**19 - Pediatrics**

**Chapter 268. Approach to the Care of Normal Infants and Children**

## Introduction

Routine care for infants and children aims to promote healthy development through education, routine vaccination, and early detection and treatment of disease.

## Evaluation and Care of the Normal Neonate

Hand washing is critical for all personnel to prevent transmission of infection.

Active participation in the birth by the mother and her partner helps them adapt to parenting.

### The First Few Hours

Immediately at delivery, the neonate's respiratory effort, heart rate, color, tone, and reflex irritability should be assessed; all are key components of the Apgar score assigned at 1 min and 5 min after birth (see Table 274-2 on p. 2770). Apgar scores between 8 and 10 indicate that the neonate is making a smooth transition to extrauterine life; scores ≤ 7 at 5 min (particularly if sustained beyond 10 min) are linked to higher neonatal morbidity and mortality rates. Many normal neonates have cyanosis 1 min after birth that clears by 5 min. Cyanosis that does not clear may indicate congenital cardiopulmonary anomalies or CNS depression.

In addition to Apgar scoring, neonates should be evaluated for gross deformities (eg, clubfoot, polydactyly) and other important abnormalities (eg, heart murmurs). The evaluation should ideally be done under a radiant warmer with the family close by.

Preventive interventions include administration into both eyes of an antimicrobial agent (eg, 0.5% erythromycin 1 cm ribbon, 1% tetracycline 1 cm ribbon, 1% silver nitrate solution 2 drops; in some countries, 2.5% povidone iodine drops) to prevent gonococcal and chlamydial ophthalmia and administration of vitamin K 1 mg IM to prevent hemorrhagic disease of the newborn.

Subsequently, the neonate is bathed, wrapped, and brought to the family. The head should be covered with a cap to prevent heat loss. Rooming-in and early breastfeeding should be encouraged so the family can get to know the baby and can receive guidance from staff members during the hospital stay. Breastfeeding is more likely to be successful when the family is given frequent and adequate support.

### The First Few Days

#### Physical Examination

A thorough physical examination should be done within 24 h. Doing the examination with the mother and other family members present allows them to ask questions and the clinician to point out physical findings and provide anticipatory guidance.

Basic measurements include length, weight, and head circumference (see p. 2756). Length is measured from crown to heel; normal values are based on gestational age and should be plotted on a standard growth chart. When gestational age is uncertain or when the infant seems large or small for age, the gestational age can be precisely determined using physical and neuromuscular findings (see Fig. 268-1). These methods are typically accurate to ± 2 wk.

Many clinicians begin with examination of the heart and lungs, followed by a systematic head-to-toe examination, looking particularly for signs of birth trauma and congenital abnormalities.

**Cardiorespiratory system:** The heart and lungs are evaluated when the infant is quiet.

The clinician should identify where the heart sounds are loudest to exclude dextrocardia. Heart rate (normal: 100 to 160 beats/min) and rhythm are checked. Rhythm should be regular, although an irregular rhythm from premature atrial or ventricular contractions is not uncommon. A murmur heard in the first 24 h is most commonly caused by a patent ductus arteriosus. Daily heart examination confirms the disappearance of this murmur, usually within 3 days. Femoral pulses are checked and compared with brachial pulses. A weak or delayed femoral pulse suggests aortic coarctation or other left ventricular outflow tract obstruction. Central cyanosis suggests congenital heart disease, pulmonary disease, or sepsis.

The respiratory system is evaluated by counting respirations over a full minute because breathing in neonates is irregular; normal rate is 40 to 60 breaths/min. The chest wall should be examined for symmetry, and lung sounds should be equal throughout. Grunting, nasal flaring, and retractions are signs of respiratory distress.

[**Fig. 268-1.** Assessment of gestational age—new Ballard score.]

**Head and neck:** In a vertex delivery, the head is commonly molded with overriding of the cranial bones at the sutures and some swelling and ecchymosis of the scalp (caput succedaneum). In a breech delivery, the head has less molding, with swelling and ecchymosis occurring in the presenting part (ie, buttocks, genitals, or feet). The fontanelles vary in diameter from a fingertip breadth to several centimeters. A large anterior fontanelle may be a sign of hypothyroidism.

A cephalohematoma is a common finding; blood accumulates between the periosteum and the bone, producing a swelling that does not cross suture lines. It may occur over one or both parietal bones and occasionally over the occiput. Cephalohematomas usually are not evident until soft-tissue edema subsides; they gradually disappear over several months.

Head size and shape are inspected to detect congenital hydrocephalus.

Numerous genetic syndromes cause craniofacial abnormalities (see p. 2970). The face is inspected for symmetry and normal development (particularly of the mandible, palate, pinnae, and external auditory canals).

The eyes may be easier to examine the day after birth because the birth process causes swelling around the eyelids. Eyes should be examined for the red reflex; its absence may indicate glaucoma, cataracts, or retinoblastoma. Subconjunctival hemorrhages are common and caused by forces exerted during delivery.

Low-set ears may indicate genetic anomalies, including trisomy 21. Malformed ears, external auditory canals, or both may be present in many genetic syndromes. Clinicians should look for external ear pits or tags, which are sometimes associated with hearing loss and kidney abnormalities.

The clinician should inspect and palpate the palate to check for soft or hard palate defects. Orofacial clefts are among the most common congenital defects. Some neonates are born with an epulis (a benign hamartoma of the gum), which, if large enough, can cause feeding difficulties and may obstruct the airway. These lesions can be removed; they do not recur. Some neonates are born with primary or natal teeth. Natal teeth do not have roots and may need to be removed to prevent them from falling out and being aspirated. Inclusion cysts called Epstein's pearls may occur on the roof of the mouth.

When examining the neck, the clinician must lift the chin to look for abnormalities such as cystic hygromas, goiters, and branchial arch remnants. Torticollis can be caused by a sternocleidomastoid hematoma due to birth trauma.

**Abdomen and pelvis:** The abdomen should be round and symmetric. A scaphoid abdomen may indicate a diaphragmatic hernia, allowing the intestine to migrate through it to the chest cavity in utero; pulmonary hypoplasia and postnatal respiratory distress may result. An asymmetric abdomen suggests an abdominal mass. Splenomegaly suggests congenital infection or hemolytic anemia. The kidneys may be palpable with deep palpation; the left is more easily palpated than the right. Large kidneys may indicate obstruction, tumor, or cystic disease. The liver is normally palpable 1 to 2 cm below the costal margin. An

umbilical hernia, due to a weakness of the umbilical ring musculature, is common but rarely significant. The presence of a normally placed, patent anus should be confirmed.

In boys, the penis should be examined for hypospadias or epispadias. In term boys, the testes should be in the scrotum. Scrotal swelling may signify hydrocele, inguinal hernia, or, more rarely, testicular torsion. With hydrocele, the scrotum transilluminates. Torsion, a surgical emergency, causes ecchymosis and firmness.

In term girls, the labia are prominent. Mucoid vaginal and serosanguineous secretions (pseudomenses) are normal; they result from exposure to maternal hormones in utero and withdrawal at birth. A small tag of hymenal tissue at the posterior fourchette, believed to be due to maternal hormonal stimulation, is sometimes present but disappears over a few weeks.

Ambiguous genitals (intersex) may indicate several uncommon disorders (eg, congenital adrenal hyperplasia; 5α-reductase deficiency; Klinefelter's, Turner's, or Swyer syndrome). Referral to an endocrinologist is indicated for evaluation and a discussion with the family about benefits and risks of immediate vs delayed sex assignment.

**Musculoskeletal system:** The extremities are examined for deformities, amputations (incomplete or missing limbs), contractures, and maldevelopment. Brachial nerve palsy due to birth trauma may manifest as limited or no spontaneous arm movement on the affected side, sometimes with adduction and internal rotation of the shoulder and pronation of the forearm.

The spine is inspected for signs of spina bifida, particularly exposure of the meninges, spinal cord, or both (meningomyelocele).

Orthopedic examination includes palpation of long bones for birth trauma (particularly clavicle fracture) but focuses on detection of hip dysplasia. Risk factors for dysplasia include female sex, breech position in utero, twin gestation, and family history. The Barlow and Ortolani maneuvers are used to check for dysplasia. These maneuvers must be done when neonates are quiet. The position is the same for both: Neonates are placed on their back with their hips and knees flexed to 90° (the feet will be off the bed), feet facing the clinician, who places an index finger on the greater trochanter and a thumb on the lesser trochanter.

For the Barlow maneuver, the clinician adducts the hip (ie, the knee is drawn across the body) while pushing the thigh posteriorly. A clunk indicates that the head of the femur has moved out of the acetabulum; the Ortolani maneuver then relocates it and confirms the diagnosis.

For the Ortolani maneuver, the hip is returned to the starting position; then the hip being tested is abducted (ie, the knee is moved away from the midline toward the examining table into a frog-leg position) and gently pulled anteriorly. A palpable clunk of the femoral head with abduction signifies movement of an already dislocated femoral head into the acetabulum and constitutes a positive test for hip dysplasia.

The maneuver may be falsely negative in infants > 3 mo because of tighter hip muscles and ligaments. If the examination is equivocal or the infant is at high risk (eg, girls who were in the breech position), hip ultrasonography should be done at 4 to 6 wk; some experts recommend screening ultrasonography at 4 to 6 wk for all infants with risk factors.

**Neurologic system:** The neonate's tone, level of alertness, movement of extremities, and reflexes are evaluated. Typically, neonatal reflexes, including the Moro, suck, and rooting reflexes, are elicited:

- **Moro reflex:** The neonate's response to startle is elicited by pulling the arms slightly off the bed and releasing suddenly. In response, the neonate extends the arms with fingers extended, flexes the hips, and cries.

- **Rooting reflex:** Stroking the neonate's cheek or lateral lip prompts the neonate to turn the head toward the touch and open the mouth.

• **Suck reflex:** A pacifier or gloved finger is used to elicit this reflex.

These reflexes are present for several months after birth and are markers of a normal peripheral nervous system.

**Skin:** A neonate's skin is usually ruddy; cyanosis of fingers and toes is common in the first few hours. Vernix caseosa covers most neonates > 24 wk gestation. Dryness and peeling often develop within days, especially at wrist and ankle creases.

Petechiae may occur in areas traumatized during delivery, such as the face when the face is the presenting part; however, neonates with diffuse petechiae should be evaluated for thrombocytopenia.

Many neonates have erythema toxicum, a benign rash with an erythematous base and a white or yellow papule. This rash, which usually appears 24 h after birth, is scattered over the body and can last for up to 2 wk.

### Screening

Screening recommendations vary by clinical context and state requirements.

Blood typing is indicated when the mother has type O or Rh-negative blood or when minor blood antigens are present because hemolytic disease of the newborn (see p. 2665) is a risk.

All neonates are evaluated for jaundice throughout the hospital stay and before discharge. The risk of hyperbilirubinemia is assessed using risk criteria, measurement of bilirubin, or both (see also p. 2788). Bilirubin can be measured transcutaneously or in serum. Many hospitals screen all neonates and use a predictive nomogram to determine the risk of extreme hyperbilirubinemia. Follow-up is based on age at discharge, predischarge bilirubin level, and risk of developing jaundice.

Most states test for specific inherited diseases (see p. 3009), including phenylketonuria, tyrosinemia, biotinidase deficiency, homocystinuria, maple syrup urine disease, galactosemia, congenital adrenal hyperplasia, sickle cell disease, and hypothyroidism. Some states also include testing for cystic fibrosis, disorders of fatty acid oxidation, and other organic acidemias.

HIV screening is required by some states and is indicated for children of mothers known to be HIV-positive or those engaging in HIV high-risk behaviors.

Toxicology screening is indicated when any of the following are present: maternal history of drug use, unexplained placental abruption, unexplained premature labor, poor prenatal care, or evidence of drug withdrawal in the neonate.

**Hearing screening** varies by state. Some screen only high-risk neonates (see Table 268-1); others screen all. Initial screening often involves using a handheld device to test for echoes produced by healthy ears in response to soft clicks (otoacoustic emissions); if this test is abnormal, auditory brain stem response (ABR) testing is done. Some institutions use ABR testing as an initial screening test. Further testing by an audiologist may be needed.

### Routine Care and Observation

Neonates can be bathed (if the parents wish) once their temperature has stabilized at 37° C for 2 h. The umbilical cord clamp can be removed when the cord appears dry, usually at 24 h. The umbilical stump should be kept clean and dry to prevent infection. Some centers apply isopropyl alcohol several times a day or a single dose of triple dye, a bacteriostatic agent believed to decrease bacterial colonization of the cord. The cord should be observed daily for redness or drainage because it can be a portal for infection.

[**Table 268-1.** High-Risk Factors for Hearing Deficits in Neonates]

Circumcision, if desired by the family, can be safely done, using a local anesthetic, within the first few

days of life. Circumcision should be delayed if the mother has taken anticoagulants or aspirin, if there is a family history of bleeding disorders, or if the neonate has displacement of the urethral meatus, hypospadias, or any other abnormality of the glans or penis (because the prepuce may be used later in plastic surgical repair). Circumcision should not be done if the neonate has hemophilia or another bleeding disorder.

Most neonates lose 5 to 7% of their birth weight during the first few days of life, primarily because fluid is lost in urine and insensibly and secondarily because meconium is passed, vernix caseosa is lost, and the umbilical cord dries.

In the first 2 days, urine may stain the diaper orange or pink because of urate crystals, which are a normal result of urine concentration. Most neonates void within 24 h after birth; the average time of first void is 7 to 9 h after birth, and most void at least 2 times in the 2nd 24 h of life. A delay in voiding is more common among male neonates and may result from a tight foreskin; a male neonate's inability to void may indicate posterior urethral valves. Circumcision is usually delayed until at least after the first void; not voiding within 12 h of the procedure may indicate a complication.

If meconium has not been passed within 24 h, the clinician should consider evaluating the neonate for anatomic abnormalities, such as imperforate anus, Hirschsprung's disease, and cystic fibrosis, which can cause meconium ileus.

### Hospital Discharge

Neonates discharged within 48 h should be evaluated within 2 to 3 days to assess feeding success (breast or formula), hydration, and jaundice (for those at increased risk). Follow-up for neonates discharged after 48 h should be based on risk factors, including those for jaundice and for breastfeeding difficulties.

## Nutrition in Infants

If the delivery was uncomplicated and the neonate is alert and healthy, the neonate can be brought to the mother for feeding immediately. Successful breastfeeding is enhanced by putting the neonate to the breast as soon as possible after delivery. Spitting mucus after feeding is common (because gastroesophageal smooth muscle is lax) but should subside within 48 h. If spitting mucus or emesis persists past 48 h or if vomit is bilious, complete evaluation of the upper GI and respiratory tracts is needed to detect congenital GI anomalies (see p. 2975).

Daily fluid and calorie requirements vary with age and are proportionately greater in neonates and infants than in older children and adults (see
Tables 268-2 and
268-3). Relative requirements for protein and energy (g or kcal/kg body weight) decline progressively from the end of infancy through adolescence (see
Table 1-4 on p. 5), although absolute requirements increase. For example, protein requirements decrease from 1.2 g/kg/day at 1 yr to 0.9 g/kg/day at 18 yr, and mean relative energy requirements decrease from 100 kcal/kg at 1 yr to 40 kcal/kg in late adolescence. Nutritional recommendations are generally not evidence-based. Requirements for vitamins depend on the intake of calories, protein, fat, carbohydrate, and amino acids.

**Feeding problems:** Minor variations in day-to-day food intake are common and, although often of concern to parents, usually require only reassurance and guidance unless there are signs of disease or changes in growth parameters, particularly weight (changes in the child's percentile rank on standard growth curves are more significant than absolute changes).

[**Table 268-2.** Range of Average Water Requirements of Children at Different Ages Under Ordinary Conditions]

Loss of > 5 to 7% of birth weight in the first week indicates undernutrition. Birth weight should be regained by 2 wk, and a subsequent gain of about 20 to 30 g/day (1 oz/day) is expected for the first few

months. Infants should double their birth weight by about 6 mo.

**Breastfeeding**

Breast milk is the nutrition of choice. The American Academy of Pediatrics (AAP) recommends exclusive breastfeeding for a minimum of 6 mo and introduction of appropriate solid food from 6 mo to 1 yr. Beyond 1 yr, breastfeeding continues for as long as both infant and mother desire, although after 1 yr breastfeeding should complement a full diet of solid foods and fluids. To encourage breastfeeding, practitioners should begin discussions prenatally, mentioning the multiple advantages:

- **For the child:** Nutritional and cognitive advantages and protection against infection, allergies, obesity, Crohn's disease, and diabetes

- **For the mother:** Reduced fertility during lactation, more rapid return to normal prepartum condition (eg, uterine involution, weight loss), and protection against osteoporosis, obesity, and ovarian and premenopausal breast cancers

Milk production is fully established in primiparas by 72 to 96 h and in less time in multiparas. The first milk produced is colostrum, a high-calorie, high-protein, thin yellow fluid that is immunoprotective because it is rich in antibodies, lymphocytes, and macrophages; colostrum also stimulates passage of meconium. Subsequent breast milk has the following characteristics:

- Has a high lactose content, providing a readily available energy source compatible with neonatal enzymes

- Contains large amounts of vitamin E, an important antioxidant that may help prevent anemia by increasing erythrocyte life span

- Has a Ca:P ratio of 2:1, which prevents Ca-deficiency tetany

- Favorably changes the pH of stools and the intestinal flora, thus protecting against bacterial diarrhea

- Transfers protective antibodies from mother to infant

- Contains cholesterol and taurine, which are important to brain growth, regardless of the mother's diet

- Is a natural source of ω-3 and ω-6 fatty acids

These fatty acids and their very long-chain polyunsaturated derivatives (LC-PUFAS), arachidonic acid (ARA) and docosahexaenoic acid (DHA), are believed to contribute to the enhanced visual and cognitive outcomes of breastfed compared with formula-fed infants.

If the mother's diet is sufficiently diverse, no dietary or vitamin supplementation is needed

[Table 268-3. Calorie Requirements at Different Ages*]

for the mother or her term breastfed infant, with the exception of vitamin D 200 units once/day beginning in the first 2 mo for all infants exclusively breastfed. Premature and dark-skinned infants and infants with limited sunlight exposure (residence in northern climates) are especially at risk. After 6 mo, breastfed infants in homes where the water does not have adequate fluoride (supplemental or natural) should be given fluoride drops. Clinicians can obtain information about fluoride content from a local dentist.

Infants < 6 mo should not be given additional water because hyponatremia is a risk.

**Technique**

The mother should use whatever comfortable, relaxed position works best and should support her breast with her hand to ensure that it is centered in the infant's mouth, minimizing any soreness. The center of

the infant's lower lip should be stimulated with the nipple so that rooting occurs and the mouth opens wide. The infant should be encouraged to take in as much of the breast and areola as possible, placing the lips 2.5 to 4 cm from the base of the nipple. The infant's tongue then compresses the nipple against the hard palate. Initially, it takes at least 2 min for the let-down reflex to occur. Volume of milk increases as the infant grows and stimulation from suckling increases. Feeding duration is usually determined by the infant. Some mothers require a breast pump to increase or maintain milk production; in most mothers, a total of 90 min/day of breast pumping divided into 6 to 8 sessions produces enough milk for an infant who is not directly breastfed.

The infant should nurse on one breast until the breast softens and suckling slows or stops. The mother can then break suction with a finger before removing the infant from one breast and offering the infant the second. In the first days after birth, infants may nurse on only one side; then the mother should alternate sides with each feeding. If the infant tends to fall asleep before adequately nursing, the mother can remove the infant when suckling slows, burp the infant, and move the infant to the other side. This switch keeps the infant awake for feedings and stimulates milk production in both breasts.

Mothers should be encouraged to feed on demand or about every 1 1/2 to 3 h (8 to 12 feedings/day), a frequency that gradually decreases over time; some neonates < 2500 g may need to feed even more frequently to prevent hypoglycemia. In the first few days, neonates may need to be wakened and stimulated; small infants and late preterm infants should not be allowed to sleep long periods at night. Large full-term infants who are feeding well (as evidenced by stooling pattern) can sleep longer. Eventually, a schedule that allows infants to sleep as long as possible at night is usually best for the infant and family.

Mothers who work outside the home can pump breast milk to maintain milk production while they are separated from their infants. Frequency varies but should approximate the infant's feeding schedule. Pumped breast milk should be immediately refrigerated if it is to be used within 48 h and immediately frozen if it is to be used after 48 h. Refrigerated milk that is not used within 96 h should be discarded because risk of bacterial contamination is high. Frozen milk should be thawed by placing it in warm water; microwaving is not recommended.

### Infant Complications

The primary complication is underfeeding, which may lead to dehydration and hyperbilirubinemia. Risk factors for underfeeding include small or premature infants and mothers who are primiparous, who become ill, or who have had difficult or operative deliveries. A rough assessment of feeding adequacy can be made by daily diaper counts. By age 5 days, a normal neonate wets at least 6 diapers/day and soils at least 4 diapers/day; lower numbers suggest underhydration and undernutrition. Also, stools should have changed from dark meconium at birth to light brown and then yellow. Weight is also a reasonable parameter to follow (see p. 2704); not attaining growth landmarks suggests undernutrition. Constant fussiness before age 6 wk (when colic may develop unrelated to hunger or thirst) may also indicate underfeeding. Dehydration should be suspected if vigor of the infant's cry decreases or skin becomes turgid; lethargy and sleepiness are extreme signs of dehydration and should prompt testing for hypernatremia.

### Maternal Complications

Common maternal complications include breast engorgement, sore nipples, plugged ducts, mastitis, and anxiety.

**Breast engorgement**, which occurs during early lactation and may last 24 to 48 h, may be minimized by early frequent feeding. A comfortable nursing brassiere worn 24 h/day can help, as can applying cool compresses after breastfeeding and taking a mild analgesic (eg, ibuprofen). Just before breastfeeding, mothers may have to use massage and warm compresses and express breast milk manually to allow

[
**Table 268-4.** Some Drugs Contraindicated for Breastfeeding Mothers]

infants to get the swollen areola into their mouth. Excessive expression of milk between feedings facilitates engorgement, so expression should be done only enough to relieve discomfort.

For **sore nipples**, the infant's position should be checked; sometimes the infant draws in a lip and sucks it, which irritates the nipple. The mother can ease the lip out with her thumb. After feedings, she can express a little milk, letting the milk dry on the nipples. After breastfeeding, cool compresses reduce engorgement and provide further relief.

**Plugged ducts** manifest as mildly tender lumps in the breasts of lactating women who have no other systemic signs of illness. The lumps appear in different places and are not tender. Continued breastfeeding ensures adequate emptying of the breast. Warm compresses and massage of the affected area before breastfeeding may further aid emptying. Women may also alternate positions because different areas of the breast empty better depending on the infant's position at the breast. A good nursing brassiere is helpful because regular brassieres with wire stays or constricting straps may contribute to milk stasis in a compressed area.

**Mastitis** is common and manifests as a tender, warm, swollen, wedge-shaped area of breast. It is caused by engorgement, blocking, or plugging of an area of the breast; infection may occur secondarily, most often with penicillin-resistant *Staphylococcus aureus* and less commonly with *Streptococcus* sp or *Escherichia coli*. With infection, fever ≥ 38.5° C, chills, and flu-like aching may develop. Diagnosis is by history and examination. Cell counts (WBCs > $10^6$/mL) and cultures of breast milk (bacteria > $10^3$/mL) may distinguish infectious from noninfectious mastitis. If symptoms are mild and present < 24 h, conservative management (milk removal via breastfeeding or pumping, compresses, analgesics, a supportive brassiere, and stress reduction) may be sufficient. If symptoms do not lessen in 12 to 24 h or if the woman is acutely ill, antibiotics that are safe for breastfeeding infants and effective against *S. aureus* (eg, dicloxacillin, cloxacillin, or cephalexin 500 mg po qid) should be started; duration of treatment is 10 to 14 days. Community-acquired methicillin-resistant *S. aureus* should be considered if cases do not respond promptly to these measures or if an abscess is present. Complications of delayed treatment are recurrence and abscess formation. Breastfeeding may continue during treatment.

**Maternal anxiety**, frustration, and feelings of inadequacy may result from lack of experience with breastfeeding, mechanical difficulties holding the infant and getting the infant to latch on and suck, fatigue, difficulty assessing whether nourishment is adequate, and postpartum physiologic changes. These factors and emotions are the most common reasons mothers stop breastfeeding. Early follow-up with a pediatrician or consultation with a lactation specialist is helpful and effective for preventing early breastfeeding termination.

### Drugs

Breastfeeding mothers should avoid taking drugs if possible. When drug therapy is necessary, the mother should avoid contraindicated drugs and drugs that suppress lactation (eg, bromocriptine, levodopa, trazodone). The US National Library of Medicine maintains an extensive database regarding drugs and breastfeeding, which should be consulted regarding use of or exposure to specific drugs or classes of drugs. For some common drugs contraindicated for breastfeeding mothers, see Table 268-4.

When drug treatment is necessary, the safest known alternative should be used; when possible, most drugs should be taken immediately after breastfeeding or before the infant's longest sleep period, although this strategy is less helpful with neonates who nurse frequently and exclusively. Knowledge of the adverse effects of most drugs comes from case reports and small studies. Safety of some (eg, acetaminophen, ibuprofen, cephalosporins, insulin) has been determined by extensive research, but others are considered safe only because there are no case reports of adverse effects. Drugs with a long history of use are generally safer than newer drugs for which few data exist.

### Weaning

Weaning can occur whenever the mother and infant mutually desire, although preferably not until the infant is at least 12 mo old. Gradual weaning over weeks or months during the time solid food is

introduced is most common; some mothers and infants stop abruptly without problems, but others continue breastfeeding 1 or 2 times/day for 18 to 24 mo or longer. There is no correct schedule.

**Formula Feeding**

The only acceptable alternative to breastfeeding during the first year is formula; water can cause hyponatremia, and whole cow's milk is not nutritionally complete. Advantages of formula feeding include the ability to quantify the amount of nourishment and the ability of family members to participate in feedings. But all other factors being equal, these advantages are outweighed by the undisputed health benefits of breastfeeding.

Commercial infant formulas are available as powders, concentrated liquids, and prediluted (ready-to-feed) liquids; each contains vitamins, and most are supplemented with iron. Formula should be prepared with fluoridated water; fluoride drops (0.25 mg/day po) should be given after age 6 mo in areas where fluoridated water is unavailable and when using prediluted liquid formula, which is prepared with nonfluoridated water.

Choice of formula is based on infant need. Cow's milk-based formula is the standard choice unless excessive fussiness, spitting up, or gas suggests sensitivity to cow's milk protein or lactose intolerance (extremely rare in neonates); then, a soy formula may be recommended. All soy formulas in the US are lactose free, but some infants allergic to cow's milk protein may also be allergic to soy protein; then, a hydrolyzed formula is indicated. This formula may be derived from cow's milk but has triglycerides, proteins, and monosaccharides predigested to smaller, nonallergenic components. True elemental formulas (proteins broken down to amino acids) are available for the few infants who have allergic reactions to hydrolyzed formula. Special carbohydrate-free formulas are also available.

Bottle-fed infants are fed on demand, but because formula is digested more slowly than breast milk, they typically can go longer between feedings, initially every 3 to 4 h. Initial volumes of 15 to 60 mL (0.5 to 2 oz) can be increased gradually during the first week of life up to 90 mL (3 oz) about 6 times/day, which supplies about 120 kcal/kg at 1 wk for a 3-kg infant.

**Solid Foods**

The WHO recommends exclusive breastfeeding for about 6 mo, with introduction of solid foods thereafter. Other organizations suggest introducing solid food between age 4 mo and 6 mo while continuing breastfeeding or bottle-feeding. Before 4 mo, solid food is not needed nutritionally, and the extrusion reflex, in which the tongue pushes out anything placed in the mouth, makes feeding of solids difficult.

Initially, solid foods should be introduced after breastfeeding or bottle-feeding to ensure adequate nourishment. Iron-fortified rice cereal is traditionally the first food introduced because it is nonallergenic, easily digested, and a needed source of iron. It is generally recommended that one new, single-ingredient food be introduced per week so that food allergies can be identified. Foods need not be introduced in any specific order, although in general they can gradually be introduced by increasingly coarser textures—eg, from rice cereal to soft table food to chopped table food. Meat, pureed to prevent aspiration, is a good source of iron and zinc (both of which can be limited in the diet of an exclusively breastfed infant) and is therefore a good early complementary food. Vegetarian infants can get adequate iron from iron-fortified cereals and grains, peas, and dried beans and adequate zinc from yeast-fermented whole-grain breads and fortified infant cereals.

Home preparations are equivalent to commercial foods, but commercial preparations of carrots, beets, turnips, collard greens, and spinach are preferable before 1 yr if available because they are screened for nitrates. High nitrate levels, which can induce methemoglobinemia in young children, are present when vegetables are grown using water supplies contaminated by fertilizer.

Foods to avoid include

• Eggs, peanuts, and cow's milk, usually until children are 1 yr to prevent food sensitivities

- Honey until 1 yr because infant botulism is a risk

- Foods that, if aspirated, could obstruct the child's airway (eg, nuts, round candies, popcorn, hot dogs, meat unless it is pureed, grapes unless they are cut into small pieces)

Nuts should be avoided until age 2 or 3 because they do not fully dissolve with mastication and small pieces can be aspirated whether bronchial obstruction is present or not, causing pneumonia and other complications.

At or after 1 yr, children can begin drinking whole cow's milk; reduced-fat milk is avoided until 2 yr, when their diet essentially resembles that of the rest of the family. Parents should be advised to limit milk intake to 16 to 20 oz/day in young children; higher intake can reduce intake of other important sources of nutrition and contribute to iron deficiency.

Juice is a poor source of nutrition, contributes to dental caries, and should be limited to 4 to 6 oz/day or avoided altogether.

By about 1 yr, growth rate usually slows. Children require less food and may refuse it at some meals. Parents should be reassured and advised to assess a child's intake over a week rather than at a single meal or during a day. Underfeeding of solid food is only a concern when children do not achieve expected weights at an appropriate rate.

## Health Supervision of the Well Child

Well-child visits aim to do the following:

- Promote health

- Prevent disease through routine vaccinations and education

- Detect and treat disease early

- Guide parents to optimize the child's emotional and intellectual development

The American Academy of Pediatrics (AAP) has recommended preventive health care schedules (see Tables 268-5, 268-6, and 268-7) for children who have no significant health problems and who are growing and developing satisfactorily. Those who do not meet these criteria should have more frequent and intensive visits. If children come under care for the first time late on the schedule or if any items are not done at the suggested age, children should be brought up to date as soon as possible. Children who have developmental, psychosocial, or chronic disease may require more frequent counseling and treatment visits that are separate from preventive care visits. If parents are high risk, are parents for the first time, or wish to have a conference, a prenatal visit with the pediatrician is appropriate.

In addition to physical examination, practitioners should evaluate the child's motor, cognitive, and social development and parent-child interactions. These assessments can be made by taking a thorough history from parents and child, making direct observations, and sometimes seeking information from outside sources such as teachers and child care providers. Tools are available for office use to facilitate evaluation of cognitive and social development (see p. 2757).

Both physical examination and screening are important parts of preventive health care in infants and children. Most parameters, such as weight, are included for all children; others are applicable to selected patients, such as lead screening in 1- and 2-yr-olds.

**Anticipatory guidance** is also important to preventive health care. It includes

- Obtaining information about the child and parents (eg, via questionnaire, interview, or evaluation)

- Working with parents to promote health (forming a therapeutic alliance)
- Teaching parents what to expect in their child's development, how they can help enhance development (eg, by establishing a healthy lifestyle), and what the benefits of a healthy lifestyle are

[**Table 268-5.** Recommendations for Preventive Care During Infancy[a]]

[**Table 268-6.** Recommendations for Preventive Care During Early and Middle Childhood[a]]

[**Table 268-7.** Recommendations for Preventive Care During Adolescence[a]]

**Physical Examination**

**Growth:** Length (crown-heel) or height (once children can stand) and weight should be measured at each visit. Head circumference should be measured at each visit through 24 mo. Growth rate should be monitored using a growth curve with percentiles; deviations in these parameters should be evaluated (see Ch. 271).

**Blood pressure:** Starting at age 3 yr, BP should be routinely checked by using an appropriatesized cuff. The width of the inflatable rubber bag portion of the BP cuff should be about 40% of the circumference of the upper arm, and its length should cover 80 to 100% of the circumference. If no available cuff fits the criteria, using the larger cuff is better.

Systolic and diastolic BPs are considered normal if they are < 90th percentile; actual values for each percentile vary by sex, age, and size (as height percentile), so reference to published tables is essential. Systolic and diastolic BP measurements between the 90th and 95th percentiles should prompt continued observation and assessment of hypertensive risk factors. If measurements are consistently ≥ 95th percentile, children should be considered hypertensive, and a cause should be determined.

**Head:** The most common abnormality is fluid in the middle ear (otitis media with effusion), manifesting as a change in the appearance of the tympanic membrane. Clinicians should screen for hearing deficits (see p. 2717).

Eyes should be assessed at each visit. Clinicians should check for esotropia or exotropia; for abnormalities in globe size (suggesting congenital glaucoma); for a difference in pupil size, iris color, or both (suggesting Horner's syndrome, trauma, or neuroblastoma; asymmetric pupils may be normal or represent an ocular, autonomic, or intracranial disorder); and for absence or distortion of the red reflex (suggesting cataract or retinoblastoma).

Ptosis and eyelid hemangioma obscure vision and require attention. Infants born at < 32 wk gestation should be assessed by an ophthalmologist for evidence of retinopathy of prematurity (see p. 2781) and for refractive errors, which are more common. By age 3 or 4 yr, vision testing by Snellen charts or newer testing machines can be used. E charts are better than pictures; visual acuity of < 20/30 should be evaluated by an ophthalmologist.

Detection of dental caries is important, and referral to a dentist should be made if cavities are present, even in children who have only deciduous teeth. Thrush is common among infants and not usually a sign of immunosuppression.

**Heart:** Auscultation is done to identify new murmurs, heart rate abnormalities, or rhythm disturbances; benign flow murmurs are common and need to be distinguished from pathologic murmurs. The chest wall is palpated for the apical impulse to check for cardiomegaly; femoral pulses are palpated to check for asymmetry, which suggests aortic coarctation.

**Abdomen:** Palpation is repeated at every visit because many masses, particularly Wilms' tumor and neuroblastoma, may be apparent only as children grow. Stool is often palpable in the left lower quadrant.

**Spine and extremities:** Children old enough to stand should be screened for scoliosis by observing posture, shoulder tip and scapular symmetry, torso list, and especially paraspinal asymmetry when children bend forward (see p. 2912).

At each visit before children start to walk, they should be checked for developmental dysplasia of the hip. The Barlow and Ortolani maneuvers (see p. 2701) are used until about age 4 mo. After that, dysplasia may be suggested by unequal leg length, adductor tightness, or asymmetry of abduction or leg creases.

Toeing-in can result from adduction of the forefoot, tibial torsion, or femoral torsion. Only pronounced cases require therapy and referral to an orthopedist.

**Genital examination:** Girls should be offered a pelvic examination and Papanicolaou (Pap) testing at age 18 or when they become sexually active—whichever occurs first. All sexually active patients should be screened for sexually transmitted diseases.

Testicular and inguinal evaluation should be done at every visit, specifically looking for undescended testes in infants and young boys, testicular masses in older adolescents, and inguinal hernia in boys of all ages.

### Screening

**Blood tests:** To detect iron deficiency, clinicians should determine Hct or Hb at age 9 to 12 mo in term infants, at age 5 to 6 mo in premature infants, and annually in menstruating adolescents. Testing for Hb S can be done at age 6 to 9 mo (see p. 944) if not done as part of neonatal screening.

Recommendations for blood testing for lead exposure vary by state. In general, testing should be done between ages 9 mo and 1 yr in children at risk of exposure (those living in housing built before 1980) and should be repeated at 24 mo. If the clinician is not sure of a child's risk, testing should be done. Levels > 10 µg/dL (> 0.48 µmol/L) pose a risk of neurologic damage (see p. 3343), although some experts question this threshold because they believe that any lead in the system can be toxic.

Cholesterol screening is indicated for children > 2 yr who are at high risk because of family history. If other risk factors are present or family history is uncertain, testing is at the discretion of the physician.

**Hearing tests:** (See also Ch. 47.) Parents may suspect a hearing deficit if their child ceases responding appropriately to noises or voices or does not understand or develop speech (see Table 268-8). Because hearing deficits impair language development, hearing problems must be remedied as early as possible. The clinician therefore should seek parental input about hearing at every visit during early childhood and be prepared to do formal testing or refer to an audiologist whenever there is any question of the child's ability to hear.

Audiometry can be done in the primary care setting; most other audiologic procedures (eg, otoacoustic emission testing, brain stem auditory evoked response) should be done by an audiologist. Conventional audiometry can be used for children beginning at about age 3 yr; young children can also be tested by observing their responses to sounds made through headphones, watching their attempts to localize the sound or complete a simple task. Tympanometry, another in-office procedure (see p. 435), can be used with children of any age and is useful for evaluating middle ear function. Abnormal tympanograms often denote eustachian tube dysfunction or the presence of middle ear fluid that cannot be detected during otoscopic examination. Pneumatic otoscopy is helpful in evaluating middle ear status, but combining it with tympanometry is more informative than either procedure alone.

[**Table 268-8.** Normal Hearing in Very Young Children*]

[
**Table 268-9.** Case Rates of Some Diseases Preventable by Vaccines]

**Other screening tests:** Tuberculin testing should be done if children have been exposed to TB (eg, to

an infected family member or close contact), if they have had a family member with a positive tuberculin test, if they were born in developing countries, or if their parents are new immigrants from those countries or have been recently incarcerated.

For sexually active adolescents, dipstick analysis for leukocytes and urinary testing for chlamydial infection should be done annually. Screening for cervical dysplasia should be begun within 3 yr of onset of sexual activity.

**Prevention**

Preventive counseling is part of every well-child visit and covers a broad spectrum of topics, such as recommendations to have infants sleep on their backs, injury prevention, nutritional and exercise advice, and discussions of violence, firearms, and substance abuse.

[
Table 268-10. Recommended Immunization Schedule for Ages 0-6 yr]

[
Table 268-11. Recommended Immunization Schedule for Ages 7-18 yr]

**Safety:** Recommendations for injury prevention vary by age. Some examples follow.

For infants from birth to 6 mo:

• Using a rear-facing car seat

• Reducing home water temperature to < 49° C (< 120° F)

• Preventing falls

• Using sleeping precautions: Placing infants on their back, not sharing a bed, using a firm mattress, and not allowing stuffed animals, pillows, and blankets in the crib

• Avoiding foods and objects that children can aspirate

For infants from 6 to 12 mo:

• Continuing to use a rear-facing car seat

• Continuing to place infants on their back to sleep

• Not using baby walkers

• Using safety latches on cabinets

• Preventing falls from changing tables and around stairs

• Vigilantly supervising children when in bathtubs and while learning to walk

For children aged 1 to 4 yr:

• Using an age- and weight-appropriate car seat (infants can face forward when they reach 9 kg [20 lb] and age 12 mo, but rear-facing is still the safest position)

• Reviewing automobile safety both as passenger and pedestrian

• Tying window cords

• Using safety caps and latches

• Preventing falls

• Removing handguns from the home

[
Table 268-12. Catch-Up Immunization Schedule for Ages 4 Mo-18 yr]

For children ≥ 5 yr:

• All of the above

• Using a bicycle helmet and protective sports gear

• Instructing children about safe street crossing

• Closely supervising swimming and sometimes requiring the use of life jackets during swimming

**Nutrition:** Poor nutrition underlies the epidemic of obesity in children (see p. 60). Recommendations vary by age; for children up to 2 yr, see p. 2703. As children grow older, parents can allow them some discretion in food choices, while keeping the diet within healthy parameters. Children should be guided away from frequent snacking and foods that are high in calories, salt, and sugar. Soda has been implicated as a major contributor to obesity.

**Exercise:** Physical inactivity also underlies the epidemic of obesity in children, and the benefits of exercise in maintaining good physical and emotional health should induce parents to make sure their children develop good habits early in life. During infancy and early childhood, children should be allowed to roam and explore in a safe environment under close supervision. Outdoor play should be encouraged from infancy.

As children grow older, play becomes more complex, often evolving to formal school-based athletics. Parents should set good examples and encourage both informal and formal play, always keeping safety issues in mind and promoting healthy attitudes about sportsmanship and competition. Participation in sports and activities as a family provides children with exercise and has important psychologic and developmental benefits. Screening of children before sports participation is recommended (see p. 3295).

Limits to television watching, which is linked directly to inactivity and obesity, should start at birth and be maintained throughout adolescence. Similar limits should be set for video games and noneducational computer time as children grow older.

## Vaccination

**Effectiveness of vaccination:** Vaccination has been profoundly effective in preventing serious disease (see Table 268-9). Many health care practitioners currently in practice have seen few or no cases of diseases that were once extremely common and fatal.

**Vaccination schedule:** Vaccination follows a schedule recommended by the Centers for Disease Control and Prevention, the American Academy of Pediatrics, and the American Academy of Family Physicians (see Tables 268-10, 268-11, and 268-12). The latest recommendations can be obtained at www.cdc.gov/vaccines; vaccination status should be reassessed at every visit. For adverse effects and details of administration of specific vaccines, see Ch. 131.

## Colic

**Colic is paroxysms of crying and irritability in an infant.**

Although the term colic suggests an intestinal origin, etiology is unknown. Colic often begins at about 6

wk and spontaneously abates between 3 and 4 mo. Paroxysms of crying and unhappiness develop at about the same time of day or night and continue for hours for no apparent reason. A few infants cry almost incessantly. Excessive crying may cause aerophagia, which results in flatulence and abdominal distention. Typically, colicky infants eat and gain weight well, although vigorous nonnutritive sucking may suggest excessive hunger. Colic probably has no relation to development of an insistent, impatient personality.

### Evaluation

**History and physical examination:** History should establish whether the infant's crying is outside the normal range (up to 3 h/day in a 6-wk-old infant). Then it must distinguish colic from other causes of excessive crying (see p. 2735), including fever, UTI, ear infection, and maltreatment. Thorough questioning may reveal that crying is not the chief concern but a symptom that the parents have used to justify their visiting the physician to present another problem—eg, concern over the death of a previous child or over their feelings of inability to cope with a new infant. A thorough physical examination typically detects no abnormalities but reassures parents. Physicians should also offer reassurance that they understand how stressful a colicky infant can be for parents.

**Testing:** No testing is necessary unless specific abnormalities are detected by history and examination.

### Treatment

Parents should be reassured that the infant is healthy, that the irritability is not due to poor parenting, and that colic will resolve on its own with no long-term adverse effects. The following may help:

- For infants who cry for short periods: Being held, rocked, or patted gently
- For infants who have a strong sucking urge and who fuss soon after a feeding: Opportunity to suck more (eg, a pacifier)
- If bottle-feeding takes < 15 to 20 min: Nipples with smaller holes, a pacifier, or both
- For very active, restless infants: Paradoxically, being swaddled tightly

An infant swing, music, and white noise (eg, from a vacuum cleaner, car engine, or clothes or hair dryer) may also be calming.

A milk-substitute formula may be tried briefly to determine whether infants have milk intolerance, but frequent formula switching should be avoided. Sometimes in breastfed infants, removing milk or another food from the mother's diet brings relief.

## Constipation

Constipation is responsible for up to 5% of pediatric office visits. It is defined as delay or difficulty in the passing of hard, sometimes large stools for ≥ 2 wk.

The frequency of normal bowel movements varies for infants. In the first year, the average number of bowel movements ranges from 2 to 4/day. This number also varies depending on whether infants are breastfed or formula-fed (breastfed infants have more frequent bowel movements). In general, signs of effort (eg, straining) do not signify constipation; infants only gradually develop the muscles to assist a bowel movement. After age 1 yr, children average 1 bowel movement/day.

### Etiology

Constipation in children is divided into 2 main types:

- Organic (5%)

• Functional (95%)

**Organic:** Organic causes involve specific structural, neurologic, toxic/metabolic, or intestinal disorders. They are rare but important to recognize (see Table 268-13).

The most common cause is

• Hirschsprung's disease

Other organic causes that may manifest in the neonatal period or later include

• Anorectal malformations

• Cystic fibrosis

• Metabolic disorders (eg, hypothyroidism, hypercalcemia, hyperkalemia)

• Spinal cord abnormalities

**Functional:** Functional constipation is difficulty passing stools for reasons other than organic causes.

In infants, the use of formula can lead to small, hard stools.

In older children, diets low in fiber and high in dairy lead to hard stools that are uncomfortable to pass and can cause anal fissures. Children sometimes put off having bowel movements because they have discomfort caused by fissures or because they do not want to interrupt play. To avoid having a bowel movement, children may tighten the external sphincter muscles, pushing the stool higher in the rectal vault. If this behavior is repeated, the rectum stretches to accommodate the retained stool. The urge to defecate is then decreased, and the stool becomes harder, leading to a vicious circle of painful defecation and worsened constipation. Occasionally, soft stool passes around the impacted stool and leads to stool incontinence.

Stress, toilet training, desire for control, and sexual abuse are also some of the functional causes of stool retention and subsequent constipation.

**Evaluation**

Evaluation should focus on differentiating functional constipation from constipation with an organic cause.

**History: History of present illness** in neonates should determine whether meconium has been passed at all and, if so, when. For older infants and children, history should note onset and duration of constipation, frequency and consistency of stools, and timing of symptoms—whether they began after a specific event, such as introduction of certain foods or a stressor that could lead to stool retention (eg, introduction of toilet training). Important associated symptoms include soiling (stool incontinence), discomfort during defecation, and blood on or in the stool. The composition of the diet, especially the amount of fluids and fiber, should be noted.

**Review of systems** should ask about symptoms that suggest an organic cause, including new onset of poor suck, hypotonia, and ingestion of honey before age 12 mo (infantile botulism); cold intolerance, dry skin, fatigue, hypotonia, prolonged neonatal hyperbilirubinemia, urinary frequency, and excessive thirst (endocrinopathies); change in gait, pain or weakness in lower extremities, and urinary incontinence (spinal cord defects); night sweats, fever, and weight loss (cancer); and vomiting, abdominal pain, poor growth, intermittent diarrhea, and constipation (intestinal disorders).

**Past medical history** should ask about known disorders that can cause constipation, including cystic fibrosis and celiac sprue. Exposure to constipating drugs or lead paint dust should be noted. Clinicians should ask about delayed passage of meconium within the first 24 to 48 h of life, as well as previous

episodes of constipation and family history of constipation.

**Physical examination:** The physical examination begins with general assessment of the

[**Table 268-13.** Organic Causes of Constipation in Infants and Children]

child's level of comfort or distress and overall appearance (including skin and hair condition). Height and weight should be measured and plotted on growth charts.

Examination should focus on the abdomen and anus and on the neurologic examination.

The abdomen is inspected for distention, auscultated for bowel sounds, and palpated for masses and tenderness. The anus is inspected for a fissure (taking care not to spread the buttocks so forcefully as to cause one). A digital rectal examination is done gently to check stool consistency and to obtain a sample for occult blood testing. Rectal examination should note the tightness of the rectal opening and presence or absence of stool in the rectal vault. Examination includes placement of the anus and presence of any hair tuft or pit superior to the sacrum.

[
**Table 268-14.** Treatment of Constipation]

In infants, neurologic examination focuses on tone and muscle strength. In older children, the focus is on gait, deep tendon reflexes, and signs of weakness in the lower extremities.

**Interpretation of findings:** A primary finding that suggests an organic cause in neonates is constipation from birth; those who have had a normal bowel movement are unlikely to have a significant structural disorder.

In older children, clues to an organic cause include constitutional symptoms (particularly weight loss, fever, or vomiting), poor growth (decreasing percentile on growth charts), an overall ill appearance, and any focal abnormalities detected during examination (see Table 268-13). A well-appearing child who has no other complaints besides constipation, who is not on any constipating drugs, and who has a normal examination likely has a functional disorder.

A distended rectum filled with stool or the presence of an anal fissure is consistent with functional constipation in an otherwise normal child. Constipation that began after starting a constipating drug or that coincides with a dietary change can be attributed to that drug or food. Foods that are known to be constipating include dairy (eg, milk, cheese, yogurt) and starches and processed foods that do not contain fiber. However, if constipation complaints begin after ingestion of wheat, celiac sprue should be considered. History of a new stress (eg, a new sibling) or other potential causes of stool retention behavior, with normal physical findings, support a functional etiology.

**Red flags:** The following findings are of particular concern:

• Delayed passage of meconium (> 24 to 48 h after birth)

• Hypotonia and poor suck (suggesting infant botulism)

• Abnormal gait and deep tendon reflexes (suggesting spinal cord involvement)

**Testing:** For patients whose histories are consistent with functional constipation, no tests are needed unless there is no response to conventional treatment. An abdominal x-ray should be done if patients have been unresponsive to treatment or an organic cause is suspected. Tests for organic causes should be done based on the history and physical examination (see Table 268-13):

• Barium enema, rectal manometry, and biopsy (Hirschsprung's disease)

• Plain x-rays of lumbosacral spine; MRI considered (tethered spinal cord or tumor)

- Thyroid-stimulating hormone and thyroxine (hypothyroidism)
- Blood lead level (lead poisoning)
- Stool for botulinum toxin (infant botulism)
- Sweat test and genetic testing (cystic fibrosis)
- Ca and electrolytes (metabolic derangement)
- IgA and IgG antigliadin antibodies, IgA antiendomysium antibodies, IgA antitissue glutaminase (celiac disease)

**Treatment**

Specific organic causes should be treated.

Functional constipation is ideally initially treated with

- Dietary changes
- Behavior modification

**Dietary changes** include adding prune juice to formula for infants, increasing fruits and vegetables for older infants and children, increasing water intake, and decreasing the amount of constipating foods (eg, milk, cheese).

**Behavior modification** for older children involves encouraging regular stool passage after meals if they are toilet trained and providing a reinforcement chart and encouragement to them. For children who are in the process of toilet training, it is sometimes worthwhile to give them a break from training until the constipation concern has passed.

Unresponsive constipation is treated by disimpacting the bowel and maintaining a regular diet and stool routine. Disimpaction can occur through oral or rectal agents. Oral agents require consumption of large volumes of liquid. Rectal agents can feel invasive and can be difficult to give. Both methods can be done by parents under medical supervision; however, disimpaction sometimes requires hospitalization if outpatient management is unsuccessful. Usually, infants do not require extreme measures, but if intervention is required, a glycerin suppository is typically adequate. For maintenance of healthy bowels, some children may require OTC dietary fiber supplements. These supplements require consuming 32 to 64 oz of water/day to be effective (see Table 268-14).

**Key Points**

- Functional constipation accounts for about 95% of cases.
- Organic causes are rare but need to be considered.
- Delayed passage of meconium for > 24 to 48 h after birth raises suspicion of structural disorders, especially Hirschsprung's disease.
- Early intervention with dietary and behavior changes can successfully treat functional constipation.

## Cough

Cough is a reflex that helps clear the airways of secretions, protects the airway from foreign body aspiration, and can be the manifesting symptom of a disease. Cough is one of the most common complaints for which parents bring their children to a health care practitioner.

### Etiology

Causes of cough differ depending on whether the symptoms are acute (< 4 wk) or chronic (see Table 268-15).

For **acute cough**, the most common cause is

• Viral URI

For **chronic cough**, the most common causes are

• Asthma (most common)

• Gastroesophageal reflux disorder (GERD)

• Postnasal drip

Foreign body aspiration and diseases such as cystic fibrosis and primary ciliary dyskinesia are less common, although they can all result in persistent cough.

### Evaluation

**History: History of present illness** should cover duration and quality of cough (barky, staccato, paroxysmal) and onset (sudden or indolent). The physician should ask about associated symptoms, some of which are ubiquitous (eg, runny nose, sore throat, fever). Other associated symptoms suggest a cause; they include headache, itchy eyes, and sore throat (postnasal drip); wheezing and cough with exertion (asthma); night sweats (TB); post-tussive emesis, spitting up after feedings, or apparent discomfort or arching with lying down (GERD). For children 6 mo to 4 yr, the parents should be asked about potential for foreign body aspiration, including older siblings or visitors with small toys, access to

[**Table 268-15.** Some Causes of Cough in Children]

small objects, and consumption of small, smooth foods (eg, peanuts, grapes).

**Review of systems** should note symptoms of possible causes, including abdominal pain (some bacterial pneumonias), weight loss or poor weight gain and foul-smelling stools (cystic fibrosis), and muscle soreness (possible association with viral illness or atypical pneumonia but usually not with bacterial pneumonia).

**Past medical history** should cover recent respiratory infections, repeated pneumonias, history of known allergies or asthma, risk factors for TB (eg, exposure to person who has known or suspected TB infection, exposure to prisons, HIV infection, travel to or immigration from countries that have endemic infection), and exposure to respiratory irritants.

**Physical examination:** Vital signs, including respiratory rate, temperature, and $O_2$ saturation, should be noted. Signs of respiratory distress (eg, nasal flaring, intercostal retractions, cyanosis, grunting, stridor, marked anxiety) should be noted.

Head and neck examination should focus on presence and amount of nasal discharge and the condition of the nasal turbinates (pale, boggy, or inflamed). The pharynx should be checked for postnasal drip.

The cervical and supraclavicular areas should be inspected and palpated for lymphadenopathy.

Lung examination focuses on presence of stridor, wheezing, rales, rhonchi, decreased breath sounds, and signs of consolidation (eg, egophony, E to A change, dullness to percussion).

Abdominal examination should focus on presence of abdominal pain, especially in the upper quadrants

(indicating possible left or right lower lobe pneumonia).

Examination of extremities should note clubbing or cyanosis of nail beds (cystic fibrosis).

**Red flags:** The following findings are of particular concern:

• Cyanosis or hypoxia on pulse oximetry

• Stridor

• Respiratory distress

• Toxic appearance

• Abnormal lung examination

**Interpretation of findings:** Clinical findings frequently indicate a specific cause (see Table 268-15); the distinction between acute and chronic cough is particularly helpful.

Other characteristics of the cough are helpful but less specific. A barky cough suggests croup or tracheitis; it can also be characteristic of psychogenic cough or a postrespiratory tract infection cough. A staccato cough is consistent with a viral or atypical pneumonia. A paroxysmal cough is characteristic of pertussis or certain viral pneumonias (adenovirus). Failure to thrive or weight loss can occur with TB or cystic fibrosis. Nighttime cough can indicate postnasal drip or asthma. Coughing at the beginning of sleep and in the morning with waking usually indicates sinusitis; coughing in the middle of the night is more consistent with asthma. In young children with sudden cough and no fever or URI symptoms, the examiner should have a high index of suspicion for foreign body aspiration.

**Testing:** Children with red flag findings should have pulse oximetry and chest x-ray, as should those whose symptoms are prolonged (eg, > 4 wk) or worsening.

Children with stridor, drooling, fever, and marked anxiety need to be evaluated for epiglottitis, typically in the operating room by an ENT specialist prepared to immediately place an endotracheal or tracheostomy tube. If foreign body aspiration is suspected, chest x-ray with inspiratory and expiratory views should be done.

Children with TB risk factors or weight loss should have a chest x-ray and PPD testing for TB.

Children with repeated episodes of pneumonia, poor growth, or foul-smelling stools should have a chest x-ray and sweat testing for cystic fibrosis.

Acute cough in children with URI symptoms and no red flag findings is usually caused by a viral infection, and testing is rarely indicated. Many other children without red flag findings have a presumptive diagnosis after the history and physical examination. Testing is not necessary in such cases; however, if empiric treatment has been instituted and has not been successful, testing may be necessary. For example, if allergic sinusitis is suspected and treated with an antihistamine that does not alleviate symptoms, a head CT may be necessary for further evaluation. Suspected GERD unsuccessfully treated with an $H_2$ blocker may require evaluation with a pH probe and a swallowing study.

**Treatment**

Treatment is management of the underlying disorder. For example, antibiotics should be given for bacterial pneumonia; bronchodilators and anti-inflammatory drugs should be given for asthma. Children with viral infections should receive supportive care, including $O_2$ and bronchodilators as needed.

Little evidence exists to support the use of cough suppressants and mucolytic agents. Coughing is an important mechanism for clearing secretions from the airways and can assist in recovery from respiratory infections. Use of nonspecific drugs for cough suppression is discouraged in children.

### Key Points

• Clinical diagnosis is usually adequate.

• A high index of suspicion for foreign body aspiration is needed if children are age 6 mo to 4 yr.

• Antitussives and expectorants lack proof of effect in most cases.

• Chest x-rays should be taken in patients with red flag findings or chronic cough.

## Crying

All infants and young children cry as a form of communication; it is the only means they have to express a need. Thus, most crying is in response to hunger, discomfort (eg, a wet diaper), or separation, and it ceases when the needs are met (eg, by feeding, changing, cuddling). This crying is normal and tends to lessen in duration and frequency after 3 mo of age. However, crying that persists after attempts to address routine needs and efforts to console or that is prolonged in relation to the child's baseline should be investigated to identify a specific cause.

### Etiology

Cause of crying is

• Organic in < 5%

• Functional in 95%

**Organic:** Organic causes, although rare, must always be considered. Causes to consider are classified as cardiac, GI, infectious, and traumatic (see Table 268-16). Of these, potential life threats include heart failure, intussusception, volvulus, meningitis, and intracranial bleeding due to head trauma.

Colic (see p. 2725) is excessive crying that has no identifiable organic cause and that occurs at least 3 h/day > 3 days/wk for > 3 wk.

### Evaluation

**History: History of present illness** focuses on onset of crying, duration, response to attempts to console, and frequency or uniqueness of episodes. Parents should be asked about associated events or conditions, including recent immunizations, trauma (eg, falls), interaction with a sibling, infections, drug use, and relationship of crying with feedings and bowel movements.

**Review of systems** focuses on symptoms of causative disorders, including constipation, diarrhea, vomiting, arching of back, explosive stools, and bloody stools (GI disorders); fever, cough, wheezing, nasal congestion, and difficulty breathing (respiratory infection); and apparent pain during bathing or changing (trauma).

**Past medical history** should note previous episodes of crying and conditions that can potentially predispose to crying (eg, history of heart disease, developmental delay).

**Physical examination:** Examination begins with a review of vital signs, particularly for fever and tachypnea. Initial observation assesses the infant or child for signs of lethargy or distress and notes how the parents are interacting with the child.

The infant or child is undressed and observed for signs of respiratory distress (eg, super-clavicular and subcostal retractions, cyanosis). The entire body surface is inspected for swelling, bruising, and abrasions.

Auscultatory examination focuses on signs of respiratory infection (eg, wheezing, rales, decreased breath sounds) and cardiac compromise (eg, tachycardia, gallop, holosystolic murmur, systolic click). The abdomen is palpated for signs of tenderness. The diaper is removed for examination of the genitals and anus to look for signs of testicular torsion (eg, red-ecchymotic scrotum, pain on palpation), hair tourniquet on the penis, inguinal hernia (eg, swelling in the inguinal region or scrotum), and anal fissures.

Extremities are examined for signs of fracture (eg, swelling, erythema, tenderness, pain with passive motion). Fingers and toes are checked for hair tourniquets.

The ears are examined for signs of trauma (eg, blood in the canal or behind the tympanic membrane) or infection (eg, red, bulging tympanic membrane). The corneas are stained with fluorescein and examined with a blue light to rule out corneal abrasion, and the fundi are examined with an ophthalmoscope for signs of hemorrhage. (If retinal hemorrhages are suspected, examination by an ophthalmologist is advised.) The oropharynx is examined for signs of thrush or oral abrasions. The skull is gently palpated for signs of fracture.

**Red flags:** The following findings are of particular concern:

• Respiratory distress

• Bruising and abrasions

• Extreme irritability

• Fever and inconsolability (meningitis)

• Fever in an infant ≤ 6 wk of age

[**Table 268-16.** Some Causes of Crying]

**Interpretation of findings:** A high index of suspicion is warranted when evaluating crying. Parental concern is an important variable. When concern is high, the clinician should be wary even when there are no conclusive findings because the parents may be reacting subconsciously to subtle but significant changes. Conversely, a very low level of concern, particularly if there is lack of parental interaction with the infant or child, can indicate a bonding problem or an inability to assess and manage the child's needs. Inconsistency of the history and the child's clinical presentation should raise concerns about possible abuse.

It is helpful to distinguish the general area of concern. For example, with fever, the most likely etiology is infectious; respiratory distress without fever indicates possible cardiac etiology or pain. Abnormalities in stool history or abdominal pain during examination is consistent with a GI etiology. Specific findings often suggest certain causes (see Table 268-16).

The time frame is also helpful. Crying that has been intermittent over a number of days is of less concern than sudden, constant crying. Whether the cry is exclusive to a time of day or night is helpful. For example, recent onset of crying at night in an otherwise happy, healthy infant or child may be consistent with night terrors or constipation.

The character of the cry is also revealing. Parents frequently can distinguish a cry that is painful in character from a frantic or scared cry. It is also important to determine the level of acuity. An inconsolable infant or child is of more concern than an infant or child who is well-appearing and consolable in the office.

**Testing:** Testing is targeted at the suspected cause (see Table 268-16) and pays particular attention to potential life threats, unless the history and physical examination are sufficient for diagnosis. When there are few or no specific clinical findings and no testing is immediately indicated, close follow-up and reevaluation are appropriate.

### Treatment

The underlying organic disorder should be treated. Support and encouragement are important for parents when the infant or child has no apparent underlying disorder. Swaddling an infant in the first month of life can be helpful. Holding an infant or child and responding to crying as quickly as possible are helpful in decreasing the duration of crying. It is also valuable to encourage parents, if they are feeling frustrated, to take a break from a crying baby and put the infant or child down in a safe environment for a few minutes. Educating parents and "giving permission" to take a break are helpful in preventing abuse. Supplying resources for support services to parents who seem overwhelmed may prevent future concerns.

### Key Points

• Crying is part of normal development and is most prevalent during the first 3 mo of life.

• Excessive crying with organic causes needs to be differentiated from colic.

• Less than 5% of crying has an organic cause.

• When no organic cause is identified, parents may need support.

## Diarrhea

Diarrhea is frequent loose or watery bowel movements that deviate from a child's normal pattern. However, breastfed infants who are not yet receiving solid food often have frequent loose bowel movements that are considered normal.

Diarrhea may be accompanied by anorexia, vomiting, acute weight loss, fever, or passage of blood. If diarrhea is severe or prolonged, dehydration is likely. Even in the absence of dehydration, chronic diarrhea usually results in weight loss or failure to gain weight.

Diarrhea is a very common pediatric concern and causes 2 to 3 million deaths/yr worldwide. It accounts for about 9% of hospitalizations in the US among children aged < 5 yr.

For diarrhea in adults, see p. 88.

### Pathophysiology

Mechanisms of diarrhea may include the following:

• Osmotic

• Secretory

• Inflammatory

• Malabsorptive

**Osmotic diarrhea** results from the presence of nonabsorbable solutes in the GI tract, as with lactose intolerance. Fasting for 2 to 3 days stops osmotic diarrhea.

**Secretory diarrhea** results from substances (eg, bacterial toxins) that increase secretion of Cl ions and water into the intestinal lumen. Secretory diarrhea does not stop with fasting.

**Inflammatory diarrhea** is associated with conditions that cause inflammation or ulceration of the intestinal mucosa (eg, Crohn's disease, ulcerative colitis). The resultant out-pouring of plasma, serum proteins, blood, and mucous increases fecal bulk and fluid content.

**Malabsorption** may result from osmotic or secretory mechanisms or conditions that lead to less surface area in the bowel. Conditions such as short bowel syndrome and conditions that speed up transit time cause diarrhea due to decreased absorption.

### Etiology

The causes and significance of diarrhea (see Table 268-17) differ depending on whether it is acute (< 2 wk) or chronic (> 2 wk). Most cases of diarrhea are acute.

**Acute diarrhea** usually is caused by

• Gastroenteritis

• Antibiotic use

• Food allergies

• Food poisoning

Most gastroenteritis is caused by a virus; however, any enteric pathogen can cause acute diarrhea.

**Chronic diarrhea** usually is caused by

• Dietary factors

• Infection

• Celiac disease

Chronic diarrhea can also be caused by anatomic disorders and disorders that interfere with absorption or digestion.

[**Table 268-17.** Some Causes of Diarrhea]

### Evaluation

**History: History of present illness** focuses on quality, frequency, and duration of stools, as well as on any accompanying fever, vomiting, abdominal pain, or blood in the stool. Parents are asked about current or recent (within 2 mo) antibiotic use. Elements of the diet should be established; they include amounts of juice, foods high in sugar, and processed foods. Any history of hard stools or constipation should be noted. Risk factors for infection should be assessed; they include recent travel; exposure to questionable food sources; and recent contact with animals at a petting zoo, reptiles, or someone with similar symptoms.

**Review of systems** should seek symptoms of complications and causes. Symptoms of complications include weight loss and decreased frequency of urination and fluid intake (dehydration). Symptoms of causes include urticarial rash associated with food intake (food allergy); nasal polyps, sinusitis, and poor growth (cystic fibrosis); arthritis and anal fissures (inflammatory bowel disease); and anorexia, anemia, and rash (celiac sprue).

**Past medical history** should assess known causative disorders (eg, immunocompromise, cystic fibrosis, celiac sprue, inflammatory bowel disease) in the patient and family members. Drug history should be reviewed for current or recent antibiotic use.

**Physical examination:** Vital signs should be reviewed for indications of dehydration (eg, tachycardia, hypotension) and fever.

General assessment includes checking for signs of lethargy or distress. Growth parameters should be noted.

Because the abdominal examination may elicit discomfort, it is advisable to begin the examination with the head. Examination should focus on the mucous membranes to assess whether they are moist or dry. Nasal polyps; psoriasiform dermatitis around the eyes, nose, and mouth; and oral ulcerations should be noted.

Examination of the extremities focuses on skin turgor, capillary refill time, and presence of petechiae or purpura. Other forms of rash and signs of erythematous, swollen joints should be noted.

Abdominal examination focuses on distention, tenderness, and quality of bowel sounds (eg, high-pitched, normal, absent). Examination of the genitals focuses on presence of rashes and signs of anal fissures or ulcerative lesions.

**Red flags:** The following findings are of particular concern:

• Tachycardia, hypotension, and lethargy (significant dehydration)

• Bloody stools and extreme abdominal tenderness (volvulus, intussusception, partial obstruction)

• Bloody stool, fever, petechiae, and purpura (hemolytic-uremic syndrome)

**Interpretation of findings:** Antibiotic-related, postinfectious, and anatomic-related causes of diarrhea are typically clear from the history. Determination of the time frame helps establish whether diarrhea is acute or chronic. Establishing the level of acuity is also important. Most cases of acute diarrhea have a viral etiology, are low acuity, and cause fever and nonbloody diarrhea. However, bacterial diarrhea can lead to serious consequences; manifestations include fever, bloody diarrhea, and possibly a petechial or purpuric rash.

Symptoms associated with chronic diarrhea can vary and those of different conditions can overlap. For example, Crohn's disease and celiac sprue can cause oral ulcerations, a number of conditions can cause rashes, and any condition can lead to a poor growth pattern. If the cause is unclear, further tests are done based on clinical findings (see Table 268-17).

**Testing:** Testing is unnecessary in most cases of acute self-limited diarrhea. However, if the evaluation suggests an etiology other than viral gastroenteritis, testing should be directed by the suspected etiology (see Table 268-17).

If dehydration is suspected, screening laboratory tests should be done (for electrolytes).

**Treatment**

Specific causes are treated (eg, gluten-free diet for children with celiac disease).

General treatment focuses on hydration, which can usually be done orally; IV hydration is rarely essential. (CAUTION: *Antidiarrheal drugs [eg, loperamide] are not recommended for infants and young children.* )

**Rehydration:** Oral rehydration solution (ORS) should contain complex carbohydrate or 75 mEq/L glucose and 75 mEq/L Na (total 245 mOsm/L solution). Sports drinks, sodas, juices, and similar drinks do not meet these criteria and should not be used. They generally have too little Na and too much carbohydrate to take advantage of Na/glucose cotransport, and the osmotic effect of the excess carbohydrate may result in additional fluid loss.

ORS is recommended by the WHO and is widely available in the US without a prescription. Premixed solutions are also available at most pharmacies and supermarkets.

Small, frequent amounts are used, starting with 5 mL q 5 min and increasing gradually as tolerated (see

also p.
2809). Generally, 50 mL/kg is given over 4 h for mild dehydration, and 100 mL/kg is given over 4 h for moderate dehydration. For each diarrheal stool, an additional 10 mL/kg (up to 240 mL) is given. After 4 h, the patient is reassessed. If signs of dehydration persist, the same volume is repeated.

**Diet and nutrition:** Children should eat an age-appropriate diet as soon as they have been rehydrated and are not vomiting. Infants may resume breast milk or formula.

For chronic diarrhea, adequate nutrition must be maintained, particularly of fat-soluble vitamins.

### Key Points

• Diarrhea is a common pediatric concern.

• Gastroenteritis is the most common cause.

• Testing is rarely necessary in acute diarrhea.

• Dehydration is likely if diarrhea is severe or prolonged.

• Oral rehydration is effective in most cases.

• Antidiarrheal drugs (eg, loperamide) are not recommended for infants and young children.

## Fever

Normal body temperature varies from person to person and throughout the day, but fever usually is defined as a core body (rectal) temperature ≥ 38.0° C.

Significance of fever depends on clinical context rather than peak temperature; some minor illnesses cause high fever, whereas some serious illnesses cause only a mild temperature elevation. Although parental assessment is frequently clouded by fear of fever, the history of a temperature taken at home should be considered equivalent to a temperature taken in the office.

### Pathophysiology

Normal body temperature varies during the day by as much as 0.5° C and, in a child with a febrile illness, by as much as 1.0° C.

Fever occurs in response to the release of endogenous pyogenic mediators called cytokines. Cytokines stimulate the production of prostaglandins by the hypothalamus, which readjust and elevate the temperature set point (see p. 1152).

Fever plays an integral role in fighting infection and, although it is uncomfortable, does not necessitate treatment in an otherwise healthy child. Some studies even indicate that lowering the temperature can prolong some illnesses. However, fever increases the metabolic rate and the demands on the cardiopulmonary system. Therefore, fever can be detrimental to children with pulmonary or cardiac compromise or neurologic impairment. It can also be the catalyst for febrile seizures, a typically benign childhood condition (see p. 2898).

### Etiology

Causes of fever (see
Table 268-18) differ based on whether the fever is acute (≤ 7 days) or chronic (> 7 days). Response to antipyretics and height of the temperature have no direct relationship to the etiology or its seriousness.

**Acute:** Most acute fevers in infants and young children are caused by infection. The most common are

• Viral respiratory or GI infections (most common causes overall)

• Certain bacterial infections (otitis media, pneumonia, UTIs)

However, potential causes vary with the child's age. Causes vary because neonates (infants < 28 days) and young infants have decreased immunologic function and are therefore at greater risk of infection and because neonates may have perinatally acquired infection. Common perinatal infections include those with group B streptococci, *Escherichia coli, Listeria monocytogenes*, and herpes simplex virus; these organisms can cause bacteremia, pneumonia, meningitis, or sepsis.

Febrile children < 36 mo are at special risk of occult bacteremia (pathogenic bacteria in the bloodstream but without focal symptoms or signs). The most common causative organisms of occult bacteremia used to be *Streptococcus pneumoniae* and *Haemophilus influenzae*; vaccination against both is now widespread in the US and Europe, making occult bacteremia less common and potentially changing the common causative organisms.

Rare, noninfectious causes of acute fevers include heatstroke and toxic ingestions (eg, of drugs with anticholinergic effects). Some vaccinations can cause fever for days (eg, with pertussis vaccination) and even 1 or 2 wk (eg, with measles vaccination) after administration. These fevers typically last from a few hours to a day. If the child is otherwise well, no evaluation is necessary. Teething does not cause fever.

**Chronic:** Chronic fever suggests various potential causes, including autoimmune disorders, collagen vascular diseases (eg, juvenile idiopathic arthritis, inflammatory bowel disease), cancer (eg, leukemia, lymphoma), and chronic infections (eg, osteomyelitis, TB). Miscellaneous causes include factitious fever and cases in which etiology is not identified.

The most common causes include

• Benign infectious causes (prolonged viral illnesses, back-to-back illnesses—especially in young children)

Collagen vascular diseases, autoimmune disorders, and cancer are much less common.

**Evaluation**

**History: History of present illness** should note degree and duration of fever, method of

[Table 268-18. Some Common Causes of Fever in Children*]

measurement, and the dose and frequency of antipyretics (if any). Important associated symptoms that suggest serious illness include poor appetite, irritability, lethargy, and change in crying (eg, duration, character). Associated symptoms that may suggest the cause include vomiting, diarrhea (including presence of blood or mucus), cough, difficulty breathing, favoring of an extremity or joint, and strong or foul-smelling urine. Drug history should be reviewed for indications of drug-induced fever.

Factors that predispose to infection are identified. In neonates, these factors include prematurity, prolonged rupture of membranes, maternal fever, and positive prenatal tests (usually for group B streptococcal infections, cytomegalovirus infections, or sexually transmitted diseases). For all children, predisposing factors include recent exposures to infection (including family and caretaker infection), in-dwelling medical devices (eg, catheters, ventriculoperitoneal shunts), recent surgery, and travel and environmental exposures (eg, to ticks, mosquitoes, cats, farm animals, or reptiles).

**Review of systems** should note symptoms suggesting possible causes, including runny nose and congestion (viral URI), headache (sinusitis, Lyme disease, meningitis), ear pain or waking in the night with signs of discomfort (otitis media), cough or wheezing (pneumonia, bronchiolitis), abdominal pain (pneumonia, gastroenteritis, UTI, abdominal abscess), back pain (pyelonephritis), and any history of joint swelling or redness (Lyme disease, osteomyelitis). A history of repeated infections (immunodeficiency) or symptoms that suggest a chronic illness, such as poor weight gain or weight loss (TB, cancer), is

identified. Certain symptoms can help direct the evaluation toward noninfectious causes; they include heart palpitations, sweating, and heat intolerance (hyperthyroidism) and recurrent or cyclic symptoms (a rheumatoid, inflammatory, or hereditary disorder).

**Past medical history** should note previous fevers or infections and known conditions predisposing to infection (eg, congenital heart disease, sickle cell anemia, cancer, immunodeficiency). A family history of an autoimmune disorder or other hereditary conditions (eg, familial dysautonomia, familial Mediterranean fever) is sought. Vaccination history is reviewed to identify patients at risk of infections that can be prevented by a vaccine.

**Physical examination:** Vital signs are reviewed, noting abnormalities in temperature and respiratory rate. In ill-appearing children, BP should also be measured. Temperature should be measured rectally in infants for accuracy. Any child with cough, tachypnea, or labored breathing requires pulse oximetry.

The child's overall appearance and response to the examination are important. A febrile child who is overly compliant or listless is of more concern than one who is unco-operative. However, an irritable infant or child who is inconsolable is also of concern. The febrile child who looks quite ill, especially when the temperature has come down, is of great concern and requires in-depth evaluation and continued observation. However, children who appear more comfortable after antipyretic therapy do not always have a benign disorder.

The examination seeks signs of causative disorders (see Table 268-19).

**Red flags:** The following findings are of particular concern:

• Age < 1 mo

• Lethargy, listlessness, or toxic appearance

• Respiratory distress

• Petechiae or purpura

• Inconsolability

**Interpretation of findings:** Although serious illness does not always cause high fever, and many high fevers result from self-limited viral infections, a temperature of ≥ 39° C in children < 3 yr indicates higher risk of occult bacteremia.

**Acute fever** is infectious in most cases, and of these, most are viral. History and examination are adequate to make a diagnosis in older children who are otherwise well and not toxic-appearing. Typically, they have a viral respiratory illness (recent ill contact, runny nose, wheeze, or cough) or GI illness (ill contact, diarrhea, and vomiting). Other findings also suggest specific causes (see Table 268-19).

However in infants < 36 mo, the possibility of occult bacteremia, plus the frequent absence of focal findings in neonates and young infants with serious bacterial infection, necessitates a different approach. Evaluation varies by age group. Accepted categories are neonates (≤ 28 days), young infants (1 to 3 mo), and older infants and children (3 to 36 mo). Regardless of clinical findings, a neonate with fever requires immediate hospitalization and testing to rule out a dangerous infection. Young infants may require hospitalization depending on screening laboratory results and the likelihood that they will be brought in for follow-up.

**Chronic fever** requires a high index of suspicion for the many potential causes. However, certain findings can suggest the disorder: erythema chronicum migrans rash, intermittent joint swelling, and neck pain (Lyme disease); intermittent headaches with runny nose or congestion (sinusitis); weight loss, high-risk exposure, and night sweats (TB); weight loss or difficulty gaining weight, heart palpitations, and sweating (hyperthyroidism); and weight loss, anorexia, and night sweats (cancer). Certain conditions (eg,

granulomatous diseases) may manifest with non-specific symptoms and a history that involves repeated infections (eg, pneumonia, skin infections, abscesses, septicemia).

**Testing:** Testing depends on whether fever is acute or chronic.

For **acute fever**, testing for infectious causes is directed by the age of the child (see Fig. 280-1 on p. 2842 and Fig. 280-2 on p. 2843).

**All febrile children < 3 mo** require a WBC count with a manual differential, blood cultures, and urinalysis and urine culture (urine obtained by catheterization, not an external bag). Lumbar puncture is mandatory for children < 28 days; expert opinion varies about the need for the test in children aged 29 days to

[**Table 268-19.** Examination of the Febrile Child]

2 mo. Chest x-ray, stool swabs for WBCs, stool cultures, and acute-phase reactant tests (eg, ESR, C-reactive protein) are done depending on symptoms and degree of suspicion.

**Febrile children between 3 mo and 36 mo** who look well and can be watched carefully do not require laboratory testing. If the child has symptoms or signs of specific infections, clinicians should order appropriate tests (eg, chest x-ray when there is hypoxemia, dyspnea, or grunting; urinalysis and culture when there is foul-smelling urine; lumbar puncture when there is abnormal behavior or meningismus). If the child looks ill or has a temperature > 39° C but has no localizing signs, blood counts and cultures and urine tests should be considered as well as a lumbar puncture.

For **febrile children > 36 mo**, testing should be directed by history and examination; screening blood cultures and WBC counts are not indicated.

For **chronic fever**, testing for noninfectious causes should be directed by history, physical examination, and suspected disorder (eg, thyroid-stimulating hormone [TSH] and thyroxine [$T_4$] for suspected hyperthyroidism; antinuclear antibodies and Rh factor for suspected juvenile idiopathic arthritis).

Children without focal findings should have initial screening tests, including

• CBC with differential

• Urinalysis and culture

• ESR (C-reactive protein is also considered, although one is not necessarily better than the other)

• PPD for TB screening

An elevated ESR suggests inflammation (infection, TB, autoimmune disorder, cancer), and further testing can be done. If the WBC count is normal, indolent infection is less likely; however, if infection is suspected clinically, serologic testing for possible causes (eg, Lyme disease, cat-scratch disease, mononucleosis, cytomegalovirus) can be done, as well as blood cultures. Imaging tests can be helpful in detecting tumors, collections of purulent material, or osteomyelitis. The type of test is determined by the specific concern. For example, head CT is used for diagnosis of sinusitis; both CT and MRI are used for identification of a tumor and metastatic lesions, and bone scanning is used for detection of osteomyelitis. Bone marrow aspiration can be done to detect cancers such as leukemia.

**Treatment**

Treatment is directed at the underlying disorder.

Fever in an otherwise healthy child does not necessarily require treatment. Although antipyretics can provide comfort, they do not change the course of an infection. In fact, fever is an integral part of the

inflammatory response to infection and can help the child fight the infection. However, most clinicians use antipyretics to help alleviate discomfort and to reduce physiologic stresses in children who have cardiopulmonary disorders, neurologic disorders, or a history of febrile seizures.

**Antipyretic drugs** that are typically used include

• Acetaminophen

• Ibuprofen

Acetaminophen tends to be preferred because ibuprofen decreases the protective effect of prostaglandins in the stomach and, if used chronically, can lead to gastritis. The dosage of acetaminophen is 10 to 15 mg/kg po or rectally q 4 to 6 h. Ibuprofen dosage is 10 mg/kg po q 6 h. Use of one antipyretic at a time is preferred; however, some clinicians alternate the 2 drugs to treat high fever (eg, acetaminophen at 6 AM, 12 PM, and 6 PM and ibuprofen at 9 AM, 3 PM, and 9 PM). This approach is not encouraged because caregivers may become confused and inadvertently exceed the recommended daily dose. Aspirin should be avoided because it increases the risk of Reye's syndrome (see p. 2937) if certain viral illnesses such as influenza and varicella are present.

**Nondrug approaches** to fever include putting the child in a warm or tepid bath, using cool compresses, and undressing the child. Caregivers should be cautioned not to use a cold water bath, which is uncomfortable and, by inducing shivering, may paradoxically elevate body temperature. As long as the temperature of the water is slightly cooler than the temperature of the child, a bath provides temporary relief.

**Things to avoid:** Wiping the body down with isopropyl alcohol should be strongly discouraged because alcohol can be absorbed through the skin and cause toxicity. Numerous folk remedies exist, ranging from the harmless (eg, putting onions or potatoes in socks) to the uncomfortable (eg, coining, cupping).

### Key Points

• Most acute fever is caused by viral infections.

• Causes and evaluation of acute fever differ depending on the age of a child.

• Children < 36 mo can have a bacterial bloodstream infection without localizing signs (occult bacteremia).

• Teething does not cause fever.

• Antipyretics do not alter the outcome but may make children feel better.

## Nausea and Vomiting

Nausea is the sensation of impending emesis and is frequently accompanied by autonomic changes, such as increased heart rate and salivation. Nausea and vomiting typically occur in sequence; however, they can occur separately (eg, vomiting can occur without preceding nausea as a result of increased intracranial pressure).

Vomiting is uncomfortable and can cause dehydration because fluid is lost and because the ability to rehydrate by drinking is limited.

### Pathophysiology

Vomiting is the final part of a sequence of events coordinated by the emetic center located in the medulla. The emetic center can be activated by afferent neural pathways from digestive (eg, pharynx, stomach, small bowel) and nondigestive (eg, heart, testes) organs, the chemoreceptor trigger zone located in the area postrema on the floor of the 4th ventricle (containing dopamine and serotonin receptors), and other CNS centers (eg, brain stem, vestibular system).

### Etiology

The causes of vomiting vary with age and range from relatively benign to potentially life threatening (see Table 268-20). Vomiting is a protective mechanism that provides a means to expel potential toxins; however, it can also indicate serious disease (eg, intestinal obstruction). Bilious vomiting indicates a high intestinal obstruction and, especially in an infant, requires immediate evaluation.

**Infants:** Infants normally spit up small amounts (usually < 5 to 10 mL) during or soon after feedings, often when being burped. Rapid feeding, air swallowing, and overfeeding may be causes, although spitting up occurs even without these factors. Occasional vomiting may also be normal, but repeated vomiting is abnormal.

The most common causes of vomiting in infants and neonates include the following:

• Acute viral gastroenteritis

• Gastroesophageal reflux disease

Other important causes in infants and neonates include the following:

• Pyloric stenosis

• Intestinal obstruction (eg, meconium ileus, volvulus, intestinal atresia, stenosis)

• Intussusception (should be considered in an infant ≥ 3 mo)

Less common causes of recurrent vomiting include sepsis and food intolerance. Metabolic disorders (eg, urea cycle disorders, organic acidemias) are uncommon but can manifest with vomiting.

**Older children:** The most common cause is

• Acute viral gastroenteritis

Non-GI infections may cause a few episodes of vomiting. Other causes to consider include serious infection (eg, meningitis, pyelonephritis), acute abdomen (eg, appendicitis), increased intracranial pressure secondary to a space-occupying lesion (eg, caused by trauma or tumor), and cyclic vomiting.

In adolescents, causes of vomiting also include pregnancy, eating disorders, and toxic ingestions.

### Evaluation

Evaluation includes assessment of severity (eg, presence of dehydration, surgical or other life-threatening disorder) and diagnosis of cause.

**History: History of present illness** should determine when vomiting episodes started, frequency, and character of episodes (particularly whether vomiting is projectile, bilious, or small in amount and more consistent with spitting up). Any pattern to the vomiting (eg, after feeding, only with certain foods, primarily in the morning or in recurrent cyclic episodes) should be established. Important associated symptoms include diarrhea (with or without blood), fever, anorexia, and abdominal pain, distention, or both. Stool frequency and consistency and urinary output should be noted.

**Review of systems** should seek symptoms of causative disorders, including weakness, poor suck, and failure to thrive (metabolic disorders); delay in passage of meconium, abdominal distention, and lethargy (intestinal obstruction); headache, nuchal rigidity, and vision change (intracranial disorders); food bingeing or signs of distorted body image (eating disorders); missed periods and breast swelling (pregnancy); rashes (eczematous suggests food intolerance, petechial suggests CNS infection, urticarial suggests food allergy); ear pain and sore throat (focal non-GI infection); and fever with headache, back

pain, or abdominal pain (meningitis, pyelonephritis, or appendicitis).

**Past medical history** should note history of travel (possible infectious gastroenteritis), any recent head trauma, and unprotected sex (pregnancy).

[**Table 268-20.** Some Causes of Vomiting in Infants, Children, and Adolescents]

**Physical examination:** Vital signs are reviewed for indicators of infection (eg, fever) and volume depletion (eg, tachycardia, hypotension).

During the general examination, signs of distress (eg, lethargy, irritability, inconsolable crying) and signs of weight loss (cachexia) or gain are noted.

Because the abdominal examination may cause discomfort, the physical examination should begin with the head. The head and neck examination should focus on signs of infection (eg, red, bulging tympanic membrane; bulging anterior fontanelle; erythematous tonsils) and dehydration (eg, dry mucous membranes, lack of tears). The neck should be passively flexed to detect resistance or discomfort, suggesting meningeal irritation.

Cardiac examination should note presence of tachycardia (eg, dehydration, fever, distress). Abdominal examination should note distention; presence and quality of bowel sounds (eg, high-pitched, normal, absent); tenderness and any associated guarding, rigidity, or rebound (peritoneal signs); and presence of organomegaly or mass.

The skin and extremities are examined for petechiae or purpura (severe infection) or other rashes (possible viral infection or signs of atopy), jaundice (possible metabolic disorder), and signs of dehydration (eg, poor skin turgor, delayed capillary refill).

Growth parameters and signs of developmental progress should be noted.

**Red flags:** The following findings are of particular concern:

• Lethargy and listlessness

• Inconsolability and bulging fontanelle in infant

• Nuchal rigidity, photophobia, and fever in older child

• Peritoneal signs or abdominal distention ("surgical" abdomen)

• Persistent vomiting with poor growth or development

**Interpretation of findings:** Initial findings help determine severity of diagnosis and need for immediate intervention.

• Any neonate or infant with recurrent or bilious (yellow or green) emesis or projectile vomiting most likely has a GI obstruction and probably requires surgical intervention.

• An infant or young child with colicky abdominal pain, signs of intermittent pain or listlessness, and absent or bloody stools needs to be evaluated for an intussusception.

• A child or adolescent with fever, nuchal rigidity, and photophobia should be evaluated for meningitis.

• A child or adolescent with fever and abdominal pain followed by vomiting, anorexia, and decreased bowel sounds should be evaluated for appendicitis.

• Recent history of head trauma or progressive headaches and visual changes indicate intracranial hypertension.

Other findings can be interpreted primarily depending on age (see Table 268-20).

In **infants**, irritability, choking, and respiratory signs (eg, stridor) may be manifestations of gastroesophageal reflux. A history of poor development or neurologic manifestations suggests a CNS or metabolic disorder. Delayed passage of meconium, later onset of vomiting, or both may indicate Hirschsprung's disease or an intestinal stenosis.

In **children and adolescents**, fever suggests infection; the combination of vomiting and diarrhea suggests acute gastroenteritis. Lesions on fingers and erosion of tooth enamel or an adolescent unconcerned about weight loss suggests an eating disorder. Morning nausea and vomiting, amenorrhea, and possibly weight gain suggest pregnancy. Vomiting that has occurred in the past and is episodic, short-lived, and has no other accompanying symptoms suggests cyclic vomiting.

**Testing:** Testing should be directed by suspected causative disorders (see Table 268-20). Imaging studies are typically done to evaluate abdominal pathology. Various specific blood tests are done to diagnose inherited metabolic disorders.

If dehydration is suspected, serum electrolytes should be measured.

#### Treatment

Treatment is targeted at the causative disorder. Drugs frequently used in adults to decrease nausea and vomiting are rarely used in children because the usefulness of treatment has not been proved and because they have potential risks of adverse effects and of masking an underlying condition.

Rehydration is important (see p. 2809).

#### Key Points

• In general, the most common cause of vomiting is acute viral gastroenteritis.

• Not all vomiting is caused by gastroenteritis.

• Diarrhea suggests an infectious GI cause.

• Bloody stools or lack of bowel movements suggests an obstructive cause.

• Persistent vomiting (especially in an infant) requires immediate evaluation.

### Separation and Stranger Anxiety

**Separation anxiety:** Separation anxiety is crying when a parent leaves the room. It is normal when it starts at about 8 mo, peaks in intensity between 10 and 18 mo, and generally resolves by 24 mo. It should be distinguished from separation anxiety disorder (see p. 3052), which occurs at an older age, when such a reaction is developmentally inappropriate; refusal to go to school (or preschool) is a common manifestation.

Separation anxiety occurs at a time when infants start to become emotionally attached to their parents. Because they have no object permanence (incomplete memory and no sense of time), children fear that the departure of their parents is permanent. Separation anxiety resolves as children develop a sense of memory; they can keep an image of their parents in mind when the parents are gone and can recall that in the past, the parents returned.

Parents should be advised not to limit or forego separations in response to separation anxiety; this response could compromise the child's maturation and development. When parents leave the home (or leave the child at a child care center), they can try the following strategies:

- Encouraging the person caring for the child to create distractions
- Leaving without responding at length to a child's crying
- Remaining calm and reassuring
- Establishing routines at separations to ease the child's anxiety
- Feeding the child and letting the child nap before parents leave (because separation anxiety may be worse when a child is hungry or tired)

If the parents must momentarily go to another room in the home, they should call to the child while in the other room to reassure the child. This strategy gradually teaches the child that parents are still present even though the child cannot see them.

Separation anxiety causes no long-term harm to children if it resolves by age 2 yr. If it persists beyond age 2, separation anxiety may or may not be a problem depending how much it interferes with the child's development. For children, feeling some fear when they leave for preschool or kindergarten is normal. This feeling should diminish with time. Rarely, excessive fear of separations inhibits children from attending child care or preschool or keeps them from playing normally with peers. This anxiety is probably abnormal (separation anxiety disorder—see p. 3052). In such cases, children require medical attention.

**Stranger anxiety:** Stranger anxiety is manifested by crying when an unfamiliar person approaches. It is normal when it starts at about 8 to 9 mo and usually abates by age 2 yr. Stranger anxiety is linked with the infant's developmental task of distinguishing the familiar from the unfamiliar. Both the duration and intensity of the anxiety vary greatly among children.

Some infants and young children show a strong preference for one parent over another at a given age, and grandparents may suddenly be viewed as strangers. Anticipating these occurrences during well-child visits helps prevent misinterpretation of the behavior. Comforting the child and avoiding overreaction to the behavior are usually the only therapy needed.

Common sense should dictate management. If a new sitter is coming, having that person spend some time with the family before the actual day makes sense. When the event arrives, having parents spend some time with the child and sitter before they leave is prudent. If grandparents are coming to watch the child for a few days while parents go away, they should arrive a day or two early. Similar techniques can be used in anticipation of hospitalization.

Stranger anxiety of pronounced intensity or extended duration may be a sign of more generalized anxiety and should prompt evaluation of the family situation, parenting techniques, and the child's overall emotional state.

## Sleeping

Sleep behaviors are culturally determined, and problems tend to be defined as behaviors that vary from accepted customs or norms. In cultures where children sleep separately from their parents in the same house, sleep problems are among the most common that parents and children face.

Infants usually adapt to a day-night sleep schedule between 4 and 6 mo. Sleep problems beyond these ages take many forms, including difficulty falling asleep at night, frequent nighttime awakening, atypical daytime napping, and dependence on feeding or on being held before being able to go to sleep. These problems are related to parental expectations, the child's temperament and biologic rhythms, and child-parent interactions.

Factors that influence sleep patterns vary by age. For infants, inborn biologic patterns are central. At 9 mo and again around 18 mo, sleep disturbances become common for these reasons:

- Separation anxiety develops.

• Children can move independently and control their environment.

• They may take long late-afternoon naps.

• They may become overstimulated while playing before bedtime.

• Nightmares tend to become more common.

In toddlers and older children, emotional factors and established habits become more important. Stressful events (eg, moving, illness) may cause acute sleep problems in older children.

### Evaluation

**History:** History focuses on the child's sleeping environment, consistency of bedtime, bedtime routines, and parental expectations. A detailed description of the child's average day can be useful. The history should probe for stressors in the child's life, such as difficulties in school, as well as exposure to unsettling television programs and caffeinated beverages (eg, sodas). Reports of inconsistent bedtimes, a noisy or chaotic environment, or frequent attempts by the child to manipulate parents by using sleep behaviors suggest the need for lifestyle changes. Extreme parental frustration suggests tension within the family or parents who are having difficulty being consistent and firm.

A sleep diary compiled over several nights may help identify unusual sleep patterns and sleep disorders (eg, sleepwalking, night terrors—see p. 1713). Careful questioning of older children and adolescents about school, friends, anxieties, depressive symptoms, and overall state of mind often reveals a source for a sleep problem.

**Physical examination and testing:** Examination and diagnostic testing generally yield little useful information.

### Treatment

The clinician's role in treatment is to present explanations and options to parents, who must implement changes to get the child on an acceptable sleep schedule. Approaches vary with age and circumstances. Infants are often comforted by swaddling, ambient noise, and movement. However, always rocking infants to sleep does not allow them to learn how to fall asleep on their own, which is an important developmental task. As a substitute for rocking, the parent can sit quietly by the crib until the infant falls asleep; the infant eventually learns to be comforted and to fall asleep without being held. All children awaken during the night, but children who have been taught to fall asleep by themselves usually settle themselves back to sleep. When children cannot get back to sleep, parents can check on them to make sure they are safe and to reassure them, but children should then be allowed to settle themselves back to sleep.

In older children, a period of winding down with quiet activities such as reading at bedtime facilitates sleep. A consistent bedtime is important, and a fixed ritual is helpful for young children. Asking fully verbal children to recount the events of the day often eliminates nightmares and waking. Encouraging exercise in the daytime, avoiding scary television programs and movies, and refusing to allow bedtime to become an element of manipulation can also help prevent sleep problems.

If stressful events are the cause, reassurance and encouragement are always ultimately effective. Allowing children to sleep in their parents' bed in such instances almost always prolongs rather than resolves the problem.

## Toilet Training

Toilet training involves recognition of readiness for and implementation of the separate steps of toileting: discussion, undressing, eliminating, dressing again, flushing, and hand washing. Most children can be trained for bowel control between age 2 yr and 3 yr and for urinary control between age 3 yr and 4 yr. By

age 5 yr, the average child can go to the toilet alone. For children ≥ 4 yr, see p. 2923 for incontinence of urine (enuresis) and p. 2928 for incontinence of stool (encopresis).

The key to successful toilet training is recognizing signs of readiness to train (usually at age 18 to 24 mo):

- Children can remain dry for several hours.
- They show interest in sitting on a potty chair and express visible signs of preparing to urinate or defecate.
- They want to be changed after either.
- They can place things where they belong and can understand and carry out simple verbal commands.

Approaches to toilet training must be consistent among all caregivers.

The **timing method** is the most common approach. Once children have demonstrated readiness, the parent discusses with them what will be happening, selecting words that they can readily understand and say. Children are gradually introduced to the potty chair and briefly sit on it fully clothed; they then practice taking their pants down, sitting on the potty chair for ≤ 5 or 10 min, and redressing. The purpose of the exercise is explained repeatedly and emphasized by placing wet or dirty diapers in the potty. Once this connection between the potty and elimination has been made, the parent should try to anticipate children's need to eliminate and provide positive reinforcement for successful elimination. Children are also encouraged to practice using the potty whenever the need to eliminate is sensed. They should be taught about flushing and hand washing after each elimination. For children with an unpredictable schedule, this type of plan is difficult, and training must be delayed until they can anticipate elimination themselves. Anger or punishment for accidents or lack of success is counterproductive.

Children who resist sitting on the potty should try again after a meal. If resistance continues for days, postponing toilet training for at least several weeks is the best strategy. Behavior modification with a reward given for successful toileting is one option; once the pattern is established, rewards are gradually withdrawn. Power struggles must be avoided because they often cause regression from any progress that has been made and may strain the parent-child relationship. Toilet-trained children may also regress when they are ill or emotionally upset or when they feel the need for more attention, as when a new sibling arrives. Refusal to use the potty may also represent manipulation. In these situations, parents are advised to avoid pressuring children, offer incentives, and, if possible, give children more care and attention at times other than when toileting is involved.

## Chapter 269. Approach to the Care of Adolescents

Adolescence is a developmental period during which dependent children grow into independent adults. This period usually begins at about 10 yr and lasts until the late teens or early 20s. During adolescence, children undergo striking physical, intellectual, and emotional growth. Guiding adolescents through this period is a challenge for parents as well as clinicians. Preventive care is also important (see Table 268-7 on p. 2714).

Fortunately, most adolescents enjoy good physical health. Psychosocial adjustment is a hallmark of this phase of development because even normal individuals struggle with issues of identity, autonomy, sexuality, and relationships. "Who am I, where am I going, and how do I relate to all of these people in my life?" are constant preoccupations for most adolescents. Psychosocial disorders are more common during adolescence than during childhood, and many unhealthy behaviors that begin during adolescence (eg, smoking, drug use, violence) can lead to acute health problems, chronic disorders, or morbidity later in life.

### Physical Growth

All organ systems and the body as a whole undergo major growth during adolescence; breasts in girls and genitals and body hair in both sexes undergo the most obvious changes. Even when this process goes normally, substantial emotional adjustments are required. If the timing is atypical, particularly in a boy whose physical development is delayed or in a girl whose development occurs early, additional emotional stress is likely. Most boys who grow slowly have a constitutional delay and catch up eventually. Evaluation to exclude pathologic causes and reassurance are needed.

Guidance concerning nutrition, fitness, and lifestyle should be given to all adolescents, with special attention paid to the role of activities such as sports, the arts, social activities, and community service in the adolescent's life. Relative requirements for protein and energy (g or kcal/kg body weight) decline progressively from the end of infancy through adolescence (see Table 1-4 on p. 5), although absolute requirements increase. Protein requirements are 0.9 g/kg/day in late adolescence; mean relative energy requirements are 40 kcal/kg.

### Sexuality

In addition to adapting to bodily changes, the adolescent must become comfortable with the role of adult and must put sexual urges, which can be very strong and sometimes frightening, into perspective. Some adolescents struggle with the issue of sexual identity and may be afraid to reveal their sexual orientation to friends or family members. Acceptance from a clinician and, if indicated, a referral for supportive counseling, may help the adolescent adjust to life as a healthy adult.

Few elements of the human experience combine physical, intellectual, and emotional aspects as thoroughly as sexuality. Helping adolescents put sexuality into a healthy context through honest answers regarding reproduction and sexually transmitted diseases is extremely important. Adolescents and their parents should be encouraged to speak openly regarding their attitudes toward sex and sexuality; parents' opinions remain an important determinant of adolescent behavior.

### Intellectual Growth

As adolescents encounter schoolwork that is more complex, they begin to identify areas of interest as well as relative strengths and weaknesses. Adolescence is a period during which young people begin to consider career options, although most do not have a clearly defined goal. Parents and clinicians must be aware of the adolescent's capabilities, help the adolescent formulate realistic expectations, and be prepared to identify impediments to learning that need remediation, such as learning disabilities, attention problems, or inappropriate learning environments. Parents and clinicians should facilitate apprenticeships and experiences that expose older adolescents to potential career opportunities either during school or during school vacations. These opportunities may help adolescents focus their career choices and future studies.

### Emotional Growth

The emotional aspect of growth is most trying, often taxing the patience of parents, teachers, and clinicians. Emotional lability is a direct result of neurologic development during this period, as the parts of the brain that control emotions mature. Frustration may also arise from growth in multiple domains. A major area of conflict arises from the adolescent's desire for more freedom, which clashes with the parents' strong instincts to protect their children from harm. Parents may need help in renegotiating their role and slowly allowing their adolescents more privileges as well as expecting them to accept greater responsibility for themselves and within the family. Communication within even stable families can be difficult and is worsened when families are divided or parents have emotional problems of their own. Clinicians can be of great help by offering adolescents and parents sensible, practical, concrete, supportive help while facilitating communication within the family.

### Physical Problems

Although adolescents are susceptible to the same kinds of illness that afflict younger children, generally they are a healthy group. Adolescents should continue to receive vaccinations according to the recommended schedule (see
Table 268-11 on p. 2720).

Acne is extremely common and needs to be addressed because of its impact on self-esteem.

Trauma is very common among adolescents, with sports and motor vehicle injuries most frequent. Violence, sometimes involving weapons, is an everyday threat among certain adolescent groups.

Obesity is one of the most common reasons for visits to adolescent clinics. Most cases of obesity are due to eating more than is needed, often in conjunction with a sedentary lifestyle. Genetic influences are common, and responsible genes are now being identified (see also Ch. 6). Determination of the body mass index (BMI) is recognized as an important aspect of physical assessment. Primary endocrine (eg, hyperadrenocorticism, hypothyroidism) or metabolic causes are uncommon. Hypothyroidism should be ruled out as a cause and should be suspected if height growth slows significantly. If the child is short and has hypertension, Cushing's syndrome should be considered. Type 2 diabetes mellitus is occurring with increasing frequency due to obesity in adolescents. Despite many therapeutic approaches, obesity is one of the most difficult and discouraging problems to treat, and long-term success rates remain low.

Infectious mononucleosis is particularly prevalent among adolescents. Sexually transmitted diseases become an important concern, and UTIs are common among girls. Some endocrine disorders, particularly thyroid disorders, are common among adolescents, as are menstrual abnormalities. Iron deficiency is relatively common among adolescent girls. Pregnancy also is not a rare occurrence and must be kept in mind when treating adolescent girls. Although not common, neoplastic diseases such as leukemia, lymphoma, bone cancers, and brain tumors also occur.

### Psychosocial Disorders

Clinicians must be aware of the high frequency of psychosocial disorders that occur during this unsettled stage of life. Depression is common and should be looked for actively (see p. 3055). Although suicide is a rare occurrence (5/100,000), suicidal ideation is common (as many as 1 in 10 in some studies). Anxiety often manifests during adolescence (see p. 3049), as do bipolar disease and problems with anger management. Adolescence is also a time when some people who will develop a psychotic disorder experience their first psychotic break. Eating disorders, especially in girls, are common (see p. 1535). Some patients go to extraordinary lengths to hide an anorexic or bulimic state.

School problems, especially when related to learning or attention difficulties, can be dealt with by clinicians, who must work closely with school personnel and parents. Learning disorders may manifest for the first time as school becomes more demanding, particularly among bright children who previously had been able to accommodate for their areas of weakness. If a learning disorder is suspected, the clinician should recommend a complete learning evaluation followed by provision of appropriate services. Environmental changes and sometimes drug therapy can be of great help to struggling students.

A constant concern is substance use, which begins as a psychosocial problem but may develop into a physiologic disorder. Alcohol and cigarette use is extremely common, followed by marijuana and a long list of other substances available in all strata of society. Inhalant use is also a problem, particularly among young adolescents. Prescription and OTC drugs are now misused by adolescents more than any other substances other than alcohol and marijuana. All of these psychoactive substances are addictive, and delaying the onset of substance use from adolescence into adulthood both prevents the acute problems associated with substance use and decreases the lifetime risk of developing a substance use disorder. Clinicians should screen for use of alcohol and other drugs at every health maintenance visit and also should advise both adolescents and parents about safely using and monitoring OTC and prescription drugs.

The clinician who has developed an open, trusting relationship with an adolescent often can identify these problems, can supply support and practical advice, and can get the adolescent to accept a referral to specialized care if necessary.

# Chapter 270. Caring for Sick Children and Their Families

## Introduction

Illness and death cause emotional stresses in children and their families.

## Sick Neonates

Difficulties arise when a sick or premature infant must be taken away from the family after birth because of illness. The parents may not be able to see a critically ill infant during stabilization and may be separated from the infant because of transport to a different hospital. Some infants require prolonged separation from their families because of lengthy hospitalizations and treatments.

Many hospitals have recognized the importance of encouraging contact between infants and their families. In most places, parents are encouraged to visit, taking precautions to minimize the risk of spreading infections. Many hospitals have unlimited visiting hours for parents. Some hospitals have areas in which parents can stay for prolonged periods to be near their infants.

In most hospitals, parents are encouraged to interact with their sick infant as much as possible. *No infant, even one on a respirator, is too ill for the parents to see and touch*.

Parents are also encouraged to provide direct care for the infant as a way to get to know the infant and to prepare for taking the infant home. Some hospitals increase contact between parents and premature or sick infants by encouraging skin-to-skin contact; this may help parents feel more confident about taking care of their infant at home. Infants who experience skin-to-skin contact gain weight faster when compared with those who do not receive such care. Mothers can also provide breast milk directly or pumped to be given through a feeding tube.

When an infant has a birth defect, the parents should see the infant as soon after birth as possible, regardless of the medical condition. Otherwise, they may imagine the appearance and condition to be much worse than the reality. Intensive parental support is essential, with as many counseling sessions as are needed for parents to understand their infant's condition and recommended treatment and to accept the infant psychologically. To balance discussion of abnormalities, the physician should emphasize what is normal about the infant and the infant's potential.

When neonates die without having been seen or touched by their parents, the parents may later feel as though they never really had a child. Such parents have reported exaggerated feelings of emptiness and may develop prolonged depression because they could not mourn the loss of a "real" child. Parents who have not been able to see or hold their infant while alive will usually be helped in the long term if allowed to do so after the infant has died. In all cases, follow-up visits with the physician and a social worker are helpful to review the circumstances of the infant's illness and death, answer questions that often arise later, and assess and alleviate feelings of guilt. The physician can also evaluate the parents' grieving process and provide appropriate guidance or a referral for more extensive support if necessary.

## Children with Chronic Health Conditions

Chronic health conditions (both chronic illnesses and chronic physical disabilities) are generally defined as those conditions that last > 12 mo and are severe enough to create some limitations in usual activity. It has been estimated that chronic health conditions affect 10 to 30% of children, depending on the criteria. Examples of chronic illnesses include asthma, cystic fibrosis, congenital heart disease, diabetes mellitus, attention-deficit/hyperactivity disorder, and depression. Examples of chronic physical disabilities include meningomyelocele, hearing or visual impairments, cerebral palsy, and loss of limb function.

**Effects on the children:** Children with chronic health conditions may experience limitations in some activities; frequent pain or discomfort; abnormal growth and development; and more hospitalizations, outpatient visits, and medical treatments. Those with severe disabilities may be unable at times to participate in school and peer activities.

Children's response to a chronic health condition largely depends on their developmental stage when the condition occurs. Children with chronic conditions that appear in infancy will respond differently than children who develop conditions during adolescence. School-aged children may be most affected by the inability to attend school and form relationships with peers. Adolescents may struggle with their inability to achieve independence if they require assistance from parents and others for many of their daily needs; parents should encourage self-reliance within the adolescent's capability and avoid overprotection. Adolescents also find it particularly difficult to be viewed as different from their peers.

Health care practitioners can be advocates for appropriate hospital services for children with chronic health conditions. Age-appropriate playrooms can be set up and a school program can be initiated with the oversight of a trained child life specialist. Children can be encouraged to interact with peers whenever possible. All procedures and plans should be explained to families and children whenever possible so the families know what to expect during the hospitalization, thus relieving the anxiety that can be created by uncertainty.

**Effects on the family:** For families, having a child who has a chronic health condition can lead to loss of their hope for an "ideal" child, neglected siblings, major expense and time commitment, confusion caused by conflicting systems of health care management, lost opportunities (eg, family members providing primary care to the child are therefore unable to return to work), and social isolation. Siblings may resent the extra attention the ill child receives. Such stress may cause family breakup, especially when there are preexisting difficulties with family function.

Conditions that affect the physical appearance of an infant (eg, cleft lip and palate, hydrocephalus) can affect the bond between the infant and family members or caretakers. Once the diagnosis of abnormality is made, parents may react with shock, denial, anger, sadness or depression, guilt, and anxiety. These reactions may occur at any time in the child's development, and each parent may be at a different stage of acceptance, making communication between them difficult. Parents may express their anger at the health care practitioner, or their denial may cause them to seek many opinions about their child's condition.

**Care coordination:** Without coordination of services, care is crisis-oriented. Some services will be duplicated, whereas others will be neglected. Care coordination requires knowledge of the children's condition, their family and support systems, and the community in which they function.

All professionals who care for children with chronic health conditions must ensure that someone is coordinating care. Sometimes the coordinator can be the child's parent. However, the systems that must be negotiated are often so complex that even the most capable parents need assistance. Other possible coordinators include the primary care physician, the subspecialty program staff, the community health nurse, and staff of the 3rd-party payer. Regardless of who coordinates services, families and children must be partners in the process. In general, children from low-income families who have chronic conditions fare worse than others, in part because of lack of access to health care and care coordination services. Some children with terminal illness benefit from hospice care.

## Death and Dying

Families often have difficulty dealing with an ill and dying child. Children who are trying to make sense of the death of a friend or family member may have particular difficulty (see also Ch. 353).

**Death of a child:** Most often the death of a child happens in the hospital or emergency department. Death can occur after a prolonged illness, such as cancer, or suddenly and unexpectedly, such as following injury or sudden infant death. The death of a child can be difficult for families to comprehend and accept. For parents, the death of a child means that they must give up their dreams and hopes for their child. The grieving process may also mean that they are unable to attend to the needs of other family members, including other children. Health care practitioners can help in the process by being available to the family for consultation and to provide comfort whenever possible. In some circumstances, referral to specialists skilled in working with families who have experienced the death of a child is appropriate.

**Death of a family member or friend:** Many children experience the death of a loved one. The way children perceive the event (and hence the best response by parents and health care practitioners) is affected by their developmental level. Preschool children may have limited understanding of death. Relating the event to previous experience with a beloved pet may be helpful. Older children may be able to understand the event more easily. Death should never be equated with going to sleep and never waking up because children may become fearful of sleeping.

Parents should discuss with health care practitioners whether to have children visit severely ill children or adults. Some children may express a specific desire to visit family members or friends who are dying. Children should be adequately prepared for such a visit so they will know what to expect. In the same way, adults often wonder whether to bring children to a funeral. This decision should be made individually, in consultation with the children whenever possible. When children attend a funeral, a close friend or relative should accompany them to provide support throughout, and children should be allowed to leave if necessary.

# Chapter 271. Physical Growth and Development

## Introduction

Physical growth is an increase in size. Development is growth in function and capability. Both processes are highly dependent on genetic, nutritional, and environmental factors.

## Physical Growth

(See also Failure to Thrive on p. 2931.)

Physical growth includes attainment of full height and appropriate weight and an increase in size of all organs (except lymphatic tissue, which decreases in size). Growth from birth to adolescence occurs in 2 distinct phases. The 1st phase (from birth to about age 1 to 2 yr) is one of rapid growth, although the rate of growth decreases over that period. In the 2nd phase (from about 2 yr to the onset of puberty), growth occurs in relatively constant annual increments. Puberty is the process of physical maturation from child to adult. Adolescence defines an age group; puberty occurs during adolescence. At puberty, a 2nd growth spurt occurs, affecting boys and girls slightly differently. All growth parameters can be charted on standard growth curves available from the Centers for Disease Control and Prevention.

**Length:** Length is measured in children too young to stand; height is measured once the child can stand. In general, length in normal term infants increases about 30% by 5 mo and > 50% by 12 mo; infants grow 25 cm during the 1st yr; and height at 5 yr is about double birth length. In boys, half the adult height is attained by about age 2; in girls, height at 19 mo is about half the adult height.

Rate of change in height (height velocity) is a more sensitive measure of growth than time-specific height measures. In general, healthy term infants and children grow about 2.5 cm/mo between birth and 6 mo, 1.3 cm/mo from 7 to 12 mo, and about 7.6 cm/yr between 12 mo and 10 yr. Before 12 mo, height velocity varies and is due in part to perinatal factors (eg, prematurity). After 12 mo, height is mostly genetically determined, and height velocity stays constant until puberty; a child's height relative to peers tends to remain the same. Some small-for-gestationalage infants tend to be shorter throughout life than infants whose size is appropriate for their gestational age. Boys and girls show little difference in height and growth rate during infancy and childhood.

Extremities grow faster than the trunk, leading to a gradual change in relative proportions; the crown-to-pubis/pubis-to-heel ratio is 1.7 at birth, 1.5 at 12 mo, 1.2 at 5 yr, and 1.0 after 7 yr.

A growth spurt in boys occurs sometime between ages 12 and 17, with the peak typically between ages 13 and 15; a gain of > 10 cm can be expected in the year of peak velocity. A growth spurt in girls occurs sometime between ages 9 1/2 and 14 1/2, with the peak typically between ages 11 and 13 1/2; gain may reach 9 cm in the year of peak velocity. If puberty is delayed (see p. 2894), growth in height may slow considerably. If the delay is not pathologic, the adolescent growth spurt occurs later and growth catches up, with height crossing percentile lines until the child reaches a genetically determined stature. At age 18, almost 2.5 cm of growth remains for boys and slightly less for girls, for whom growth is 99% complete. In girls with true precocious puberty (prior to age 6 1/2), an early growth spurt occurs along with menarche at a young age and, ultimately, short stature results because of early closure of growth plates.

**Weight:** Weight follows a similar pattern. Normal term neonates generally lose 5 to 8% of birth weight in the days after delivery but regain their birth weight within 2 wk. They then gain 14 to 28 g/day until 3 mo, then 4000 g between 3 and 12 mo, doubling their birth weight by 5 mo, tripling it by 12 mo, and almost quadrupling it by 2 yr. Between age 2 yr and puberty, weight increases 2 kg/yr. The recent epidemic of childhood obesity has involved markedly greater weight gain, even among very young children. In general, boys are heavier and taller than girls when growth is complete because boys have a longer prepubertal growth period, increased peak velocity during the pubertal growth spurt, and a longer adolescent growth spurt.

**Head circumference:** Head circumference reflects brain size and is routinely measured up to 2 yr. At birth, the brain is 25% of adult size, and head circumference averages 35 cm. Head circumference

increases an average 1 cm/mo during the 1st yr; growth is more rapid in the 1st 8 mo, and by 12 mo, the brain has completed half its postnatal growth and is 75% of adult size. Head circumference increases 3.5 cm over the next 2 yr; the brain is 80% of adult size by age 3 yr and 90% by age 7 yr.

**Body composition:** Body composition (proportions of body fat and water) changes and affects volume of distribution of drugs (see p. 2762). Proportion of fat increases rapidly from 13% at birth to 20 to 25% by 12 mo, accounting for the chubby appearance of most infants. Subsequently, a slow fall occurs until preadolescence, when body fat returns to about 13%. There is a slow rise again until the onset of puberty, when body fat may again fall, especially in boys. After puberty, the percentage generally stays stable in girls, whereas in boys there tends to be a slight decline.

Body water measured as a percentage of body weight is 70% at birth, dropping to 61% at 12 mo (about equal to the adult percentage). This change is fundamentally due to a decrease in ECF from 45% to 28% of body weight. ICF stays relatively constant. After age 12 mo, there is a slow and variable fall in ECF to adult levels of about 20% and a rise in ICF to adult levels of about 40%. The relatively larger amount of body water, its high turnover rate, and the comparatively high surface losses (due to a proportionately large surface area) make infants more susceptible to fluid deprivation than older children and adults.

**Tooth eruption:** Tooth eruption is variable (see Table 271-1), primarily because of genetic factors. On average, normal infants should have 6 teeth by 12 mo, 12 teeth by 18 mo, 16 teeth by 2 yr, and all teeth (20) by 2 1/2 yr; deciduous teeth are replaced by permanent teeth between the ages of 5 and 13 yr. Eruption of deciduous teeth is similar in both sexes; permanent teeth tend to appear earlier in girls. Tooth eruption may be delayed by familial patterns or by conditions such as rickets, hypopituitarism, hypothyroidism, or Down syndrome. Supernumerary teeth and congenital absence of teeth are probably normal variants.

[**Table 271-1.** Tooth Eruption Times]

## Development

(See also Ch. 304.)

Development is often divided into specific domains, such as gross motor, fine motor, language, cognition, and social/emotional growth. These designations are useful, but substantial overlap exists. Studies have established average ages at which specific milestones are reached, as well as ranges of normality. In a normal child, progress within the different domains varies, as in the toddler who walks late but speaks in sentences early (see Table 271-2).

Environmental influences, ranging from nutrition to stimulation and from the impact of disease to the effects of psychologic factors, interact with genetic factors to determine the pace and pattern of development.

Assessment of development occurs constantly as parents, school personnel, and clinicians evaluate children. Many tools are available for monitoring development more specifically. The Denver Developmental Screening Test

[**Table 271-2.** Developmental Milestones*]

facilitates evaluation in several domains. The scoring sheet indicates the average ages for achieving certain milestones and nicely shows the critical concept of a range of normality. Other tools can also be used (see Table 271-2).

**Motor development:** Motor development includes fine motor (eg, picking up small objects, drawing) and gross motor (eg, walking, climbing stairs) skills. It is a continuous process that depends on familial patterns, environmental factors (eg, when activity is limited by prolonged illness), and specific disorders (eg, cerebral palsy, intellectual disability, muscular dystrophy). Children typically begin to walk at 12 mo,

can climb stairs at 21 mo, and run well at 2 yr, but the age at which these milestones are achieved by normal children varies widely. Motor development cannot be significantly accelerated by applying increased stimulation.

**Language development:** The ability to understand language precedes the ability to speak; children with few words usually can understand a great deal. Although delays in expressive speech are typically not accompanied by other developmental delays, all children with excessive language delays should be evaluated for the presence of other delays in development. Children who have delays in both receptive and expressive speech more often have additional developmental problems. Evaluation of any delay should start with an assessment of hearing. Most children who experience speech delay have normal intelligence. In contrast, children with accelerated speech development are often of above-average intelligence.

Speech progresses from the utterance of vowel sounds (cooing) to the introduction of syllables that start with consonants (ba-ba-ba). Most children can say "Dada" and "Mama" specifically by 12 mo, use several words by 18 mo, and combine words into some sentences by 2 yr. The average 3-yr-old can carry on a conversation. These milestones are highly variable.

**Cognitive and social/emotional development:** Cognitive and social/emotional development refers to the intellectual and psychologic maturation of children as their physical development allows them to interact more with other people and the external world. There are multiple theories of these forms of development in children and adolescents; the oldest and most famous are those proposed by Freud, Piaget, and Erikson. All are based on clinical observations, but none has been tested in large groups of children. In general, these models are considered useful for describing aspects of development in some children, but none is universally applicable. Increasingly, appropriate attachments and nurturing in infancy and early childhood are recognized as critical factors in cognitive growth and emotional health. For example, reading to children from an early age, providing intellectually stimulating experiences, and providing warm and nurturing relationships all have a major impact on growth in these domains. Intellect is appraised in young children by observations of language skills, curiosity, and problem-solving abilities. As children become more verbal, intellectual functioning becomes easier to assess using a number of specialized clinical tools. Once children start school, they undergo constant monitoring as part of the academic process.

Emotional growth and the acquisition of social skills are assessed by watching children interact with others in everyday situations. When children acquire speech, the understanding of their emotional state becomes much more accurate. As with intellect, emotional functioning can be delineated more precisely with specialized tools.

## Sexual Development

Sexual maturation generally proceeds in an established sequence in both sexes. The age at onset and rapidity of sexual development vary and are influenced by genetic and environmental factors. Sexual maturity begins earlier today than a century ago, probably because of improvements in nutrition, general health, and living conditions—eg, the average age of menarche has decreased by about 3 yr over the past 100 yr. The physiologic changes that underlie sexual maturation are discussed in Chs. 229 and 245.

In boys, sexual changes begin with enlargement of the scrotum and testes, followed by lengthening of the penis and enlargement of the seminal vesicles and prostate. Next, pubic hair appears. Axillary and facial hair appears about 2 yr after pubic hair. The growth spurt usually begins a year after the testes start enlarging. The median age for first ejaculation (between 12 1/2 and 14 yr in the US) is affected by psychologic, cultural, and biologic factors. First ejaculation takes place about 1 yr after penis growth accelerates. Gynecomastia, usually in the form of breast buds, is common among young adolescent boys and usually resolves within several years.

In most girls, breast budding is the first visible sign of sexual maturation, followed closely by the initiation of the growth spurt. Shortly thereafter, pubic and axillary hair appears. Menarche generally occurs about 2 yr after onset of breast development and when growth in height slows after reaching its peak. Menarche occurs within a wide range, with most girls in the US starting their periods at 12 or 13 yr. The

stages of breast growth and pubic hair development can be detailed using Tanner's method (see Figs. 245-2 and 245-3 on p. 2498).

If the order of sexual changes is disturbed, growth may be abnormal, and the physician should consider pathologic reasons.

# Chapter 272. Principles of Drug Treatment in Children

## Introduction

Drug treatment in children differs from that in adults, most obviously because it is usually based on weight or surface area. Doses (and dosing intervals) differ because of age-related variations in drug absorption, distribution, metabolism, and elimination. A child cannot safely receive an adult drug dose, nor can it be assumed that a child's dose is proportional to an adult's dose (ie, that a 7-kg child requires one tenth the dose of a 70-kg adult). Most drugs have not been adequately studied in children, although federal legislation (the Best Pharmaceuticals for Children Act of 2001 and the Pediatric Research Equity Act of 2003 [both renewed in 2007]) provides the statutory and regulatory authority to begin those studies.

**Adverse effects and toxicity:** Children are generally subject to the same adverse effects as adults (see p. 3184), but they have increased risk with certain drugs because of differences in pharmacokinetics or because of drug effects on growth and development. Common drugs with unique or higher risk of adverse effects in children are listed in Table 272-1.

Younger children are at especially high risk of accidental poisoning when they discover and take caregivers' vitamins or drugs. Infants are at risk of toxicity from drugs used by adults; toxicity can occur prenatally when they are exposed via placental transfer or postnatally when exposed through breast milk (numerous agents—see p. 2708 and Table 268-4 on p. 2706) or skin contact with caregivers who have recently applied certain topical drugs (eg, scopolamine for motion sickness, malathion for lice, diphenhydramine for poison ivy).

Adverse effects, including death, have occurred in children receiving OTC cough and cold preparations containing some combination of an antihistamine, sympathomimetic decongestant, and the antitussive dextromethorphan. Current recommendations are that such products should not be given to children < 4 yr.

## Pharmacokinetics in Children

Pharmacokinetics refers to the processes of drug absorption, distribution, metabolism, and elimination (see p. 3172).

[**Table 272-1.** Drugs Manifesting Unusual Toxicity in Children]

**Absorption:** Absorption from the GI tract is affected by

• Gastric acid secretion

• Bile salt formation

• Gastric emptying time

• Intestinal motility

• Bowel length and effective absorptive surface

• Microbial flora

All these factors are reduced in neonates and all may be reduced or increased in an ill child of any age. Reduced gastric acid secretion increases bioavailability of acid-labile drugs (eg, penicillin) and decreases bioavailability of weakly acidic drugs (eg, phenobarbital). Reduced bile salt formation decreases bioavailability of lipophilic drugs (eg, diazepam). Reduced gastric emptying and intestinal motility increase the time it takes to reach therapeutic concentrations when enteral drugs are given to infants < 3 mo. Drug-metabolizing enzymes present in the intestines of young infants are another cause of reduced drug absorption. Infants with congenital atretic bowel or surgically removed bowel or who have jejunal feeding

tubes may have specific absorptive defects depending on the length of bowel lost or bypassed and the location of the lost segment.

Injected drugs are often erratically absorbed because of

• Variability in their chemical characteristics

• Differences in absorption by site of injection (IM or sc)

• Variability in muscle mass among children

• Illness (eg, compromised circulatory status)

IM injections are generally avoided in children because of pain and the possibility of tissue damage, but, when needed, water-soluble drugs are best because they do not precipitate at the injection site.

Transdermal absorption may be enhanced in neonates and young infants because the stratum corneum is thin and because the ratio of surface area to weight is much greater than for older children and adults. Skin disruptions (eg, abrasions, eczema, burns) increase absorption in children of any age.

Transrectal drug therapy is generally appropriate only for emergencies when an IV route is not available (eg, use of rectal diazepam for status epilepticus). Site of placement of the drug within the rectal cavity may influence absorption because of the difference in venous drainage systems. Expulsion of the drug may also be enhanced in the young infant.

Absorption of drugs from the lungs (eg, β-agonists for asthma, pulmonary surfactant for respiratory distress syndrome) varies less by physiologic parameters and more by reliability of the delivery device and patient or caregiver technique.

**Distribution:** The volume of distribution of drugs changes in children with aging. These age-related changes are due to changes in body composition (especially the extracellular and total body water spaces) and plasma protein binding.

Higher doses (per kg of body weight) of water-soluble drugs are required in younger children because a higher percentage of their body weight is water (see Fig. 272-1). Conversely, lower doses are required to avoid toxicity as children grow older because of the decline in water as a percentage of body weight.

Many drugs bind to proteins (primarily albumin, $\alpha_1$-acid glycoprotein, and lipoproteins); protein binding limits distribution of

[**Fig. 272-1.** Changes in body proportions of body composition with growth and aging.]

free drug throughout the body. Albumin and total protein concentrations are lower in neonates but approach adult levels by 10 to 12 mo. Decreased protein binding in neonates is also due to qualitative differences in binding proteins and to competitive binding by molecules such as bilirubin and free fatty acids, which circulate in higher concentrations in neonates and infants. The net result may be increased free drug concentrations, greater drug availability at receptor sites, and both pharmacologic effects and higher frequency of adverse effects at lower drug concentrations.

**Metabolism and elimination:** Drug metabolism and elimination vary with age and depend on the substrate or drug, but most drugs, and most notably phenytoin, barbiturates, analgesics, and cardiac glycosides, have plasma half-lives 2 to 3 times longer in neonates than in adults.

The cytochrome P-450 (CYP450) enzyme system in the small bowel and liver is the most important known system for drug metabolism. CYP450 enzymes inactivate drugs via

• Oxidation, reduction, and hydrolysis (phase I metabolism)

• Hydroxylation and conjugation (phase II metabolism)

Phase I activity is reduced in neonates, increases progressively during the first 6 mo of life, exceeds adult rates by the first few years for some drugs, slows during adolescence, and usually attains adult rates by late puberty. However, adult rates of metabolism may be achieved for some drugs (eg, barbiturates, phenytoin) 2 to 4 wk postnatally. CYP450 activity can also be induced (reducing drug concentrations and effect) or inhibited (augmenting concentrations and effect) by coadministered drugs. These drug interactions may lead to drug toxicity when CYP450 activity is inhibited or an inadequate drug level when CYP450 activity is induced. Kidneys, lungs, and skin also play a role in the metabolism of some drugs, as do intestinal drug-metabolizing enzymes in neonates. Phase II metabolism varies considerably by substrate. Maturation of enzymes responsible for bilirubin and acetaminophen conjugation is delayed; enzymes responsible for morphine conjugation are fully mature even in preterm infants.

Drug metabolites are eliminated primarily through bile or the kidneys. Renal elimination depends on

• Plasma protein binding

• Renal blood flow

• GFR

• Tubular secretion

All of these factors are altered in the first 2 yr of life. Renal plasma flow is low at birth (12 mL/min) and reaches adult levels of 140 mL/min by age 1 yr. Similarly, GFR is 2 to 4 mL/min at birth, increases to 8 to 20 mL/min by 2 to 3 days, and reaches adult levels of 120 mL/min by 3 to 5 mo.

**Drug dosing:** Because of the above factors, drug dosing in children < 12 yr is always a function of age, body weight, or both. This approach is practical but not ideal. Even within a population of similar age and weight, drug requirements may differ because of maturational differences in absorption, metabolism, and elimination. Thus, when practical, dose adjustments should be based on plasma drug concentration. Unfortunately, these adjustments are not feasible for most drugs. Studies done as a result of federal legislation (the Best Pharmaceuticals for Children Act of 2001 and the Pediatric Research Equity Act of 2003 [both renewed in 2007]) have provided dosing for > 150 drugs that previously did not have pediatric dosing information.

## Nonadherence in Children

Nonadherence with drug recommendations (see also p. 3166) may occur at any age because of cost; painful or inconvenient administration; or the need for frequent doses, complex regimens, or both. But many unique factors contribute to nonadherence in children. Children < 6 yr may have difficulty swallowing pills and may resist taking forms of drugs that taste bad. Older children often resist drugs or regimens (eg, insulin, metered-dose inhalers) that require them to leave their classes or activities or that make them appear different from their peers. Adolescents may express rebellion and assert independence from parents by not taking their drugs. Parents or caregivers of younger children may only partially remember or understand the rationale and instructions for taking a drug, and their work schedules may preclude their being available to give children their scheduled doses. Some may wish to try folk or herbal remedies initially. Some caregivers have limited incomes and are forced to spend their money on other priorities, such as food; others have beliefs and attitudes that prevent them from giving children drugs.

To minimize nonadherence, a prescribing provider can do the following:

• Ascertain whether the patient or caregiver agrees with the diagnosis, perceives it as serious, and believes the treatment will work.

• Correct misunderstandings and guide the patient or caregiver toward reliable sources of information.

- Give written as well as oral instructions in a language the patient or caregiver can review and understand.
- Make early follow-up telephone calls to families to answer residual questions.
- Assess progress and remind the patient or caregiver of follow-up visits.
- Review drug bottles at follow-up office visits for pill counts.
- Educate the patient or caregiver about how to keep a daily symptom or drug diary.

Adolescents in particular need to feel in control of their illness and treatment and should be encouraged to communicate freely and to take as much responsibility as is possible for their own treatment. Regimens should be simplified (eg, synchronizing multiple drugs and minimizing the number of daily doses while maintaining efficacy) and matched to the patient's and caregivers' schedules. Critical aspects of the treatment should be emphasized (eg, taking the full course of an antibiotic). If lifestyle changes (eg, in diet or exercise) are also needed, such changes should be introduced incrementally over several visits, and realistic goals should be set (eg, to lose 1 of 14 kg [2 of 30 lb] by a 2-wk follow-up visit). Success in achieving a goal should be reinforced with praise, and only then should the next goal be added. For patients who require expensive long-term regimens, a list of pharmaceutical patient-assistance programs is available at www.needymeds.org.

## Chapter 273. Perinatal Physiology

The transition from life in utero to life outside the womb involves multiple changes in physiology and function.

### Bilirubin Metabolism

Aged or damaged fetal RBCs are removed from the circulation by reticuloendothelial cells, which convert heme to bilirubin (1 g of Hb yields 35 mg of bilirubin). This bilirubin is transported to the liver, where it is transferred into hepatocytes. Glucuronyl transferase then conjugates the bilirubin with uridine diphosphoglucuronic acid (UDPGA) to form bilirubin diglucuronide (conjugated bilirubin), which is secreted actively into the bile ducts. Bilirubin diglucuronide makes its way into meconium in the GI tract but cannot be eliminated from the body, because the fetus does not normally pass stool. The enzyme β-glucuronidase, present in the fetus' small-bowel luminal brush border, is released into the intestinal lumen, where it deconjugates bilirubin glucuronide; free (unconjugated) bilirubin is then reabsorbed from the intestinal tract and reenters the fetal circulation. Fetal bilirubin is cleared from the circulation by placental transfer into the mother's plasma following a concentration gradient. The maternal liver then conjugates and excretes the fetal bilirubin.

At birth, the placenta is "lost," and although the neonatal liver continues to take up, conjugate, and excrete bilirubin into bile so it can be eliminated in the stool, neonates lack proper intestinal bacteria for oxidizing bilirubin to urobilinogen in the gut; consequently, unaltered bilirubin remains in the stool, imparting a typical bright-yellow color. Additionally, the neonatal GI tract (like that of the fetus) contains β-glucuronidase, which deconjugates some of the bilirubin. In many neonates, feedings cause the gastrocolic reflex, and bilirubin is excreted in stool before most of it can be deconjugated and reabsorbed. However in many other neonates, the unconjugated bilirubin is reabsorbed and returned to the circulation from the intestinal lumen (enterohepatic circulation of bilirubin), contributing to physiologic hyperbilirubinemia and jaundice (see p. 2788).

### Cardiovascular Function

Fetal circulation is marked by right-to-left shunting of blood around the unventilated lungs through a patent ductus arteriosus (connecting the pulmonary artery to the aorta) and foramen ovale (connecting the right and left atria). Shunting is encouraged by high pulmonary arteriolar resistance and relatively low resistance to blood flow in the systemic (including placental) circulation. About 90 to 95% of the right heart output bypasses the lungs and goes directly to the systemic circulation. The fetal ductus arteriosus is kept open by low fetal systemic $PaO_2$ (about 25 mm Hg) along with locally produced prostaglandins. The foramen ovale is kept open by differences in atrial pressures: left atrial pressure is relatively low because little blood is returned from the lungs, but right atrial pressure is relatively high because large volumes of blood return from the placenta.

Profound changes to this system occur after the first few breaths, resulting in increased pulmonary blood flow and closure of the foramen ovale. Pulmonary arteriolar resistance drops acutely as a result of vasodilation caused by lung expansion, increased $PaO_2$, and reduced $PaCO_2$. The elastic forces of the ribs and chest wall decrease pulmonary interstitial pressure, further enhancing blood flow through pulmonary capillaries. Increased venous return from the lungs raises left atrial pressure, thus reducing the pressure differential between left and right atria; this effect contributes to closure of the foramen ovale.

As pulmonary blood flow is established, venous return from the lungs increases, raising left atrial pressure. Air breathing increases the $PaO_2$, which constricts the umbilical arteries. Placental blood flow is reduced or stops, reducing blood return to the right atrium. Thus, right atrial pressure decreases while left atrial pressure increases; as a result, the foramen ovale closes.

Soon after birth, systemic resistance becomes higher than pulmonary resistance, a reversal from the fetal state. Therefore, the direction of blood flow through the patent ductus arteriosus reverses, creating left-to-right shunting of blood (called transitional circulation). This state lasts from moments after birth (when the pulmonary blood flow increases and functional closure of the foramen ovale occurs) until about 24 to

72 h of age, when the ductus arteriosus usually closes. Blood entering the ductus and its vasa vasorum from the aorta has a high $PO_2$, which, along with alterations in prostaglandin metabolism, leads to constriction and closure of the ductus arteriosus. Once the ductus arteriosus closes, an adult-type circulation exists. The 2 ventricles now pump in series, and there are no major shunts between the pulmonary and systemic circulations.

During the days immediately after birth, a stressed neonate may revert to a fetal-type circulation. Asphyxia with hypoxia and hypercarbia causes the pulmonary arterioles to constrict and the ductus arteriosus to dilate, reversing the processes described previously and resulting in right-to-left shunting through the now-patent ductus arteriosus, the reopened foramen ovale, or both. Consequently, the neonate becomes severely hypoxemic, a condition called persistent pulmonary hypertension or persistent fetal circulation (although there is no umbilical circulation). The goal of treatment is to reverse the conditions that caused pulmonary vasoconstriction.

### Endocrine Function

The fetus depends completely on the maternal supply of glucose via the placenta and does not contribute to glucose production. The fetus begins to build a hepatic glycogen supply early in gestation, accumulating most glycogen stores during the 2nd half of the 3rd trimester. The neonate's glucose supply terminates when the umbilical cord is cut; concurrently, levels of circulating epinephrine, norepinephrine, and glucagon surge, while insulin levels decline. These changes stimulate gluconeogenesis and mobilization of hepatic glycogen stores. In healthy, term neonates, glucose levels reach a nadir 30 to 90 min after birth, after which neonates are typically able to maintain normal glucose homeostasis. Infants at highest risk of neonatal hypoglycemia include those with reduced glycogen stores (small-for-gestationalage and premature infants), critically ill infants with increased glucose catabolism, and infants of diabetic mothers (secondary to temporary fetal hyperinsulinemia).

### Hematopoietic Function

In utero, RBC production is controlled exclusively by fetal erythropoietin produced in the liver; maternal erythropoietin does not cross the placenta. About 55 to 90% of fetal RBCs contain fetal Hb, which has high $O_2$ affinity. As a result, a high $O_2$ concentration gradient is maintained across the placenta, resulting in abundant $O_2$ transfer from the maternal to the fetal circulation. This increased $O_2$ affinity is less useful after birth, because fetal Hb gives up $O_2$ to tissues less readily, and it may be deleterious if severe pulmonary or cardiac disease with hypoxemia exists. The transition from fetal to adult Hb begins before birth; at delivery, the site of erythropoietin production changes from the liver to the kidney by an unknown mechanism. The abrupt increase in $PaO_2$ from about 25 to 30 mm Hg in the fetus to 90 to 95 mm Hg in the neonate just after delivery causes serum erythropoietin to fall, and RBC production shuts down between birth and about 6 to 8 wk, causing physiologic anemia and contributing to anemia of prematurity (see p. 2783).

### Immunologic Function

At term, most immune mechanisms are not fully functional, more so with increasing prematurity. Thus, all neonates and young infants are immunodeficient relative to adults and are at increased risk of overwhelming infection. This risk is enhanced by prematurity, maternal illness, neonatal stress, and drugs (eg, immunosuppressants, anticonvulsants). Neonates' decreased immune response may explain the absence of localized clinical signs (eg, fever or meningismus) with infection.

In the fetus, phagocytic cells, present at the yolk sac stage of development, are critical for the inflammatory response that combats bacterial and fungal infection. Granulocytes can be identified in the 2nd mo of gestation and monocytes can be identified in the 4th mo of gestation. Their level of function increases with gestational age but is still low at term.

At birth, the ultrastructure of neutrophils is normal, but in most neonates, chemotaxis of neutrophils and monocytes is decreased because of an intrinsic abnormality of cellular locomotion and adherence to

surfaces. These functional deficits are more pronounced in premature infants.

By about the 14th wk of gestation, the thymus is functioning and producing lymphocytes. Also by 14 wk, T cells are present in the fetal liver and spleen, indicating that mature T cells are established in the peripheral lymphoid organs by this age. The thymus is most active during fetal development and in early postnatal life. It grows rapidly in utero and is readily noted on chest x-ray in a healthy neonate, reaching a peak size at age 10 yr then involuting gradually over many years.

The number of T cells in the fetal circulation gradually increases during the 2nd trimester and reaches nearly normal levels by 30 to 32 wk gestation. At birth, neonates have a relative T lymphocytosis compared to adults. However, neonatal T cells do not function as effectively as adult T cells. For example, neonatal T cells may not respond adequately to antigens and may not produce cytokines.

B cells are present in fetal bone marrow, blood, liver, and spleen by the 12th wk of gestation. Trace amounts of IgM and IgG can be detected by the 20th wk and trace amounts of IgA can be detected by the 30th wk; because the fetus is normally in an antigen-free environment, only small amounts of immunoglobulin (predominantly IgM) are produced in utero. Elevated levels of cord serum IgM indicate in utero antigen challenge, usually caused by congenital infection. Almost all IgG is acquired maternally from the placenta. After 22 wk gestation, placental transfer of IgG increases to reach maternal levels or greater at term. IgG levels at birth in premature infants are decreased relative to gestational age.

The passive transfer of maternal immunity from transplacental IgG and secretory IgA and antimicrobial factors in breast milk (eg, IgG, secretory IgA, WBCs, complement proteins, lysozyme, lactoferrin) compensate for the neonate's immature immune system and confer immunity to many bacteria and viruses. Protective immune factors in breast milk coat the GI and upper respiratory tracts via mucosa-associated lymphoid tissue and prevent invasion of mucous membranes by respiratory and enteric pathogens.

Over time, passive immunity begins to wane, reaching a nadir when the infant is 3 to 6 mo old. Premature infants, in particular, may become profoundly hypogammaglobulinemic during the first 6 mo of life. By 1 yr, the IgG level rises to about 60% of average adult levels. IgA, IgM, IgD, and IgE, which do not cross the placenta and therefore are detectable only in trace amounts at birth, increase slowly during childhood. IgG, IgM, and IgA reach adult levels by about age 10 yr.

### Pulmonary Function

Fetal lungs develop throughout gestation, and fairly well-developed alveoli are present by the 25th wk. The lungs continually produce fluid—a transudate from pulmonary capillaries plus surfactant secreted by type II pneumocytes. For normal gas exchange to occur at birth, pulmonary alveolar fluid and interstitial fluid must be cleared promptly by compression of the fetal thorax during delivery and by absorption of fluid into cells in the lung. Transient tachypnea of the newborn (see p. 2877) is probably caused by delay in this clearance process.

On delivery, when elastic recoil of ribs and strong inspiratory efforts draw air into the pulmonary tree, air-fluid interfaces are formed in alveoli. At the first breath, large amounts of surfactant are released into the air-fluid interfaces of infants ≥ 34 to 35 wk. Surfactant, a mixture of phospholipids (phosphatidylcholine, phosphatidyl glycerol, phosphatidylinositol), neutral lipids, and 3 surface active proteins all stored in lamellar inclusions in type II pneumocytes, reduces high surface tension, which would otherwise cause atelectasis and increase the work of breathing. Surfactant works more effectively in small alveoli than in large alveoli, thus opposing the normal tendency of small alveoli to collapse into large alveoli (per Laplace's law, which states that in an elastic cavity, pressure *decreases* as volume increases).

Before 34 to 35 wk gestation, surfactant is often not produced in sufficient quantities to prevent diffuse atelectasis, and respiratory distress syndrome develops (see p. 2876).

### Renal Function

At birth, renal function is generally reduced, particularly in premature infants. GFR increases

progressively during gestation, particularly during the 3rd trimester. GFR rapidly increases in the first months of life; however, GFR, urea clearance, and maximum tubular clearances do not reach adult levels until age 1 to 2 yr.

# Chapter 274. Perinatal Problems

## Introduction

Extensive physiologic changes accompany the birth process, sometimes revealing conditions that posed no problem during intrauterine life. For that reason, a person with resuscitation skills must attend each birth. Each neonate is classified as premature, full-term, or postmature to help determine the risk of various complications.

Gestational age, the primary determinant of organ maturity, can be determined in the days immediately after birth using the Ballard score (see Fig. 268-1 on p. 2700). Through plotting of weight vs gestational age (see Fig. 274-1), each infant is classified as small, appropriate, or large for gestational age. Head circumference and length are also plotted against gestational

[**Fig. 274-1.** Level of intrauterine growth based on birth weight and gestational age of live-born, single, white infants.]

age (see Fig. 274-2). These parameters are influenced by genetic factors and intrauterine conditions. They also help to predict subsequent growth and development.

## Neonatal Resuscitation

About 10% of neonates require some degree of resuscitation at delivery. Causes are numerous (see Table 274-1), but most involve asphyxia or respiratory depression. Incidence rises significantly if birth weight is < 1500 g.

**Assessment:** The Apgar score assigns 0 to 2 points for each of 5 measures of neonatal health (Appearance, Pulse, Grimace, Activity, Respiration—see Table 274-2). Scores depend on physiologic maturity, maternal perinatal therapy, and fetal cardiorespiratory and neurologic conditions. A score of 7 to 10 at 5 min is considered normal; 4 to 6, intermediate; and 0 to 3, low. A low Apgar score is not *by itself* diagnostic of perinatal asphyxia but is associated with a risk of long-term neurologic dysfunction. An unduly prolonged (> 10 min) low Apgar score predicts increased risk of mortality in the first year of life.

The earliest sign of asphyxia is acral (peripheral) cyanosis, followed by decreases in respiration, muscle tone, reflex response, and heart rate. Effective resuscitation leads initially to increased heart rate, followed by improved reflex response, color, respiration, and muscle tone. Evidence of intrapartum fetal distress, persistence of an Apgar score of 0 to 3 for > 5 min; an umbilical arterial blood pH < 7; and a sustained neonatal neurologic syndrome that includes hypotonia, coma, seizures, and evidence of multiorgan dysfunction are manifestations of perinatal asphyxia. The severity and prognosis of posthypoxic encephalopathy can be estimated with the Sarnat classification (see Table 274-3) in conjunction with EEG, neuroradiologic imaging, and brain stem auditory and cortical evoked responses.

**Resuscitation:** Initial measures for all neonates include suctioning and tactile stimulation. Suctioning requires appropriately sized catheters (see Table 223-3 on p. 2264) and pressure limits of 100 mm Hg (136 cm $H_2O$). Tactile stimulation (eg, flicking the soles of the feet, rubbing the back) may be necessary to encourage regular, spontaneous breathing. Infants not responding with appropriate respirations and heart rate require $O_2$ therapy, bag-mask ventilation, sometimes endo-tracheal intubation, and much less commonly, chest compressions (see Fig. 274-3 and Fig. 223-2 on p. 2268).

[**Fig. 274-2.** Level of intrauterine growth based on gestational age, body length (*A*), and head

circumference (*B*) at birth.]

[**Table 274-1.** Problems that may Require Resuscitation]

The infant is quickly dried and placed supine under a preheated overhead warmer in the delivery room. The neck is supported in the neutral position with a rolled towel under the shoulders.

$O_2$ should be given at 10 L/min through a face mask attached to a self-inflatable or anesthesia bag; if no mask is available, $O_2$ tubing may be placed adjacent to the face and set to deliver 5 L/min. If spontaneous respirations are absent or heart rate is < 100 beats/min, respirations are assisted with the bag-mask. *Bradycardia in a distressed child is a sign of impending cardiac arrest; neonates tend to develop bradycardia with hypoxemia.* Advanced resuscitation techniques, including endotracheal intubation, and selection of equipment size, drugs and dosages, and CPR parameters are discussed elsewhere (see p. 2266).

## Birth Injuries

The forces of labor and delivery occasionally cause physical injury to the infant. The incidence of neonatal injury from difficult or traumatic deliveries is decreasing due to increasing use of cesarean section in place of difficult versions, vacuum extractions, or mid- or high-forceps deliveries.

A traumatic delivery is anticipated when the mother has small pelvic measurements, when the infant seems large for gestational age (often the case with diabetic mothers), or when there is a breech or other abnormal presentation, especially in a primipara. In such situations, labor and the fetal condition should be monitored closely. If fetal distress is detected, the mother should be positioned on her side and given $O_2$. If fetal distress persists, an immediate cesarean section should be done.

### Head Injuries

Head molding is common in vaginal delivery due to the high pressure exerted by uterine contractions on the infant's malleable cranium as it passes through the birth canal. This molding rarely causes problems or requires treatment.

**Caput succedaneum** is edema of the presenting portion of the scalp. It occurs when the area is forced against the uterine cervix. Subgaleal hemorrhage results from greater trauma and is characterized by a boggy feeling over the entire scalp, including the temporal regions. Treatment is not required.

**Cephalhematoma,** or hemorrhage beneath the periosteum, can be differentiated from subgaleal hemorrhage because it is sharply limited to the area overlying a single bone, the periosteum being adherent at the sutures. Cephalhematomas are commonly unilateral and parietal. In a small percentage, there is a linear fracture of the underlying bone. Treatment is not required, but anemia or hyperbilirubinemia may result.

**Depressed skull fractures** are uncommon. Most result from forceps pressure or rarely from the head resting on a bony prominence in utero. Infants with depressed skull fractures or other head trauma may also have subdural bleeding, subarachnoid hemorrhage, or contusion or laceration of the brain itself (see p. 2773). Depressed skull fractures cause a palpable (and sometimes visible) step-off deformity,

[**Table 274-2.** Apgar Score]

which must be differentiated from the palpable elevated periosteal rim occurring with cephalhematomas. CT is done to confirm the diagnosis and rule out complications. Neuro-surgical elevation may be needed.

### Cranial Nerve Injury

The facial nerve is injured most often. Although frequently attributed to forceps pressure, most injuries probably result from pressure on the nerve in utero, which may be due to fetal positioning (eg, from the

head lying against the shoulder, the sacral promontory, or a uterine fibroid).

Facial nerve injury usually occurs at or distal to its exit from the stylomastoid foramen and results in facial asymmetry, especially during crying. Identifying which side of the face is affected can be confusing, but the facial muscles on the side of the nerve injury cannot move. Injury can also occur to individual branches of the nerve, most often the mandibular. Another cause of facial asymmetry is mandibular asymmetry resulting from intrauterine pressure; in this case, muscle innervation is intact and both sides of the face can move. In mandibular asymmetry, the maxillary and the mandibular occlusal surfaces are not parallel, which differentiates it from a facial nerve injury.

Testing or treatment is not needed for peripheral facial nerve injuries or mandibular asymmetry. They usually resolve by age 2 to 3 mo.

**Brachial Plexus Injuries**

Brachial plexus injuries follow stretching caused by shoulder dystocia, breech extraction, or hyperabduction of the neck in cephalic presentations. Injuries can be due to simple stretching, hemorrhage within a nerve, tearing of the nerve or root, or avulsion of the roots with accompanying cervical cord injury. Associated injuries (eg, fractures of the clavicle or humerus or subluxations of the shoulder or cervical spine) may occur.

Injuries of the upper brachial plexus (C5 to C6) affect muscles around the shoulder and elbow, whereas lesions of the lower plexus (C7 to C8 and T1) primarily affect muscles of the forearm and hand. The site and type of nerve root injury determine the prognosis.

Erb's palsy is an upper brachial plexus injury causing adduction and internal rotation of the shoulder with pronation of the forearm. Ipsilateral paralysis of the diaphragm is common. Treatment includes protecting the shoulder from excessive motion by immobilizing the arm across the upper abdomen and preventing contractures by passive range-of-motion exercises to involved joints done gently every day starting at 1 wk of age.

Klumpke's palsy is a lower plexus injury resulting in paralysis of the hand and wrist, often with ipsilateral Horner's syndrome (miosis, ptosis, facial anhidrosis). Passive range-of-motion exercises are the only treatment needed.

Neither Erb's palsy nor Klumpke's palsy usually causes demonstrable sensory loss, which suggests a tear or avulsion. These conditions usually improve rapidly, but deficits can persist. If a significant deficit persists > 3 mo, MRI is done to determine the extent of injury to the plexus, roots, and cervical cord. Surgical exploration and repair have sometimes been helpful.

[**Table 274-3.** Clinical Staging of Posthypoxic Encephalopathy]

When the entire brachial plexus is injured, the involved upper extremity cannot move, and sensory loss is usually present. Ipsilateral pyramidal signs indicate spinal cord trauma; an MRI should be done. The involved extremity's subsequent growth may be impaired. The prognosis for recovery is poor. Management may include neurosurgical exploration. Passive range-of-motion exercises can prevent contractures.

**Other Peripheral Nerve Injuries**

Injuries to other peripheral nerves (eg, the radial, sciatic, obturator) are rare in neonates and are usually not related to labor and delivery. They are usually secondary to a local traumatic event (eg, an injection in or near the sciatic nerve). Treatment includes placing the muscles antagonistic to those paralyzed at rest until recovery. Neurosurgical exploration of the nerve is seldom indicated. In most peripheral nerve injuries, recovery is complete.

**Spinal Cord Injury**

Spinal cord injury (see also p. 3231) is rare and involves variable degrees of cord disruption, often with hemorrhage. Complete disruption of the cord is very rare. Trauma usually occurs in breech deliveries after excess longitudinal traction to the spine. It can also follow

[**Fig. 274-3.** Algorithm for resuscitation of neonates.]

hyperextension of the fetal neck in utero (the "flying fetus"). Injury usually affects the lower cervical region (C5 to C7). When the injury is higher, lesions are usually fatal because respiration is completely compromised. Sometimes a click or snap is heard at delivery.

Spinal shock with flaccidity below the level of injury occurs initially. Usually, there is patchy retention of sensation or movement below the lesion. Spasticity develops within days or weeks. Breathing is diaphragmatic because the phrenic nerve remains intact as its origin is higher (at C3 to C5) than the typical cord lesion. When the spinal cord lesion is complete, the intercostal and abdominal muscles become paralyzed and rectal and bladder sphincters cannot develop voluntary control. Sensation and sweating are lost below the involved level, which can cause fluctuations of body temperature with environmental changes.

An MRI of the cervical cord may show the lesion and excludes surgically treatable lesions, such as congenital tumors or hematomas pressing on the cord. The CSF is usually bloody.

With appropriate care, most infants survive for many years. The usual causes of death are recurring pneumonia and progressive loss of renal function. Treatment includes nursing care to prevent skin ulcerations, prompt treatment of urinary and respiratory infections, and regular evaluations to identify obstructive uropathy early.

**Intracranial Hemorrhage**

Hemorrhage in or around the brain can occur in any neonate but is particularly common in those born prematurely; about 20% of premature infants < 1500 g have intracranial hemorrhage. Hypoxia-ischemia, variations in BP, and pressures exerted on the head during labor are major causes. The presence of the germinal matrix (a mass of embryonic cells lying over the caudate nucleus on the lateral wall of the lateral ventricles and present only in the fetus) makes hemorrhage more likely. Risk also is increased by hematologic disorders (eg, vitamin K deficiency, hemophilia, disseminated intravascular coagulation).

Hemorrhage can occur in several CNS spaces. Small hemorrhages in the subarachnoid space, falx, and tentorium are frequent incidental findings at autopsy of neonates that have died from non-CNS causes. Larger hemorrhages in the subarachnoid or subdural space, brain parenchyma, or ventricles are less common but more serious.

**Subarachnoid hemorrhage** probably is the most common type of intracranial hemorrhage. Neonates may present with apnea, seizures, lethargy, or an abnormal neurologic examination. With large hemorrhages, the associated meningeal inflammation may lead to a communicating hydrocephalus as the infant grows.

**Subdural hemorrhage,** which is now less common because of improved obstetric techniques, results from tears in the falx, tentorium, or bridging veins. Such tears tend to occur in neonates of primiparas, in large neonates, or after difficult deliveries—conditions that can produce unusual pressures on intracranial vessels. The presenting finding may be seizures; a rapidly enlarging head; or an abnormal neurologic examination with hypotonia, a poor Moro reflex, or extensive retinal hemorrhages.

**Intraventricular and/or intraparenchymal hemorrhage** usually occurs during the 1st 3 days of life and is the most serious type of intracranial bleeding. Hemorrhages occur most often in premature infants, are often bilateral, and usually arise in the germinal matrix. Most bleeding episodes are subependymal or intraventricular and involve a small amount of blood. In severe hemorrhage, there may be bleeding into the parenchyma or a cast of the ventricular system with large amounts of blood in the cisterna magna and basal cisterns. Hypoxia-ischemia often precedes intraventricular and subarachnoid bleeding. Hypoxia-ischemia damages the capillary endothelium, impairs cerebral vascular autoregulation, and can increase

cerebral blood flow and venous pressure, all of which make hemorrhage more likely. Most intraventricular hemorrhages are asymptomatic, but larger hemorrhages may cause apnea, cyanosis, or sudden collapse.

**Diagnosis**

• CT

Intracranial hemorrhage should be suspected in any neonate with apnea, seizures, lethargy, or an abnormal neurologic examination; such infants should have head CT. Although cranial ultrasonography is risk free, requires no sedation, and can readily identify blood within the ventricles or brain substance, CT is more sensitive for thin layers of blood in the subarachnoid or subdural spaces. However, for screening of very premature infants (eg, < 30 wk gestation), some clinicians prefer the logistical simplicity of ultrasonography. If the diagnosis is in doubt, the CSF can be examined for RBCs: it usually contains gross blood. However, some RBCs are often present in the CSF of term neonates. In subdural hemorrhage, transillumination of the skull may reveal the diagnosis after the blood has lysed.

Additionally, clotting studies, a CBC, and metabolic studies to identify other causes of neurologic dysfunction (eg, hypoglycemia, hypocalcemia, electrolyte imbalance) should be done. An EEG may help establish prognosis if the infant survives the acute bleeding episode.

**Prognosis**

The prognosis for subarachnoid hemorrhage is usually good. The prognosis for subdural hemorrhage is guarded, but some infants do well. Most infants with small intraventricular hemorrhages survive the acute bleeding episode and do well. Infants with large intraventricular hemorrhages have a poor prognosis, especially if the hemorrhage extends into the parenchyma. Preterm infants with a history of severe intraventricular hemorrhage are at risk of developing posthemorrhagic hydrocephalus and must be monitored carefully with serial cranial ultrasound examinations and frequent serial head circumference measurements. Infants with progressive hydrocephalus require neurosurgical evaluation for the placement of a subcutaneous ventricular reservoir (to aspirate CSF) or for the placement of a ventriculoperitoneal shunt. The CSF associated with posthemorrhagic hydrocephalus has a very low glucose concentration known as hypoglycorrhachia. Because many infants will be left with neurologic deficits, careful follow-up and referral for early intervention services are important.

**Treatment**

Treatment is mostly supportive unless a hematologic abnormality contributed to the bleeding. All infants should receive vitamin K if not previously given. If deficient, platelets or clotting factors should be given. Subdural hematomas should be managed by a neuro-surgeon; evacuation of the hemorrhage may be needed.

**Fractures**

Midclavicular fracture, the most common fracture during birth, occurs with shoulder dystocia and with normal, nontraumatic deliveries. Initially, the neonate is irritable and does not move the arm on the involved side either spontaneously or when the Moro reflex is elicited. Most clavicular fractures are greenstick and heal rapidly and uneventfully. A large callus forms at the fracture site within a week, and remodeling is completed within a month. Treatment consists of making a sling by pinning the shirt sleeve of the involved side to the opposite side of the infant's shirt.

The humerus and femur may be fractured in difficult deliveries. Most of these are green-stick, mid-shaft fractures, and excellent remodeling of the bone usually follows, even if moderate angulation occurs initially. A long bone may be fractured through its epiphysis, but prognosis is excellent.

**Soft-Tissue Injuries**

All soft tissues are susceptible to injury during birth if they have been the presenting part or the fulcrum for the forces of uterine contraction. Edema and ecchymosis often follow injury, particularly of the

periorbital and facial tissues in face presentations and of the scrotum or labia during breech deliveries. Breakdown of blood within the tissues and conversion of heme to bilirubin result whenever a hematoma develops. This added burden of bilirubin may cause sufficient neonatal hyperbilirubinemia to require phototherapy, and rarely, exchange transfusion (see p. 2793). No other treatment is needed.

## Hypothermia

**Hypothermia is a core temperature < 35 to 35.5° C. The condition may be purely environmental or represent intercurrent illness. Treatment is rewarming.**

Thermal equilibrium is affected by relative humidity, air flow, proximity of cold surfaces, and ambient air temperature. Neonates are particularly prone to rapid heat loss and consequent hypothermia because of a high surface area to volume ratio, which is particularly high in low-birth-weight neonates. Radiant heat loss occurs when bare skin is exposed to an environment containing objects of cooler temperature. Evaporative heat loss occurs when neonates are wet with amniotic fluid. Conductive heat loss occurs when the neonate is placed in contact with a cool surface or object. Hypothermia also may be caused by pathologic conditions that impair thermoregulation (eg, sepsis, intracranial hemorrhage).

### Pathophysiology

Prolonged, unrecognized cold stress may divert calories to produce heat, impairing growth. Neonates respond to cooling by sympathetic nerve discharge of norepinephrine in the brown fat. This specialized tissue of the neonate, located in the nape of the neck, between the scapulae, and around the kidneys and adrenals, responds by lipolysis followed by oxidation or re-esterification of the fatty acids that are released. These reactions produce heat locally, and a rich blood supply to the brown fat helps transfer this heat to the rest of the neonate's body. This reaction increases the metabolic rate and $O_2$ consumption 2- to 3-fold. Thus, in neonates with respiratory insufficiency (eg, the preterm infant with respiratory distress syndrome), cold stress may also result in tissue hypoxia and neurologic damage. Additionally, hypothermia can result in hypoglycemia, metabolic acidosis, and death.

### Treatment

Hypothermia is treated by rewarming in an incubator or under a radiant warmer. The neonate should be monitored and treated as needed for hypoglycemia, hypoxemia, and apnea. Underlying conditions such as sepsis or intracranial hemorrhage require specific treatment.

### Prevention

Hypothermia can be prevented by immediately drying and then swaddling the neonate (including the head) in a warm blanket. A neonate exposed for resuscitation or observation should be placed under a radiant warmer. Sick neonates should be maintained in a neutral thermal environment to minimize the metabolic rate. The proper incubator temperature varies depending on the neonate's birth weight and postnatal age. Alternatively, heating can be adjusted with a servomechanism set to maintain skin temperature at 36.5° C.

## Large-for-Gestational-Age Infant

**Infants whose weight is > the 90th percentile for gestational age are classified as large for gestational age (LGA). The predominant cause is maternal diabetes. Complications include birth trauma, hypoglycemia, and hyperbilirubinemia.**

Other than genetically determined size, the major cause of an infant's being LGA is maternal diabetes mellitus. The macrosomia results from the anabolic effects of high fetal insulin levels produced in response to excessive blood glucose during gestation. The less well controlled the mother's diabetes during pregnancy, the more severe is the fetal macrosomia. A rare nongenetic cause of macrosomia is Beckwith-Wiedemann syndrome (characterized by macrosomia, omphalocele, macroglossia, and hypoglycemia).

### Symptoms, Signs, and Treatment

LGA infants are large, obese, and plethoric. These infants are often listless and limp and may feed poorly. Delivery complications can occur in any LGA infant. Metabolic and respiratory complications are specific to LGA infants of diabetic mothers.

**Delivery complications:** Because of the infant's large size, vaginal delivery may be difficult and occasionally results in birth injury. Shoulder dystocia, fractures of the clavicles or limbs, and perinatal asphyxia may occur. Therefore, cesarean section should be considered when the fetus is thought to be LGA, especially if the mother's pelvic measurements are at the lower end of normal.

**Infants of diabetic mothers:** These infants are very likely to become hypoglycemic in the first 1 to 2 h after delivery because of the state of hyperinsulinism and the sudden termination of maternal glucose when the umbilical cord is cut. Neonatal hypoglycemia can be prevented by close prenatal control of the mother's diabetes and by the prophylactic IV infusion of 10% dextrose in water into the infant until early frequent feedings can be established. Blood glucose levels should be closely monitored by bedside testing during the transition period.

Hyperbilirubinemia (see also p. 2788) is common because of intolerance for oral feedings in the earliest days of life, which increases the enterohepatic circulation of bilirubin. Hyperbilirubinemia can also result from the infant's high Hct (another accompanying problem in infants of diabetic mothers).

Because surfactant production (and hence pulmonary maturation) may be delayed until late in gestation, respiratory distress syndrome may develop even if the infant is delivered only a few weeks prematurely. The lecithin/sphingomyelin ratio, and especially the presence of phosphatidyl glycerol, in amniotic fluid obtained by amniocentesis can evaluate fetal lung maturity and help determine the optimal time for safe delivery. Lung maturity can be assumed only if phosphatidyl glycerol is present. Treatment is discussed on p. 2877.

## Postmature Infant

**A postmature infant is an infant born after 42 wk gestation.**

The cause of postmaturity is generally unknown. Very rarely, it may be caused by abnormalities that affect the fetal pituitary-adrenal axis (eg, anencephaly or adrenal agenesis).

### Pathophysiology

Past term, the placenta involutes, and multiple infarcts and villous degeneration cause placental insufficiency syndrome. In this syndrome, the fetus receives inadequate nutrients from the mother, resulting in soft-tissue wasting. During labor, postmature infants are prone to develop asphyxia; meconium aspiration syndrome, which may be unusually severe because post-term amniotic fluid volume is decreased and the aspirated meconium is less diluted; and neonatal hypoglycemia caused by insufficient glycogen stores at birth. Because anaerobic metabolism rapidly uses the remaining glycogen stores, hypoglycemia is exaggerated if perinatal asphyxia has occurred.

### Symptoms and Signs

Postmature infants are alert and appear mature but have a decreased amount of soft-tissue mass, particularly subcutaneous fat. The skin may hang loosely on the extremities and is often dry and peeling. The fingernails and toenails are long. The nails and umbilical cord may be stained with meconium passed in utero.

### Diagnosis

Diagnosis is by clinical appearance (see Fig. 268-1 on p. 2700) and estimated date of delivery.

### Treatment

Prognosis and treatment depend on complications. Neonates with meconium aspiration may have chronic respiratory insufficiency and secondary pulmonary hypertension if untreated; surfactant replacement therapy is frequently helpful.

## Premature Infant

**A premature infant is an infant born before 37 wk gestation.**

Full-term gestation is 40 wk. Infants born before 37 wk have an increased incidence of complications and mortality roughly proportional to the degree of prematurity. Preterm delivery occurs in about 12.5% of pregnancies in the US and is one of the chief causes of neonatal morbidity and mortality. The rate of prematurity for black infants is 17.9%.

Previously, any infant weighing < 2.5 kg was termed premature. This definition is inappropriate because many infants weighing < 2.5 kg are mature or postmature but small for gestational age; they have a different appearance and different problems. Infants < 2.5 kg at birth are considered low-birth-weight infants, and those < 1500 g are considered very low-birth-weight infants.

### Etiology

The cause of premature labor and delivery, whether preceded by premature rupture of the membranes or not, is usually unknown. However, maternal history commonly shows low socioeconomic status; inadequate prenatal care; poor nutrition; poor education; unwed state; previous preterm birth; and intercurrent, untreated illness or infection (eg, bacterial vaginosis). Other risk factors include placental abruption, preeclampsia, multiple pregnancies, cervical incompetence, and multiple abortions.

### Symptoms and Signs

The premature infant is small, usually weighing < 2.5 kg, and tends to have thin, shiny, pink skin through which the underlying veins are easily seen. Little subcutaneous fat, hair, or external ear cartilage exists. Spontaneous activity and tone are reduced, and extremities are not held in the flexed position typical of term infants. In males, the scrotum may have few rugae, and the testes may be undescended. In females, the labia majora do not yet cover the labia minora. Reflexes develop at different times during gestation. The Moro reflex begins by 28 to 32 wk gestation and is well established by 37 wk. The palmar reflex starts at 28 wk and is well established by 32 wk. The tonic neck reflex starts at 35 wk and is most prominent at 1 mo postterm.

### Diagnosis

Findings on physical examination correlate with gestational age (see Fig. 268-1 on p. 2700). Estimated date of delivery and prenatal ultra-sonography, if done, also determine gestational age.

**Initial testing:** Along with appropriate testing for any identified problems or disorders, routine evaluations include pulse oximetry, serum Ca and electrolytes, CBC, bilirubin level, blood culture, hearing evaluation, cranial ultra-sonography to screen for intraventricular hemorrhage and periventricular leukomalacia, and screening by an ophthalmologist for retinopathy of prematurity. Weight, length, and head circumference should be plotted on an appropriate growth chart at weekly intervals.

**Subsequent screening:** Preterm infants must be monitored for apnea and bradycardia until they are 34.5 to 35 wk adjusted age. Before discharge from the hospital, premature infants should undergo a car seat monitoring evaluation using pulse oximetry to make sure that they can maintain a patent airway and good $O_2$ saturation while positioned in the car seat. After discharge, premature infants should receive careful neurodevelopmental follow-up and appropriate early referral to intervention programs as needed for physical, occupational, and language therapy.

### Complications

Most complications relate to dysfunction of immature organ systems. In some cases, complications resolve completely; in others, there is residual organ dysfunction.

**Lungs:** Surfactant production is often inadequate to prevent alveolar collapse and atelectasis, which result in respiratory distress syndrome (see p. 2876). Surfactant replacement therapy is used to both prevent and treat respiratory distress syndrome. In spite of this therapy, many premature infants develop a chronic form of lung disease known as bronchopulmonary dysplasia with a prolonged need for ventilator therapy and supplemental $O_2$ therapy. Palivizumab prophylaxis for respiratory syncytial virus is important for infants with chronic lung disease (see p. 2870).

**CNS:** Infants born before 34 wk gestation have inadequate coordination of sucking and swallowing reflexes and need to be fed intravenously or by gavage. Immaturity of the respiratory center in the brain stem results in apneic spells (central apnea—see p. 2869). Apnea may also result from hypopharyngeal obstruction alone (obstructive apnea). Both may be present (mixed apnea).

The periventricular germinal matrix (a mass of embryonic cells on the lateral wall of the lateral ventricles and present only in the fetus) is prone to hemorrhage, which may extend into the cerebral ventricles (intraventricular hemorrhage). Infarction of the periventricular white matter (periventricular leukomalacia) may also occur for reasons that are incompletely understood. Hypotension, inadequate or unstable brain perfusion, and BP peaks (as when fluid or colloid is given rapidly IV) may contribute to cerebral infarction or hemorrhage. Periventricular white matter injury is a major risk factor for cerebral palsy and neuro-developmental delays.

Premature infants, particularly those with a history of sepsis, hypoxia, and intraventricular or periventricular hemorrhages, are at risk of developmental and cognitive delays. These infants require careful follow-up during the first year of life to identify auditory, visual, and neurodevelopmental delays. Careful attention must be paid to developmental milestones, muscle tone, language skills, and growth (weight, length, and head circumference). Infants with identified delays in visual skills should be referred to a pediatric ophthalmologist. Infants with auditory and neurodevelopmental delays (including increased muscle tone and abnormal protective reflexes) should be referred to early intervention programs that provide physical, occupational, and speech therapy. Infants with severe neurodevelopmental problems may need to be referred to a pediatric neurologist.

**Infection:** Sepsis (see p. 2832) or meningitis (see p. 2830) is about 4 times more likely in the premature infant. The increased likelihood results from indwelling intravascular catheters and endotracheal tubes, areas of skin breakdown, and markedly reduced serum immunoglobulin levels (see p. 2766).

**Cardiac:** The ductus arteriosus is more likely to fail to close after birth in premature infant. The incidence of patent ductus arteriosus (PDA—see p. 2955) increases with increasing prematurity; PDA occurs in almost half of infants < 1750 g birth weight and in about 80% of those < 1200 g. About one third to one half of those with PDA have some degree of heart failure. Premature infants ≤ 29 wk gestation at birth who have respiratory distress syndrome have a 65 to 88% risk of a symptomatic PDA.

**Temperature regulation:** Premature infants have an exceptionally large body surface area to volume ratio. Therefore, when exposed to temperatures below the neutral thermal environment (see p. 2774), they rapidly lose heat and have difficulty maintaining body temperature.

**GI tract:** The small stomach and immature sucking and swallowing reflexes hinder oral or NGT feedings and create a risk of aspiration. Necrotizing enterocolitis (see p. 2803) usually manifests with bloody stool, feeding intolerance, and a distended, tender abdomen. Necrotizing enterocolitis is the most common surgical emergency in the premature infant. Complications of neonatal necrotizing enterocolitis include bowel perforation with pneumoperitoneum, intra-abdominal abscess formation, stricture formation, and short bowel syndrome.

**Kidneys:** Renal function is limited, so the concentrating and diluting limits of urine are decreased. Late metabolic acidosis and growth failure may result from the immature kidneys' inability to excrete fixed acids, which accumulate with high-protein formula feedings and as a result of bone growth. Na and $HCO_3$ are lost in the urine.

**Eyes:** Retinal vascularization is not complete until near term. Preterm delivery may interfere with this process, resulting in abnormal vessel development and sometimes defects in vision (retinopathy of prematurity—(see p. 2781). Incidence of myopia and strabismus increases independently of retinopathy of prematurity.

**Metabolic problems:** Hypoglycemia (see p. 2796) and hyperglycemia (see p. 2795) are discussed elsewhere.

Hyperbilirubinemia (see also p. 2788) occurs more commonly in the premature as compared to the term infant, and kernicterus may occur at serum bilirubin levels as low as 10 mg/dL (170 µmol/L) in small, sick, premature infants. The higher bilirubin levels may be partially due to inadequately developed hepatic excretion mechanisms, including deficiencies in the uptake of bilirubin from the serum, its hepatic conjugation to bilirubin diglucuronide, and its excretion into the biliary tree. Decreased intestinal motility enables more bilirubin diglucuronide to be deconjugated within the intestinal lumen by the luminal enzyme β-glucuronidase, thus permitting increased reabsorption of unconjugated bilirubin (enterohepatic circulation of bilirubin). Conversely, early feedings increase intestinal motility and reduce bilirubin reabsorption and can thereby significantly decrease the incidence and severity of physiologic jaundice. Uncommonly, delayed clamping of the umbilical cord increases the risk of significant hyperbilirubinemia by allowing the transfusion of a large RBC mass, thus increasing RBC breakdown and bilirubin production.

### Prognosis

Prognosis varies with presence and severity of complications, but usually mortality and likelihood of complications decrease greatly with increasing gestational age and birth weight (see Table 274-4).

### Treatment

• Supportive care

Specific disorders are treated as discussed elsewhere in THE MANUAL. General supportive care of the premature infant is best provided in a neonatal ICU or special care nursery and involves careful attention to the thermal environment, using servo-controlled incubators. Scrupulous adherence is paid to handwashing before and after all patient contact. Infants are continually monitored for apnea, bradycardia, and hypoxemia until 34.5 or 35 wk gestation.

Parents should be encouraged to visit and interact with the infant as much as possible within the constraints of the infant's medical condition.

Preterm infants should be transitioned to the supine sleeping position before hospital discharge. Parents should be instructed to keep cribs free of fluffy materials including blankets, quilts, pillows, and stuffed toys, which have been associated with an increased risk of SIDS.

**Feeding:** Feeding should be by NGT until coordination of sucking, swallowing, and breathing is established at about 34 wk gestation, at which time breastfeeding is strongly encouraged. Most premature infants tolerate breast milk, which provides immunologic and nutritional factors that are absent in cow's milk formulas. However, breast milk does not provide sufficient Ca, phosphorus, and protein for very low-birth-weight infants (ie, < 1500 g), for whom it should be mixed with a breast milk fortifier. Alternatively, specific premature infant formulas that contain 20 to 24 kcal/oz (2.8 to 3.3 joules/mL) can be used.

In the initial 1 or 2 days, if adequate fluids and calories cannot be given by mouth or NGT because of the infant's condition, a 10% glucose solution with maintenance electrolytes is given IV to prevent dehydration and undernutrition. Continuous breast milk or formula feeding via NGT or nasojejunal tube can satisfactorily maintain caloric intake in small, sick, premature infants, especially those with respiratory distress or recurrent apneic spells. Feedings are begun with small amounts (eg, 1 to 2 mL q 3 to 6 h) to

stimulate the GI tract. If tolerated, the volume and concentration of feedings are slowly increased over 7 to 10 days. In very small or critically sick infants, total parenteral hyperalimentation via a peripheral IV or a percutaneously or surgically placed central catheter may be required until full enteral feedings can be tolerated.

### Prevention

The risk of preterm delivery can be reduced by ensuring that all women, especially those in high-risk groups, have access to early and appropriate prenatal care, including advice on the importance of avoiding alcohol, tobacco,

[**Table 274-4.** Survival Estimates for Premature Infants]

and illicit drugs. The use of tocolytics to arrest premature labor and provide time for prenatal administration of corticosteroids to hasten lung maturation is discussed elsewhere (see p. 2683).

## Retinopathy of Prematurity

(Retrolental Fibroplasia)

**Retinopathy of prematurity (ROP) is a bilateral disorder of abnormal retinal vascularization in premature infants, especially those of lowest birth weight. Outcomes range from normal vision to blindness. Diagnosis is by ophthalmoscopy. Treatment of severe disease may include cryotherapy or photocoagulation; other treatment is directed at complications (eg, retinal detachment).**

The inner retinal blood vessels start growing about midpregnancy, but the retina is not fully vascularized until term. ROP results if these vessels continue their growth in an abnormal pattern, forming a ridge of tissue between the vascularized central retina and the nonvascularized peripheral retina. In severe ROP, these new vessels invade the vitreous. Sometimes the entire vasculature of the eye becomes engorged (plus disease).

Susceptibility to ROP correlates with the proportion of retina that remains avascular at birth. More than 80% of neonates weighing < 1 kg at birth develop ROP. The percentage is higher when many medical complications exist. Excessive (especially prolonged) $O_2$ therapy increases the risk. However, supplemental $O_2$ is often needed to adequately oxygenate the infant even though a safe level and duration of $O_2$ therapy have not been determined.

### Diagnosis

• Ophthalmoscopy

Diagnosis is made by ophthalmoscopic examination, which shows a line of demarcation and a ridge in mild cases and proliferation of retinal vessels in more severe cases. Because significant ROP is rare in appropriately managed infants weighing > 1500 g at birth, alternative diagnoses should be considered in these infants (eg, familial exudative retinopathy, Norrie's disease).

### Prognosis

Abnormal vessel growth often subsides spontaneously but, in about 4% of survivors weighing < 1 kg at birth, progresses to produce retinal detachments and vision loss within 2 to 12 mo postpartum. Children with healed ROP have a higher incidence of myopia, strabismus, and amblyopia. A few children with moderate, healed ROP are left with cicatricial scars (eg, dragged retina or retinal folds) and are at risk of retinal detachments later in life; rarely, glaucoma and cataracts can also occur.

### Treatment

• Cryotherapy or laser photocoagulation

In severe ROP, cryotherapy or laser photo-coagulation to ablate the peripheral avascular retina reduces the incidence of retinal fold and detachment. Therefore, all high-risk infants should be examined by an ophthalmologist before 6 wk of age. Retinal vascularization must be followed at 1- to 2-wk intervals until the vessels have matured sufficiently. If retinal detachments occur in infancy, scleral buckling surgery or vitrectomy with lensectomy may be considered, but these procedures are late rescue efforts with low benefit.

Patients with residual scarring should be followed at least annually for life. Treatment of amblyopia and refractive errors in the 1st year optimizes vision. Infants with total retinal detachments should be monitored for secondary glaucoma and poor eye growth and referred to intervention programs for the visually impaired.

### Prevention

Prevention of premature birth is the best way to prevent ROP. After a preterm birth, $O_2$ should be supplemented only as needed to avoid hypoxia documented by ABG or pulse oximetry. Vitamin E and restricted light are not effective.

## Small-for-Gestational-Age Infant

(Dysmaturity; Intrauterine Growth Restriction)

**Infants whose weight is < the 10th percentile for gestational age are classified as small for gestational age (SGA). Complications include perinatal asphyxia, meconium aspiration, and hypoglycemia.**

### Etiology

An infant may be small at birth because of genetic factors. Nongenetic factors that can restrict intrauterine growth usually are not apparent before 32 to 34 wk gestation; these factors include placental insufficiency from maternal disease involving the small blood vessels (as in preeclampsia, primary hypertension, renal disease, or long-standing diabetes); placental involution accompanying postmaturity; and infectious agents such as cytomegalo-virus, rubella virus, or *Toxoplasma gondii*. An infant may also be SGA if the mother is an opioid or cocaine addict or a heavy user of alcohol or, to a lesser degree, if she smoked cigarettes during pregnancy.

### Symptoms and Signs

Despite their size, SGA infants have physical characteristics (eg, skin appearance, ear cartilage, sole creases) and behavior (eg, alertness, spontaneous activity, zest for feeding) similar to those of normal-sized infants of like gestational age.

If growth restriction is caused by placental insufficiency and, therefore, undernutrition, the infant's weight is most affected, with a relative sparing of growth of the brain, cranium, and long bones (asymmetric growth restriction). In contrast, many genetic disorders and congenital infections cause symmetric growth restriction, in which height, weight, and head circumference are about equally affected.

**Complications:** Full-term SGA infants do not have the complications related to organ system immaturity that premature infants of similar size have. They are, however, at risk of perinatal asphyxia, meconium aspiration, and hypoglycemia.

**Perinatal asphyxia** is the most serious potential complication. It is a risk during labor if intrauterine growth restriction is caused by placental insufficiency (with marginally adequate placental perfusion), because each uterine contraction slows or stops maternal placental perfusion by compressing the spiral arteries. Therefore, when placental insufficiency is suspected, the fetus should be assessed before labor and the fetal heart rate monitored during labor. If fetal compromise is detected, rapid delivery, often by

cesarean section, is indicated.

**Meconium aspiration** may occur during perinatal asphyxia. SGA infants, especially those who are postmature, may pass meconium into the amniotic sac and begin deep gasping movements. The consequent aspiration is likely to result in meconium aspiration syndrome (often most severe in growth-restricted or postmature infants, because the meconium is contained in a smaller volume of amniotic fluid —see p. 2872).

**Hypoglycemia** often occurs in the early hours and days of life due to a lack of adequate glycogen stores (see p. 2796).

**Polycythemia** may occur when SGA fetuses experience chronic mild hypoxia caused by placental insufficiency. Erythropoietin release is increased, leading to an increased rate of erythrocyte production. The neonate with polycythemia at birth appears ruddy and may be tachypneic or lethargic.

### Prognosis

If asphyxia can be avoided, neurologic prognosis is quite good.

Infants who are SGA because of genetic factors, congenital infection, or maternal drug use often have a worse prognosis, depending on the specific diagnosis. If intrauterine growth restriction is caused by chronic placental insufficiency, adequate nutrition may allow SGA infants to demonstrate remarkable "catch-up" growth after delivery.

### Treatment

Underlying conditions and complications are treated. There is no specific intervention for the SGA state, but prevention is aided by prenatal advice on the importance of avoiding alcohol, tobacco, and illicit drugs.

# Chapter 275. Perinatal Hematologic Disorders

## Introduction

Anemia and polycythemia are the most common hematologic disorders diagnosed at birth. Prenatal and perinatal changes in erythropoiesis are discussed in Ch. 273.

## Perinatal Anemia

(See also Ch. 104.)

Anemia is Hb or Hct > 2 standard deviations below the mean for age. Both Hb and Hct change rapidly as a neonate matures, so lower limits of normal also change (see Table 275-1). Variables such as gestational age, sampling site (capillary vs vein), and position of the neonate relative to the placenta before

[**Table 275-1.** Age-Specific Values for Hemoglobin and Hematocrit]

cord clamping (lower position causes blood to transfer in to the neonate; higher position causes blood to transfer out of the neonate) also affect test results.

### Etiology

Causes of anemia in neonates include

• Physiologic processes

• Blood loss

• Decreased RBC production

• Increased RBC destruction (hemolysis)

**Physiologic anemia:** Normal physiologic processes often cause normocytic-normochromic anemia in term and preterm infants. Physiologic anemias do not generally require extensive evaluation or treatment.

In term infants, the increase in oxygenation that occurs with normal breathing after birth causes an abrupt rise in tissue $O_2$ level, resulting in negative feedback on erythropoietin production and erythropoiesis. This reduction in erythropoiesis, as well as the shorter life span of neonatal RBCs (60 to 70 days vs 120 days in adults), causes Hb concentration to fall over the first 2 to 3 mo of life, usually to no lower than 9.4 g/dL. Hb remains stable over the next several weeks, and then slowly rises in the 4th to 6th mo secondary to renewed erythropoietin stimulation.

The same mechanism causes anemia in preterm infants during the first 4 to 12 wk, but lower erythropoietin production, shorter RBC life span (35 to 50 days), rapid growth, and more frequent phlebotomy contribute to a faster and lower Hb nadir (8 to 10 g/dL). Infants < 32 wk gestation are most affected.

**Blood loss:** Anemia may develop because of prenatal, perinatal (at delivery), or postpartum hemorrhage. In neonates, absolute blood volume is low (eg, preterm, 90 to 105 mL/kg; term, 78 to 86 mL/kg); therefore, acute loss of as little as 15 to 20 mL of blood may result in anemia. An infant with chronic blood loss can compensate physiologically and is typically more clinically stable than an infant with acute blood loss.

**Prenatal hemorrhage** may be caused by

• Fetal-to-maternal hemorrhage

- Twin-to-twin transfusion
- Cord malformations
- Placental abnormalities
- Diagnostic procedures

Fetal-to-maternal hemorrhage occurs spontaneously or as a result of maternal trauma, amniocentesis, external cephalic version, or placental tumor. It affects about 50% of pregnancies, although in most cases the volume of blood lost is extremely small (about 2 mL); "massive" blood loss, defined as > 30 mL, occurs in 3/1000 pregnancies.

Twin-to-twin transfusion is the unequal sharing of blood supply between twins that affects 13 to 33% of monozygotic, monochorionic twin pregnancies. When significant blood transfer occurs, the donor twin may become very anemic and develop heart failure, while the recipient may become polycythemic and develop hyperviscosity syndrome (see p. 2787).

Cord malformations include velamentous insertion of the umbilical cord, vasa previa, or abdominal or placental insertion; the mechanism of hemorrhage, which is often massive and rapid, is by cord vessel shearing or rupture.

The 2 important placental abnormalities causing hemorrhage are placenta previa and abruptio placentae.

Diagnostic procedures causing hemorrhage include amniocentesis, chorionic villus sampling, and umbilical cord blood sampling.

**Perinatal hemorrhage** may be caused by

- Precipitous delivery (ie, rapid, spontaneous delivery < 3 h after onset of labor, which causes hemorrhage due to umbilical cord tearing)
- Obstetric accidents (eg, incision of the placenta during cesarean delivery, birth trauma)
- Coagulopathies

Cephalhematomas resulting from procedures such as vacuum or forceps delivery are usually relatively harmless, but subgaleal bleeds can extend into soft tissue, sequestering sufficient blood volumes to result in anemia, hypotension, shock, and death. Far less often, rupture of the liver, spleen, or adrenal gland during delivery may lead to internal bleeding. Intraventricular hemorrhage, most common among preterm infants (see p. 2773), as well as subarachnoid and subdural bleeding also can result in a significantly lowered Hct.

Hemorrhagic disease of the newborn (see also Vitamin K Deficiency on p. 46) is hemorrhage within a few days of a normal delivery caused by transient physiologic deficiency in vitamin K-dependent coagulation factors. Other possible causes of hemorrhage in the first few days of life are other coagulopathies (eg, hemophilia), disseminated intravascular coagulation caused by sepsis, vascular malformations, or prenatal maternal use of vitamin K antagonists (eg, phenytoin, warfarin, isoniazid).

**Decreased RBC production:** Defects in RBC production may be

- Congenital
- Acquired

**Congenital defects** are extremely rare, but Diamond-Blackfan anemia and Fanconi's anemia are the most common.

Diamond-Blackfan anemia is characterized by lack of RBC precursors in bone marrow, macrocytic RBCs, lack of reticulocytes in peripheral blood, and lack of involvement of other blood cell lineages. It is often part of a syndrome of congenital anomalies including microcephaly, cleft palate, eye anomalies, thumb deformities, and webbed neck. Up to 25% of affected infants are anemic at birth, and low birth weight occurs in about 10%. It is thought to be caused by defective stem cell differentiation.

Fanconi's anemia is an autosomal recessive disorder of bone marrow progenitor cells that causes macrocytosis and reticulocytopenia with progressive failure of all hematopoietic cell lines. It is usually diagnosed after the neonatal period. The cause is a genetic defect that prevents cells from repairing damaged DNA or removing toxic free radicals that damage cells.

Other congenital anemias include Pearson's syndrome, a rare, multisystem disease involving mitochondrial defects that cause refractory sideroblastic anemia, pancytopenia, and variable hepatic, renal, and pancreatic insufficiency or failure; and congenital dyserythropoietic anemia, in which chronic anemia (typically macrocytic) results from ineffective or abnormal RBC production, and hemolysis caused by RBC abnormalities.

**Acquired defects** are those that occur after birth. The most common causes are

• Infections

• Nutritional deficiencies

Infections (eg, malaria, rubella, syphilis, HIV, cytomegalovirus, adenovirus, bacterial sepsis) may impair RBC production in the bone marrow. Congenital parvovirus B19 infection may result in the absence of RBC production.

Nutritional deficiencies of iron, copper, folate (folic acid), and vitamins E and $B_{12}$ may cause anemia in the early months of life but not usually at birth. The incidence of iron deficiency, the most common nutritional deficiency, is higher in less developed countries where it results from dietary insufficiency and exclusive and prolonged breastfeeding. Iron deficiency is common among neonates whose mothers have an iron deficit and among premature infants who have not been transfused and whose formula is not supplemented with iron; premature infants deplete iron stores by 10 to 14 wk if not supplemented.

**Hemolysis:** Hemolysis (see also p. 934) may be caused by

• Immune-mediated disorders

• RBC membrane disorders

• Enzyme deficiencies

• Hemoglobinopathies

• Infections

All also cause hyperbilirubinemia, which may cause jaundice and kernicterus (see p. 2793).

**Immune-mediated hemolysis** may occur when fetal RBCs with surface antigens (most commonly Rh and ABO blood antigens but also Kell, Duffy, and other minor group antigens) that differ from maternal RBC antigens enter the maternal circulation and stimulate production of IgG antibody directed against fetal RBCs. The most common severe scenario is that an Rh (D antigen)-negative mother becomes sensitized to the D antigen during a previous pregnancy with an Rh-positive fetus; a 2nd Rh-positive pregnancy may then prompt an IgG response that may result in fetal and neonatal hemolysis (see also Erythroblastosis Fetalis on p. 2665). Intrauterine hemolysis may be severe enough to cause hydrops or death; postpartum, there may be significant anemia and hyperbilirubinemia with ongoing hemolysis secondary to persistent maternal IgG (half-life about 28 days). With widespread prophylactic use of anti-Rh D to prevent sensitization (see p. 2666), < 0.11% of pregnancies in Rh-negative women are affected.

ABO incompatibility may cause hemolysis by a similar mechanism. ABO incompatibility usually occurs in type O mothers. Mothers with type A, B, or AB blood make anti-A or anti-B antibodies that are predominantly IgM and are incapable of crossing the placenta. Hemolysis caused by ABO incompatibility can occur in a first pregnancy because mothers are often sensitized by antigens in foods or bacteria.

**RBC membrane disorders** alter RBC shape and deformability, resulting in premature removal of RBCs from the circulation. The most common disorders are hereditary spherocytosis and hereditary elliptocytosis (see p. 940).

**Enzyme deficiencies** of G6PD (see p. 941) and pyruvate kinase (see also Embden-Meyerhof Pathway Defects on p. 941) are the most common enzyme disorders causing hemolysis.

**Hemoglobinopathies** are caused by deficiencies and structural abnormalities of globin chains. At birth, 55 to 90% of the neonate's Hb is composed of 2 α and 2 γ globin chains (fetal Hb or Hb F [$\alpha^2\gamma^2$]). After birth, γ-chain production decreases (to < 2% by 2 to 4 yr of age) and β-chain production increases until adult Hb (Hb A [$\alpha^2\beta^2$]) becomes predominant. α-Thalassemia (see p. 946) is a genetically inherited disorder of depressed α globin chain production and is the most common hemoglobinopathy causing anemia in the neonatal period. β-Thalassemia is an inherited decrease in β-chain production. Because β globin is naturally low at birth, β-thalassemia and structural abnormalities of the β globin chain (eg, Hb S [sickle cell disease], Hb C) are rarely apparent at birth and symptoms do not appear until fetal Hb levels have fallen to sufficiently low levels at 3 to 4 mo of age.

**Intrauterine infections** by certain bacteria, viruses, fungi, and protozoa (most notably toxoplasmosis and malaria) also may trigger hemolytic anemia. In malaria, the *Plasmodium* parasite invades and ultimately ruptures the RBC. Immune-mediated destruction of parasitized RBCs and excess removal of nonparasitized cells occur. Associated bone marrow dyserythropoiesis results in inadequate compensatory erythropoiesis. Intravascular hemolysis, extravascular phagocytosis, and dyserythropoiesis can lead to anemia.

### Symptoms and Signs

Symptoms and signs are similar regardless of the cause but vary with severity and rate of onset of the anemia. Neonates are generally pale and, if anemia is severe, have tachypnea, tachycardia, and sometimes a flow murmur; hypotension is present with acute blood loss. Jaundice may be present with hemolysis.

### Evaluation

**History:** History should focus on maternal factors (eg, bleeding diatheses, hereditary RBC disorders, nutritional deficiencies, drugs), family history of hereditary disorders that may cause neonatal anemia (eg, hemoglobinopathies, enzyme deficiencies, red cell membrane disorders, RBC aplasias), and obstetric factors (eg, infections, vaginal bleeding, obstetric interventions, mode of delivery, blood loss, treatment and appearance of the cord, placental pathology, fetal distress, number of fetuses).

Nonspecific maternal factors may provide additional clues. Splenectomy would indicate a possible history of hemolysis, red cell membrane disorder, or autoimmune anemia; cholecystectomy might indicate a history of hemolysis-induced gallstones. Important neonatal factors include gestational age at delivery, age at presentation, sex, race, and ethnicity.

**Physical examination:** Tachycardia and hypotension suggest acute, significant blood loss. Jaundice suggests hemolysis, either systemic (caused by ABO incompatibility or G6PD deficiency) or localized (caused by breakdown of sequestered blood in cephalhematomas). Hepatosplenomegaly suggests hemolysis, congenital infection, or heart failure. Hematomas, ecchymoses, or petechiae suggest bleeding diathesis. Congenital anomalies may suggest a bone marrow failure syndrome.

**Testing:** Anemia may be suspected prenatally if ultrasonography shows hydrops fetalis, which, by definition, is abnormal, excessive fluid in 2 or more body compartments (eg, pleura, peritoneum,

pericardium); cardiac, hepatic, and splenic enlargement may be present.

After birth, if anemia is suspected, initial testing consists of

- Reticulocyte count
- Peripheral smear examination

If the **reticulocyte count is low**, anemia is caused by acquired or congenital bone marrow dysfunction, and the infant should be evaluated for causes of bone marrow suppression with

- Titers or PCR studies for congenital infection (rubella, syphilis, HIV, cytomegalovirus, adenovirus, parvovirus)
- Folate and vitamin $B_{12}$ levels
- Iron and copper levels

If these studies do not identify a cause of anemia, a bone marrow biopsy, genetic testing for congenital disorders of RBC production, or both may be necessary.

If the **reticulocyte count is elevated or normal** (reflecting an appropriate bone marrow response), anemia is caused by blood loss or hemolysis. If there is no apparent blood loss or if signs of hemolysis are noted on the peripheral smear, a direct antiglobulin test (DAT [Coombs' test]) should be done.

If the **DAT is positive**, anemia is likely secondary to Rh, ABO, or other blood group incompatibility.

If the **DAT is negative**, the RBC mean corpuscular volume (MCV) may prove helpful. A significantly low MCV suggests α-thalassemia or chronic intrauterine blood loss. With a normal or high MCV, peripheral blood smear may show abnormal RBC morphology compatible with a membrane disorder, microangiopathy, disseminated intravascular coagulation, vitamin E deficiency, or hemoglobinopathy. If the smear is normal, blood loss, enzyme deficiency, or infection should be considered and an appropriate assessment, including testing for fetal-to-maternal hemorrhage, should ensue.

Fetal-to-maternal hemorrhage can be diagnosed by testing for fetal RBCs in maternal blood. The Kleihauer-Betke acid elution technique is the most frequently used test, but other tests include fluorescent antibody techniques and differential or mixed agglutination testing. In the Kleihauer-Betke technique, citric acid-phosphate buffer of pH 3.5 elutes Hb from adult but not fetal RBCs; thus, fetal RBCs stain with eosin and are visible on microscopy, whereas adult RBCs appear as red cell ghosts. The Kleihauer-Betke technique is not useful when the mother has a hemoglobinopathy.

**Treatment**

Need for treatment varies with degree of anemia and associated medical conditions. Mild anemia in otherwise healthy term and preterm infants generally does not require specific treatment; treatment is directed at the underlying diagnosis. Some patients require transfusion or exchange transfusion of packed RBCs.

**Transfusion:** Transfusion is indicated to treat severe anemia. Infants should be considered for transfusion if symptomatic due to anemia or if a decrease in tissue $O_2$ delivery is suspected. The decision to transfuse should be based on symptoms, patient age, and degree of illness. Hct alone should not be the deciding factor regarding transfusion because some infants may be asymptomatic with lower levels and others may be symptomatic with higher levels.

Guidelines for when to transfuse vary, but one accepted set is described in Table 275-2.

Before the first transfusion, if not already done, maternal and fetal blood should be screened for ABO and

Rh types and the presence of atypical RBC antibodies, and a DAT should be done on the infant's RBCs.

Blood for transfusion should be the same as or compatible with the neonate's ABO and Rh group and with any ABO or RBC antibody present in maternal or neonatal serum. Neonates produce RBC antibodies only rarely, so in cases where the need for transfusion persists, repeat antibody screening is usually not necessary until 4 mo of age.

[**Table 275-2.** Transfusion Guidelines for Infants < 4 Mo]

Packed RBCs used for transfusion should be filtered (leukocyte depleted), irradiated, and given in aliquots of 10 to 20 mL/kg derived from a single donation; sequential transfusions from the same unit of blood minimize recipient exposure and transfusion complications. Blood from cytomegalovirus-negative donors should be considered for extremely premature infants.

**Exchange transfusion:** Exchange transfusion, in which blood from the neonate is removed in aliquots in sequence with packed RBC transfusion, is indicated for some cases of hemolytic anemia with elevation of serum bilirubin and some cases of severe anemia with heart failure. This procedure decreases plasma antibody titers and bilirubin levels and minimizes fluid overload. Serious adverse effects (eg, thrombocytopenia; necrotizing enterocolitis; hypoglycemia; hypocalcemia; shock, pulmonary edema, or both [caused by shifts in fluid balance]) are common, so the procedure should be done by experienced staff. Guidelines for when to begin exchange transfusion differ and are not evidence based.

**Other treatments:** Recombinant human erythropoietin is not routinely recommended, in part because it has not been shown to reduce transfusion requirements in the first 2 wk of life.

Iron therapy is restricted to cases of repetitive blood loss (eg, hemorrhagic diathesis, GI bleeding, frequent phlebotomy). Oral iron supplements are preferred; parenteral iron sometimes causes anaphylaxis, so therapy should be guided by a hematologist.

Treatment of more unusual causes of anemia is disorder specific (eg, corticosteroids in Diamond-Blackfan anemia, and vitamin $B_{12}$ for $B_{12}$ deficiency).

## Perinatal Polycythemia and Hyperviscosity Syndrome

**Polycythemia is an abnormal increase in RBC mass, defined in neonates as a venous Hct ≥ 65%; this increase can lead to hyperviscosity with sludging of blood within vessels and sometimes thrombosis. The main symptoms and signs of neonatal polycythemia are nonspecific and include ruddy complexion, feeding difficulties, lethargy, hypoglycemia, hyperbilirubinemia, cyanosis, respiratory distress, and seizures. Diagnosis is made clinically and with an Hct measurement. Treatment is with partial exchange transfusion.**

The terms polycythemia and hyperviscosity are often used interchangeably but are not equivalent. Polycythemia is significant only because it increases risk of hyperviscosity syndrome. Hyperviscosity is a clinical syndrome caused by sludging of blood within vessels. Sludging occurs because increased RBC mass causes a relative decrease in plasma volume and a relative increase in proteins and platelets.

Incidence of polycythemia is about 3 to 4% (range 0.4 to 12%), and about half of infants with polycythemia have hyperviscosity.

### Etiology

Dehydration causing relative hemoconcentration and an elevated Hct mimics polycythemia, but RBC mass is not increased. Causes of true polycythemia include intrauterine hypoxia, perinatal asphyxia, placental transfusion (including twin-to-twin transfusion), some congenital abnormalities (eg, cyanotic congenital heart disease, renovascular malformations, congenital adrenal hyperplasia), certain delivery procedures (eg, delayed cord clamping, holding neonate below the level of the mother before cord clamping, stripping the cord toward the neonate at delivery), maternal insulin-dependent diabetes, Down syndrome, Beckwith-Wiedemann syndrome, and intrauterine growth restriction. Polycythemia is also more

common when the mother resides at a high altitude. Premature infants rarely develop hyperviscosity syndrome.

### Symptoms and Signs

Symptoms and signs of hyperviscosity syndrome are those of heart failure, thrombosis (cerebral and renal vessels), and CNS dysfunction, including tachypnea, respiratory distress, cyanosis, plethora, apnea, lethargy, irritability, hypotonia, tremulousness, seizures, and feeding problems. Renal vein thrombosis may also cause renal tubular damage, proteinuria, or both.

### Diagnosis

• Hct

• Clinical evaluation

Diagnosis of polycythemia is by Hct. Diagnosis of hyperviscosity syndrome is clinical. Capillary samples often overestimate Hct, so a venous or arterial Hct should be obtained before the diagnosis is made; most published studies of polycythemia use spun Hcts, which are no longer routinely done and are generally higher than those done on automated counters. Laboratory measure of viscosity is not readily available.

Other laboratory abnormalities may include low blood glucose and $Ca^{++}$ levels, maternal diabetes, or both; RBC lysis; thrombocytopenia (secondary to consumption with thrombosis); hyperbilirubinemia (caused by turnover of a higher number of RBCs); and reticulocytosis and increased peripheral nucleated RBCs (caused by increased erythropoiesis secondary to fetal hypoxia).

### Treatment

• IV hydration

• Sometimes phlebotomy plus saline replacement

Asymptomatic infants should be treated with IV hydration (see p. 2807). Symptomatic infants with Hct > 65 to 70% should undergo an isovolemic hemodilution (sometimes called partial exchange transfusion, although no blood products are given) to reduce the Hct to ≤ 55% and thereby decrease blood viscosity. Partial exchange is done by removing blood in aliquots of 5 mL/kg (about 10 to 12 mL) and immediately replacing it with an equal volume of 0.9% saline. Asymptomatic infants whose Hct remains persistently > 70% despite hydration may also benefit from this procedure.

Although many studies show immediate measurable effects of partial exchange, the long-term benefits remain in question. Most studies have failed to document differences in long-term growth or neurodevelopment between children who have received a partial exchange transfusion in the neonatal period and those who have not.

# Chapter 276. Metabolic, Electrolyte, and Toxic Disorders in Neonates

## Introduction

Inherited disorders of metabolism are discussed in Ch. 301. Electrolyte disorders also are discussed elsewhere in THE MANUAL.

## Neonatal Hyperbilirubinemia

Jaundice is a yellow discoloration of the skin and eyes caused by hyperbilirubinemia (elevated serum bilirubin concentration). The serum bilirubin level required to cause jaundice varies with skin tone and body region, but jaundice usually becomes visible on the sclera at a level of 2 to 3 mg/dL (34 to 51 µmol/L) and on the face at about 4 to 5 mg/dL (68 to 86 µmol/L). With increasing bilirubin levels, jaundice seems to advance in a head-to-foot direction, appearing at the umbilicus at about 15 mg/dL (258 µmol/L) and at the feet at about 20 mg/dL (340 µmol/L). Slightly more than half of all neonates become visibly jaundiced in the first week of life.

**Consequences of hyperbilirubinemia:** Hyperbilirubinemia may be harmless or harmful depending on its cause and the degree of elevation. Some causes of jaundice are intrinsically dangerous whatever the bilirubin level. But hyperbilirubinemia of any etiology is a concern once the level is high enough. The threshold for concern varies by age (see
Fig. 276-1), degree of prematurity, and health status;

[**Fig. 276-1.** Risk of hyperbilirubinemia in neonates ≥ 35 wk gestation.]

however, among term infants, the threshold typically is considered to be a level > 18 mg/dL (> 308 µmol/L).

**Kernicterus** (see p. 2793) is the major consequence of neonatal hyperbilirubinemia. Although it is now rare, kernicterus still occurs and can nearly always be prevented. Kernicterus is brain damage caused by unconjugated bilirubin deposition in basal ganglia and brain stem nuclei, caused by either acute or chronic hyperbilirubinemia. Normally, bilirubin bound to serum albumin stays in the intravascular space. However, bilirubin can cross the blood-brain barrier and cause kernicterus in certain situations:

• When serum bilirubin concentration is markedly elevated

• When serum albumin concentration is markedly low (eg, in preterm infants)

• When bilirubin is displaced from albumin by competitive binders

Competitive binders include drugs (eg, sulfisoxazole, ceftriaxone, aspirin) and free fatty acids and hydrogen ions (eg, in fasting, septic, or acidotic infants).

### Pathophysiology

The majority of bilirubin is produced from the breakdown of Hb into unconjugated bilirubin (and other substances). Unconjugated bilirubin binds to albumin in the blood for transport to the liver, where it is taken up by hepatocytes and conjugated with glucuronic acid by the enzyme uridine diphosphogluconurate glucuronosyltransferase (UGT) to make it water-soluble. The conjugated bilirubin is excreted in bile into the duodenum. In adults, conjugated bilirubin is reduced by gut bacteria to urobilin and excreted. Neonates, however, have sterile digestive tracts. They do have the enzyme β-glucuronidase, which deconjugates the conjugated bilirubin, which is then reabsorbed by the intestines and recycled into the circulation. This is called enterohepatic circulation of bilirubin (see p. 2764).

**Mechanisms of hyperbilirubinemia:** Hyperbilirubinemia can be caused by one or more of the following processes:

• Increased production

• Decreased hepatic uptake

• Decreased conjugation

• Impaired excretion

• Impaired bile flow (cholestasis)

• Increased enterohepatic circulation

**Etiology**

**Classification:** There are several ways to classify and discuss causes of hyperbilirubinemia. Because transient jaundice is common among healthy neonates (unlike adults, in whom jaundice always signifies a disorder), hyperbilirubinemia can be classified as physiologic or pathologic. It can be classified by whether the hyperbilirubinemia is unconjugated, conjugated, or both. It also can be classified by mechanism (see
Table 276-1).

**Causes:** Most cases involve unconjugated hyperbilirubinemia. Some of the most common causes of neonatal jaundice include

• Physiologic hyperbilirubinemia

• Breastfeeding jaundice

• Breast milk jaundice

• Pathologic hyperbilirubinemia due to hemolytic disease

Liver dysfunction (eg, caused by parenteral alimentation causing cholestasis, neonatal sepsis, neonatal hepatitis) may cause a conjugated or mixed hyperbilirubinemia.

**Physiologic hyperbilirubinemia** occurs in almost all neonates. Shorter neonatal RBC life span increases bilirubin production; deficient conjugation due to the deficiency of UGT decreases clearance; and low bacterial levels in the intestine combined with increased hydrolysis of conjugated bilirubin increase enterohepatic circulation. Bilirubin levels can rise up to 18 mg/dL by 3 to 4 days of life (7 days in Asian infants) and fall thereafter.

**Breastfeeding jaundice** develops in one sixth of breastfed infants during the first week of life. Breastfeeding increases enterohepatic circulation of bilirubin in some infants who have decreased milk intake and who also have dehydration or low caloric intake. The increased enterohepatic circulation also may result from reduced intestinal bacteria that convert bilirubin to nonresorbed metabolites.

**Breast milk jaundice** is different from breastfeeding jaundice. It develops after the first 5 to 7 days of life and peaks at about 2 wk. It is thought to be caused by an increased concentration of β-glucuronidase in breast milk, causing an increase in the deconjugation and reabsorption of bilirubin.

**Pathologic hyperbilirubinemia** in term infants is diagnosed if

• Jaundice appears in the first 24 h, after the first week of life, or lasts > 2 wk

• Total serum bilirubin (TSB) rises by > 5 mg/dL/day

• TSB is > 18 mg/dL

• Infant shows symptoms or signs of a serious illness

Some of the most common pathologic causes are

[Table 276-1. Causes of Neonatal Hyperbilirubinemia]

• Immune and nonimmune hemolytic anemia

• G6PD deficiency

• Hematoma resorption

• Sepsis

• Hypothyroidism

**Evaluation**

**History: History of present illness** should note age of onset and duration of jaundice. Important associated symptoms include lethargy and poor feeding (suggesting possible kernicterus), which may progress to stupor, hypotonia, or seizures and eventually to hypertonia. Patterns of feeding can be suggestive of possible breastfeeding failure or underfeeding. Therefore, history should include what the infant is being fed, how much and how frequently, urine and stool production (possible breastfeeding failure or underfeeding), how well the infant is latching on to the breast or taking the nipple of the bottle, whether the mother feels that her milk has come in, and whether the infant is swallowing during feedings and seems satiated after feedings.

**Review of systems** should seek symptoms of causes, including respiratory distress, fever, and irritability or lethargy (sepsis); hypotonia and poor feeding (hypothyroidism, metabolic disorder); and repeated episodes of vomiting (intestinal obstruction).

**Past medical history** should focus on maternal infections (toxoplasmosis, other pathogens, rubella, cytomegalovirus, and herpes simplex [TORCH] infections), disorders that can cause early hyperbilirubinemia (maternal diabetes), maternal Rh factor and blood group (maternofetal blood group incompatibility), and a history of a prolonged or difficult birth (hematoma or forceps trauma).

Family history should note known inherited disorders that can cause jaundice, including G6PD deficiency, thalassemias, and spherocytosis, and also any history of siblings who have had jaundice.

Drug history should specifically note drugs that may promote jaundice (eg, ceftriaxone, sulfonamides, antimalarials).

**Physical examination:** Overall clinical appearance and vital signs are reviewed.

The skin is inspected for extent of jaundice. Gentle pressure on the skin can help reveal the presence of jaundice. Also, ecchymoses or petechiae (suggestive of hemolytic anemia) are noted.

The physical examination should focus on signs of causative disorders.

The general appearance is inspected for plethora (maternofetal transfusion); macrosomia (maternal diabetes); lethargy or extreme irritability (sepsis or infection); and any dysmorphic features such as macroglossia (hypothyroidism) and flat nasal bridge or bilateral epicanthal folds (Down syndrome).

For the head and neck examination, any bruising and swelling of the scalp consistent with a cephalohematoma are noted. Lungs are examined for crackles, rhonchi, and decreased breath sounds (pneumonia). The abdomen is examined for distention, mass (hepatosplenomegaly), or pain (intestinal obstruction). Neurologic examination should focus on signs of hypotonia or weakness (metabolic disorder, hypothyroidism, sepsis).

**Red flags:** The following findings are of particular concern:

• Jaundice in the first day of life

• TSB > 18 mg/dL

• Rate of rise of TSB > 0.2 mg/dL/h (> 3.4 µmol/L/h) or > 5 mg/dL/day

• Conjugated bilirubin concentration > 1 mg/dL (> 17 µmol/L) if TSB is < 5 mg/dL or > 20% of TSB (suggests neonatal cholestasis)

• Jaundice after 2 wk of age

• Lethargy, irritability, respiratory distress

**Interpretation of findings:** Evaluation should focus on distinguishing physiologic from pathologic jaundice. History, physical examination, and timing can help (see Table 276-2), but typically TSB and conjugated serum bilirubin levels are measured.

**Timing:** Jaundice that develops in the first 24 to 48 h, or that persists > 2 wk, is most likely pathologic. Jaundice that does not become evident until after 2 to 3 days is more consistent with physiologic, breastfeeding, or breast milk jaundice. An exception is undersecretion of bilirubin due to metabolic factors (eg, Crigler-Najjar syndrome, hypothyroidism, drugs), which may take 2 to 3 days to become evident. In such cases, bilirubin typically peaks in the first week, accumulates at a rate of < 5 mg/dL/day, and can remain evident for a prolonged period. Because most neonates are now discharged from the hospital or nursery within 48 h, many cases of hyperbilirubinemia are detected only after discharge.

**Testing:** Diagnosis is suspected by the infant's color and is confirmed by measurement of serum bilirubin. Noninvasive techniques for transcutaneous measurement of bilirubin levels in infants are being used increasingly, with good correlation with serum bilirubin measurements. Risk of hyperbilirubinemia is based on age-specific TSB levels.

A bilirubin concentration > 10 mg/dL (> 170 µmol/L) in preterm infants or > 18 mg/dL in term infants warrants additional testing,

[**Table 276-2.** Physical Findings in Neonatal Jaundice]

including Hct, blood smear, reticulocyte count, direct Coombs' test, TSB and direct serum bilirubin concentrations, and blood type and Rh group of the infant and mother.

Other tests, such as blood, urine, and CSF cultures to detect sepsis and measurement of RBC enzyme levels to detect unusual causes of hemolysis, may be indicated by the history and physical examination. Such tests also may be indicated for any neonates with an initial bilirubin level > 25 mg/dL (> 428 µmol/L).

**Treatment**

Treatment is directed at the underlying disorder. In addition, treatment for hyperbilirubinemia itself may be necessary.

**Physiologic jaundice** usually is not clinically significant and resolves within 1 wk. Frequent formula feedings can reduce the incidence and severity of hyperbilirubinemia by increasing GI motility and frequency of stools, thereby minimizing the enterohepatic circulation of bilirubin. The type of formula does not seem important in increasing bilirubin excretion.

**Breastfeeding jaundice** may be prevented or reduced by increasing the frequency of feedings. If the bilirubin level continues to increase > 18 mg/dL in a term infant with early breastfeeding jaundice, a temporary change from breast milk to formula may be appropriate; phototherapy also may be indicated at higher levels. Stopping breastfeeding is necessary for only 1 or 2 days, and the mother should be

encouraged to continue expressing breast milk regularly so she can resume nursing as soon as the infant's bilirubin level starts to decline. She also should be assured that the hyperbilirubinemia has not caused any harm and that she may safely resume breastfeeding. It is not advisable to supplement with water or dextrose because that may disrupt the mother's production of milk.

**Definitive treatment** involves

• Phototherapy

• Exchange transfusion

**Phototherapy:** This treatment remains the standard of care, most commonly using fluorescent white light. (Blue light is most effective for intensive phototherapy.) Phototherapy is the use of light to photoisomerize unconjugated bilirubin into forms that are more water-soluble and can be excreted rapidly by the liver and kidney without glucuronidation. It provides definitive treatment of neonatal hyperbilirubinemia and prevention of kernicterus. Photo-therapy is an option when unconjugated bilirubin is > 12 mg/dL (> 205.2 µmol/L) and may be indicated when unconjugated bilirubin is > 15 mg/dL at 25 to 48 h, 18 mg/dL at 49 to 72 h, and 20 mg/dL at > 72 h (see Fig. 276-1). Phototherapy is not indicated for conjugated hyperbilirubinemia. Because visible jaundice may disappear during phototherapy though serum bilirubin remains elevated, skin color cannot be used to evaluate jaundice severity. Blood taken for bilirubin determinations should be shielded from bright light, because bilirubin in the collection tubes may rapidly photo-oxidize.

**Exchange transfusion:** This treatment can rapidly remove bilirubin from circulation and is indicated for severe hyperbilirubinemia, which most often occurs with immune-mediated hemolysis. Small amounts of blood are withdrawn and replaced through an umbilical vein catheter to remove partially hemolyzed and antibody-coated RBCs as well as circulating Igs. The blood is replaced with uncoated donor RBCs. Only unconjugated hyperbilirubinemia can cause kernicterus, so if conjugated bilirubin is elevated, the level of unconjugated rather than total bilirubin is used to determine the need for exchange transfusion.

Specific indications are serum bilirubin ≥ 20 mg/dL at 24 to 48 h or ≥ 25 mg/dL at > 48 h and failure of phototherapy to result in a 1- to 2-mg/dL (17- to 34-µmol/L) decrease within 4 to 6 h of initiation or at the first clinical signs of kernicterus regardless of bilirubin levels. If the serum bilirubin level is > 25 mg/dL when the neonate is initially examined, preparation for an exchange transfusion should be made in case intensive phototherapy fails to lower the bilirubin level. An alternative approach uses the weight of the neonate in grams divided by 100 to determine the bilirubin level (in mg/dL) at which exchange transfusion is indicated. Thus, a 1000-g neonate would receive an exchange transfusion at a bilirubin level of ≥ 10 mg/dL, and a 1500-g neonate would receive an exchange transfusion at a bilirubin level of ≥ 15 mg/dL.

Most often, 160 mL/kg (twice the infant's total blood volume) of packed RBCs is exchanged over 2 to 4 h; an alternative is to give 2 successive exchanges of 80 mL/kg each over 1 to 2 h. To do an exchange, 20 mL of blood is withdrawn and then immediately replaced by 20 mL of transfused blood. This procedure is repeated until the total desired volume is exchanged. For critically ill or premature infants, aliquots of 5 to 10 mL are used to avoid sudden major changes in blood volume. The goal is to reduce bilirubin by nearly 50%, with the knowledge that hyperbilirubinemia may rebound to about 60% of pretransfusion level within 1 to 2 h. It is also customary to lower the target level by 1 to 2 mg/dL in conditions that increase the risk of kernicterus (eg, fasting, sepsis, acidosis). Exchange transfusions may need to be repeated if bilirubin levels remain high. Finally, there are risks and complications with the procedure, and the success of phototherapy has reduced the frequency of exchange transfusion.

**Key Points**

• Neonatal jaundice is caused by increased bilirubin production, decreased bilirubin clearance, or increased enterohepatic circulation.

• Some jaundice is normal in neonates.

• Risk varies with postnatal age, TSB value, prematurity, and health of the neonate.

• Treatment depends on cause and degree of elevation.

• Definitive treatments include phototherapy and exchange transfusion.

**Kernicterus**

(Bilirubin Encephalopathy)

**Kernicterus is brain damage caused by unconjugated bilirubin deposition in basal ganglia and brain stem nuclei.**

Normally, bilirubin bound to serum albumin stays in the intravascular space. However, bilirubin can cross the blood-brain barrier and cause kernicterus when serum bilirubin concentration is markedly elevated; serum albumin concentration is markedly low (eg, in preterm infants); or bilirubin is displaced from albumin by competitive binders (eg, sulfisoxazole, ceftriaxone, and aspirin; free fatty acids and hydrogen ions in fasting, septic, or acidotic infants).

In preterm infants, kernicterus may not cause recognizable clinical symptoms or signs. Early symptoms in term infants are lethargy, poor feeding, and vomiting. Opisthotonos, oculogyric crisis, seizures, and death may follow. Kernicterus may result in intellectual disability, choreoathetoid cerebral palsy, sensorineural hearing loss, and paralysis of upward gaze later in childhood. It is unknown whether minor degrees of kernicterus can cause less severe neurologic impairment (eg, perceptual-motor problems, learning disorders).

There is no reliable test to determine the risk of kernicterus, and the diagnosis is made presumptively. A definite diagnosis can be made only by autopsy.

There is no treatment once kernicterus develops; it can be prevented by treating hyperbilirubinemia (see p. 2788).

## Neonatal Hypercalcemia

**Hypercalcemia is total serum Ca > 12 mg/dL (> 3 mmol/L) or ionized Ca > 6 mg/dL (> 1.5 mmol/L). The most common cause is iatrogenic. GI signs may occur (eg, anorexia, vomiting, constipation) and sometimes lethargy or seizures. Treatment is IV normal saline plus furosemide and sometimes corticosteroids, calcitonin, and bisphosphonates.**

**Etiology**

The **most common cause** is

• Iatrogenic

Iatrogenic causes usually involve excess Ca or vitamin D, or phosphate deprivation, which can result from prolonged feeding with incorrectly prepared formula or from dairy milk containing excess vitamin D.

**Other causes** include maternal hypoparathyroidism, subcutaneous fat necrosis, parathyroid hyperplasia, abnormal renal function, Williams syndrome, and idiopathic. Williams syndrome includes supravalvular aortic stenosis, an elfin facies, and hypercalcemia of unknown pathophysiology; infants may also be small for gestational age, and hypercalcemia can be noted early in infancy, usually resolving by age 12 mo. Idiopathic neonatal hypercalcemia is a diagnosis of exclusion and is difficult to differentiate from Williams syndrome. Neonatal hyperparathyroidism is very rare. Subcutaneous fat necrosis may occur after major trauma and causes hypercalcemia that usually resolves spontaneously. Maternal hypoparathyroidism or maternal hypocalcemia may cause secondary fetal hyperparathyroidism, with changes in fetal mineralization (eg, osteopenia).

**Symptoms and Signs**

Symptoms and signs may be noted when total serum Ca is > 12 mg/dL (> 3 mmol/L). These signs can include anorexia, GI reflux, nausea, vomiting, lethargy or seizures or generalized irritability, and hypertension. Other symptoms and signs include constipation, abdominal pain, dehydration, feeding intolerance, and failure to thrive. Some neonates have vague symptoms of muscle or joint aches and weakness. With subcutaneous fat necrosis, firm purple nodules may be observed on trunk, buttocks, or legs.

**Diagnosis**

Diagnosis is made by measuring total serum Ca concentration.

**Treatment**

• IV normal saline plus furosemide

• Sometimes corticosteroids, calcitonin, and bisphosphonates

Marked elevation of serum Ca may be treated with normal saline 20 mL/kg IV plus furosemide 2 mg/kg IV and, when persistent, with corticosteroids and calcitonin. Bisphosphonates are also increasingly used in this context (eg, etidronate by mouth or pamidronate IV). Treatment of subcutaneous fat necrosis is with a low-Ca formula; fluids, furosemide, calcitonin, and corticosteroids are used as indicated by the degree of hypercalcemia. Fetal hypercalcemia caused by maternal hypoparathyroidism can be treated expectantly, because it usually resolves spontaneously within a few weeks. Treatment of chronic conditions includes a low-Ca, low-vitamin D formula.

## Neonatal Hypocalcemia

**Hypocalcemia is a serum total Ca concentration < 8 mg/dL (< 2 mmol/L) in term infants or < 7 mg/dL (< 1.75 mmol/L) in preterm infants. It is also defined as an ionized Ca level < 3.0 to 4.4 mg/dL (< 0.75 to 1.10 mmol/L), depending on the method (type of electrode) used. Signs are primarily neurologic and include hypotonia, apnea, and tetany. Treatment is IV or oral Ca supplementation.**

**Etiology**

Neonatal hypocalcemia occurs in 2 forms:

• Early onset (in the first 2 days of life)

• Late onset (> 3 days), which is rare

Some infants with congenital hypoparathyroidism (eg, caused by DiGeorge syndrome with agenesis or dysgenesis of the parathyroid glands [see p. 1103]) have both early and late (prolonged) hypocalcemia.

**Early-onset hypocalcemia:** Risk factors for early-onset hypocalcemia include prematurity, being small for gestational age, maternal diabetes, and perinatal asphyxia. Mechanisms vary. Normally, parathyroid hormone helps maintain normal Ca levels when the constant infusion of ionized Ca across the placenta is interrupted at birth. A transient, relative hypoparathyroidism may cause hypocalcemia in preterm and some small-for-gestational-age neonates, who have parathyroid glands that do not yet function adequately, and in infants of mothers with diabetes or hyperparathyroidism, because these women have higher-than-normal ionized Ca levels during pregnancy. Perinatal asphyxia may also increase serum calcitonin, which inhibits Ca release from bone and results in hypocalcemia. In other neonates, the normal phosphaturic renal response to parathyroid hormone is absent; the elevated phosphate ($PO_4$) level leads to hypocalcemia.

**Late-onset hypocalcemia:** The cause of late-onset hypocalcemia is usually ingestion of cow's milk or formula with a too-high $PO_4$ load; elevated serum $PO_4$ leads to hypocalcemia.

### Symptoms and Signs

Symptoms and signs rarely occur unless total serum Ca is < 7 mg/dL (< 1.75 mmol/L) or the ionized Ca is < 3.0 mg/dL (< 0.75 mmol/L). Signs include hypotonia, tachycardia, tachypnea, apnea, poor feeding, jitteriness, tetany, and seizures. Similar symptoms may occur with hypoglycemia and opioid withdrawal.

### Diagnosis

• Total or ionized serum Ca level

Diagnosis is by measurement of serum total or ionized Ca; ionized Ca is the more physiologic measurement, because it obviates concerns about protein concentration and pH. Prolongation of the corrected QT interval ($QT_C$) on ECG also suggests hypocalcemia.

### Treatment

• Early onset: IV 10% Ca gluconate

• Late onset: Oral calcitriol or Ca

Early-onset hypocalcemia ordinarily resolves in a few days, and asymptomatic neonates with serum Ca levels > 7 mg/dL or ionized Ca > 3.5 mg/dL rarely require treatment. Those term infants with levels < 7 mg/dL and preterm infants with Ca < 6 mg/dL (< 1.5 mmol/L) should be treated with 2 mL/kg of 10% Ca gluconate (200 mg/kg) by slow IV infusion over 30 min. Too-rapid infusion can cause bradycardia, so heart rate should be monitored during the infusion. The IV site should also be watched closely because tissue infiltration by a Ca solution is irritating and may cause local tissue damage or necrosis. Manifestations of Ca infiltration include skin redness, calcification, and necrosis or slough; there can be radial nerve damage at the wrist.

After acute correction of hypocalcemia, Ca gluconate may be mixed in the maintenance IV infusion and given continuously. Starting with 400 mg/kg/day of Ca gluconate, the dose may be increased gradually to 800 mg/kg/day, if needed, to prevent a recurrence. When oral feedings are begun, the formula may be supplemented with the same daily dose of Ca gluconate, if needed, by adding the 10% Ca gluconate solution into the day's formula. Supplementation is usually required for only a few days.

Treatment of late-onset hypocalcemia is addition of calcitriol or additional Ca to infant formula to provide a 4:1 molar ratio of Ca:$PO_4$ until normal Ca levels are maintained. Oral Ca preparations have a high sucrose content, which may lead to diarrhea in preterm infants.

## Neonatal Hyperglycemia

**Hyperglycemia is a serum glucose concentration > 150 mg/dL (> 8.3 mmol/L).**

The **most common cause** of neonatal hyperglycemia is

• Iatrogenic

Iatrogenic causes usually involve too-rapid IV infusions of dextrose during the first few days of life in very low-birth-weight infants (< 1.5 kg).

The other important cause is physiologic stress caused by surgery, hypoxia, respiratory distress syndrome, or sepsis; fungal sepsis poses a special risk. In premature infants, partially defective processing of proinsulin to insulin and relative insulin resistance may cause hyperglycemia. In addition, transient neonatal diabetes mellitus is a rare self-limited cause that usually occurs in small-for-gestational-age infants; corticosteroid therapy may also result in transient hyperglycemia. Hyperglycemia is less common than hypoglycemia, but it is important because it increases morbidity and mortality of the underlying causes.

Symptoms and signs are those of the underlying disorder; diagnosis is by serum glucose testing. Additional laboratory findings may include glycosuria and marked serum hyperosmolarity.

**Treatment**

• Reduction of IV dextrose concentration, rate, or both

• Sometimes IV insulin

Treatment of iatrogenic hyperglycemia is reduction of the IV dextrose concentration (eg, from 10% to 5%) or of the infusion rate; hyperglycemia persisting at low dextrose infusion rates (eg, 4 mg/kg/min) may indicate relative insulin deficiency or insulin resistance. Treatment of other causes is fast-acting insulin. One approach is to add fast-acting insulin to an IV infusion of 10% dextrose at a uniform rate of 0.01 to 0.1 unit/kg/h, then titrate the rate until the glucose level is normalized. Another approach is to add insulin to a separate IV of 10% D/W given simultaneously with the maintenance IV infusion so that the insulin can be adjusted without changing the total infusion rate. Responses to insulin are unpredictable, and it is extremely important to monitor serum glucose levels and to titrate the insulin infusion rate carefully.

In transient neonatal diabetes mellitus, glucose levels and hydration should be carefully maintained until hyperglycemia resolves spontaneously, usually within a few weeks.

Any fluid or electrolytes lost through osmotic diuresis should be replaced.

## Neonatal Hypoglycemia

**Hypoglycemia is a serum glucose concentration < 40 mg/dL (< 2.2 mmol/L) in term neonates or < 30 mg/dL (< 1.7 mmol/L) in preterm neonates. Risk factors include prematurity, being small for gestational age, and perinatal asphyxia. The most common causes are deficient glycogen stores, delayed feeding, and hyperinsulinemia. Signs include tachycardia, cyanosis, seizures, and apnea. Diagnosis is suspected empirically and is confirmed by glucose testing. Prognosis depends on the underlying condition. Treatment is enteral feeding or IV dextrose.**

**Etiology**

Neonatal hypoglycemia may be transient or persistent.

Causes of **transient hypoglycemia** are

• Inadequate substrate

• Immature enzyme function leading to deficient glycogen stores

Causes of **persistent hypoglycemia** include

• Hyperinsulinism

• Defective counter-regulatory hormone release

• Inherited disorders of metabolism (eg, glycogen storage diseases, disorders of gluconeogenesis, fatty acid oxidation disorders—see Ch. 301)

Deficiency of glycogen stores at birth is common in very low-birth-weight preterm infants, infants who are small for gestational age (SGA) because of placental insufficiency, and infants who have perinatal asphyxia. Anaerobic glycolysis consumes glycogen stores in these infants, and hypoglycemia may develop at any time in the first few days, especially if there is a prolonged interval between feedings or if nutritional intake is poor. A sustained input of exogenous glucose is therefore important to prevent hypoglycemia.

Transient hyperinsulinism most often occurs in infants of diabetic mothers and is inversely related to the degree of maternal diabetic control. It also commonly occurs in physiologically stressed infants who are SGA. Less common causes include congenital hyperinsulinism (genetic conditions transmitted in both autosomal dominant and recessive fashion), severe erythroblastosis fetalis, and Beckwith-Wiedemann syndrome (in which islet cell hyperplasia accompanies features of macroglossia and umbilical hernia). Hyperinsulinemia characteristically results in a rapid fall in serum glucose in the first 1 to 2 h after birth when the continuous supply of glucose from the placenta is interrupted.

Hypoglycemia may also occur if an IV infusion of D/W is abruptly interrupted. Finally, hypoglycemia can be due to malposition of an umbilical catheter or sepsis.

**Symptoms and Signs**

Many infants remain asymptomatic. Prolonged or severe hypoglycemia causes both adrenergic and neuroglycopenic signs. Adrenergic signs include diaphoresis, tachycardia, lethargy or weakness, and shakiness. Neuroglycopenic signs include seizure, coma, cyanotic episodes, apnea, bradycardia or respiratory distress, and hypothermia. Listlessness, poor feeding, hypotonia, and tachypnea may occur.

**Diagnosis**

• Bedside glucose check

All signs are nonspecific and also occur in neonates who have asphyxia, sepsis or hypocalcemia, or opioid withdrawal (see p. 2800). Therefore, at-risk neonates with or without these signs require an immediate bedside serum glucose check from a capillary sample. Abnormally low levels are confirmed by a venous sample.

**Treatment**

• IV dextrose (for prevention and treatment)

• Enteral feeding

• Sometimes IM glucagon

Most high-risk neonates are treated preventively. For example, infants of diabetic women who have been using insulin are often started at birth on a 10% D/W infusion IV or given oral glucose, as are those who are sick, are extremely premature, or have respiratory distress. Other at-risk neonates who are not sick should be started on early, frequent formula feedings to provide carbohydrates.

Any neonate whose glucose falls to ≤ 50 mg/dL (≤ 2.75 mmol/L) should begin prompt treatment with enteral feeding or with an IV infusion of up to 12.5% D/W, 2 mL/kg over 10 min; higher concentrations of dextrose can be infused if necessary through a central catheter. The infusion should then continue at a rate that provides 4 to 8 mg/kg/min of glucose (ie, 10% D/W at about 2.5 to 5 mL/kg/h). Serum glucose levels must be monitored to guide adjustments in the infusion rate. Once the neonate's condition has improved, enteral feedings can gradually replace the IV infusion while the glucose concentration continues to be monitored. IV dextrose infusion should always be tapered, because sudden discontinuation can cause hypoglycemia.

If starting an IV infusion promptly in a hypoglycemic neonate is difficult, glucagon 100 to 300 µg/kg IM (maximum, 1 mg) usually raises the serum glucose rapidly, an effect that lasts 2 to 3 h, except in neonates with depleted glycogen stores. Hypoglycemia refractory to high rates of glucose infusion may be treated with hydrocortisone 2.5 mg/kg IM bid. If hypoglycemia is refractory to treatment, other causes (eg, sepsis) and possibly an endocrine evaluation for persistent hyperinsulinism and disorders of defective gluconeogenesis or glycogenolysis should be considered.

## Neonatal Hypernatremia

(See also p. 829.)

**Hypernatremia is a serum Na concentration > 150 mEq/L, usually caused by dehydration. Signs include lethargy and seizures. Treatment is cautious hydration with IV saline solution.**

### Etiology

Hypernatremia develops when

• Water is lost in excess of Na (hypernatremic dehydration)

• Na intake exceeds Na losses (salt poisoning)

• Both

Water loss in excess of Na intake is most commonly caused by diarrhea, vomiting, or high fever. It may also be caused by poor feeding in the early days of life (eg, when mother and infant are both learning to breastfeed) and may occur in very low-birth-weight (VLBW) infants born at 24 to 28 wk. In VLBW infants, insensible water losses through an immature, water-permeable stratum corneum combine with immature renal function and a reduced ability to produce concentrated urine to facilitate free water loss. Insensible water loss through the skin is also significantly increased by radiant warmers and phototherapy lights; exposed VLBW infants may require up to 250 mL/kg/day of water IV in the first few days, after which the stratum corneum develops and insensible water loss decreases. A rare cause is central or nephrogenic diabetes insipidus. Infants with hypernatremia and dehydration are often more dehydrated than is apparent by physical examination, because the increased osmolality helps maintain the extracellular fluid space (and hence circulating blood volume).

Solute overload most commonly results from adding too much salt when preparing homemade infant formula or from giving hyperosmolar solutions. Fresh frozen plasma and human albumin contain Na and can contribute to hypernatremia when given repeatedly to very premature infants.

### Symptoms and Signs

Symptoms and signs include lethargy, restlessness, hyperreflexia, spasticity, and seizures. Skin texture may be doughy rather than diminished. Intracranial hemorrhage, venous sinus thrombosis, and acute renal tubular necrosis are major complications.

### Diagnosis

• Serum Na concentration

Diagnosis is suspected by symptoms and signs and is confirmed by measuring serum Na concentration.

Additional laboratory findings may include an increase in BUN, a modest increase in serum glucose, and, if serum K is low, a depression in the level of serum Ca.

### Treatment

• IV 0.9% saline, then hypotonic saline (0.3% or 0.45% saline)

Severely dehydrated infants must have their circulating blood volume restored first, usually with 0.9% saline in aliquots of 20 mL/kg IV. Treatment is then with 5% D/W/0.3% to 0.45% saline solution IV in volumes equal to the calculated fluid deficit (see p. 2807), given over 2 to 3 days to avoid a rapid fall in serum osmolality, which would cause rapid movement of water into cells and potentially lead to cerebral edema. Maintenance fluids should be provided concurrently. The goal of treatment is to decrease serum Na by about 10 mEq/L/day. Body weight, serum electrolytes, and urine volume and specific gravity must be monitored regularly so that fluid therapy can be adjusted appropriately. Once adequate urine output is

shown, K is added to provide maintenance requirements or replace urinary losses.

Extreme hypernatremia (Na > 200 mEq/L) caused by salt poisoning should be treated with peritoneal dialysis, especially if poisoning causes a rapid rise in serum Na.

### Prevention

Prevention requires attention to the volume and composition of unusual fluid losses and of solutions used to maintain homeostasis. In neonates and young infants, who are unable to signal thirst effectively and to replace losses voluntarily, the risk of dehydration is greatest. The composition of feedings whenever mixing is involved (eg, some infant formulas and concentrated preparations for tube feeding) requires particular attention, especially when the potential for developing dehydration is high, such as during episodes of diarrhea, poor fluid intake, vomiting, or high fever.

## Neonatal Hyponatremia

(See also p. 823.)

**Hyponatremia is a serum Na concentration < 135 mEq/L. Significant hyponatremia may cause seizures or coma. Treatment is cautious Na replacement with IV 0.9% saline solution; rarely, 3% saline solution is required, particularly if seizures are occurring.**

### Etiology

The most frequent cause of neonatal hyponatremia is hypovolemic dehydration caused by vomiting, diarrhea, or both, when large GI losses are replaced with fluids that have little or no Na (eg, some juices).

A less frequent cause is euvolemic hyponatremia caused by inappropriate ADH secretion and consequent water retention. Possible causes of inappropriate ADH secretion include CNS tumors and infection. Also, overdilution of infant formula can lead to water intoxication.

Finally, hypervolemic hyponatremia occurs in the setting of water retention and excess Na retention, such as in heart failure or renal failure.

### Symptoms and Signs

Symptoms and signs include nausea and vomiting, apathy, headache, seizures, and coma; other symptoms include cramps and weakness. Infants with hyponatremic dehydration may appear quite ill, because hyponatremia causes disproportionate reductions in ECF volume. Symptoms and signs are related to duration and degree of hyponatremia.

### Diagnosis

• Serum Na concentration

Diagnosis is suspected because of symptoms and signs and confirmed by measuring serum Na concentration. In dehydration, an increase in BUN may be observed.

### Treatment

• IV 5% D/W/0.45% to 0.9% saline solution

• Rarely IV hypertonic (3%) saline solution

Treatment is with 5% D/W/0.45% to 0.9% saline solution IV in volumes equal to the calculated deficit, given over as many days as it takes to correct the Na concentration by no more than 10 to 12 mEq/L/day to avoid rapid fluid shifts in the brain. Neonates with hypovolemic hyponatremia need volume expansion, using a solution containing salt to correct the Na deficit (10 to 12 mEq/kg of body weight or even 15

mEq/kg in young infants with severe hyponatremia) and include Na maintenance needs (3 mEq/kg/day in 5% D/W solution). Neonates with symptomatic hyponatremia (eg, lethargy, confusion) require emergency treatment with 3% saline solution IV to prevent seizure or coma. (For prevention, see Prevention in left column.)

## Prenatal Drug Exposure

Alcohol and illicit drugs are toxic to the placenta and developing fetus and can cause congenital syndromes and withdrawal symptoms. Prescription drugs also may have adverse effects on the fetus (see Table 262-2 on p. 2626). For effects of cigarette smoking, see p. 2655.

Although some toxic substances used by the mother are not illegal, many are. In any case, the home situation should be evaluated to determine whether the infant will be safely cared for after discharge. With the supportive help of relatives, friends, and visiting nurses, the mother may be able to care for her infant. If not, foster home care or an alternative care plan may be best.

**Alcohol:** Alcohol exposure in utero increases the risk of spontaneous abortion, decreases birth weight, and can cause fetal alcohol syndrome (FAS), a constellation of variable physical and cognitive abnormalities. At birth, infants with FAS can be identified by small stature and a typical set of facial traits including microcephaly, microphthalmia, short palpebral fissures, epicanthal folds, a small or flat midface, a flat elongated philtrum, a thin upper lip, and a small chin. Abnormal palmar creases, cardiac defects, and joint contractures may also be evident. After birth, cognitive deficits become apparent. The most serious manifestation is severe intellectual disability, thought to be a teratogenic effect of alcohol given the high number of intellectually disabled infants of alcoholic women; FAS may be the most common cause of noninherited intellectual disability. No single physical or cognitive finding is pathognomonic; lesser degrees of alcohol use cause less severe manifestations, and the diagnosis of mild cases can be difficult because partial expression occurs. It is often difficult to distinguish the effects of alcohol on the developing fetus from those of other exposures (eg, tobacco, other drugs) and factors (eg, poor nutrition, lack of health care, violence) that affect women who drink excessively.

Diagnosis is given to infants with characteristic findings born to women who used alcohol excessively during pregnancy.

Because it is unknown when during pregnancy alcohol is most likely to harm the fetus and whether there is a lower limit of alcohol use that is completely safe, pregnant women should be advised to avoid all alcohol intake. Siblings of an infant diagnosed with FAS should be examined for subtle manifestations of the disorder.

**Amphetamines:** Prenatal exposure to amphetamines has lasting subtle effects on neonatal brain structure and function. Some studies have shown decreased volume of the caudate, putamen, and globus pallidus (anatomic components of brain) in methamphetamine-exposed children, whereas other studies have not uniformly confirmed these findings. Other studies indicate that prenatal methamphetamine exposure may be associated with abnormal neurobehavioral patterns or fetal growth restriction, but these findings are not yet fully established.

**Barbiturates:** Prolonged maternal abuse of barbiturates may cause neonatal drug withdrawal with jitteriness, irritability, and fussiness that often do not develop until 7 to 10 days postpartum, after the neonate has been discharged home. Sedation with phenobarbital 0.75 to 1.5 mg/kg po or IM q 6 h may be required and then tapered over a few days or weeks, depending on the duration of symptoms.

**Cocaine:** Cocaine inhibits reuptake of the neurotransmitters norepinephrine and epinephrine; it crosses the placenta and causes vasoconstriction and hypertension in the fetus. Cocaine abuse in pregnancy is associated with a higher rate of placental abruption and spontaneous abortion, perhaps caused by reduced maternal blood flow to the placental vascular bed; abruption may also lead to intrauterine fetal death or to neurologic damage if the infant survives. Neonates born to addicted mothers have low birth weight, reduced body length and head circumference, and lower Apgar scores. Cerebral infarcts may occur, and rare anomalies associated with prenatal cocaine use include limb amputations; GU malformations, including prune-belly syndrome; and intestinal atresia or necrosis. All are caused by

vascular disruption, presumably secondary to local ischemia caused by the intense vasoconstriction of fetal arteries caused by cocaine. In addition, a pattern of mild neurobehavioral effects has also been observed, including decreases in attention and alertness, lower IQ, and impaired gross and fine motor skills.

Some neonates may show withdrawal symptoms if the mother used cocaine shortly before delivery, but symptoms are less common and less severe than for opioid withdrawal, and signs and treatment are the same.

**Marijuana:** Marijuana does not consistently seem to increase risk of congenital malformations, fetal growth restriction, or postnatal neurobehavioral abnormalities. However, women who use marijuana during pregnancy often also use alcohol, cigarettes, or both, which can cause fetal problems.

**Opioids:** Opioid exposure in utero can cause withdrawal on delivery. The neonate of a woman addicted to opioids should be observed for withdrawal symptoms, which usually occur within 72 h after delivery. Characteristic signs of withdrawal include irritability, jitteriness, hypertonicity, vomiting, diarrhea, sweating, seizures, and hyperventilation that causes respiratory alkalosis. Prenatal benzodiazepine exposure may cause similar effects.

Mild withdrawal symptoms are treated by a few days of swaddling and soothing care to alleviate the physical overarousal and giving frequent feedings to reduce restlessness. With patience, most problems resolve in no more than a week. Severe symptoms can be controlled by diluting tincture of opium (which contains 10 mg morphine/mL) 25-fold with water and giving 2 drops (0.1 mL)/kg po q 4 h. The dose can be increased by 0.1 mL/kg q 4 h as needed. Phenobarbital 0.75 to 1.5 mg/kg po q 6 h may also control withdrawal symptoms. Treatment is tapered and stopped over several days or weeks as symptoms subside.

The incidence of sudden infant death syndrome is greater among infants born to women addicted to opioids but still is < 10/1000 infants, so routine use of home cardiorespiratory monitors is not recommended for these infants.

# Chapter 277. Gastrointestinal Disorders in Neonates and Infants

## Introduction

Infectious gastroenteritis is the most common pediatric GI disorder. About 1 billion episodes occur worldwide each year, most commonly in developing countries among children < 5 yr. Death due to dehydration occurs in 3 to 6 million cases/yr. In the US, 25 to 35 million cases occur annually, resulting in 300 to 400 deaths. In addition, infectious gastroenteritis in the US results in an estimated 200,000 hospitalizations and 1.5 million outpatient visits at a cost in excess of 1 billion dollars. For a full discussion of causative agents, evaluation, and treatment, see Ch. 16. For dehydration and fluid therapy in children, see Ch. 278.

## Hypertrophic Pyloric Stenosis

**Hypertrophic pyloric stenosis is obstruction of the pyloric lumen due to pyloric muscular hypertrophy.**

Hypertrophic pyloric stenosis may cause almost complete gastric outlet obstruction. It affects 1 of 250 infants and is more common among males by a 4:1 ratio, particularly first-born males. It occurs most often between 3 to 5 wk of age and rarely after 12 wk. The exact etiology is uncertain, but a genetic component is likely because siblings and offspring of affected people are at increased risk. Proposed mechanisms include lack of neuronal nitric oxide synthase and abnormal innervation of the muscular layer. Infants exposed to certain macrolide antibiotics in the first few weeks of life are at significantly increased risk.

### Symptoms and Signs

Symptoms can develop between 2 and 6 wk of life. Projectile vomiting (without bile) occurs shortly after eating. Until dehydration sets in, the child feeds avidly and otherwise appears well, unlike many of those with vomiting caused by systemic illness. Gastric peristaltic waves may be visible, crossing the epigastrium from left to right. A discrete, 2- to 3-cm, firm, movable, and olive-like pyloric mass is sometimes palpable deep in the right side of the epigastrium. With progression of illness, the child fails to gain weight, and signs of dehydration (see p. 2806) appear.

### Diagnosis

Diagnosis is by abdominal ultrasonography showing increased thickness of the pylorus (typically to ≥ 4 mm; normal, < 2 mm) along with an elongated pylorus (> 16 mm). If the diagnosis remains uncertain, ultrasonography can be repeated serially or an upper GI series can be done, which typically shows delayed gastric emptying and a "string" sign or "railroad track" sign of a markedly narrowed, elongated pyloric lumen. In rare cases, upper endoscopy is required for confirmation. The classic electrolyte pattern of an infant with pyloric stenosis is that of hypochloremic metabolic alkalosis. About 5% of infants are jaundiced.

### Treatment

Initial treatment is directed at hydration and correcting electrolyte abnormalities. Definitive treatment is a longitudinal pyloromyotomy, which leaves the mucosa intact and separates the incised muscle fibers. Postoperatively, the infant usually tolerates feeding within a day.

## Intussusception

**Intussusception is telescoping of one portion of the intestine (intussusceptum) into an adjacent segment (intussuscipiens), causing intestinal obstruction and sometimes intestinal ischemia.**

Intussusception generally occurs between ages 3 mo and 3 yr, with 65% of cases occurring before age 1. It is the most common cause of intestinal obstruction in this age group. Most cases are idiopathic. However, there is a slight male predominance as well as a seasonal variation; peak incidence coincides with the viral enteritis season. In older children, there may be a lead point (ie, a mass or other intestinal

abnormality that triggers the telescoping). Examples include polyps, lymphoma, Meckel's diverticulum, and Henoch-Schonlein purpura. Cystic fibrosis is also a risk factor.

The telescoping segment obstructs the intestine and ultimately impairs blood flow (see Fig. 277-1), causing ischemia, gangrene, and perforation.

### Symptoms and Signs

The initial symptoms are recurrent colicky abdominal pain that occurs every 15 to 20 min, often with vomiting. The child appears relatively well between episodes. Later, as intestinal ischemia develops, pain becomes steady, the child becomes lethargic, and mucosal hemorrhage causes heme-positive stool on rectal examination and sometimes spontaneous passage of a currant-jelly stool. The latter, however, is a late occurrence, and physicians should not wait for this symptom to occur to suspect intussusception. A palpable abdominal mass, described as sausage-shaped, is sometimes present. Perforation results in signs of peritonitis, with significant tenderness, guarding, and rigidity. Pallor, tachycardia, and diaphoresis indicate shock.

[**Fig. 277-1.** Intussusception.]

### Diagnosis

• Ultrasonography

Studies and intervention must be done urgently, because survival and likelihood of non-operative reduction decrease significantly with time. Approach depends on clinical findings. Ill children with signs of peritonitis require fluid resuscitation (see p. 2809), broad-spectrum antibiotics (eg, ampicillin, gentamicin, clindamycin), nasogastric suction, and surgery. Others require imaging studies to confirm diagnosis and treat the disorder.

Barium enema was once the preferred initial study because it revealed the classic "coiled spring" appearance around the intussusceptum. In addition to being diagnostic, barium enema was also usually therapeutic; the pressure of the barium often reduced the telescoped segments. However, barium occasionally enters the peritoneum through a clinically unsuspected perforation and causes significant peritonitis. Currently, ultrasonography is the preferred means of diagnosis; it is easily done, relatively inexpensive, and safe.

### Treatment

If intussusception is confirmed, an air enema is used for reduction, which lessens the likelihood and consequences of perforation. The intussusceptum can be successfully reduced in 75 to 90% of children. Children are observed overnight after reduction to rule out occult perforation. If reduction is unsuccessful, immediate surgery is required. Without surgery, the recurrence rate is 5 to 10%.

## Meconium Ileus

**Meconium ileus is obstruction of the terminal ileum by abnormally tenacious meconium; it almost universally occurs in neonates with cystic fibrosis. Meconium ileus accounts for up to 33% of neonatal small-bowel obstructions. Symptoms include emesis that may be bilious, abdominal distention, and failure to pass meconium. Diagnosis is based on clinical presentation and x-rays. Treatment is enemas with dilute contrast under fluoroscopy and surgery if enemas fail.**

Meconium ileus is almost always an early manifestation of cystic fibrosis, which causes GI secretions to be extremely viscid and adherent to the intestinal mucosa. These secretions are the presenting manifestation of cystic fibrosis in 10 to 25% of cases. Obstruction occurs at the level of the terminal ileum (unlike the colonic obstruction caused by meconium plug syndrome) and may be diagnosed by prenatal ultrasonography. Distal to the obstruction, the colon is narrow and empty or contains small amounts of desiccated meconium pellets. The relatively empty, small-caliber colon is called a microcolon.

About 50% of cases are complicated by malrotation, intestinal atresia, or perforation. The distended loops of small bowel may twist to form a volvulus in utero. If the intestine loses its vascular supply and infarcts, sterile meconium peritonitis can result. The infarcted intestinal loop may be resorbed, leaving an area or areas of intestinal atresia.

### Symptoms and Signs

After birth, infants fail to pass meconium in the first 12 to 24 h, which is typical for normal neonates. They have signs of intestinal obstruction, including bilious emesis and abdominal distention. Loops of distended small bowel sometimes can be palpated through the abdominal wall and may feel characteristically doughy. Meconium peritonitis with respiratory distress and ascites can occur secondary to perforation.

### Diagnosis

• Plain x-rays

• If positive, tests for cystic fibrosis

Prenatal ultrasonography can detect changes in utero suggestive of cystic fibrosis and meconium ileus, but these changes are not specific. Diagnosis is suspected in a neonate with signs of intestinal obstruction, particularly if a family history of cystic fibrosis exists. Patients should undergo abdominal x-rays, which show dilated intestinal loops; however, fluid levels are often absent. A "soap bubble" or "ground glass" appearance due to small air bubbles mixed with the meconium is diagnostic of meconium ileus. If meconium peritonitis is present, calcified meconium flecks may line the peritoneal surfaces and even the scrotum. A barium enema reveals a microcolon with an obstruction in the terminal ileum.

Patients diagnosed with meconium ileus should be tested for cystic fibrosis (see p. 2881).

### Treatment

• Radiographic contrast enema

• Sometimes surgery

Obstruction may be relieved in uncomplicated cases (eg, without perforation, volvulus, or atresia) by giving ≥ 1 enema with a dilute radiographic contrast medium plus *N*-acetylcysteine under fluoroscopy; hypertonic contrast material may cause large GI water losses requiring IV rehydration. If the enema does not relieve the obstruction, laparotomy is required. A double-barreled ileostomy with repeated *N*-acetylcysteine lavage of the proximal and distal loops is usually required to liquefy and remove the abnormal meconium.

## Meconium Plug Syndrome

(Small Left Colon Syndrome)

**Meconium plug syndrome is colonic obstruction caused by thick meconium.**

Meconium plug syndrome usually occurs in infants who are otherwise healthy, but it is more common among infants of diabetic mothers and toxemic mothers treated with Mg sulfate. It is generally regarded as a functional immaturity of the colon, resulting in failure to pass the first stool.

### Symptoms and Signs

Infants present in the first few days of life with failure to pass stools, abdominal distention, and vomiting. Thick, inspissated, rubbery meconium forms a cast of the colon, resulting in complete obstruction.

### Diagnosis

• Radiographic contrast enema

• Sometimes testing for Hirschsprung's disease

Diagnosis is of exclusion and should be differentiated primarily from Hirschsprung's disease (see p. 2980).

Plain abdominal x-rays are nonspecific and can show signs of low intestinal obstruction. Conversely, contrast enema shows the characteristic appearance of the outline of the inspissated meconium against the wall of the colon, providing a double-contrast impression. Unlike meconium ileus, microcolon is not typically seen on x-ray with meconium plug syndrome.

### Treatment

• Radiographic contrast enema

The water-soluble contrast enema can be therapeutic by separating the plug from the intestinal wall and expelling it. Occasionally, repeated enemas are required. Rarely, surgical decompression is required. Although most infants are healthy thereafter, diagnostic studies may be needed to rule out Hirschsprung's disease (see p. 2980) or cystic fibrosis (see p. 2883).

## Necrotizing Enterocolitis

**Necrotizing enterocolitis (NEC) is an acquired disease, primarily of preterm or sick neonates, characterized by mucosal or even deeper intestinal necrosis. It is the most common GI emergency among neonates. Symptoms and signs include feeding intolerance, lethargy, temperature instability, ileus, bloating, bilious emesis, hematochezia, reducing substances in the stool, apnea, and sometimes signs of sepsis. Diagnosis is clinical and is confirmed by imaging studies. Treatment is primarily supportive and includes nasogastric suction, parenteral fluids, TPN, antibiotics, isolation in cases of infection, and, often, surgery.**

Over 85% of cases of NEC occur in premature infants. It occurs in about 1 to 8% of neonatal ICU admissions. Risk factors include prolonged rupture of the membranes with amnionitis, birth asphyxia, small-for-gestational-age infants, congenital heart disease, and exchange transfusions. The incidence may also be higher in infants fed hypertonic formulas.

### Etiology

In infants who develop NEC, 3 intestinal factors are usually present: a preceding ischemic insult, bacterial colonization, and intraluminal substrate (ie, enteral feedings).

The exact etiology is not clear. It is believed that an ischemic insult damages the intestinal lining, leading to increased intestinal permeability and leaving the intestine susceptible to bacterial invasion. NEC rarely occurs before enteral feedings and is less common among breastfed infants. However, once feedings are begun, ample substrate is present for proliferation of luminal bacteria, which can penetrate the damaged intestinal wall, producing hydrogen gas. The gas may collect within the intestinal wall (pneumatosis intestinalis) or enter the portal veins.

The initial ischemic insult may result from vasospasm of the mesenteric arteries, which can be caused by an anoxic insult triggering the primitive diving reflex that markedly diminishes intestinal blood flow. Intestinal ischemia may also result from low blood flow during an exchange transfusion, during sepsis, or from the use of hyperosmolar formulas. Similarly, congenital heart disease with reduced systemic blood flow or arterial $O_2$ desaturation may lead to intestinal hypoxia/ischemia and predispose to NEC.

Necrosis begins in the mucosa and may progress to involve the full thickness of the intestinal wall,

causing perforation with subsequent peritonitis and often free intra-abdominal air. Perforation occurs most commonly in the terminal ileum; the colon and the proximal small bowel are involved less frequently. Sepsis occurs in 33% of infants, and death may occur.

NEC may occur as clusters of cases or as outbreaks in neonatal ICUs. Some clusters appear to be associated with specific organisms (eg, *Klebsiella, Escherichia coli,* coagulase-negative staphylococci), but often no specific pathogen is identified.

**Symptoms and Signs**

Infants may present with feeding difficulties, bilious gastric residuals (after feedings) that may progress to bilious emesis, ileus manifested by abdominal distention, or gross or microscopic blood in stool. Sepsis may be manifested by lethargy, temperature instability, increased apneic spells, and metabolic acidosis.

**Diagnosis**

• Detection of blood in stool

• Usually abdominal x-rays

Screening the stools of enterally fed premature infants for occult blood or reducing substances may help diagnose NEC early. Early x-rays may be nonspecific and reveal only ileus. However, a fixed, dilated intestinal loop that does not change on repeated x-rays indicates NEC. X-ray signs diagnostic of NEC are pneumatosis intestinalis and portal vein gas. Pneumoperitoneum indicates bowel perforation and an urgent need for surgery.

**Treatment**

• Stoppage of feedings

• NGT

• Fluid resuscitation

• Broad-spectrum antibiotics

• TPN

• Possibly surgery

The mortality rate is 20 to 30%. Aggressive support and judicious timing of surgical intervention maximize the chance of survival.

**Support:** Nonsurgical support is sufficient in over 75% of cases. Feedings must be stopped immediately if NEC is suspected, and the intestine should be decompressed with a double-lumen NGT attached to intermittent suction. Appropriate colloid and crystalloid parenteral fluids must be given to support circulation, because extensive intestinal inflammation and peritonitis may lead to considerable 3rd-space fluid loss. TPN is needed for 14 to 21 days while the intestine heals. Systemic antibiotics should be started at once with a β-lactam antibiotic (eg, ampicillin, ticarcillin) and an aminoglycoside. Additional anaerobic coverage (eg, clindamycin, metronidazole) may also be considered and should continue for 10 days (for dosage, see
Table 279-1 on p. 2812). Because some outbreaks may be infectious, patient isolation should be considered, particularly if several cases occur within a short time.

The infant requires close monitoring; frequent complete reevaluation (eg, at least every 12 h); and serial abdominal x-rays, CBCs, platelet counts, and blood gases. Intestinal strictures are the most common long-term complication of NEC, occurring in 10 to 36% of infants who survive the initial event. Strictures typically manifest within 2 to 3 mo of an NEC episode. Strictures are most commonly noted in the colon,

especially on the left side. Resection of the stricture is then required.

**Surgery:** Surgical intervention is needed in < 25% of infants. Absolute indications are intestinal perforation (pneumoperitoneum), signs of peritonitis (absent intestinal sounds and diffuse guarding and tenderness or erythema and edema of the abdominal wall), or aspiration of purulent material from the peritoneal cavity by paracentesis. Surgery should be considered for an infant with NEC whose clinical and laboratory condition worsens despite nonsurgical support. During surgery, gangrenous bowel is resected, and ostomies are created. (Primary reanastomosis may be done if the remaining intestine shows no signs of ischemia.) With resolution of sepsis and peritonitis, intestinal continuity can be reestablished several weeks or months later.

**Prevention:** Risk may be decreased by delaying feedings for several days to weeks in tiny or sick premature infants while providing TPN; feedings are slowly advanced over weeks. However, in some studies this approach was not beneficial. Breast milk seems to offer protection. For this and other reasons, breast milk should be encouraged for enteral feeding. Hypertonic formula, drugs, or contrast material should be avoided. Umbilical catheters, if required, should be placed below the renal arteries. Polycythemia should be treated promptly. Recent evidence suggests that probiotics (eg, *Bifidus infantis, Lactobacillus acidophilus*) may help prevent NEC, but further studies are required before they can be recommended routinely.

## Neonatal Cholestasis

**Cholestasis is failure of bilirubin secretion, resulting in conjugated hyperbilirubinemia and jaundice. There are numerous causes, which are identified by laboratory testing, hepatobiliary scan, and, sometimes, liver biopsy and surgery. Treatment depends on cause.**

### Etiology

Cholestasis (see also p. 212) may result from extrahepatic or intrahepatic disorders, although some conditions overlap. The most common extrahepatic disorder is biliary atresia. There are numerous intrahepatic disorders, collectively termed the neonatal hepatitis syndrome.

**Biliary atresia** is obstruction of the biliary tree due to progressive sclerosis of the extrahepatic bile duct. In most cases, biliary atresia develops several weeks after birth, probably after inflammation and scarring of the extrahepatic (and sometimes intrahepatic) bile ducts. It is rarely present in premature infants or in neonates at birth. The cause of the inflammatory response is unknown, but infectious organisms have been implicated.

**Neonatal hepatitis syndrome** (giant cell hepatitis) is an inflammatory condition of the neonatal liver. It has numerous metabolic, infectious, and genetic causes; some cases are idiopathic. Metabolic diseases include $\alpha_1$-antitrypsin deficiency, cystic fibrosis, neonatal iron storage disease, respiratory chain defects, and fatty acid oxidation defects. Infectious causes include congenital syphilis, echovirus, and some herpesviruses (simplex and cytomegalovirus); the classic hepatitis viruses (A, B, and C) are less common causes. There are also a number of less common genetic defects, such as Alagille syndrome and progressive familial intrahepatic cholestasis.

### Pathophysiology

In cholestasis, the primary failure is of bilirubin excretion, resulting in excess conjugated bilirubin in the bloodstream and decreased bile salts in the GI tract. As a result of inadequate bile in the GI tract, there is malabsorption of fat and fat-soluble vitamins (A, D, E, and K), leading to vitamin deficiency, undernutrition, and growth failure.

### Symptoms and Signs

Cholestasis typically is noted in the first 2 wk of life. Infants are jaundiced and often have dark urine (containing conjugated bilirubin), acholic stools, and hepatomegaly. If cholestasis persists, chronic pruritus is common, as are symptoms and signs of fat-soluble vitamin deficiency; progression on growth

charts may show a decline. If the underlying disorder causes hepatic fibrosis and cirrhosis, portal hypertension with subsequent abdominal distention from ascites, dilated abdominal veins, and upper GI bleeding from esophageal varices may develop.

**Diagnosis**

• Total and direct bilirubin

• Liver function tests

• Tests for metabolic, infectious, and genetic causes

• Hepatobiliary scan

• Occasionally liver biopsy

Any infant who is jaundiced after age 2 wk should be evaluated for cholestasis. The initial approach should be directed at diagnosing treatable conditions (eg, extrahepatic biliary atresia, in which early surgical intervention improves outcome).

Cholestasis is identified by an elevation in both total and direct bilirubin. Tests that are needed to further evaluate liver function include albumin, fractionated serum bilirubin, liver enzymes, PT, and PTT. Once cholestasis is confirmed, testing is required to determine etiology (see Table 277-1).

A hepatobiliary scan should also be done; excretion of contrast into the intestine rules out biliary atresia, but lack of excretion can occur with both biliary atresia and severe neonatal hepatitis. An abdominal ultrasound can aid in assessing liver size and in attempting to visualize the gallbladder and common bile duct but is nonspecific. When no diagnosis has been made, a liver biopsy is generally performed relatively early on. Patients with biliary atresia typically have enlarged portal triads, bile duct proliferation, and increased fibrosis. Neonatal hepatitis is characterized by lobular disarray with multinucleated giant cells. Sometimes diagnosis remains unclear, and surgical exploration with operative cholangiography is required.

**Prognosis**

Biliary atresia is progressive and, if untreated, results in liver failure, cirrhosis with portal hypertension by several months of age, and death by 1 yr of age.

[**Table 277-1.** Diagnostic Evaluation for Neonatal Cholestasis]

Prognosis of cholestasis due to specific disorders (eg, metabolic disease) is variable, ranging from a completely benign course to a progressive disease resulting in cirrhosis.

Idiopathic neonatal hepatitis syndrome usually resolves slowly, but permanent liver damage may result and lead to death.

**Treatment**

• Specific cause treated

• Vitamin A, D, E, and K supplements

• Medium-chain triglycerides

• Sometimes ursodeoxycholic acid

Specific treatment is directed at the cause. If there is no specific therapy, treatment is supportive and

consists primarily of nutritional therapy, including supplements of vitamins A, D, E, and K. For formula-fed infants, a formula that is high in medium-chain triglycerides should be used because it is absorbed better in the presence of bile salt deficiency. Adequate calories are required; infants may need > 130 calories/kg day. In infants with some bile flow, ursodeoxycholic acid 10 to 15 mg/kg once/day or bid may relieve itching.

Infants with presumed biliary atresia require surgical exploration with an intraoperative cholangiogram. If biliary atresia is confirmed, a portoenterostomy (Kasai procedure) should be done. Ideally, this procedure should be done in the first 1 to 2 mo of life. After this period, the prognosis significantly worsens. Postoperatively, many patients have significant chronic problems, including persistent cholestasis, recurrent ascending cholangitis, and failure to thrive. Even with optimal therapy, many infants develop cirrhosis and require liver transplantation.

## Miscellaneous Surgical Emergencies

**Inguinal hernia:** Inguinal hernias (see p. 113) develop most often in male neonates, particularly if they are premature. About 10% of inguinal hernias are bilateral. Because inguinal hernias can become incarcerated, repair should be done shortly after diagnosis. For premature infants, repair typically is not done until they have reached a weight of 2 kg. In contrast, umbilical hernias rarely become incarcerated, close spontaneously after several years, and do not ordinarily need surgical repair.

**Gastric perforation:** In neonates, gastric perforations are often spontaneous and may be due to a congenital defect in the stomach wall, usually along the greater curvature. The abdomen suddenly becomes distended, and massive pneumoperitoneum is seen on abdominal x-ray. Treatment with corticosteroids increases risk of this disorder. Giving an $H_2$ blocker raises the gastric pH in premature infants and may reduce risk by inhibiting HCl production. Prognosis is usually good after surgical repair of the perforation.

**Ileal perforation:** In premature infants, ileal perforation has been reported after indomethacin has been given to close a patent ductus arteriosis. Ileal perforation is probably related to local ischemia resulting from vasoconstriction caused by indomethacin.

**Mesenteric arterial occlusion:** Mural thrombi or emboli may occlude a mesenteric artery after high placement of an umbilical artery catheter. Such an occurrence is extremely rare but can cause extensive intestinal infarction requiring surgery and intestinal resection.

# Chapter 278. Dehydration and Fluid Therapy

## Introduction

(See also Neonatal Hypernatremia on p. 2797; and Neonatal Hyponatremia on p. 2798.)

Unlike in adults, fluid management in children is based on weight and on specific guidelines, because children are more sensitive to fluid depletion (and excess). All guidelines are approximations; individualized adjustments based on close monitoring are essential.

## Dehydration

**Dehydration is significant depletion of body water and, to varying degrees, electrolytes. Symptoms and signs include thirst, lethargy, dry mucosae, decreased urine output, and, as the degree of dehydration progresses, tachycardia, hypotension, and shock. Diagnosis is based on history and physical examination. Treatment is with oral or IV replacement of fluid and electrolytes.**

Dehydration, usually caused by diarrhea, remains a major cause of morbidity and mortality in infants and young children worldwide. Infants are particularly susceptible to the ill effects of dehydration because of their greater baseline fluid requirements (due to a higher metabolic rate), higher evaporative losses (due to a higher ratio of surface area to volume), and inability to communicate thirst or seek fluid.

### Etiology

Dehydration results from increased fluid loss, decreased fluid intake, or both.

The most common source of increased fluid loss is the GI tract from vomiting, diarrhea, or both (eg, gastroenteritis). Other sources are renal (eg, diabetic ketoacidosis), cutaneous (eg, excessive sweating, burns), and 3rd-space losses (eg, into the intestinal lumen in bowel obstruction). All types of lost fluid contain electrolytes in varying concentrations, so fluid loss is always accompanied by electrolyte loss.

Decreased fluid intake is common during serious illness of any kind and is particularly problematic when the child is vomiting and during hot weather. It may also be a sign of neglect.

### Symptoms and Signs

Symptoms and signs vary according to degree of deficit (see Table 278-1) and are affected by serum Na concentration: hemodynamic findings are exaggerated by hyponatremia and reduced by hypernatremia.

### Diagnosis

• Clinical evaluation

In general, dehydration without hemodynamic changes is considered mild (about 5% body wt in infants and 3% in adolescents); tachycardia defines moderate dehydration (about 10% body wt in infants and 6% in adolescents); and hypotension with impaired perfusion defines severe dehydration (about 15% body wt in infants and 9% in adolescents). A more accurate method in children with acute dehydration is change in body weight; all short-term weight loss > 1%/day is presumed to represent fluid deficit. However, this method depends on knowing a precise, recent preillness weight. Parental estimates are usually inadequate; a 1-kg error in a 10-kg child causes a 10% error in the calculated percentage of dehydration —the difference between mild and severe dehydration.

Laboratory testing is usually reserved for moderately or severely ill children, in whom electrolyte disturbances (eg, hypernatremia, hypokalemia, metabolic acidosis) are more common. Other laboratory abnormalities include relative polycythemia from hemoconcentration, elevated BUN, and increased urine specific gravity.

### Treatment

• Fluid replacement (oral if possible)

Treatment is best approached by considering separately the fluid resuscitation requirements, current deficit, ongoing losses, and maintenance requirements. The volume (eg, amount of fluid), composition, and rate of replacement differ for each. Formulas and estimates used to determine treatment parameters provide a starting place, but treatment requires ongoing monitoring of vital signs, clinical appearance, urine output and specific gravity, weight, and sometimes serum electrolyte levels. Children with severe dehydration (eg, evidence of circulatory compromise) should receive fluids IV. Those unable or unwilling to drink or who have repetitive vomiting can receive fluid replacement IV, through an NGT, or sometimes orally through frequently repeated small amounts (see p. 2809).

**Resuscitation:** Patients with signs of hypoperfusion should receive fluid resuscitation with boluses of isotonic fluid (eg, 0.9% saline or Ringer's lactate). The goal is to restore adequate circulating volume to restore BP and perfusion. The resuscitation phase should reduce moderate or severe dehydration to a deficit of about 8% body wt. If dehydration is moderate, 20 mL/kg (2% body wt) is given IV over 20 to 30 min, reducing a 10% deficit to 8%. If dehydration is severe, 3 boluses of 20 mL/kg (2% body wt) will likely be required. The end point of the fluid resuscitation phase is restoring peripheral perfusion and BP and returning increased heart rate toward normal.

**Deficit replacement:** Total deficit volume is estimated clinically as described previously. Na deficits are usually about 80 mEq/L of fluid deficit, and K deficits are usually about 30 mEq/L of fluid deficit. The resuscitation phase should have reduced moderate or severe dehydration to a deficit of about 8% body wt;

[**Table 278-1.** Clinical Correlates of Dehydration]

this remaining deficit can be replaced by providing 10 mL/kg (1% body wt)/h for 8 h. Because 0.45% saline has 77 mEq Na per liter, it is usually an appropriate fluid choice. K replacement (usually by adding 20 to 40 mEq K per liter of replacement fluid) should not begin until adequate urine output is established.

Dehydration with significant hypernatremia (eg, serum Na > 160 mEq/L) or hyponatremia (eg, serum Na < 120 mEq/L) requires special consideration to avoid complications (see p. 2798).

**Ongoing losses:** Volume of ongoing losses should be measured directly (eg, NGT, catheter, stool measurements) or estimated (eg, 10 mL/kg per diarrheal stool). Replacement should be milliliter for milliliter in time intervals appropriate for the rapidity and extent of the loss. Ongoing electrolyte losses can be estimated by source or cause (see Table 278-2). Urinary electrolyte losses vary with intake and disease process but can be measured if deficits fail to respond to replacement therapy.

**Maintenance requirements:** Fluid and electrolyte needs from basal metabolism must also be accounted for. Maintenance requirements are related to metabolic rate and affected by body temperature. Insensible losses (evaporative free water losses from the skin and respiratory tract in a ratio of 2:1) account for about one half of maintenance needs.

Volume rarely must be exactly determined but generally should aim to provide an amount of water that does not require the kidney to significantly concentrate or dilute the urine. The most common estimate uses patient weight to calculate metabolic expenditure in kcal/24 h, which approximates fluid needs in mL/24 h (see Table 278-3). A simpler calculation (the Holliday-Segar formula) uses 3 weight classes (see Table 278-4). Body surface area derived from a nomogram (see Fig. 278-2) also can be used, allowing 1500 to 2000 $mL/m^2/24$ h. More complex calculations are rarely required. These fluid volumes can be given as a separate simultaneous infusion, so that the infusion rate for replacing deficits and ongoing losses can be set and adjusted independently of the maintenance infusion rate.

[Table 278-2. Standard Basal Metabolic Rates Used for Calculating Maintenance Fluid Requirements*]

[Table 278-3. Estimated Electrolyte Deficits by Cause]

Baseline estimates are affected by fever (increasing by 12% for each degree > 37.8° C), hypothermia, and activity (eg, increased for hyperthyroidism or status epilepticus, decreased for coma).

Composition differs from solutions used to replace deficits and ongoing losses. Patients require Na 3 mEq/100 kcal/24 h (3 mEq/100

[Table 278-4. Holliday-Segar Formula for Maintenance Fluid Requirements by Weight]

mL/24 h) and K 2 mEq/100 kcal/24 h (2 mEq/100 mL/24 h). This need is met by using 0.2% to 0.3% saline with 20 mEq/L of K in a 5% dextrose solution. Other electrolytes (eg, Mg, Ca) are not routinely added. It is inappropriate to replace deficits and ongoing losses solely by increasing the amount or rate of maintenance fluids.

**Practical Example**

A 7-mo-old infant has diarrhea for 3 days with weight loss from 10 kg to 9 kg. The infant is currently producing 1 diarrheal stool every 3 h and refusing to drink. Clinical findings of dry mucous membranes, poor skin turgor, markedly decreased urine output, and tachycardia with normal BP and capillary refill suggest 10% fluid deficit. Rectal temperature is 37° C; serum Na, 136 mEq/L; K, 4 mEq/L; Cl, 104 mEq/L; and $HCO_3$, 20 mEq/L.

**Fluid volume** is estimated by deficits, ongoing losses, and maintenance requirements.

The total fluid deficit given 1 kg wt loss = 1 L.

Ongoing diarrheal losses are measured as they occur by weighing the infant's diaper before application and after the diarrheal stool.

Baseline maintenance requirements by the weight-based Holliday-Segar method are 100 mL/kg × 10 kg = 1000 mL/day = 1000/24 or 40 mL/h.

**Electrolyte losses** from diarrhea (see Table 278-2) are an estimated 80 mEq of Na and 80 mEq of K.

**Procedure**

**Resuscitation:** The patient is given an initial bolus of Ringer's lactate 200 mL (20 mL/kg × 10 kg) over 30 min. This amount replaces 26 mEq of the estimated 80 mEq Na deficit.

**Deficits:** Residual fluid deficit is 800 mL (1000 initial - 200 mL resuscitation), and Na deficit is 54 mEq (80-26 mEq). This residual amount is given over 8 h as 5% dextrose/0.45% saline at 100 mL/h. This amount replaces the Na deficit (0.8 L × 77 mEq Na/L = 62 mEq Na). When urine output is established, K is added at a concentration of 20 mEq/L (for safety reasons, no attempt is made to replace complete K deficit acutely).

**Ongoing losses:** Five percent dextrose/0.45% saline also is used to replace ongoing losses; volume and rate are determined by the amount of diarrhea.

**Maintenance fluid:** Five percent dextrose/0.2% saline is given at 40 mL/h with 20 mEq/L of K added when urine output is established. Alternatively, the deficit could be replaced during the initial 8 h followed by the entire day's maintenance fluid in the next 16 h (ie, 60 mL/h); 24 h of maintenance fluid given in 16 h reduces mathematically to a rate of 1.5 times the usual maintenance rate and obviates the need for simultaneous infusions (which may require 2 rate-controlling pumps).

## Oral Rehydration

Oral fluid therapy is effective, safe, convenient, and inexpensive compared with IV therapy. It should be used for children with mild to moderate dehydration who are accepting fluids orally unless prohibited by copious vomiting or underlying disorders (eg, surgical abdomen, intestinal obstruction).

**Solutions:** Oral rehydration solution should contain complex carbohydrate or 2% glucose and 50 to 90 mEq/L of Na. Sports drinks, sodas, juices, and similar drinks do not meet these criteria and should not be used. They generally have too little Na and too much carbohydrate to take advantage of Na/glucose cotransport, and the osmotic effect of the excess carbohydrate may result in additional fluid loss.

Oral rehydration solution (ORS) is recommended by the WHO and is widely available in the US without prescription. Most solutions come as powders that are mixed with tap water. Premixed solutions also are available in most pharmacies and supermarkets. An ORS packet is dissolved in 1 L of water to produce a solution containing (in mmol/L) Na 90, K 20, Cl 80, citrate 10, and glucose 111 (standard WHO ORS) or Na 75, K 20, Cl 65, citrate 10, and glucose 75 (WHO reduced-osmolarity

[**Fig. 278-2.** Nomogram for calculating the body surface area of children.]

ORS). It can also be made manually by adding 1 L of water to 3.5 g NaCl, 2.9 g trisodium citrate (or 2.5 g $NaHCO_3$), 1.5 g KCL, and 20 g glucose. ORS is effective in patients with dehydration regardless of age, cause, or type of electrolyte imbalance (hyponatremia, hypernatremia, or isonatremia) as long as their kidneys are functioning adequately. After rehydration, this solution must be replaced by a lower-Na fluid to avoid hypernatremia.

If specific rehydration solutions (powders or premixed) are unavailable, some clinicians advise caretakers to prepare a homemade solution using sugar and table salt. However, even with written instructions (and in some cases, dispensing 2 color-coded scoops), errors in preparation have at times caused fatal hypernatremia. Therefore, if specific rehydration solutions are unavailable, infants with mild to moderate dehydration should be continued on breast milk or formula, but the threshold for using IV hydration in those with moderate dehydration should be lower. Clinicians in practice situations where patients may be unable to obtain appropriate ORS on their own should explore alternative means of making the solution available.

**Administration:** Generally, 50 mL/kg is given over 4 h for mild dehydration and 100 mL/kg for moderate. For each diarrheal stool, an additional 10 mL/kg (up to 240 mL) is given. After 4 h, the patient is reassessed. If signs of dehydration persist, the same volume is repeated. Patients with cholera may require many liters of fluid/day.

Vomiting usually should not deter oral rehydration (unless there is bowel obstruction or other contraindication). Small, frequent amounts are used, starting with 5 mL q 5 min and increasing gradually as tolerated.

Once the deficit has been replaced, an oral maintenance solution containing less Na should be used. Children should eat an age-appropriate diet as soon as they have been rehydrated and are not vomiting. Infants may resume breastfeeding or formula. Infants with diarrhea who develop signs or symptoms of malabsorption (see p. 152) should be given lactose-free formula.

# Chapter 279. Infections in Neonates

## Introduction

Neonatal infection can be acquired in utero transplacentally, through the birth canal during delivery (intrapartum), and from external sources after birth (postpartum).

In utero infection, which can occur any time before birth, results from overt or subclinical maternal infection. Consequences depend on the agent and timing of infection in gestation and include spontaneous abortion, intrauterine growth restriction, premature birth, stillbirth, congenital malformation (eg, rubella), and symptomatic neonatal infection (eg, cytomegalovirus [CMV], toxoplasmosis, syphilis).

Common viral agents include herpes simplex, HIV, CMV, and hepatitis B. Intrapartum infection with HIV or hepatitis B occurs from passage through an infected birth canal or by ascending infection if delivery is delayed after rupture of membranes; these viruses can less commonly be transmitted transplacentally. CMV is commonly transmitted transplacentally. Bacterial agents include group B streptococci, enteric gram-negative organisms (primarily *Escherichia coli*), gonococci, and chlamydiae.

Postpartum infections are acquired from contact with an infected mother either directly (eg, TB, which also is sometimes transmitted in utero) or through breastfeeding (eg, HIV, CMV) or from contact with health care practitioners and the hospital environment (numerous organisms—see p. 2828).

**Risk factors:** Risk of contracting intrapartum and postpartum infection is inversely proportional to gestational age. Neonates are immunologically immature, with decreased polymorphonuclear leukocyte and monocyte function; premature infants are particularly so (see p. 2766). Maternal IgG antibodies are actively transported across the placenta, but effective levels for all organisms are not achieved until near term. IgM antibodies do not cross the placenta. Premature infants have decreased intrinsic antibody production and reduced complement activity. Premature infants are also more likely to require invasive procedures (eg, endotracheal intubation, prolonged IV access) that predispose to infection.

### Symptoms and Signs

Symptoms and signs in neonates tend to be nonspecific (eg, vomiting, fever, petechiae, rashes, diarrhea, fever, hypothermia). Many congenital infections acquired before birth can cause or be accompanied by various symptoms or abnormalities (eg, growth restriction, deafness, microcephaly, anomalies, failure to thrive, hepatosplenomegaly, neurologic abnormalities).

### Diagnosis

A wide variety of infections should be considered in neonates who are ill, febrile, or hypothermic. Infections such as congenital rubella, syphilis, toxoplasmosis, and CMV should be considered, particularly in neonates with abnormalities such as growth restriction, deafness, microcephaly, anomalies, failure to thrive, hepatosplenomegaly, or neurologic abnormalities.

### Treatment

• Antimicrobial therapy

The primary treatment is usually antimicrobial therapy. Drug selection is similar to that in adults, because infecting organisms and their sensitivities are not specific to neonates. However, numerous factors, including age and weight, affect dose and frequency (see Tables 279-1 and 279-2).

In neonates, the ECF constitutes up to 45% of total body weight, requiring relatively larger doses of certain antibiotics (eg, aminoglycosides) compared with adults. Lower serum albumin concentrations in premature infants may reduce antibiotic protein binding. Drugs that displace bilirubin from albumin (eg, sulfonamides, ceftriaxone) increase the risk of kernicterus.

Absence or deficiency of certain enzymes in neonates may prolong the half-life of certain antibiotics (eg, chloramphenicol) and increase the risk of toxicity. Changes in GFR and renal tubular secretion during the first month of life necessitate dosing changes for other drugs (eg, penicillins, aminoglycosides, vancomycin).

## Congenital and Perinatal Cytomegalovirus Infection

(See also Cytomegalovirus Infection on p. 1416.)

**Cytomegalovirus (CMV) infection may be acquired prenatally or perinatally and is the most common congenital viral infection. Signs at birth, if present, are intrauterine growth restriction, prematurity,**

[**Table 279-1.** Recommended Dosages of Selected Parenteral Antibiotics for Neonates]

[**Table 279-2.** Recommended Dosages of Selected Oral Antibiotics for Neonates*]

**microcephaly, jaundice, petechiae, hepatosplenomegaly, periventricular calcifications, chorioretinitis, and pneumonitis. If acquired later in infancy, signs may include pneumonia, hepatosplenomegaly, hepatitis, thrombocytopenia, and atypical lymphocytosis. Diagnosis of neonatal infection is best made by virus isolation. Treatment is supportive. Parenteral ganciclovir can prevent hearing deterioration, but its use remains controversial.**

CMV is frequently isolated from neonates. Although most infants shedding this virus are asymptomatic, others have life-threatening illness and devastating long-term sequelae.

It is not known when a woman with primary CMV can safely conceive. Because risk to the fetus is difficult to assess, women who develop primary CMV during pregnancy should be counseled, but few experts recommend routine serologic testing for CMV before or during pregnancy in healthy women.

### Etiology

**Congenital CMV infection**, which occurs in 0.2 to 2.2% of live births worldwide, may result from transplacental acquisition of either a primary or recurrent maternal infection. Clinically apparent disease in the neonate is much more likely to occur after a primary maternal exposure, particularly in the first half of pregnancy. In some higher socioeconomic groups in the US, 50% of young women lack antibody to CMV, making them susceptible to primary infection.

**Perinatal CMV infection** is acquired by exposure to infected cervical secretions, breast milk, or blood products. Maternal antibody is thought to be protective, and most exposed term infants are asymptomatic or not infected. In contrast, preterm infants (who lack antibody to CMV) can develop serious infection or can die, particularly when transfused with CMV-positive blood. Efforts should be made to transfuse these infants with only CMV-negative blood or components or to use blood that has been filtered to remove leukocytes (leukoreduced).

### Symptoms and Signs

Many women who become infected with CMV during pregnancy are asymptomatic, but some develop a mononucleosis-like illness.

About 10% of infants with congenital CMV infection are symptomatic at birth. Manifestations include the following:

• Intrauterine growth restriction

• Prematurity

- Microcephaly
- Jaundice
- Petechiae
- Hepatosplenomegaly
- Chorioretinitis
- Pneumonitis

Infants who acquire CMV after birth, especially if they are premature, may develop a sepsis-like syndrome, pneumonia, hepatosplenomegaly, hepatitis, thrombocytopenia, and atypical lymphocytosis, as well as sensorineural hearing loss.

**Diagnosis**

- Viral culture using urine, saliva, or tissue
- PCR using urine, saliva, blood, or tissue

Symptomatic congenital CMV infection must be distinguished from other congenital infections, including toxoplasmosis, rubella, and syphilis.

In neonates, viral culture of a urine, saliva, or tissue sample is the primary diagnostic tool; maternal diagnosis can also be made by serologic testing (see p. 1416). Culture specimens should be refrigerated until inoculation of fibroblast cells. Congenital CMV is diagnosed if the virus is isolated from urine or other body fluids obtained within the first 3 wk of life. After 3 wk, positive cultures may indicate perinatal or congenital infection. Infants may shed CMV for several years after either type of infection. A positive PCR result using neonatal urine, saliva, blood, or tissue is helpful in making a diagnosis, but a negative PCR result does not rule out an infection. PCR can also establish maternal infection.

A CBC and differential and liver function tests may be helpful but are not specific. Cranial ultrasonography or CT and an ophthalmologic evaluation should also be done. Periventricular calcifications are commonly found on CT. Hearing tests should be routinely done at birth in all infected neonates, but close monitoring is required because hearing loss may be progressive.

**Prognosis**

Symptomatic neonates have a mortality rate of up to 30%, and 70 to 90% of survivors have some neurologic impairment, including

- Hearing loss
- Intellectual disability
- Visual disturbances

Among asymptomatic neonates, 10% eventually develop neurologic sequelae.

**Treatment**

No specific therapy is available. Ganciclovir decreases viral shedding in neonates with congenital CMV and may prevent hearing deterioration at 6 mo. When therapy stops, the virus is again shed; therefore, its role in treatment remains controversial.

**Prevention**

Nonimmune pregnant women should attempt to limit exposure to the virus. For instance, because CMV infection is common among children attending day care centers, pregnant women should always wash their hands thoroughly after exposure to urine and oral or respiratory secretions from children.

Transfusion-associated perinatal CMV disease can be avoided by giving preterm neonates blood products from CMV-seronegative donors or leukoreduced products.

A vaccine to prevent congenital CMV is being developed. Using CMV hyper immune globulin in pregnant women with primary CMV infection to prevent or treat congenital infection is also under investigation.

## Congenital Rubella

(See also Rubella on p. 1462.)

**Congenital rubella is a viral infection acquired from the mother during pregnancy. Signs are multiple congenital anomalies that can result in fetal death. Diagnosis is by serology and viral culture. There is no specific treatment. Prevention is by routine vaccination.**

Congenital rubella typically results from a primary maternal infection. Congenital rubella is rare in the US.

Rubella is believed to invade the upper respiratory tract, with subsequent viremia and dissemination of virus to different sites, including the placenta. The fetus is at highest risk of developmental abnormalities when infected during the first 16 wk of gestation, particularly the first 8 to 10 wk. Early in gestation, the virus is thought to establish a chronic intrauterine infection. Its effects include endothelial damage to blood vessels, direct cytolysis of cells, and disruption of cellular mitosis.

### Symptoms and Signs

Rubella in a pregnant woman may be asymptomatic or characterized by upper respiratory tract symptoms, fever, lymphadenopathy (especially in the suboccipital and posterior auricular areas), and a maculopapular rash. This illness may be followed by joint symptoms.

In the fetus there may be no effects, multiple anomalies, or death in utero. The most frequent abnormalities include intrauterine growth restriction, microcephaly, meningoencephalitis, cataracts, retinopathy, hearing loss, cardiac defects (patent ductus arteriosus and pulmonary artery stenosis), hepatosplenomegaly, and bone radiolucencies. Others are thrombocytopenia with purpura, dermal erythropoiesis resulting in bluish red skin lesions, adenopathy, hemolytic anemia, and interstitial pneumonia. Close observation is needed to detect subsequent hearing loss, intellectual disability, abnormal behavior, endocrinopathies (eg, diabetes mellitus), or a rare progressive encephalitis. Infants with congenital rubella infections may develop immune deficiencies such as hypogammaglobulinemia.

### Diagnosis

• Maternal serum rubella titers

• Sometimes viral isolation from amniotic fluid

• Infant antibody titers (measured serially) and viral cultures

Pregnant women routinely have a serum rubella titer measured early in pregnancy. Titer is repeated in seronegative women who develop symptoms or signs of rubella; diagnosis is made by seroconversion or a ≥ 4-fold rise between acute and convalescent titers. Virus may be cultured from nasopharyngeal swabs but grows very slowly, making swabs an inefficient method of diagnosis.

Infants suspected of having congenital rubella should have antibody titers and viral cultures. Persistence of rubella-specific IgG in the infant after 6 to 12 mo suggests congenital infection. Increased rubella-specific IgM antibodies also indicate rubella. Specimens from the nasopharynx, urine, CSF, buffy coat,

and conjunctiva may grow virus; samples from the nasopharynx usually offer the best sensitivity, and the laboratory should be notified that rubella virus is suspected. In a few centers, diagnoses can be made prenatally by isolating the virus from amniotic fluid, detecting rubella-specific IgM in fetal blood, or applying reverse transcriptase-PCR (RTPCR) techniques to fetal blood or chorionic villus biopsy specimens.

Other tests include a CBC with differential, CSF analysis, and x-ray examination of the bones to detect characteristic radiolucencies. Thorough ophthalmologic and cardiac evaluations are also useful.

### Treatment

• Counseling

• Possibly immune globulin

No specific therapy is available for maternal or congenital rubella infection. Women exposed to rubella early in pregnancy should be informed of the potential risks to the fetus. Some experts recommend giving nonspecific immune globulin (0.55 mL/kg IM) for exposure early in pregnancy, but this treatment does not guarantee prevention, and the use of immune globulin should be considered only in women who decline termination.

### Prevention

Rubella can easily be prevented by vaccination. In the US, infants should receive vaccination for rubella together with measles and mumps vaccinations at 12 to 15 mo of age and again at entry to grade school or junior high school (see
Table 268-11 on p. 2720). Postpubertal females who are not known to be immune to rubella should be vaccinated. (CAUTION: *Rubella vaccination is contraindicated in immunodeficient or pregnant women.* ) After vaccination, women should be advised not to become pregnant for 28 days. Efforts should also be made to screen and vaccinate high-risk groups, such as hospital and child care workers, military recruits, recent immigrants, and college students. Women who are found to be susceptible during prenatal screening should be vaccinated after delivery and before hospital discharge.

## Congenital Syphilis

(See also Syphilis on p. 1475.)

**Congenital syphilis is a multisystem infection caused by *Treponema pallidum* and transmitted to the fetus via the placenta. Early signs are characteristic skin lesions, lymphadenopathy, hepatosplenomegaly, failure to thrive, blood-stained nasal discharge, perioral fissures, meningitis, choroiditis, hydrocephalus, seizures, intellectual disability, osteochondritis, and pseudoparalysis (Parrot's atrophy of newborn). Later signs are gummatous ulcers, periosteal lesions, paresis, tabes, optic atrophy, interstitial keratitis, sensorineural deafness, and dental deformities. Diagnosis is clinical, confirmed by microscopy or serology. Treatment is penicillin.**

Overall risk of transplacental infection of the fetus is about 60 to 80%, and likelihood is increased during the 2nd half of the pregnancy. Untreated primary or secondary syphilis in the mother usually is transmitted, but latent or tertiary syphilis usually is not. In neonates, manifestations of syphilis are classified as early congenital (ie, birth through age 2 yr) and late congenital (ie, after age 2 yr).

### Symptoms and Signs

Many patients are asymptomatic, and the infection may remain clinically silent throughout their life.

**Early congenital syphilis** commonly manifests during the first 3 mo of life. Manifestations include characteristic vesiculobullous eruptions or a macular, copper-colored rash on the palms and soles and papular lesions around the nose and mouth and in the diaper area, as well as petechial lesions. Generalized lymphadenopathy and hepatosplenomegaly often occur. The infant may fail to thrive and

have a characteristic mucopurulent or bloodstained nasal discharge causing snuffles. A few infants develop meningitis, choroiditis, hydrocephalus, or seizures, and others may be intellectually disabled. Within the first 8 mo of life, osteochondritis (chondroepiphysitis), especially of the long bones and ribs, may cause pseudoparalysis of the limbs with characteristic radiologic changes in the bones.

**Late congenital syphilis** typically manifests after 2 yr of life and causes gummatous ulcers that tend to involve the nose, septum, and hard palate and periosteal lesions that result in saber shins and bossing of the frontal and parietal bones. Neurosyphilis is usually asymptomatic, but juvenile paresis and tabes may develop. Optic atrophy, sometimes leading to blindness, may occur. Interstitial keratitis, the most common eye lesion, frequently recurs, often resulting in corneal scarring. Sensorineural deafness, which is often progressive, may appear at any age. Hutchinson's incisors, mulberry molars, perioral fissures (rhagades), and maldevelopment of the maxilla resulting in "bulldog" facies are characteristic, if infrequent, sequelae.

**Diagnosis**

- **Early congenital syphilis:** Clinical evaluation, darkfield microscopy of lesions and placenta or umbilical cord, infant serum quantitative nontreponemal tests, possibly CSF analysis

- **Late congenital syphilis:** Clinical evaluation, serologic testing

**Early congenital syphilis:** Diagnosis is usually suspected based on maternal serologic testing, which is routinely done early in pregnancy, and often in the 3rd trimester and at delivery. Neonates of mothers with positive tests should have a thorough examination, darkfield microscopy of any skin or mucosal lesions, and a quantitative nontreponemal serum test (eg, rapid plasma reagin [RPR], Venereal Disease Research Laboratory [VDRL]); cord blood is not used for serum testing because results are less sensitive and specific. The placenta or umbilical cord should be analyzed using darkfield microscopy or fluorescent antibody staining. Infants with clinical signs of illness or suggestive serologic test results also should have a lumbar puncture with CSF analysis for cell count, VDRL, and protein; CBC; liver function tests; and long-bone x-rays.

Diagnosis is confirmed by microscopic visualization of spirochetes in samples from the neonate or the placenta. Diagnosis based on neonatal serologic testing is complicated by the transplacental transfer of maternal IgG antibodies, which can cause a positive test in the absence of infection. However, a neonatal titer > 4 times the maternal titer would not generally result from passive transfer, and diagnosis is considered confirmed or highly probable. Maternal disease acquired late in pregnancy may be transmitted before development of antibodies. Thus, in neonates with lower titers but typical clinical manifestations, syphilis is also considered highly probable. In neonates with no signs of illness and low or (if maternal infection is diagnosed) negative serologic titers, syphilis is considered possible; subsequent approach depends on various maternal and neonatal factors (see also Follow up, below). The utility of fluorescent assays for antitreponemal IgM, which is not transferred across the placenta, is controversial, but such assays have been used to detect neonatal infection. Any positive nontreponemal test should be confirmed with a specific treponemal test to exclude false-positive results, but confirmative testing should not delay treatment in a symptomatic infant or an infant at high risk of infection.

**Late congenital syphilis:** Diagnosis is by clinical history, distinctive physical signs, and positive serologic tests (see also p. 1478). Hutchinson's triad of interstitial keratitis, Hutchinson's incisors, and 8th cranial nerve deafness is diagnostic. Sometimes the standard serologic tests for syphilis are negative, but the fluorescent treponemal antibody absorption test (FTA-ABS) is usually positive. The diagnosis should be considered in cases of unexplained deafness, progressive intellectual deterioration, or keratitis.

**Follow up:** All seropositive infants and those whose mothers were seropositive should have VDRL or RPR titers every 2 to 3 mo until the test is nonreactive or the titer has decreased 4-fold. In uninfected and successfully treated infants, nontreponemal antibody titers are usually non-reactive by 6 mo. Passively acquired treponemal antibodies may be present for longer, perhaps 15 mo. It is important to remember to use the same specific nontreponemal test to monitor titers.

If VDRL or RPR remain reactive past 6 to 12 mo or titers increase, the infant should be reevaluated (including lumbar puncture for CSF analysis, and CBC with platelet count, long-bone x-rays, and other

tests as clinically indicated).

**Treatment**

• Parenteral penicillin

**Pregnant women:** Pregnant women in the early stages of syphilis receive one dose of benzathine penicillin G (1.2 million units IM in each buttock for a total of 2.4 million units). For later stages of syphilis or neurosyphilis, the appropriate regimen for nonpregnant patients should be followed (see p. 1480). Occasionally, a severe Jarisch-Herxheimer reaction occurs after such therapy, leading to spontaneous abortion. Patients allergic to penicillin may be desensitized and then treated with penicillin. RPR and VDRL tests become negative by 3 mo after adequate treatment in most patients and by 6 mo in nearly all patients. Erythromycin therapy is inadequate for both the mother and fetus and is not recommended. Tetracycline is *contraindicated*.

**Early congenital syphilis:** In confirmed or highly probable cases, 2006 Centers for Disease Control and Prevention (CDC) guidelines recommend aqueous penicillin G 50,000 units/kg IV q 12 h for the first 7 days of life and q 8 h thereafter for a total of 10 days or procaine penicillin G 50,000 units/kg IM once/day for 10 days. This regimen also is used for infants with possible syphilis if the mother fits any of the following criteria:

• Untreated

• Treatment status is unknown

• Treated ≤ 4 wk before delivery

• Inadequately treated (a nonpenicillin regimen, or maternal titers did not decrease 4-fold)

In infants with possible syphilis and a negative evaluation, a single dose of benzathine penicillin 50,000 units/kg IM is an alternative treatment choice in selected circumstances, but only if follow-up is assured.

Infants with possible syphilis whose mothers were adequately treated and who are clinically well can also be given a single dose of benzathine penicillin 50,000 units/kg IM. Alternatively, if close follow-up is assured, some clinicians defer penicillin and do nontreponemal serologic testing monthly for 3 mo and then at 6 mo; antibiotics are given if titers rise or are positive at 6 mo.

**Older infants and children with newly diagnosed congenital syphilis:** CSF should be examined before treatment starts. The CDC recommends that any child with late congenital syphilis be treated with aqueous crystalline penicillin G 50,000 units/kg IV q 4 to 6 h for 10 days. Many patients do not revert to seronegativity but do have a 4-fold decrease in titer of reagin (eg, VDRL) antibody. Interstitial keratitis is usually treated with corticosteroid and atropine drops in consultation with an ophthalmologist. Patients with nerve deafness may benefit from penicillin plus a corticosteroid such as prednisone 0.5 mg/kg po once/day for 1 wk, followed by 0.3 mg/kg once/day for 4 wk, after which the dose is gradually reduced over 2 to 3 mo. (Corticosteroids have not been critically evaluated in these conditions.) Contacts should be traced, and patients should be kept under long-term surveillance.

**Prevention**

Pregnant women should be routinely tested for syphilis and retested if they acquire other sexually transmitted diseases during pregnancy. In 99% of cases, adequate treatment during pregnancy cures both mother and fetus. However, in some cases, treatment late in pregnancy eliminates the infection but not some signs of syphilis that appear at birth.

When congenital syphilis is diagnosed, other family members should be examined regularly for physical and serologic evidence of infection. Retreatment of the mother in subsequent pregnancies is necessary only if serologic titers remain positive. Women who remain seropositive after adequate treatment may have been reinfected and should be retreated. A mother without lesions who is seronegative but who has

had venereal exposure to a known person with syphilis should be treated, because there is a 25 to 50% chance that she acquired syphilis.

## Congenital Toxoplasmosis

(See also Toxoplasmosis on p. 1390.)

**Congenital toxoplasmosis is caused by transplacental acquisition of *Toxoplasma gondii*. Manifestations, if present, are prematurity, intrauterine growth restriction, jaundice, hepatosplenomegaly, myocarditis, pneumonitis, rash, chorioretinitis, hydrocephalus, intracranial calcifications, microcephaly, and seizures. Diagnosis is by serologic testing. Treatment is with pyrimethamine, sulfadiazine, and leucovorin.**

*Toxoplasma gondii*, a parasite found worldwide, causes congenital infection in about 1/10,000 to 80/10,000 births.

### Etiology

With rare exception, congenital toxoplasmosis is due to a primary maternal infection during pregnancy. Infection with *T. gondii* occurs primarily from ingestion of inadequately cooked meat containing cysts or from ingestion of oocysts derived from cat feces. The rate of transmission to the fetus is higher in women infected later during pregnancy. However, those infected earlier in gestation generally have more severe disease. Overall, 30 to 40% of women infected during pregnancy will have a congenitally infected child.

### Symptoms and Signs

Pregnant women infected with *T. gondii* generally do not have clinical manifestations, although some may have a mild mononucleosis-like syndrome, regional lymphadenopathy, or occasionally chorioretinitis. Similarly, infected neonates are usually asymptomatic at birth, but manifestations may include

- Prematurity
- Intrauterine growth restriction
- Jaundice
- Hepatosplenomegaly
- Myocarditis
- Pneumonitis
- Various rashes

Neurologic involvement, often prominent, includes chorioretinitis, hydrocephalus, intracranial calcifications, microcephaly, and seizures. The classic triad of findings consists of chorioretinitis, hydrocephalus, and intracranial calcifications.

### Diagnosis

- Serial IgG measurement (for maternal infection)
- Amniotic fluid PCR (for fetal infection)
- Serologic testing, brain imaging, CSF analysis, and ophthalmologic evaluation (for neonatal infection)

Serologic testing is important in diagnosing maternal and congenital infection. Maternal infection should be suspected if women have a mononucleosis-like syndrome and a negative heterophil antibody test,

isolated regional adenopathy not due to another cause (eg, HIV), or chorioretinitis. Acute maternal infection is suggested by seroconversion or a ≥ 4-fold rise between acute and convalescent IgG titers. However, maternal IgG antibodies may be detectable in the infant through the first year. PCR analysis of amniotic fluid is emerging as the method of choice for diagnosis of fetal infection. There are numerous other serologic tests, some of which are done only in reference laboratories. The most reliable are the Sabin-Feldman dye test, the indirect immunofluorescent antibody (IFA) test, and the direct agglutination assay. Tests to isolate the organism include inoculation into mice and tissue culture, but these tests are not usually done because they are expensive, not highly sensitive, and can take weeks before yielding results.

In suspected congenital toxoplasmosis, serologic tests, MRI or CT imaging of the brain, CSF analysis, and a thorough eye examination by an ophthalmologist should be done. CSF abnormalities include xanthochromia, pleocytosis, and increased protein concentration. The placenta is inspected for characteristic signs of *T. gondii* infection. Nonspecific laboratory findings include thrombocytopenia, lymphocytosis, monocytosis, eosinophilia, and elevated transaminases.

### Prognosis

Some children have a fulminant course with early death, whereas others have long-term neurologic sequelae. Occasionally, neurologic manifestations (eg, chorioretinitis, intellectual disability, deafness, seizures) develop years later in children who appeared normal at birth. Consequently, children with congenital toxoplasmosis should be closely monitored beyond the neonatal period.

### Treatment

• Sometimes spiramycin for pregnant women

• Pyrimethamine, sulfadiazine, and leucovorin for neonates

Limited data suggest that treatment of infected women during pregnancy may be beneficial to the fetus. Spiramycin (available in the US with special permission from the FDA) has been used to prevent maternofetal transmission. Pyrimethamine and sulfonamides have been used later in gestation to treat the infected fetus.

Treatment of symptomatic and asymptomatic neonates may improve outcome. Therefore, treatment is begun with pyrimethamine (initial loading dose of 1 mg/kg po bid for 2 days followed by 1 mg/kg po once/day, maximum 25 mg), sulfadiazine (50 mg/kg po bid, maximum 4 g), and leucovorin (5 to 10 mg po q 3 days). After the initial 6 mo of treatment, sulfadiazine and leucovorin are continued at the same dose, but the pyrimethamine is given less frequently (only on Monday, Wednesday, and Friday). This regimen is continued for at least 6 more mo. All treatment should be over-seen by an expert. The use of corticosteroids is controversial and should be determined case by case.

### Prevention

Pregnant women should avoid contact with cat litter boxes and other areas contaminated with cat feces. Meat should be thoroughly cooked before consumption, and hands should be washed after handling raw meat or unwashed produce. Women at risk of primary infection (eg, those frequently exposed to cat feces) should be screened during pregnancy. Those infected during the 1st or 2nd trimester should be counseled regarding available treatments.

## Neonatal Conjunctivitis

(Ophthalmia Neonatorum)

**Neonatal conjunctivitis is purulent ocular drainage due to a chemical irritant or a pathogenic organism. Prevention with antigonococcal drops at birth is routine. Diagnosis is clinical and usually confirmed by laboratory testing. Treatment is with organism-specific antimicrobials.**

### Etiology

The major causes (in decreasing order) are

• Chemical inflammation

• Bacterial infection

• Viral infection (see also p. 580)

Chemical conjunctivitis is generally secondary to the instillation of silver nitrate drops for ocular prophylaxis. Bacterial infection is acquired from infected mothers during passage through the birth canal. Chlamydial ophthalmia (caused by *Chlamydia trachomatis*) is the most common bacterial cause, occurring in 2 to 4% of births; it accounts for about 30 to 50% of conjunctivitis in neonates < 4 wk of age. The prevalence of maternal chlamydial infection ranges from 2 to 20%. About 30 to 50% of neonates born to acutely infected women develop conjunctivitis (and 5 to 20% develop pneumonia). Other bacteria, including *Streptococcus pneumoniae* and nontypeable *Haemophilus influenzae*, account for another 15% of cases. The incidence of gonorrheal ophthalmia (conjunctivitis due to *Neisseria gonorrhoeae*) in the US is 2 to 3/10,000 births. Isolation of bacteria other than *H. influenzae, S. pneumoniae*, and *N. gonorrhoeae*, including *Staphylococcus aureus*, usually represents colonization rather than infection. The major viral cause is herpes simplex virus types 1 and 2 (herpetic keratoconjunctivitis).

### Symptoms and Signs

Because they overlap in both manifestation and onset, causes of neonatal conjunctivitis are difficult to distinguish clinically. Conjunctivae are injected, and discharge (watery or purulent) is present.

**Chemical conjunctivitis** secondary to silver nitrate usually appears within 6 to 8 h after instillation and disappears spontaneously within 48 to 96 h.

**Chlamydial ophthalmia** usually occurs 5 to 14 days after birth. It may range from mild conjunctivitis with minimal mucopurulent discharge to severe eyelid edema with copious drainage and pseudomembrane formation. Follicles are not present in the conjunctiva, as they are in older children and adults.

**Gonorrheal ophthalmia** causes an acute purulent conjunctivitis that appears 2 to 5 days after birth or earlier with premature rupture of membranes. The neonate has severe eyelid edema followed by chemosis and a profuse purulent exudate that may be under pressure. If untreated, corneal ulcerations and blindness may occur.

**Conjunctivitis caused by other bacteria** has a variable onset, ranging from 4 days to several weeks.

**Herpetic keratoconjunctivitis** can occur as an isolated infection or with disseminated or CNS infection. It can be mistaken for bacterial or chemical conjunctivitis, but the presence of dendritic keratitis is pathognomonic.

### Diagnosis

• Testing of conjunctival material for gonorrhea, chlamydia, and, sometimes, herpes

Conjunctival material is Gram stained, cultured for gonorrhea (eg, on modified Thayer-Martin medium), and tested for chlamydia (eg, by culture, direct immunofluorescence, or enzyme-linked immunosorbent assay [samples must contain cells]). Conjunctival scrapings can also be examined with Giemsa stain; if blue intracytoplasmic inclusions are identified, chlamydial ophthalmia is confirmed. Viral culture is done only if viral infection is suspected because of skin lesions or maternal infection.

### Treatment

• Systemic, topical, or combined antimicrobial therapy

Neonates with conjunctivitis and known maternal gonococcal infection or with gram-negative intracellular diplococci identified in conjunctival exudates should be treated with ceftriaxone before results of confirmatory tests are available.

In chlamydial ophthalmia, systemic therapy is the treatment of choice, because at least half of affected neonates also have nasopharyngeal infection and some develop chlamydial pneumonia. Erythromycin ethylsuccinate 10 mg/kg po q 6 h for 2 wk is recommended. Efficacy of this therapy is only 80%, so a 2nd treatment course may be needed. Because use of erythromycin in neonates is associated with the development of hypertrophic pyloric stenosis (HPS—see p. 2800), all neonates treated with erythromycin should be monitored for symptoms and signs of HPS.

A neonate with gonorrheal ophthalmia is hospitalized to be evaluated for possible systemic gonococcal infection and given a single dose of ceftriaxone 25 to 50 mg/kg IM to a maximum dose of 125 mg (infants with hyperbilirubinemia or those receiving Ca-containing fluids may be given cefotaxime 100 mg/kg IV or IM). Frequent saline irrigation of the eye prevents secretions from adhering. Topical antimicrobial ointments alone are ineffective.

Conjunctivitis due to other bacteria usually responds to topical ointments containing polymyxin plus bacitracin, erythromycin, or tetracycline.

Herpetic keratoconjunctivitis should be treated (with an ophthalmologist's consultation) with systemic acyclovir 20 mg/kg q 8 h for 14 to 21 days and topical 1% trifluridine ophthalmic drops or ointment, vidarabine 3% ointment, or 0.1% iododeoxyuridine q 2 to 3 h, with a maximum of 9 doses/24 h. Systemic therapy is important, because dissemination to the CNS and other organs can occur.

Corticosteroid-containing ointments may seriously exacerbate eye infections due to *C. trachomatis*, and herpes simplex virus and should be avoided.

#### Prevention

Routine use of 1% silver nitrate drops, 0.5% erythromycin, or 1% tetracycline ophthalmic ointments or drops instilled into each eye after delivery effectively prevents gonorrheal ophthalmia. However, none of these agents prevents chlamydial ophthalmia; povidone iodine 2.5% drops may be effective against chlamydia and is effective against gonococci but is not available in the US. Silver nitrate and tetracycline ophthalmic ointments are also no longer available in the US.

Neonates of mothers with untreated gonorrhea should receive a single injection of ceftriaxone 25 to 50 mg/kg IM or IV, up to 125 mg, and both mother and neonate should be screened for chlamydia infection, HIV, and syphilis.

### Neonatal Hepatitis B Virus Infection

(See also Ch. 28.)

**Neonatal hepatitis B virus (HBV) infection is usually acquired during delivery. It is usually asymptomatic but can cause chronic subclinical disease. Symptomatic infection causes jaundice, lethargy, failure to thrive, abdominal distention, and clay-colored stools. Diagnosis is by serology. Rarely, severe illness may cause acute liver failure requiring liver transplantation. Less severe illness is treated supportively. Active and passive immunization help prevent vertical transmission.**

Of the recognized forms of primary viral hepatitis, only HBV is a major cause of neonatal hepatitis. Infection with other viruses (eg, cytomegalovirus, herpes simplex virus) may cause liver inflammation along with other manifestations.

#### Etiology

HBV infection occurs during delivery from an infected mother. Maternal acute hepatitis B occurring within 2 to 3 mo of delivery has about a 70% risk of transmission, but disease occurring during the 1st or 2nd trimester has only about a 5% risk. Risk of transmission is also high from asymptomatic hepatitis B surface antigen (HBsAg) carriers with the e antigen (HBe—see p. 251). Carriers without the e antigen or with anti-HBe are less likely to transmit the disease.

Mother-infant HBV transmission results primarily from maternofetal microtransfusions during labor or contact with infectious secretions in the birth canal. Transplacental transmission is unusual. Postpartum transmission occurs rarely through exposure to infectious maternal blood, saliva, stool, urine, or breast milk. Neonatal HBV infection may be an important viral reservoir in certain communities.

**Symptoms and Signs**

Most neonates with HBV infection are asymptomatic but develop chronic, subclinical hepatitis characterized by persistent HBsAg antigenemia and variably elevated transaminase activity. Many neonates born to women with acute hepatitis B during pregnancy are of low birth weight, regardless of whether they are infected.

Infrequently, infected neonates develop acute hepatitis B, which is usually mild and self-limited. They develop jaundice, lethargy, failure to thrive, abdominal distention, and clay-colored stools. Occasionally, severe infection with hepatomegaly, ascites, and hyperbilirubinemia (primarily conjugated bilirubin) occurs. Rarely, the disease is fulminant and even fatal. Fulminant disease occurs more often in neonates whose mothers are chronic carriers of hepatitis B.

**Diagnosis**

Diagnosis is by serologic testing (discussed on p. 251).

**Prognosis**

Long-term prognosis is unknown, although HBsAg carriage early in life seems to increase the risk of subsequent liver disease (eg, chronic hepatitis, cirrhosis, hepatocellular carcinoma).

**Treatment**

• Supportive care

Symptomatic care and adequate nutrition are needed. Neither corticosteroids nor hepatitis B immune globulin (HBIG) is valuable. No therapy prevents the development of chronic, subclinical hepatitis once infection is acquired. Because of the risk of developing significant disease, liver function should be monitored periodically.

**Prevention**

Pregnant women should be tested for HBsAg during an early prenatal visit. Failing that, they should be tested when admitted for delivery. Some women who are HBsAg-positive are treated with lamivudine during the 3rd trimester, which may prevent perinatal transmission of hepatitis B.

Neonates whose mothers are HBsAg- positive should be given 1 dose of HBIG 0.5mL IM within 12 h of birth. Recombinant hepatitis B virus vaccine should be given IM in a series of 3 doses. (NOTE: Doses vary among proprietary vaccines.) The first dose is given concurrently with HBIG but at a different site. The 2nd dose is given at 1 to 2 mo, and the 3rd dose is given 6 mo after the first. If the infant weighs < 2 kg, the first dose of vaccine may be less effective. Subsequent vaccine doses are given at age 30 days (or when discharged from the hospital), and then 2 other doses are given at 1 to 2 mo and 6 mo after the 30-day dose. Testing for HBsAg and anti-HBs at 9 to 15 mo is recommended.

Particularly where hepatitis B infection is highly endemic or HBsAg screening of mothers is impractical, all neonates should be vaccinated.

Separating a neonate from its HBsAg-positive mother is not recommended, and breastfeeding does not seem to increase the risk of postpartum HBV transmission, particularly if HBIG and hepatitis B virus vaccine have been given. However, if a mother has cracked nipples, abscesses, or other breast pathology, breast-feeding could potentially transmit HBV.

## Neonatal Herpes Simplex Virus Infection

(See also Herpes Simplex Virus Infections on p. 1417.)

**Neonatal herpes simplex virus (HSV) infection is usually transmitted during delivery. Signs are typically a vesicular eruption and subsequent disseminated disease. Diagnosis is by viral culture, PCR, immunofluorescence, or electron microscopy. Treatment is with high-dose parenteral acyclovir and supportive care.**

Neonatal HSV infection has high mortality and significant morbidity. Incidence estimates range from 1/3,000 to 1/20,000 births. HSV type 2 causes more cases than HSV type 1.

HSV is usually transmitted during delivery through an infected maternal genital tract. Transplacental transmission of virus and hospital-acquired spread from one neonate to another by hospital personnel or family may account for some cases. Mothers of neonates with HSV infection tend to have newly acquired genital infection, but many have not yet developed symptoms at the time of delivery.

### Symptoms and Signs

Manifestations generally occur between the 1st and 2nd wk of life but may not appear until as late as the 4th wk. Patients may present with local or disseminated disease. Skin vesicles are common with either type, occurring in about 55% overall. Those with no skin vesicles usually present with localized CNS disease. In patients with isolated skin or mucosal disease, progressive or more serious forms of disease frequently follow within 7 to 10 days if left untreated.

**Localized disease:** Neonates with localized disease can be divided into 2 groups. One group has encephalitis manifested by neurologic findings, CSF pleocytosis, and elevated protein concentration, with or without concomitant involvement of the skin, eyes, and mouth. The other group has only skin, eye, and mouth involvement and no evidence of CNS or organ disease.

**Disseminated disease:** Neonates with disseminated disease and visceral organ involvement have hepatitis, pneumonitis, disseminated intravascular coagulation, or a combination, with or without encephalitis or skin disease.

Other signs, which can occur singly or in combination, include temperature instability, lethargy, hypotonia, respiratory distress, apnea, and seizures.

### Diagnosis

• HSV culture or PCR

• Sometimes immunofluorescent testing of lesions or electron microscopy

Rapid diagnosis by viral culture or HSV PCR is essential. The most common site of retrieval is skin vesicles. The mouth, eyes, and CSF are also high-yield sites. In some neonates with encephalitis, virus is present only in the brain. Diagnosis also can be made by immunofluorescence of lesion scrapings, particularly with use of monoclonal antibodies; and electron microscopy. If no diagnostic virology facilities are available, a Tzanck test of the lesion base may show characteristic multinucleated giant cells and intranuclear inclusions, but this test is less sensitive than culture, and false-positives also occur.

### Prognosis

The mortality rate of untreated disseminated disease is 85%; among those with untreated encephalitis, it is about 50%. Without treatment, at least 65% of survivors have severe neurologic sequelae.

Death is uncommon in neonates with local disease limited to the skin, eyes, or mouth. However, without treatment, many of these neonates will progress to disseminated disease or CNS disease that may be unrecognized; about 30% develop neurologic impairment, which may not manifest until 2 to 3 yr of age.

**Treatment**

• Parenteral and topical acyclovir

• Supportive therapy

Acyclovir decreases the mortality rate in CNS and disseminated disease by 50% and increases the percentage of children who develop normally from about 35% to 50 to 80%; the dose is 20 mg/kg IV q 8 h for 21 days. Vigorous supportive therapy is required, including appropriate IV fluids, alimentation, respiratory support, correction of clotting abnormalities, and control of seizure disorders.

For localized disease (skin or mouth), treatment is acyclovir 20 mg/kg IV q 8 h for 14 days. Herpetic keratoconjunctivitis requires concomitant systemic acyclovir for 14 days and topical therapy with a drug such as trifluridine, iododeoxyuridine, or vidarabine (see p. 2825).

**Prevention**

Efforts to prevent neonatal transmission have not been very effective. Universal screening has not been recommended or shown to be effective, and most maternal infections with risk of transmission are asymptomatic. However, cesarean delivery for women known to have a high risk of transmission (eg, active genital lesions present at term) has been shown to decrease transmission and is recommended. Also, fetal scalp monitors should not be used during labor on infants whose mothers have suspected active genital herpes.

## Neonatal Hospital-Acquired Infection

Some infections are acquired after admission to the nursery rather than from the mother in utero or intrapartum. For some infections (eg, group B streptococci, herpes simplex virus [HSV]) it may not be clear whether the source is maternal or the hospital environment.

Hospital-acquired infection is primarily a problem for premature infants and for term infants with medical disorders requiring prolonged hospitalization. Healthy, term neonates have infection rates < 1%. For those in special care nurseries, the incidence increases as birth weight decreases. The most common infections, sepsis and pneumonia, have a combined rate of 6.2 cases per 1000 catheter or ventilator days for infants weighing 1501 to 2500 g, 8.9 cases for those weighing 1001 to 1500 g, and 13.9 cases for those weighing ≤ 1000 g.

Overall mortality rates are about 33%; for neonates whose birth weight is < 1000 g, the mortality rate is 16 to 45%, and for those whose birth weight is > 2000 g, the mortality rate is 2 to 12%.

**Etiology**

In **term neonates**, skin infection due to *Staphylococcus aureus* (both methicillin sensitive and methicillin resistant) is the most frequent hospital-acquired infection. Although nursery personnel who are *S. aureus* nasal carriers are potential sources of infection, colonized neonates are usually the reservoir. The umbilical stump and groin are most frequently colonized during the first few days of life, whereas the nares are more frequently colonized later. Often, infections do not manifest until the neonate is at home.

In **very-low-birth-weight** (VLBW; < 1500 g) infants, gram-positive organisms cause about 70% of infections, the majority being with coagulase-negative staphylococci. Gram-negative organisms, including *Escherichia coli, Klebsiella, Pseudomonas, Enterobacter*, and *Serratia*, cause about 18%. Fungi

(*Candida albicans* and *C. parapsilosis*) cause about 12%. Patterns of infection (and antibiotic resistance) vary among institutions and units and change with time. Intermittent "epidemics" sometimes occur as a particularly virulent organism colonizes a unit.

Infection is facilitated by the multiple invasive procedures VLBW infants undergo (eg, long-term arterial and venous catheterization, endotracheal intubation, continuous positive airway pressure, NGTs or nasojejunal feeding tubes). The longer the stay in special care nurseries and the more procedures done, the higher is the likelihood of infection.

**Prevention**

Bathing neonates with 3% hexachlorophene decreases frequency of *S. aureus* colonization, but this product can cause neurotoxicity, particularly in low-birth-weight infants, and is no longer used. The American Academy of Pediatrics recommends dry umbilical cord care, but this care may result in high rates of colonization with *S. aureus*, and epidemics have occurred in some hospitals. During disease outbreaks, application of triple dye to the cord area or bacitracin or mupirocin ointment to the cord, nares, and circumcision site reduces colonization. Routine cultures of personnel or of the environment are not recommended.

Prevention of colonization and infection in special care nurseries requires provision of sufficient space and personnel. In intensive care, 150 sq ft (about 14 sq m)/infant and 8 ft (about 2.4 m) between incubators or warmers, edge-to-edge in each direction, and a nurse:patient ratio of 1:1 to 1:2 are required. In intermediate care, 120 sq ft (about 11.2 sq m)/infant and 4 ft (about 1.2 m) between incubators or warmers, edge-to-edge in each direction, and a nurse:patient ratio of 1:3 to 1:4 are required. Proper techniques are required, including placement and care of invasive devices and meticulous cleaning and disinfection or sterilization of equipment. Active surveillance for infection (not colonization) and monitoring of techniques are essential.

Other preventive measures include frequent hand washing and wearing gowns and gloves. Washing with alcohol preparations is more effective than soap and water in decreasing bacterial colony counts on hands but does not eliminate *Clostridium difficile* spores. Incubators provide limited protective isolation; the exteriors and interiors of the units rapidly become heavily contaminated, and personnel are likely to contaminate their hands and forearms. Universal blood and body fluid precautions add further protection.

In an epidemic, establishing a cohort of diseased or colonized infants and assigning them a separate nursing staff are useful. Continuing surveillance for 1 mo after discharge is necessary to assess the adequacy of controls instituted to end an epidemic.

Prophylactic antimicrobial therapy is generally not effective, hastens development of resistant bacteria, and alters the balance of normal flora in the neonate. However, during a confirmed nursery epidemic, antibiotics against specific pathogens may be considered—eg, penicillin G for prophylaxis against group A streptococcal infection or oral colistin or neomycin for prophylaxis against enterotoxigenic or enteropathogenic *E. coli*.

Vaccination according to the routine schedule (see Table 268-10 on p. 2718) should be given to any infant who is in the hospital at that time.

## Neonatal Listeriosis

(See also Listeriosis on p. 1242.)

**Neonatal listeriosis is acquired transplacentally or during or after delivery. Symptoms are those of sepsis. Diagnosis is by culture of mother and infant. Treatment is antibiotics, initially ampicillin plus an aminoglycoside.**

Transplacental infection with *Listeria monocytogenes* can result in fetal dissemination with granuloma formation (eg, in the skin, liver, adrenal glands, lymphatic tissue, lungs, and brain). If a rash is present, it is referred to as granulomatosis infantisepticum. Aspiration or swallowing of amniotic fluid or vaginal

secretions can lead to perinatal infection of the lungs, manifesting in the first several days of life with respiratory distress, shock, and a fulminant course.

### Symptoms and Signs

Infections in pregnant women may be asymptomatic or characterized by a primary bacteremia manifesting first as a nonspecific flu-like illness.

In the fetus and neonate, clinical presentation depends on the timing and route of infection. Abortion, premature delivery with amnionitis (with a characteristic brown, murky amniotic fluid), stillbirth, or neonatal sepsis is common. Infection may be apparent within hours or days of birth (early onset) or it may be delayed up to several weeks. Neonates with early-onset disease frequently are of low birth weight, have associated obstetric complications, and show evidence of sepsis with circulatory or respiratory insufficiency or both. Those with the delayed-onset form are full-term, previously healthy neonates presenting with meningitis or sepsis.

### Diagnosis

• Culture of blood and cervix of febrile pregnant woman

• Culture of blood, CSF, gastric aspirate, and meconium of sick neonate

Blood and cervix specimens should be obtained from any pregnant woman with an unexplained febrile disease and cultured for *L. monocytogenes*. A sick neonate whose mother has listeriosis should be evaluated for sepsis (see p. 2832), including cultures of umbilical cord or peripheral blood; the CSF, gastric aspirate, and meconium; the mother's lochia and exudates from cervix and vagina; and grossly diseased parts of the placenta. CSF examination may show a predominance of mononuclear cells. Gram-stained smears frequently are negative but may show pleomorphic, gram-variable coccobacillary forms, which should not be disregarded as diphtheroid contaminants. Laboratory confirmation of the organism involves biochemical testing and observation of motility using a slide test or showing motility in semisolid media. To do the slide test, colonies of the organism that have grown on solid media are mixed with saline and examined under a microscope. *L. monocytogenes* exhibits a distinctive end-over-end "tumbling" motility due to the presence of flagella at both ends. Serologic tests are not useful.

### Prognosis

Mortality, ranging from 10 to 50%, is higher in neonates with early-onset disease.

### Treatment

• Initially ampicillin plus an aminoglycoside

Initial treatment is with ampicillin plus an aminoglycoside (see also p. 1198). After clinical response is observed, the aminoglycoside is stopped. A 14-day course is usually satisfactory (21 days for meningitis), but the optimal duration is unknown. Other possible drugs include ampicillin or penicillin with rifampin, trimethoprim/sulfamethoxazole, and imipenem, but they have not been well evaluated.

Neonates with sepsis require other measures (see p. 2836). In heavy infection, drainage/secretion precautions may be considered.

### Prevention

Food products that may be contaminated by *L. monocytogenes* (eg, unpasteurized dairy products or raw vegetables exposed to cattle or sheep manure) should be avoided by pregnant women. If infection during pregnancy is recognized, treatment may then be given before delivery or intrapartum to prevent vertical transmission, but the usefulness of such treatment is unproved.

## Neonatal Bacterial Meningitis

(See also Ch. 180.)

**Neonatal bacterial meningitis is inflammation of the meninges due to bacterial invasion. Signs are those of sepsis, CNS irritation (eg, lethargy, seizures, vomiting, irritability [particularly paradoxical irritability], nuchal rigidity, a bulging or full fontanelle), and cranial nerve abnormalities. Diagnosis is by lumbar puncture. Treatment is with antibiotics.**

Neonatal bacterial meningitis occurs in 2/10,000 full-term and 2/1,000 low-birth-weight (LBW) neonates, with a male predominance. It occurs in about 15% of neonates with sepsis and occasionally occurs in isolation.

### Etiology

The predominant pathogens are

• Group B streptococcus (GBS—predominantly type III)

• *Escherichia coli* (particularly those strains containing the K1 polysaccharide)

• *Listeria monocytogenes*

Enterococci, nonenterococcal group D streptococci, α-hemolytic streptococci, and other gram-negative enteric organisms (eg, *Klebsiella* sp, *Enterobacter* sp, *Citrobacter diversus*) also are common pathogens. *Haemophilus influenzae* type b, *Neisseria meningitidis*, and *Streptococcus pneumoniae* have been reported as causes.

Neonatal bacterial meningitis most frequently results from the bacteremia that occurs with neonatal sepsis; the higher the colony count in the blood culture, the higher the risk of meningitis. Neonatal bacterial meningitis may also result from scalp lesions, particularly when developmental defects lead to communication between the skin surface and the subarachnoid space, which predisposes to thrombophlebitis of the diploic veins. Rarely, there is direct extension to the CNS from a contiguous otic focus (eg, otitis media).

### Symptoms and Signs

Frequently, only those findings typical of neonatal sepsis (eg, temperature instability, respiratory distress, jaundice, apnea) are manifest. CNS signs (eg, lethargy, seizures [particularly focal], vomiting, irritability) more specifically suggest neonatal bacterial meningitis. So-called paradoxical irritability, in which cuddling and consoling by a parent irritates rather than comforts the neonate, is more specific for the diagnosis. A bulging or full fontanelle occurs in about 25% and nuchal rigidity in only 15%. The younger the patient, the less common are these findings. Cranial nerve abnormalities (particularly those involving the 3rd, 6th, and 7th nerves) may also be present.

Meningitis due to GBS may occur in the first week of life, accompanying early-onset neonatal sepsis and frequently manifesting initially as a systemic illness with prominent respiratory signs. Usually, however, GBS meningitis occurs after this period (most commonly in the first 3 mo of life) as an isolated illness characterized by absence of antecedent obstetric or perinatal complications and the presence of more specific signs of meningitis (eg, fever, lethargy, seizures).

Ventriculitis frequently accompanies neonatal bacterial meningitis, particularly when caused by gram-negative enteric bacilli. Organisms that cause meningitis together with severe vasculitis, particularly *C. diversus* and *Enterobacter sakazakii* , are likely to cause cysts and abscesses. *Pseudomonas aeruginosa*, *E. coli* K1, and *Serratia* sp also may cause brain abscesses. An early clinical sign of brain abscess is increased intracranial pressure (ICP), commonly manifested by vomiting, a bulging fontanelle, and sometimes enlarging head size. Deterioration in an otherwise stable neonate with meningitis suggests progressive increased ICP caused by abscess or hydrocephalus, or rupture of an abscess into

the ventricular system.

**Diagnosis**

• CSF glucose and protein levels, Gram stain, and culture

• Sometimes brain CT or MRI

Definitive diagnosis is made by CSF examination via lumbar puncture (LP), which should be done in any neonate suspected of having sepsis or meningitis. However, LP can be difficult to do in a neonate, and there is some risk of hypoxia. Poor clinical condition (eg, respiratory distress, shock, thrombocytopenia) makes LP risky. If LP is delayed, the neonate should be treated as though meningitis is present. Even when the clinical condition improves, the presence of inflammatory cells and abnormal electrolytes in CSF days after illness onset can still suggest the diagnosis. A needle with a trocar should be used for LP to avoid introducing epithelial rests and subsequent development of epitheliomas. The CSF, even if bloody or acellular, should be cultured. About 15 to 30% of neonates with negative blood cultures have positive CSF cultures depending on the population studied. LP should be repeated at 24 to 48 h if clinical response is questionable and at 72 h when gram-negative organisms are involved (to ensure sterilization). Repeating the CSF analysis helps guide duration of therapy and predict prognosis. Some experts believe that a repeat LP at 24 h in neonates with GBS meningitis has prognostic value. LP should not be repeated at the end of therapy if the neonate is doing well.

Normal CSF values are controversial and in part age-related. In general, both term infants and preterm infants without meningitis have ≤ 20 WBCs/µL (one fifth of which may be PMNs) in their CSF. CSF protein levels in the absence of meningitis are more variable; term infants have levels of < 100 mg/dL, whereas preterm infants have levels up to 150 mg/dL. CSF glucose levels in the absence of meningitis are > 75% of the serum value measured at the same time. These levels may be as low as 20 to 30 mg/dL (1.1 to 1.7 mmol/L).

Ventriculitis is suspected in a neonate not responding appropriately to antimicrobial therapy. The diagnosis is made when a ventricular puncture yields a WBC count greater than that from the LP, by a positive Gram stain or culture, or by increased ventricular pressure. When ventriculitis or brain abscess is suspected, an MRI or CT with contrast may aid diagnosis; dilated ventricles also confirm ventriculitis.

**Prognosis**

Without treatment, the mortality rate for neonatal bacterial meningitis approaches 100%. With treatment, prognosis is determined by birth weight, organism, and clinical severity. Mortality rate for gram-negative neonatal bacterial meningitis is 15 to 20%, and for gram-positive (eg, GBS) meningitis it is 6 to 10%. For organisms that cause vasculitis or brain abscess (necrotizing meningitis), the mortality rate may approach 75%. Neurologic sequelae (eg, hydrocephalus, hearing loss, intellectual disability) develop in 20 to 50% of infants who survive, with a poorer prognosis when gram-negative enteric bacilli are the cause.

Prognosis also depends partly on the number of organisms present in CSF at diagnosis. The duration of positive CSF cultures correlates directly with the incidence of complications. In general, CSF cultures from neonates with GBS are usually sterilized within the first 24 h of antimicrobial therapy. Those from gram-negative bacillary meningitis remain positive longer, with a median of 2 days.

GBS meningitis has a mortality rate significantly lower than that of early-onset GBS sepsis.

**Treatment**

• Empiric ampicillin plus gentamicin, cefotaxime, or both, followed by culture-specific drugs

**Empiric antibiotic therapy:** Initial empiric treatment depends on patient age and is still debated. Most experts recommend ampicillin plus an aminoglycoside, a 3rd-generation cephalosporin (eg, cefotaxime), or both. Ampicillin is active against organisms such as GBS, enterococci, and *Listeria*. Gentamicin provides synergy and added efficacy against these organisms and adequate gram-negative coverage.

Cephalosporins provide adequate gram-negative coverage but do not provide synergy with ampicillin for gram-positive organisms and may allow for some resistant organisms. Hospitalized neonates who previously received antibiotics (eg, for early-onset sepsis) may have resistant organisms; fungal disease may also be considered in a septic-appearing neonate after prolonged hospitalization. Ill neonates with hospital-acquired infection should initially receive vancomycin plus an aminoglycoside with or without a 3rd-generation cephalosporin. Antibiotics are adjusted when results of CSF culture and sensitivities are known. The results of the Gram stain should not change antibiotic therapy.

**Organism-specific antibiotic therapy:** The recommended initial treatment for GBS meningitis in neonates < 1 wk of age is penicillin G 100,000 to 150,000 units/kg IV q 8 h or ampicillin 100 mg/kg IV q 8 h, plus gentamicin 4 mg/kg IV once/day if the infant is 32 to 35 wk gestational age or 5 mg/kg IV once/day if the infant is > 35 wk gestational age. If clinical improvement occurs or sterilization of CSF is documented, gentamicin can be stopped.

For enterococci or *L. monocytogenes*, treatment is generally ampicillin plus gentamicin.

In gram-negative bacillary meningitis, treatment is difficult. The traditional regimen of ampicillin plus an aminoglycoside results in a 15 to 20% mortality rate, with a high rate of sequelae in survivors. A 3rd-generation cephalosporin (eg, cefotaxime) should be strongly considered in neonates with *proven* gram-negative meningitis (or sepsis) or those *convincingly* septic. If antibiotic resistance is a concern, both an aminoglycoside and a 3rd-generation cephalosporin may be used until sensitivities are known. However, except for initial empiric therapy, 3rd-generation cephalosporins are generally not used routinely, because certain gram-negative organisms are induced to produce β-lactamase, resulting in rapid development of resistance.

Parenteral therapy for gram-positive meningitis is given for a minimum of 14 days, and for complicated gram-positive or gram-negative meningitis, a minimum of 21 days.

**Adjunctive measures:** Because meningitis may be considered part of the continuum of neonatal sepsis, the adjunctive measures used in treating neonatal sepsis (see p. 2836) should also be used to treat neonatal meningitis. Corticosteroids are not used in treatment of neonatal meningitis. Patients should be closely monitored for neurologic complications during the first 2 yr of life.

## Neonatal Pneumonia

**Neonatal pneumonia is lung infection in a neonate. Onset may be within hours of birth and part of a generalized sepsis syndrome or after 7 days and confined to the lungs. Signs may be limited to respiratory distress or progress to shock and death. Diagnosis is by clinical and laboratory evaluation for sepsis. Treatment is initial broad-spectrum antibiotics changed to organism-specific drugs as soon as possible.**

Pneumonia is the most common invasive bacterial infection after primary sepsis. Early-onset pneumonia is part of generalized sepsis that first manifests at or within hours of birth. Late-onset pneumonia usually occurs after 7 days of age, most commonly in neonatal ICUs among infants who require prolonged endotracheal intubation because of lung disease.

### Etiology

Organisms are acquired from the maternal genital tract or the nursery. These organisms include gram-positive cocci (eg, groups A and B streptococci, *Staphylococcus aureus*) and gram-negative bacilli (eg, *Escherichia coli, Klebsiella* sp, *Proteus* sp). Methicillin-resistant *S. aureus* is common in late-onset hospital-acquired pneumonia. In infants who have received broad-spectrum antibiotics, many other pathogens may be found, including *Pseudomonas, Citrobacter, Bacillus*, and *Serratia*. Viruses or fungi cause some cases.

### Symptoms and Signs

Late-onset hospital-acquired pneumonia may begin gradually, with more secretions being suctioned from

the endotracheal tube and higher ventilator settings. Other infants may be acutely ill, with temperature instability and neutropenia. New infiltrates may be visible on chest x-ray but may be difficult to recognize if the infant has severe bronchopulmonary dysplasia.

### Diagnosis

Evaluation includes cultures of blood and tracheal aspirate, chest x-ray, and pulse oximetry. Because bacterial pneumonia in neonates may disseminate, a full evaluation for sepsis, including a lumbar puncture, should also be done.

### Treatment

• Usually vancomycin and cefotaxime

Antimicrobial therapy in early-onset disease is similar to that for neonatal sepsis. Vancomycin and cefotaxime are the initial treatment of choice for most late-onset hospital-acquired pneumonia. This regimen treats sepsis as well as pneumonia. More specific antibiotics are substituted after sensitivity results are available. General treatment is the same as that for neonatal sepsis (see p. 2836).

### Chlamydial Pneumonia

Contamination with chlamydial organisms during delivery may result in development of chlamydial pneumonia at 2 to 12 wk. Infants are tachypneic but usually not critically ill and may also have a history of conjunctivitis caused by the same organism. Eosinophilia may be present, and x-rays show bilateral interstitial infiltrates. Treatment with erythromycin leads to rapid resolution. The diagnosis of pneumonia secondary to *Chlamydia trachomatis* should prompt an evaluation of the mother and her partner because untreated maternal chlamydial infection may have complications such as pelvic inflammatory disease and sterility.

## Neonatal Sepsis

(Sepsis Neonatorum)

(See also Ch. 227.)

**Neonatal sepsis is invasive infection, usually bacterial, occurring during the neonatal period. Signs are multiple and include diminished spontaneous activity, less vigorous sucking, apnea, bradycardia, temperature instability, respiratory distress, vomiting, diarrhea, abdominal distention, jitteriness, seizures, and jaundice. Diagnosis is clinical and based on culture results. Treatment is initially with ampicillin plus either gentamicin or cefotaxime, narrowed to organism-specific drugs as soon as possible.**

Neonatal sepsis occurs in 0.5 to 8.0/1000 births. The highest rates occur in low-birth-weight (LBW) infants, those with depressed respiratory function at birth, those with maternal perinatal risk factors, males, and those with congenital anomalies.

### Etiology

Neonatal sepsis can be early onset (within 7 days of birth) or late onset (after 7 days).

**Early onset:** Early-onset sepsis usually results from organisms acquired intrapartum. Most infants have symptoms within 6 h of birth, and almost all cases occur within 72 h.

Group B streptococcus (GBS) and gram-negative enteric organisms (predominantly *Escherichia coli*) account for most cases of early-onset sepsis. Vaginal or rectal cultures of women at term may show GBS colonization rates of up to 30%. At least 35% of their infants also become colonized. The density of infant colonization determines the risk of early-onset invasive disease, which is 40 times higher with heavy colonization. Although only 1/100 of infants colonized develop invasive disease due to GBS, > 50% of

those present within the first 6 h of life. Nontypeable *Haemophilus influenzae* sepsis has been increasingly identified in neonates, especially premature neonates.

Other gram-negative enteric bacilli (eg, *Klebsiella* sp) and gram-positive organisms—*Listeria monocytogenes*, enterococci (eg, *Enterococcus faecalis, Enterococcus faecium)*, group D streptococci (eg, *Streptococcus bovis*), α-hemolytic streptococci, and staphylococci—account for most other cases. *Streptococcus pneumoniae*, *H. influenzae* type b, and, less commonly, *Neisseria meningitidis* have been isolated. Asymptomatic gonorrhea occurs occasionally in pregnancy, so *Neisseria gonorrhoeae* may be a pathogen.

**Late onset:** Late-onset sepsis is usually acquired from the environment (see also Neonatal Hospital-Acquired Infection on p. 2828). Staphylococci account for 30 to 60% of late-onset cases and are most frequently due to intravascular devices (particularly umbilical artery or vein catheters). *E. coli* is also becoming increasingly recognized as a significant cause of late-onset sepsis, especially in very LBW infants. Isolation of *Enterobacter cloacae* or *E. sakazakii* from blood or CSF suggests contaminated feedings. Contaminated respiratory equipment is suspected in outbreaks of hospital-acquired *Pseudomonas aeruginosa* pneumonia or sepsis. Although universal screening and intrapartum antibiotic prophylaxis for GBS have significantly decreased the rate of early-onset disease due to this organism, the rate of late-onset GBS sepsis has remained unchanged, which is consistent with the hypothesis that late-onset disease is usually acquired from the environment.

The role of anaerobes (particularly *Bacteroides fragilis*) in late-onset sepsis remains unclear, although deaths have been attributed to *Bacteroides* bacteremia. Anaerobes may account for some culture-negative cases in which autopsy findings indicate sepsis.

*Candida* sp are increasingly important causes of late-onset sepsis, occurring in 12 to 13% of very LBW infants.

**Early and late onset:** Certain viral infections (eg, disseminated herpes simplex, enterovirus, adenovirus, respiratory syncytial virus) may manifest as early-onset or late-onset sepsis.

**Pathophysiology**

**Early onset:** Certain maternal perinatal and obstetric factors increase risk, particularly of early-onset sepsis, such as the following:

- Premature rupture of membranes (PROM—see p. 2682) occurring ≥ 18 h before birth
- Maternal bleeding (eg, placenta previa, abruptio placentae)
- Preeclampsia
- Precipitous delivery
- Maternal infection (particularly of the urinary tract or endometrium, most commonly manifests as maternal fever shortly before or during delivery)
- Heavy colonization with GBS
- Preterm delivery

Hematogenous and transplacental dissemination of maternal infection occurs in the transmission of certain viral (eg, rubella, cytomegalovirus), protozoal (eg, *Toxoplasma gondii*), and treponemal (eg, *Treponema pallidum*) pathogens. A few bacterial pathogens (eg, *L. monocytogenes, Mycobacterium tuberculosis*) may reach the fetus transplacentally, but most are acquired by the ascending route in utero or as the fetus passes through the colonized birth canal.

Though the intensity of maternal colonization is directly related to risk of invasive disease in the neonate, many mothers with low-density colonization give birth to infants with high-density colonization who are therefore at risk. Amniotic fluid contaminated with meconium or vernix caseosa promotes growth of GBS and *E. coli*. Hence, the few organisms in the vaginal vault are able to proliferate rapidly after PROM, possibly contributing to this paradox. Organisms usually reach the bloodstream by fetal aspiration or swallowing of contaminated amniotic fluid, leading to bacteremia. The ascending route of infection helps to explain such phenomena as the high incidence of PROM in neonatal infections, the significance of adnexal inflammation (amnionitis is more commonly associated with neonatal sepsis than is central placentitis), the increased risk of infection in the twin closer to the birth canal, and the bacteriologic characteristics of neonatal sepsis, which reflect the flora of the maternal vaginal vault.

**Late onset:** The most important risk factor in late-onset sepsis is preterm delivery. Others include

• Prolonged use of intravascular catheters

• Associated illnesses (which may, however, be only a marker for the use of invasive procedures)

• Exposure to antibiotics (which selects resistant bacterial strains)

• Prolonged hospitalization

• Contaminated equipment or IV or enteral solutions

Gram-positive organisms (eg, coagulase-negative staphylococci and *Staphylococcus aureus*) may be introduced from the environment or the patient's skin. Gram-negative enteric bacteria are usually derived from the patient's endogenous flora, which may have been altered by antecedent antibiotic therapy or populated by resistant organisms transferred from the hands of personnel (the major means of spread) or contaminated equipment. Therefore, situations that increase exposure to these bacteria (eg, crowding, inadequate nurse staffing or provider hand washing) result in higher rates of hospital-acquired infection. Risk factors for *Candida* sp sepsis include prolonged (> 10 days) use of central IV catheters, hyperalimentation, use of antecedent antibiotics, necrotizing enterocolitis or other abdominal pathology, and previous surgery.

Initial foci of infection can be in the urinary tract, paranasal sinuses, middle ear, lungs, or GI tract, and may later disseminate to meninges, kidneys, bones, joints, peritoneum, and skin.

**Symptoms and Signs**

Early signs are frequently nonspecific and subtle and do not distinguish among organisms (including viral). Particularly common early signs include

• Diminished spontaneous activity

• Less vigorous sucking

• Apnea

• Bradycardia

• Temperature instability (hypothermia or hyperthermia)

Fever is present in only 10 to 15% but, when sustained (eg, > 1 h), generally indicates infection. Other symptoms and signs include respiratory distress, neurologic findings (eg, seizures, jitteriness), jaundice (especially occurring within the first 24 h without Rh or ABO blood group incompatibility and with a higher than expected direct bilirubin concentration), vomiting, diarrhea, and abdominal distention. Anaerobic infection is often indicated by foul-smelling amniotic fluid at birth.

Specific signs of an infected organ may pinpoint the primary site or a metastatic site.

- Most neonates with early-onset GBS (and many with *L. monocytogenes*) infection present with respiratory distress that is difficult to distinguish from respiratory distress syndrome.

- Periumbilical erythema, discharge, or bleeding without a hemorrhagic diathesis suggests omphalitis (infection prevents obliteration of the umbilical vessels).

- Coma, seizures, opisthotonos, or a bulging fontanelle suggests meningitis, encephalitis, or brain abscess.

- Decreased spontaneous movement of an extremity and swelling, warmth, erythema, or tenderness over a joint indicates osteomyelitis or pyogenic arthritis.

- Unexplained abdominal distention may indicate peritonitis or necrotizing enterocolitis (particularly when accompanied by bloody diarrhea and fecal leukocytes).

- Cutaneous vesicles, mouth ulcers, and hepatosplenomegaly (particularly with disseminated intravascular coagulation [DIC]) can identify disseminated herpes simplex.

Early-onset GBS infection may manifest as a fulminating pneumonia. Often, obstetric complications (particularly prematurity, PROM, or chorioamnionitis) have occurred. In > 50% of neonates, GBS infection manifests within 6 h of birth; 45% have an Apgar score of < 5. Meningitis may also be present but is not common. In late-onset GBS infection (at 1 to 12 wk), meningitis is often present. Late-onset GBS infection is generally not associated with perinatal risk factors or demonstrable maternal cervical colonization and may be acquired postpartum.

**Diagnosis**

- High index of suspicion

- Blood, urine, and CSF culture

Early diagnosis is important and requires awareness of risk factors (particularly in LBW neonates) and a high index of suspicion when any neonate deviates from the norm in the first few weeks of life. Neonates with suspected sepsis, and those whose mother was thought to have chorioamnionitis, should have a CBC, differential with smear, platelet count, blood culture, urine culture, and lumbar puncture (LP), if clinically feasible, as soon as possible. Those with respiratory symptoms require chest x-ray. Diagnosis is confirmed by isolation of a pathogen in culture. Other tests may have abnormal results but are not necessarily diagnostic.

For preterm neonates who appear well but whose mother received inadequate intrapartum antibiotics for GBS, the American Academy of Pediatrics recommends a limited evaluation (CBC and blood culture with at least a 48-h observation).

**CBC, differential, and smear:** The normal WBC count in neonates varies, but values < 4,000/µL or > 25,000/µL are abnormal. The absolute band count is not sensitive enough to predict sepsis, but a ratio of immature:total polymorphonuclear leukocytes of < 0.2 has a high negative predictive value. A precipitous fall in a known absolute eosinophil count and morphologic changes in neutrophils (eg, toxic granulation, Dohle bodies, intracytoplasmic vacuolization in noncitrated blood or ethylenediaminetetraacetic acid [EDTA]) suggest sepsis.

The platelet count may fall hours to days before the onset of clinical sepsis but more often remains elevated until a day or so after the neonate becomes ill. This fall is sometimes accompanied by other findings of DIC (eg, increased fibrin degradation products, decreased fibrinogen, prolonged INR).

Because of the large numbers of circulating bacteria, organisms can sometimes be seen in or associated with PMNs by applying Gram stain, methylene blue, or acridine orange to the buffy coat.

Regardless of the results of the CBC or LP, in all neonates with suspected sepsis (eg, those who look sick or are febrile or hypothermic), antibiotics should be started after cultures (eg, blood, urine, and CSF [if possible]) are taken.

**Lumbar puncture:** There is a risk of increasing hypoxia during an LP in already hypoxemic neonates. However, LP should be done in neonates with suspected sepsis as soon as they are able to tolerate the procedure (see also p. 2830 under Neonatal Bacterial Meningitis). Supplemental $O_2$ is given before and during LP to prevent hypoxia. Because GBS pneumonia manifesting in the first day of life can be confused with respiratory distress syndrome, LP is often done routinely in neonates suspected of having these diseases.

**Blood cultures:** Umbilical vessels are frequently contaminated by organisms on the umbilical stump, especially after a number of hours, so blood cultures from umbilical lines may not be reliable. Therefore, blood for culture should be obtained by venipuncture, preferably at 2 peripheral sites, each meticulously prepared by applying an iodine-containing liquid, then applying 95% alcohol, and finally allowing the site to dry. Blood should be cultured for both aerobic and anaerobic organisms. If catheter-associated sepsis is suspected, a culture specimen should be obtained through the catheter as well as peripherally. In > 90% of positive bacterial blood cultures, growth occurs within 48 h of incubation. Because bacteremia in neonates is associated with a high density of organisms and delayed clearance, a small amount of blood (eg, ≥ 1 mL) is usually sufficient for detecting organisms. Data on capillary blood cultures are insufficient to recommend them.

*Candida* sp grow in blood cultures and on blood agar plates, but if other fungi are suspected, a fungal culture medium should be used. For species other than *Candida*, fungal blood cultures may require 4 to 5 days of incubation before becoming positive and may be negative even in obviously disseminated disease. Proof of colonization (in mouth or stool or on skin) may be helpful before culture results are available. If disseminated candidiasis is suspected, indirect ophthalmoscopy with dilation of the pupils is done to identify retinal candidal lesions. Renal ultrasonography is done to detect renal mycetoma.

**Urinalysis and culture:** Urine should be obtained by catheterization or suprapubic aspiration, not by urine collection bags. Although only culture is diagnostic, a finding of ≥ 5 WBCs/high-power field in the spun urine or any organisms in a fresh unspun gram-stained sample is presumptive evidence of a UTI. Absence of pyuria does not rule out UTI.

**Other tests for infection and inflammation:** Numerous tests are often abnormal in sepsis and have been evaluated as possible early markers. In general, however, sensitivities tend to be low until later in illness, and specificities are suboptimal.

Acute-phase reactants are proteins produced by the liver under the influence of IL-1 when inflammation is present. The most valuable of these is quantitative C-reactive protein. A concentration of 1 mg/dL (measured by nephelometry) has both a false-positive and a false-negative rate of about 10%. Elevated levels occur within a day, peak at 2 to 3 days, and fall to normal within 5 to 10 days in neonates who recover.

The ESR is often elevated in sepsis. The micro-ESR correlates well with the standard Wintrobe method but has the same high false-negative rate (especially early in the course and with DIC) and a slow return to normal, well beyond the time of clinical cure. IL-6 and other inflammatory cytokines are being investigated as markers for sepsis.

### Prognosis

The fatality rate is 2 to 4 times higher in LBW infants than in full-term infants. The overall mortality rate of early-onset sepsis is 3 to 40% (that of early-onset GBS infection is 2 to 30%) and of late-onset sepsis is 2 to 20% (that of late-onset GBS is about 2%). More recent studies have shown lower mortality rates.

Neonates who are both septic and granulocytopenic are less likely to survive, particularly if their bone marrow neutrophil storage pool (NSP) is depleted to < 7% of total nucleated cells (mortality rate, 75%). Because NSP levels may not be readily available, the peripheral blood immature:total (I:T) neutrophil ratio

can approximate bone marrow NSP levels. I:T ratios of > 0.80 correlate with NSP depletion and death; such a ratio may identify neonates who might benefit from granulocyte transfusion.

**Treatment**

• Antibiotic therapy

• Supportive therapy

Because sepsis may manifest with non-specific clinical signs and its effects may be devastating, rapid empiric antibiotic therapy is recommended (see p. 1182); drugs are later adjusted according to sensitivities and the site of infection. If bacterial cultures show no growth by 48 h (although some pathogens may require 72 h) and the neonate appears well, antibiotics are stopped.

General supportive measures, including respiratory and hemodynamic management, are combined with antibiotic treatment.

**Antimicrobials:** In early-onset sepsis, initial therapy should include ampicillin or penicillin G plus an aminoglycoside. Cefotaxime may be added to or substituted for the aminoglycoside if meningitis is suspected. If foul-smelling amniotic fluid is present at birth, therapy for anaerobes (eg, clindamycin, metronidazole) should be added. Antibiotics may be changed as soon as an organism is identified.

Previously well infants admitted from the community with presumed late-onset sepsis should also receive therapy with ampicillin plus gentamicin or ampicillin plus cefotaxime. If gram-negative meningitis is suspected, ampicillin, cefotaxime, and an aminoglycoside may be used. In late-onset hospital-acquired sepsis, initial therapy should include vancomycin (active against methicillin-resistant *S. aureus*) plus an aminoglycoside. If *P. aeruginosa* is prevalent in the nursery, ceftazidime may be used instead of an aminoglycoside. For neonates previously treated with a full 7- to 14-day aminoglycoside course who need retreatment, a different aminoglycoside or a 3rd-generation cephalosporin should be considered.

If coagulase-negative staphylococci are suspected (eg, an indwelling catheter has been in place for > 72 h) or are isolated from blood or other normally sterile fluid and considered a pathogen, initial therapy for late-onset sepsis should include vancomycin. However, if the organism is sensitive to nafcillin, cefazolin or nafcillin should replace vancomycin. Removal of the presumptive source of the organism (usually an indwelling intravascular catheter) may be necessary to cure the infection because coagulase-negative staphylococci may be protected by a biofilm (a covering that encourages adherence of organisms to the catheter).

Because *Candida* may take 2 to 3 days to grow in blood culture, initiation of amphotericin B therapy and removal of the infected catheter without positive blood or CSF cultures may be life saving.

**Other treatment:** Exchange transfusions have been used for severely ill (particularly hypotensive and metabolically acidotic) neonates. Their purported value is to increase levels of circulating immunoglobulins, decrease circulating endotoxin, increase Hb levels (with higher 2,3-diphosphoglycerate levels), and improve perfusion. However, no controlled prospective studies of their use have been conducted.

Fresh frozen plasma may help reverse the heat-stable and heat-labile opsonin deficiencies that occur in LBW neonates, but controlled studies of its use are unavailable, and transfusion-associated risks must be considered.

Granulocyte transfusions (see p. 1039) have been used in septic and granulocytopenic neonates but have not convincingly improved outcome.

Recombinant colony-stimulating factors (granulocyte colony-stimulating factor [G-CSF]

[
**Fig. 279-1.** Indications for intrapartum antibiotic prophylaxis to prevent perinatal group B streptococcal

disease.]

and granulocyte-macrophage colony-stimulating factor [GM-CSF]) have increased neutrophil number and function in neonates with presumed sepsis but do not seem to be of routine benefit in neonates with severe neutropenia; further study is required.

### Prevention

IV immune globulin given at birth may prevent sepsis in certain high-risk LBW infants but does not help in established infection.

Because invasive disease due to GBS often manifests within the first 6 h of life, women who have previously given birth to an infant with GBS disease should receive intrapartum antibiotics, and women who have symptomatic or asymptomatic GBS bacteriuria during pregnancy should receive antibiotics at the time of diagnosis and intrapartum (see Fig. 279-1).

## Perinatal Tuberculosis

(See also Tuberculosis on p. 1302.)

**Tuberculosis (TB) can be acquired during the perinatal period. Symptoms and signs are nonspecific. Diagnosis is by culture and sometimes x-ray and biopsy. Treatment is with isoniazid and other antituberculous drugs.**

Infants may acquire TB by the following means:

• Transplacental spread through the umbilical vein to the fetal liver

• Aspiration or ingestion of infected amniotic fluid

• Airborne inoculation from close contacts (family members or nursery personnel)

About 50% of children born to mothers with active pulmonary TB develop the disease during the first year of life if chemoprophylaxis or BCG vaccine is not given.

### Symptoms and Signs

The clinical presentation of neonatal TB is nonspecific but is usually marked by multiple organ involvement. The neonate may look acutely or chronically ill and may have fever, lethargy, respiratory distress, hepatosplenomegaly, or failure to thrive.

### Diagnosis

• Culture of tracheal aspirate, gastric washings, urine, and CSF

• Chest x-ray

• Sometimes skin testing

All neonates with suspected congenital TB and infants born to mothers who have active TB should have a chest x-ray and culture of tracheal aspirates, gastric washings, urine, and CSF for acid-fast bacilli; the placenta should be examined and cultured as well. Skin testing is not extremely sensitive, particularly initially, but should be done. Biopsy of the liver, lymph nodes, lungs, or pleurae may be needed to confirm the diagnosis.

Well-appearing neonates whose mothers have a positive skin test but a negative chest x-ray and no evidence of active disease should have close follow-up and evaluation of all household members. If there is no exposure to a case of active TB, the neonate does not need treatment or testing. If significant

exposure to a case of active TB is found in the neonate's environment after birth, the neonate should be evaluated for suspected congenital TB as described previously. If the neonate is well and active and disease is reasonably excluded by the chest x-ray and physical examination, the neonate should begin treatment with isoniazid (INH) 10 mg/kg po once/day. Further follow-up and management is then identical to that for an asymptomatic neonate born to a woman with active TB (see p. 2839), including a skin test at age 3 or 4 mo.

**Treatment**

- INH for positive skin test or high-risk exposure
- Addition of other drugs (eg, rifampin, ethambutol, pyridoxine, pyrazinamide, an aminoglycoside) if TB is present

Management depends on the whether there is active TB or only a positive skin test (in mother, infant, or both).

**Pregnant women with a positive tuberculin test:** Women are evaluated for active TB. Because the hepatotoxicity of INH is increased in pregnancy, and because the risk of contracting TB from a mother with a positive tuberculin test is greater for the neonate than for the fetus, INH use may be deferred until after the postpartum period unless the woman has active TB or recent contact with a person with contagious TB (in which case the benefit outweighs the risk). Treatment is given for 9 mo, along with supplemental pyridoxine. Treatment for a pregnant woman exposed to contagious TB should be deferred until the 1st trimester is complete.

**Neonates with a positive tuberculin test:** If there is no clinical or x-ray evidence of disease, the infant should receive INH 10 mg/kg po once/day for 9 mo and should be closely monitored.

**Pregnant women with active TB:** INH, ethambutol, and rifampin use in recommended doses during pregnancy has not been shown to be teratogenic to the human fetus. The recommended initial treatment regimen in the US includes INH 300 mg po, ethambutol 15 to 25 mg/kg po, and rifampin 600 mg po. All pregnant and breastfeeding women receiving INH should also receive pyridoxine 25 mg po. All these drugs can be given once/day. The recommended duration of therapy is at least 9 mo; if the organism is drug-resistant, an infectious disease consultation is recommended, and therapy may need to be extended to 18 mo. Streptomycin is potentially ototoxic to the developing fetus and should not be used early in pregnancy unless rifampin is contraindicated. If possible, other antituberculous drugs should be avoided because of teratogenicity (eg, ethionamide) or lack of clinical experience during pregnancy. Breastfeeding is not contraindicated for mothers receiving therapy who are not infective.

Patients with active TB should be reported to the local health department. Mothers with active TB should be tested for HIV.

**Asymptomatic neonates of women with active TB:** The neonate usually is separated from the mother only until effective treatment of both mother and neonate is under way. Once the neonate is receiving INH, separation is not necessary unless the mother (or household contact) has possible multidrug-resistant organisms or poorly adheres to treatment (including not wearing a mask if TB is active) and directly observed therapy is not possible. Family contacts should be investigated for undiagnosed TB before the infant goes home.

If adherence can be reasonably assured and the family is nontuberculous (ie, the mother is being treated and no other transmission risks are present), the neonate is started on a regimen of INH 10 mg/kg po once/day and sent home at the usual time. Skin testing should be done at age 3 or 4 mo. If the neonate is tuberculin-negative, INH is stopped. If the skin test is positive, chest x-ray and cultures for acid-fast bacilli are done as described previously and, if active disease is excluded, treatment with INH is continued for a total of 9 mo. If cultures become positive for TB at any time, the neonate should be treated for TB.

If adherence in a nontuberculous environment cannot be ensured, BCG vaccine may be considered for the neonate, and INH therapy should be started as soon as possible. (Although INH inhibits the

multiplication of BCG organisms, the combination of BCG vaccine and INH is supported by clinical trials and anecdotal reports.) BCG vaccination does not ensure against exposure to and development of TB, but offers significant protection against serious and widespread invasion (eg, tuberculous meningitis). BCG should only be given if skin testing of the neonate is negative. Neonates should be monitored for development of TB, particularly during the first year. (CAUTION: *BCG vaccine is contraindicated in immunosuppressed patients and those suspected of being infected with HIV. However, in high-risk populations, the WHO recommends that asymptomatic HIV-infected neonates receive BCG vaccine at birth or shortly thereafter.*)

**Neonates with active TB:** For congenital TB, the American Academy of Pediatrics recommends treatment once/day with INH 10 to 15 mg/kg po, rifampin 10 to 20 mg/kg po, pyrazinamide 30 to 40 mg/kg po, and an aminoglycoside (eg, amikacin or streptomycin). This regimen should be modified as indicated based on results of testing for resistance.

For TB acquired after birth, the suggested regimen is treatment once/day with INH 10 to 15 mg/kg po, rifampin 10 to 20 mg/kg po, and pyrazinamide 30 to 40 mg/kg. A fourth drug such as ethambutol 20 to 25 mg/kg once/day or an aminoglycoside should be added if drug resistance or tuberculous meningitis is suspected. After the first 2 mo of treatment, INH and rifampin are continued to complete a 6- to 12-mo course (depending on disease category) and other drugs are stopped. Breastfed infants should also receive pyridoxine supplementation.

When the CNS is involved, initial therapy also includes corticosteroids (prednisone 2 mg/kg po once/day for 4 to 6 wk, then gradually tapered). Other therapy continues until all signs of meningitis have disappeared and cultures are negative on 2 successive lumbar punctures at least 1 wk apart. Therapy can then be continued with INH and rifampin once/day or twice/wk for another 10 mo. Corticosteroids may also be considered for infants and children with severe miliary disease, pleural or pericardial effusions, endobronchial disease, or those with abdominal TB.

TB in infants and children that is not congenitally acquired or disseminated; does not involve the CNS, bones, or joints; and results from drug-susceptible organisms can be treated effectively with a 6- to 9-mo (total) course of therapy. Organisms recovered from the child or mother should be tested for drug sensitivity. Hematologic, hepatic, and otologic symptoms should be monitored frequently to determine response to therapy and drug toxicity. Frequent laboratory analysis is not usually necessary.

Directly observed therapy is used whenever possible to improve adherence and the success of therapy. Many anti-TB drugs are not available in pediatric dosages. When possible, experienced personnel should give these drugs to children.

**Prevention**

Routine neonatal BCG vaccination is not routinely indicated in developed countries but may curb the incidence of childhood TB or decrease its severity in populations at increased risk of infection.

# Chapter 280. Miscellaneous Infections in Infants and Children

## Introduction

Infants and young children develop infections more frequently than do adults and older children. Infections may be present at birth (see p. 2811) but are more typically contracted afterward. A child's immune system is neither as mature nor as responsive as an adult's, perhaps because of hyporesponsiveness to T-cell-independent antigens, lower immunoglobulin concentrations, a greater proportion of naive T and B cells compared to memory lymphocytes, or other factors. Children also are exposed to more pathogens from peers in day care centers or school.

Many infectious illnesses that affect infants and children also occur in adults and are discussed elsewhere in THE MANUAL.

## Erythema Infectiosum

(Fifth Disease; Parvovirus B19 Infection)

**Erythema infectiosum, acute infection with parvovirus B19, causes mild constitutional symptoms and a blotchy or maculopapular rash beginning on the cheeks and spreading primarily to exposed extremities. Diagnosis is clinical, and treatment is generally not needed.**

The disease is caused by human parvovirus B19. It occurs mostly during the spring, commonly causing localized outbreaks every few years among children (particularly children 5 to 7 yr). Spread seems to be by respiratory droplets, with high rates of secondary infection among household contacts; infection can occur without symptoms or signs.

### Pathophysiology

Parvovirus B19 causes transient suppression of erythropoiesis that is mild and asymptomatic except in children with underlying hemoglobinopathies (eg, sickle cell disease) or other RBC disorders (eg, hereditary spherocytosis), who may develop transient aplastic crisis. Also, immunocompromised children can develop protracted viremia (lasting weeks to months), leading to severe anemia (pure RBC aplasia).

Erythema infectiosum can be transmitted transplacentally, sometimes resulting in stillbirth or severe fetal anemia with widespread edema (hydrops fetalis). However, about half of pregnant women are immune because of previous infection. The risk of fetal death is 5 to 9% after maternal infection, with risk greatest during the 2nd trimester.

### Symptoms and Signs

The incubation period is 4 to 14 days. Typical initial manifestations are nonspecific flu-like symptoms (eg, low-grade fever, slight malaise). Several days later, an indurated, confluent erythema appears over the cheeks ("slapped-cheek" appearance) and a symmetric rash appears that is most prominent on the arms, legs, and trunk, usually sparing the palms and soles. The rash is maculopapular, tending toward confluence; it forms reticular or lacy patterns of slightly raised, blotchy areas with central clearing, usually most prominent on exposed areas. The rash, and the entire illness, generally lasts 5 to 10 days. However, the rash may recur for several weeks, exacerbated by sunlight, exercise, heat, fever, or emotional stress. Mild joint pain and swelling (nonerosive arthritis) that may persist or recur for weeks to months sometimes occurs in adults.

### Diagnosis

• Clinical evaluation

The appearance and pattern of spread of the rash are the only diagnostic features; however, some enteroviruses may cause similar rashes. Rubella can be ruled out by serologic testing; an exposure history is also helpful. Serologic testing is not required in otherwise healthy children; however, in children

with transient aplastic crisis or adults with arthropathy, the presence of IgM-specific antibody to parvovirus B19 in the late acute or early convalescent phase strongly supports the diagnosis. Parvovirus B19 viremia also can be detected by quantitative PCR techniques, which are generally used for patients with transient aplastic crisis, immunocompromised patients with pure RBC aplasia, and infants with hydrops fetalis or congenital infection.

### Treatment

Only symptomatic treatment is needed. IV immune globulin has been used to curtail viremia and increase erythropoiesis in immunocompromised children with pure RBC aplasia.

## Occult Bacteremia

**Occult bacteremia is the presence of bacteria in the bloodstream of febrile young children who have no apparent foci of infection and look well. Diagnosis is by blood culture and exclusion of focal infection. Treatment is with antibiotics, either in the hospital or as outpatients; select children are treated pending blood culture results.**

About 3% (range 2 to 10%) of children aged 1 to 36 mo with a febrile illness (temperature ≥ 39° C) and no localizing abnormalities have bacteremia, which is hence considered occult. Of these, about 5 to 10% develop focal bacterial infections (eg, septic arthritis, osteomyelitis, meningitis) or sepsis (see pp. 2299 and 2832), which could be minimized by early identification and treatment of the bacteremia. The likelihood of progression to serious focal illness depends on the cause: 7 to 25% for *Haemophilus influenzae* type b (Hib) bacteremia but 4 to 6% for *Streptococcus pneumoniae* bacteremia. For further discussion of fever in infants and children, see p. 2741.

**Organisms:** In the 1980s, 80% of occult bacteremia cases were caused by *S. pneumoniae*. The remainder was caused by Hib (10%), *Neisseria meningitidis* (5%), and others (predominantly *Staphylococcus aureus* and *Salmonella* sp). In the US, since the 1990s, routine Hib conjugate vaccination in infancy essentially eliminated Hib bacteremia. More recent routine use of the *S. pneumoniae* conjugate vaccine in infancy has reduced invasive pneumococcal disease in young children by > 66%, and increased use is expected to essentially eliminate the problem. Some meningococcal conjugate vaccines also have proved effective in this age group, so that in the future occult bacteremia may be largely preventable.

### Symptoms and Signs

The major symptom is fever (temperature ≥ 38° C). By definition, children with apparent focal disease (eg, cough, dyspnea, and pulmonary crackles suggesting pneumonia; skin erythema suggesting cellulitis or septic arthritis) are excluded. A toxic appearance (eg, limpness and listlessness, lethargy, signs of poor perfusion, cyanosis, marked hypoventilation or hyperventilation) suggests sepsis or septic shock; bacteremia in such children is not classified as occult. However, early sepsis can be difficult to distinguish from occult bacteremia.

### Diagnosis

• Blood culture

Diagnosis requires blood culture. Ideally, two samples are taken (from separate sites, which helps minimize the problem of false positives due to skin contaminants), with results available within 24 h. CBC, urinalysis, and examination of the stool for leukocytes (if diarrhea is present) are done in select patients to identify specific infections and help stratify risk. Lumbar puncture for CSF analysis is done in toxic-appearing infants < 3 mo; some experts do lumbar puncture in all febrile infants < 28 days regardless of their appearance.

Recommendations regarding selection of febrile children for testing and choice of tests vary with age, temperature, and clinical appearance (see Figs. 280-1 and

280-2); the goal is to minimize testing without missing bacteremia. These algorithms are sensitive but relatively nonspecific. Thus, given the relatively low incidence of occult bacteremia in the population of febrile children, the algorithms have high negative predictive value but low positive predictive value (see p. 3391), making them much more effective in identifying children at low risk of infection who can be treated expectantly (bacteremia ruled-out) rather than in identifying children with true bacteremia.

CBC usually shows an elevated WBC count; however, only about 10% of children with WBC counts of > 15,000/µL are bacteremic, so specificity is low. Acute-phase reactants (eg, ESR, C-reactive protein) are used by some

[**Fig. 280-1.** Evaluation and management of the febrile infant aged < 3 mo.]

[**Fig. 280-2.** Fever in children aged 3 to 36 mo.]

clinicians but add little information; however, in combination with elevated procalcitonin levels, acute-phase reactants may be more specific for serious illness. In children < 3 mo, band counts > 1500/µL and either low (< 5000/µL) or high (> 15,000/µL) WBC counts may indicate bacteremia.

### Treatment

• Antibiotics (for those with positive cultures and for select patients pending culture results)

Children who receive antibiotics before bacteremia is confirmed by blood culture seem less likely to develop focal infections, although data are inconsistent. However, because of the low overall incidence of bacteremia, many children would receive unnecessary treatment if all who were tested were empirically treated. One common system for management before culture results (see Figs. 280-1 and 280-2) minimizes antibiotic use in most febrile infants and children who do not have serious bacterial infection and provides antibiotics promptly to the few who need them. Nevertheless, some authorities prefer to hospitalize all febrile infants < 1 to 2 mo of age and give parenteral antibiotics (eg, ceftriaxone) pending results of blood, urine, and CSF cultures.

All children are reexamined in 24 to 48 h. Those with persistent fever or positive blood or urine cultures have more cultures done and are hospitalized for evaluation of possible sepsis and parenteral antibiotic therapy. Children who are afebrile and well but have *S. pneumoniae* in their initial blood culture or an initial positive urine culture receive appropriate oral antibiotics (see elsewhere in THE MANUAL).

## Urinary Tract Infection

**Urinary tract infection (UTI) is defined by ≥ $5 \times 10^4$ colonies/mL in a catheterized urine specimen or, in older children, by repeated voided specimens with ≥ $10^5$ colonies/mL. In younger children, UTIs are frequently caused by anatomic abnormalities. UTI may cause fever, failure to thrive, flank pain, and signs of sepsis, especially in young children. Treatment is with antibiotics. Follow-up imaging studies of the urinary tract are done.**

UTI may involve the kidneys, bladder, or both. Sexually transmitted infections of the urethra (eg, gonococcal or chlamydial urethritis), although involving the urinary tract, are not typically termed UTI.

Mechanisms that maintain the normal sterility of the urinary tract include urine acidity and free flow, a normal emptying mechanism, intact ureterovesical and urethral sphincters, and immunologic and mucosal barriers. Abnormality of any of these mechanisms predisposes to UTI.

### Etiology

By age 6 yr, 3 to 7% of girls and 1 to 2% of boys have had a UTI. The peak age of UTI is bimodal, with one peak in infancy and the other peak between ages 2 to 4 yr (at the time of toilet training for many children). The female:male ratio ranges from 1:1 to 1:4 in the first 2 mo of life (estimates vary, likely because of different proportions of uncircumcised males in study groups and the exclusion of infants with

urologic anomalies now more commonly diagnosed in utero by prenatal ultrasonography). The female:male ratio quickly rises with age, being about 2:1 between 2 mo to 1 yr, 4:1 during the 2nd yr, and > 5:1 after 4 yr. In girls, infections usually are ascending and less often cause bacteremia. The marked female preponderance beyond infancy is attributed both to the shorter female urethra and male circumcision.

**Predisposing factors** include malformations and obstructions of the urinary tract, prematurity, indwelling catheters, and lack of circumcision. Other predisposing factors in younger children include constipation and Hirschsprung's disease. Risk factors in older children include diabetes, trauma, and, in adolescent females, sexual intercourse.

**Urinary tract abnormalities:** UTIs in children are a marker of possible urinary tract abnormalities (eg, obstruction, neurogenic bladder, ureteral duplication); these abnormalities are particularly likely to result in infection if vesicoureteral reflux (VUR—see also p. 2984) is present. The likelihood of VUR varies inversely with age at the first UTI. About 30 to 40% of infants and toddlers with UTI have VUR. Severity of reflux may determine the probability of subsequent hypertension and renal failure (caused by repeated infection and chronic pyelonephritis), but proof is lacking (see p. 2847). VUR is classified by grade (see Table 280-1).

**Organisms:** Many organisms cause infection in anatomically abnormal urinary tracts.

In relatively normal urinary tracts, the most common pathogens are strains of *Escherichia coli* with specific attachment factors for transitional epithelium of the bladder and ureters. *E. coli* causes > 75% of UTIs in all pediatric age groups. The remaining causes are other

[**Table 280-1.** Grades of Vesicoureteral Reflux*]

gram-negative enterobacteria, especially *Klebsiella, Proteus mirabilis*, and *Pseudomonas aeruginosa*. Enterococci (group D streptococci) and coagulase-negative staphylococci (eg, *Staphylococcus saprophyticus*) are the most frequently implicated gram-positive organisms. Fungi and mycobacteria are rare causes, mainly in immunocompromised hosts. Adenoviruses rarely cause UTIs, and when they do, the disorder is predominantly hemorrhagic cystitis.

### Symptoms and Signs

In neonates, symptoms and signs are non-specific and include poor feeding, diarrhea, failure to thrive, vomiting, mild jaundice, lethargy, fever, and hypothermia. Neonatal sepsis (see p. 2832) may develop.

Infants and toddlers may also present with poorly localizing signs, such as fever, GI symptoms (eg, vomiting, diarrhea, abdominal pain), or foul-smelling urine.

In children > 2 yr, the more classic picture of cystitis or pyelonephritis can occur. Symptoms of cystitis include dysuria, frequency, hematuria, urinary retention, suprapubic pain, urgency, pruritus, incontinence, foul-smelling urine, and enuresis. Symptoms of pyelonephritis include high fever, chills, and costovertebral pain and tenderness.

Physical findings suggesting associated urinary tract abnormalities include abdominal masses, enlarged kidneys, abnormality of the urethral orifice, and signs of lower spinal malformations. Diminished force of the urinary stream may be the only clue to obstruction or neurogenic bladder.

### Diagnosis

• Urine analysis and culture

• Often urinary tract imaging

**Urine tests:** Diagnosis requires culture showing significant bacteriuria in properly collected urine. Most clinicians obtain urine by transurethral catheterization in infants and young children, reserving suprapubic

aspiration of the bladder for boys with moderate to severe phimosis. Both procedures require technical expertise, but catheterization is less invasive, slightly safer, and has sensitivity of 95% and specificity of 99% compared with suprapubic aspiration. Bagged specimens are unreliable and should not be used for diagnosis.

If urine is obtained by suprapubic aspiration, the presence of any bacteria is significant. In a catheterized specimen, ≥ $5 \times 10^4$ colonies/mL commonly defines UTI. Clean-catch, midstream-voided specimens are significant when colony counts of a single pathogen (ie, not the total count of mixed flora) are ≥ $10^5$ colonies/mL. However, at times symptomatic children may have UTI despite lower colony counts on urine cultures. Urine should be examined and cultured as soon as possible or stored at 4° C if a delay of > 10 min is expected. Occasionally, UTI may be present despite colony counts lower than the described guidelines, possibly because of prior antibiotic therapy, very dilute urine (sp gr < 1.003), or obstruction to the flow of grossly infected urine. Sterile cultures generally rule out UTI unless the child is receiving antibiotics or the urine is contaminated with antibacterial skin-cleaning agents.

**Microscopic examination** of urine is useful but not definitive. Pyuria (> 5 to 10 WBCs/high-power field in spun urine sediment) is about 70% sensitive for UTI. A WBC count (using a hemocytometer) > 10/µL in unspun urine has greater sensitivity (90%) but is not used by many laboratories. Presence of bacteria on Gram stain of spun or unspun urine is about 80% sensitive. Specificity of microscopy also is about 80%.

**Dipstick tests** on urine to detect bacteria (nitrite test) or leukocytes (leukocyte esterase test) are typically done; if either is positive, the diagnostic sensitivity for UTI is about 93%. The specificity of the nitrite test is quite high; a positive result on a freshly voided specimen is highly predictive of UTI. Specificity of leukocyte esterase is much lower.

Differentiating an upper UTI from a lower UTI can be difficult. High fever, costovertebral angle tenderness, and gross pyuria with casts indicate pyelonephritis. However, many children without these symptoms and signs have an upper UTI. Tests to distinguish upper infection from lower infection are not indicated in most clinical settings, because treatment is not altered.

**Blood tests:** A CBC and tests for inflammation (eg, ESR, C-reactive protein) may help diagnose infection in children with borderline urine findings. Some authorities measure serum BUN and creatinine during a first UTI. Blood cultures are appropriate for infants with UTIs and for children > 1 to 2 yr who appear toxic.

**Urinary tract imaging:** Many major renal or urologic anomalies now are diagnosed in utero by routine prenatal ultrasonography. However, the high incidence of anatomic anomalies still warrants imaging the urinary tracts of all children 2 mo to 2 yr of age after a first UTI. If a first UTI occurs at ≥ 2 yr, most authorities recommend imaging; however, some physicians postpone imaging until after a second UTI in girls > 2 yr. Options include voiding cystourethrogram (VCUG), radionuclide cystogram (RNC) with technetium-99m pertechnetate, and ultrasonography.

VCUG and RNC are better than ultrasonography for detecting VUR and anatomic abnormalities. RNC delivers about 1% of the gonadal radiation of VCUG; it is sensitive in detecting VUR, and some recommend it as the initial test. However, most authorities prefer the better anatomic definition of contrast VCUG as the initial test, using RNC in follow up to determine when VUR has resolved. Low-dose x-ray equipment has narrowed the gap in radiation between the contrast VCUG and RNC. These tests are recommended at the earliest convenient time after clinical response, typically toward the end of therapy, when bladder reactivity has resolved and urine sterility has been regained. If imaging is not scheduled until after therapy is due to be completed, the child should continue antibiotics at prophylactic doses until VUR is excluded.

Ultrasonography helps exclude obstruction and hydronephrosis and is typically done within a week of diagnosing UTI in infants, especially if they do not respond quickly to antimicrobials. Otherwise, ultrasonography can be delayed until VCUG is done.

**Prognosis**

Properly managed children rarely progress to renal failure unless they have uncorrectable urinary tract abnormalities. However, repeated infection, particularly in the presence of VUR, is thought (but not proved) to cause renal scarring, which may lead to hypertension and end-stage renal disease. In children with high-grade VUR, long-term scarring is detected at a 4- to 6-fold greater rate than in children with low-grade VUR and at an 8- to 10-fold greater rate than in children without VUR.

**Treatment**

• Antibiotics

• For severe VUR, sometimes antibiotic prophylaxis and surgical repair

Treatment aims to eliminate the acute infection, prevent urosepsis, and preserve renal parenchymal function. Antibiotics are begun presumptively in all toxic-appearing children and in nontoxic children with likely UTI (positive leukocyte esterase or nitrite test, or microscopy showing pyuria or bacteriuria). Others can await culture results.

In infants 2 mo to 2 yr with toxicity, dehydration, or inability to retain oral intake, parenteral antibiotics are used, typically a 3rd-generation cephalosporin (eg, ceftriaxone 75 mg/kg IV/IM q 24 h, cefotaxime 50 mg/kg IV q 6 h). A 1st-generation cephalosporin (eg, cefazolin) may be used if typical local pathogens are known to be sensitive. Aminoglycosides (eg, gentamicin), although potentially nephrotoxic, are useful in complex UTIs (eg, urinary tract abnormalities, presence of indwelling catheters, recurrent UTIs) to treat potentially resistant gram-negative bacilli such as *Pseudomonas*. If blood cultures are negative and clinical response is good, an appropriate oral antibiotic (eg, a cephalosporin, trimethoprim/sulfamethoxazole [TMP/SMX], amoxicillin, or, for selected children such as those > 1 yr with complicated UTI caused by multidrug-resistant *E. coli, P. aeruginosa*, or other gram-negative bacteria, a fluoroquinolone) selected on the basis of antimicrobial sensitivities can be used to complete a 10- to 14-day course. A poor clinical response suggests a resistant organism or an obstructive lesion and warrants urgent evaluation with ultrasonography and repeat urine culture.

In nontoxic, nondehydrated infants and children who are able to retain oral intake, oral antibiotics may be given initially. The drug of choice is TMP/SMX 5 to 6 mg/kg (of TMP component) bid. Alternatives include cephalosporins such as cefixime 4 mg/kg bid or cephalexin 25 mg/kg qid. Therapy is changed based on the results of cultures and antimicrobial sensitivities. Treatment is generally for > 10 days, although many older children with uncomplicated UTI can be treated for 7 days. Urine culture is repeated 2 to 3 days after therapy starts if efficacy is not clinically apparent.

**Vesicoureteral reflux:** It is generally thought that antibiotic prophylaxis reduces UTI recurrences and prevents kidney damage. However, few long-term data are available on the actual risks of renal scarring and the effectiveness of antimicrobial prophylaxis or operative repair in preventing end-stage renal disease. An ongoing clinical trial is attempting to address these questions, but until results are available, most clinicians provide long-term antimicrobial prophylaxis to children with VUR, especially those with grades II through V. For those with grade IV or grade V VUR, open repair or endoscopic injection of polymeric bulking agents is usually recommended.

Drugs for prophylaxis include nitrofurantoin 2 mg/kg po once/day or TMP/SMX 3 mg/kg po (of TMP component) once/day, usually given at bedtime.

# Chapter 281. Human Immunodeficiency Virus Infection in Infants and Children

## Introduction

(See also Ch. 154.)

**Human immunodeficiency virus (HIV) infection is caused by the retrovirus HIV-1 (and less commonly by the related retrovirus HIV-2). Infection leads to progressive immunologic deterioration and opportunistic infections and cancers. The end stage is acquired immunodeficiency syndrome (AIDS). Diagnosis is by viral antibodies in children > 18 mo and viral PCR assay in children < 18 mo. Treatment is with combinations of antiretroviral drugs.**

The general natural history and pathophysiology of pediatric HIV infection is similar to that in adults; however, the method of infection, clinical presentations, and treatments often differ. HIV-infected children also have unique social integration issues (see Sidebar 281-1).

### Epidemiology

In the US, HIV probably occurred in children almost as early as in adults but was not clinically recognized for several years. Thus far, > 9300 cases have been reported in children and adolescents, representing only 1% of total cases.

More than 90% of US children acquired the infection from their mother, either before or around the time of birth (vertical transmission). Most of the remainder (including children with hemophilia or other coagulation disorders) received contaminated blood or blood products. A few cases are the result of sexual abuse. Fewer than 5% of cases have no clear source. Vertical transmission now accounts for almost all new cases in US preadolescents. Cases in adolescents represent survivors of vertically transmitted infection and newly acquired infection (typically from sexual contact, particularly by young men who have sex with men).

Worldwide, about 2 million children have HIV infection (6% of the total caseload worldwide), and about 370,000 more children are infected each year (14% of all new infections). In sub-Saharan Africa, where the epidemic has been present longest, some prenatal clinics report that 25 to 40% of all women of childbearing age are seropositive for HIV. HIV infection is rapidly increasing in India, China, Southeast Asia, and some areas of Eastern Europe and Russia. About 270,000 children die of HIV infection worldwide each year.

**Transmission:** Infection risk for an infant born to an HIV-positive mother who did not receive antiretroviral (ARV) therapy during pregnancy is estimated at 13 to 39%. Risk is greatest for infants born to mothers who seroconvert during pregnancy and for those with advanced disease, low peripheral CD4+ T-cell counts, prolonged rupture of membranes, and high plasma viral RNA concentrations. In vaginal deliveries, a 1st-born twin is at greater risk than a 2nd-born twin, although this relationship may not hold true in developing countries.

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### Sidebar 281-1 Integration of HIV-Infected Children

Infection in a child affects the entire family. Serologic testing of siblings and parents is recommended. The physician must provide education and ongoing counseling.

The infected child should be taught good hygiene and behavior to reduce risk to others. How much and when the child is told about the illness depends on age and maturity. Older children and adolescents should be made aware of their diagnosis and the possibility of sexual transmission and should be counseled appropriately. Families may be unwilling to share the diagnosis with people outside the immediate family because it can create social isolation. Feelings of guilt are common. Family members, including children, can become clinically depressed and require counseling.

Because HIV infection is not acquired through the typical types of contact that occur among children (eg,

through saliva or tears), most HIV-infected children should be allowed to attend school without restrictions. Similarly, there are no inherent reasons to restrict foster care, adoptive placement, or child care of HIV-infected children. Conditions that may pose an increased risk to others (eg, aggressive biting or the presence of exudative, weeping skin lesions that cannot be covered) may require special precautions.

The number of school personnel aware of the child's condition should be kept to the minimum needed to ensure proper care. The family has the right to inform the school, but people involved in the care and education of an infected child must respect the child's right to privacy. Disclosures of information should be made only with the informed consent of the parents or legal guardians and age-appropriate assent of the child.

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Cesarean delivery before onset of active labor reduces the risk of mother-to-child transmission (MTCT). However, it is clear that MTCT is reduced most significantly by giving ARV therapy (including zidovudine [ZDV, AZT]) to the mother and neonate (see p. 2858). ZDV monotherapy reduces MTCT from 25% to about 8%, and current highly active anti-retroviral therapy (HAART) reduces it to < 2%.

HIV has been detected in both the cellular and cell-free fractions of human breast milk. The incidence of transmission by breastfeeding is about 6/100 breastfed children/yr. Estimates of the overall risk of transmission through breastfeeding are 12 to 14%, reflecting varying durations of breastfeeding. Transmission by breastfeeding is greatest in mothers with high plasma viral concentrations (eg, women who become infected during pregnancy or during the period of breastfeeding).

The total number of HIV-infected US adolescents continues to increase despite the marked success in decreasing perinatal HIV infection through comprehensive diagnosis and treatment of infected pregnant women. This paradoxical increase is a result of both greater survival among perinatally infected children and the additional acquisition of new cases of HIV infection by sexual transmission among other adolescents.

**Classification:** HIV infection causes a broad spectrum of disease, of which AIDS is the most severe. Classification schemes established by the Centers for Disease Control and Prevention (CDC) define the progression of clinical and immunologic decline.

**Clinical categories** in children < 13 yr (see Table 281-1) are defined by presence or absence of certain common opportunistic infections or cancers. These categories are

N = Not symptomatic
A = Mildly symptomatic
B = Moderately symptomatic
C = Severely symptomatic

**Immunologic categories** in children < 13 yr (see Table 281-2) reflect the degree of immune suppression based on the CD4+ T-cell count (absolute count and as percentage of total lymphocyte count):

1 = No evidence of immune suppression
2 = Moderate suppression
3 = Severe suppression

Thus, a child classified in stage B3 would have moderately advanced clinical symptoms and severe immunocompromise. Clinical and immunologic categories form a unidirectional hierarchy; once classified at a certain level, children cannot be reclassified at a less severe level, regardless of clinical or immunologic improvement.

[**Table 281-1.** Clinical Categories for Children Aged < 13 yr with HIV Infection]

These clinical and immunologic categories are becoming less clinically relevant in the era of HAART, which (when taken as prescribed) almost invariably leads to a decrease in symptoms and an increase in CD4+ T-cell counts. The categories are most useful for clinical research and for describing the severity of illness at the time of diagnosis.

**Symptoms and Signs**

**Natural history in untreated children:** Infants infected perinatally usually are asymptomatic during the first few months of life. Although the median age at symptom onset is about 3 yr, some children remain asymptomatic for > 5 yr and, with appropriate ARV therapy, are expected to survive to adulthood. In the pre-ARV therapy era, about 10 to 15% of children had rapid disease progression, with symptoms occurring in the first year of life and death occurring by 18 to 36 mo; these children were thought to have acquired HIV infection earlier in utero. However, most children probably acquire infection at or near birth and have slower disease progression (surviving beyond 5 yr even before ARV therapy was used routinely).

The most common manifestations of HIV infection in children include generalized lymphadenopathy, hepatomegaly, splenomegaly, failure to thrive, oral candidiasis, CNS disease (including developmental delay, which can be progressive), lymphoid interstitial pneumonitis, recurrent bacteremia, opportunistic infections, recurrent diarrhea, parotitis, cardiomyopathy, hepatitis, nephropathy, and cancers.

**Complications:** *Pneumocystis jirovecii* pneumonia is the most common, serious, opportunistic infection among HIV-infected children and has high mortality. *Pneumocystis* pneumonia can occur as early as age 4 to 6 wk but occurs mostly in infants aged 3 to 6 mo who acquired infection before or at birth. Infants and children with *Pneumocystis* pneumonia characteristically develop a subacute, diffuse pneumonitis with dyspnea at rest, tachypnea, $O_2$ desaturation, nonproductive cough, and fever (in contrast to non-HIV-infected immunocompromised children and adults, in whom onset is often more acute and fulminant).

Other common opportunistic infections include *Candida* esophagitis, disseminated cytomegalovirus infection, and chronic or disseminated herpes simplex and varicella-zoster

[**Table 281-2.** Immunologic Categories for Children < 13 yr with HIV Infection Based on Age-Specific CD4+ T-Cell Counts and Percentages of Total Lymphocyte Counts]

virus infections, and, less commonly, *Mycobacterium tuberculosis* and *M. avium* complex infections, chronic enteritis caused by *Cryptosporidium* or other organisms, and disseminated or CNS cryptococcal or *Toxoplasma gondii* infection.

Cancers in immunocompromised children with HIV infection are relatively uncommon, but leiomyosarcomas and certain lymphomas, including CNS lymphomas and non-Hodgkin B-cell lymphomas (Burkitt's type), occur much more often than in immunocompetent children. Kaposi's sarcoma is very rare in HIV-infected children.

**Children receiving combination antiretroviral therapy:** Combination ARV therapy has significantly changed the clinical manifestations of pediatric HIV infection. Although bacterial pneumonia and other bacterial infections (eg, bacteremia, recurrent otitis media) still occur more often in HIV-infected children, opportunistic infections and growth failure are much less frequent than in the pretreatment era. New problems, such as alterations in serum lipids, hyperglycemia, fat maldistribution (lipodystrophy and lipoatrophy), nephropathy, and osteonecrosis, are reported, although with lower incidence than in HIV-infected adults. Although combination therapy clearly improves neurodevelopmental outcome, there seems to be an increased rate of behavioral, developmental, and cognitive problems in treated HIV-infected children. It is unclear whether these problems are caused by HIV infection itself, therapeutic drugs, or other bio-psychosocial factors among HIV-infected children.

**Diagnosis**

• Serum antibody tests

• Virologic assay (HIV DNA PCR or HIV RNA assays)

**HIV-specific tests:** In children > 18 mo, diagnosis is made using serum antibody tests (enzyme immunoassay [EIA] and confirmatory Western blot) as in adults. Only very rarely does an older HIV-infected child lack HIV antibody because of significant hypogammaglobulinemia.

Children < 18 mo retain maternal antibody, causing false-positive results on EIA, so diagnosis is made by HIV virologic assays such as DNA PCR, which can diagnose about 30% of cases at birth and nearly 100% by 4 to 6 mo of age. HIV viral culture has acceptable sensitivity and specificity but is technically more demanding and hazardous and has been replaced by DNA PCR in most laboratories.

HIV RNA assays (the viral load assays used for monitoring efficacy of treatment) are becoming more widely used for diagnostic testing of infants. RNA assays are probably as sensitive as DNA PCR in infants not given ARV therapy, are less expensive, and are more widely available than is DNA PCR. However, care must be taken when using RNA assays for infant diagnosis because test specificity is uncertain at very low RNA concentrations (< 10,000 copies/mL) and sensitivity is unknown in infants of mothers with complete treatment-mediated viral suppression at the time of delivery. The modified p24 antigen assay is less sensitive than either HIV DNA PCR or RNA assays and should be used only if the latter are unavailable.

An initial virologic test should be done within the first 2 wk of life, at about 1 mo of age, and between 4 mo and 6 mo. A positive test should be confirmed immediately by using the same or another virologic test. If the serial HIV virologic tests are all negative, the infant is considered uninfected with > 95% accuracy (in the absence of any AIDS-defining illness). Follow-up antibody tests (1 EIA at > 18 mo or, alternatively, 2 EIAs done between 6 mo and 18 mo) are done to exclude HIV infection and confirm seroreversion (loss of passively acquired HIV antibodies). If an infant < 18 mo with a positive antibody test but negative virologic tests develops an AIDS-defining illness (category C—see Table 281-1), HIV infection is diagnosed.

**Rapid tests** for HIV antibody are derivatives of EIAs that provide results within minutes to hours. They can be done as point-of-care tests on oral secretions, whole blood, or serum. In the US, these tests are perhaps most useful in labor and delivery suites to test women of unknown HIV serostatus, thus allowing counseling, commencement of ARV therapy to prevent MTCT, and testing of the infant to be arranged during the birth visit. Similar advantages accrue in other episodic care settings (eg, emergency departments, adolescent medicine clinics, sexually transmitted disease clinics) and in the developing world. In the US, rapid assays require confirmatory tests, such as Western blot testing. These confirmatory tests are especially important because in areas where the expected HIV prevalence is low, even a specific rapid assay yields mostly false positives (low positive predictive value by Bayes' theorem —see p. 3394). However, if the expected probability of HIV (or seroprevalence) is high, the positive predictive value increases.

Before HIV testing of a child is done, the mother or primary caregiver (and the child, if old enough) should be counseled about the possible psychosocial risks and benefits of testing. Written or oral consent should be obtained and recorded in the patient's chart, consistent with state, local, and hospital laws and regulations. Counseling and consent requirements should not deter testing if it is medically indicated; refusal of a patient or guardian to give consent does not relieve physicians of their professional and legal responsibilities, and sometimes authorization for testing must be obtained by other means (eg, court order). Test results should be discussed in person with the family, the primary caregiver, and, if old enough, the child. If the child is HIV-positive, appropriate counseling and subsequent follow-up care must be provided. In all cases, maintaining confidentiality is essential.

Children and adolescents meeting the criteria for AIDS must be reported to the appropriate public health department. In many states, HIV infection (before the development of AIDS) also must be reported.

**Other tests:** Once infection is diagnosed, other tests are done:

• CD4+ T-cell count

• CD8+ T-cell count

• Plasma viral RNA concentration

Infected children require measurement of CD4+ and CD8+ T-cell counts and plasma viral RNA concentration (viral load) to help determine their degree of illness, prognosis, and the effects of therapy. CD4+ counts may be normal (eg, above the age-specific cutoffs of category 1 in Table 281-2) initially but fall eventually. CD8+ counts usually increase initially and do not fall until late in the infection. These changes in cell populations result in a decrease in the CD4+:CD8+ cell ratio, a characteristic of HIV infection (although sometimes occurring in other infections). Plasma viral RNA concentrations in untreated children < 12 mo are typically very high (mean of about 200,000 RNA copies/mL). By 24 mo, viral concentrations in untreated children decrease (to a mean of about 40,000 RNA copies/mL). Although the wide range of HIV RNA concentrations in children make the data less predictive of morbidity and mortality than in adults, determining plasma viral concentrations in conjunction with CD4+ counts still yields more accurate prognostic information than does determining either marker alone. Less expensive alternative surrogate markers such as total lymphocyte counts and serum albumin levels may also predict AIDS mortality in children, which may be useful in developing nations.

Although not routinely measured, serum immunoglobulin concentrations, particularly IgG and IgA, often are markedly elevated, but occasionally some children develop panhypogammaglobulinemia. Patients may be anergic to skin test antigens.

**Prognosis**

In the pretherapy era, 10 to 15% of children from industrialized countries and perhaps 50 to 80% of children from developing countries died before age 4 yr; however, with appropriate HAART regimens, most perinatally infected children survive well beyond 5 yr. Many children are surviving into young adulthood; increasing numbers have given birth to or fathered their own children.

Nevertheless, opportunistic infections, particularly *Pneumocystis* pneumonia, progressive neurologic disease, and severe wasting, are associated with a poor prognosis. Mortality due to *Pneumocystis* pneumonia ranges from 5 to 40% if treated and is almost 100% if untreated. Prognosis is also poor for children in whom virus is detected early (ie, by 7 days of life) or who develop symptoms in the first year of life.

**Treatment**

• ARV drugs: 2 nucleoside analog reverse transcriptase inhibitors plus either a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor

• Supportive care

Because of the success of ARV therapy, much of the current focus is on the management of HIV infection as a chronic disease, addressing both medical and social issues. Important long-term medical issues include the need to manage HIV-related and drug-related metabolic complications and to account for age-related changes in drug pharmacokinetics and pharmacodynamics. Social issues include the need to cope with peer pressure from non-infected adolescents, ensure school success and appropriate career choice, and educate children about transmission risk. Adolescents often have difficulty seeking and following health care advice and need particular help with treatment adherence. Children and adolescents should be managed in collaboration with specialists who have experience in the management of pediatric HIV infection.

**ARV drugs:** There are > 2 dozen ARV drugs (see Table 281-3), including multidrug combination products, available in the US, each of which may have adverse effects and drug interactions with other ARV drugs or commonly used antibiotics, anticonvulsants, and sedatives. New ARV drugs, immunomodulators, and vaccines are under evaluation.

Standard treatment is with combination ARV therapy to maximize viral suppression and minimize selection of drug-resistant strains. Most commonly, ARV therapy consists of a backbone of 2 nucleoside analog reverse transcriptase inhibitors (ZDV plus lamivudine or emtricitabine, abacavir plus lamivudine or emtricitabine, didanosine plus lamivudine or emtricitabine, or, for postpubertal adolescents, tenofovir plus emtricitabine) given in combination with either a ritonavir-boosted protease inhibitor (lopinavir/ritonavir, ritonavir-boosted atazanavir, ritonavir-boosted fosamprenavir, or ritonavir-boosted darunavir) or a nonnucleoside reverse transcriptase inhibitor (efavirenz or, in some situations, nevirapine). Other combinations sometimes are used, but fewer data are available to support their use as first-line regimens. Monotherapy or dual nucleoside reverse transcriptase inhibitor therapy alone (except for ZDV chemoprophylaxis in HIV-exposed infants) is strongly discouraged. Because expert opinions on therapeutic strategies change rapidly, consultation with specialists is strongly advised.

**Indications:** Initiation of ARV therapy depends on virologic, immunologic, and clinical criteria; authorities differ on these criteria. The goal is to suppress HIV replication (as measured by plasma HIV RNA PCR viral load) and maintain or achieve age-normal $CD4^+$ counts and percentages with the least amount of drug toxicity.

**For children ≥ 12 mo**, ARV therapy is recommended for all children with significant clinical or immunologic disease (clinical category B or C [Table 281-1] or CD4+ percentage < 25% for children < 5 yr or CD4+ cell count < 350/μL for children ≥ 5 yr), regardless of the plasma HIV RNA viral load. Therapy is considered for other children who have plasma HIV RNA concentrations ≥ 100,000 copies/mL. Children who do not meet these criteria may be monitored closely without ARV therapy, but their clinical and laboratory data should be reevaluated every 3 to 4 mo.

**For children < 12 mo**, ARV therapy should be given to all regardless of clinical symptoms, CD4+ T-cell percentages or counts, or plasma HIV RNA viral load; clinical trials have shown that early therapy of infected infants decreases mortality.

**Adherence:** Therapy will be successful only if the family and child are able to adhere to a possibly complex medical regimen. Nonadherence not only leads to failure to control HIV but also selects drug-resistant HIV strains, which reduces future therapeutic choices. Barriers to adherence should be addressed before starting treatment. Barriers include availability and palatability of pills or suspensions, adverse effects (including those due to drug interactions with current therapy), pharmacokinetic factors such as need to take some drugs with food or in the fasted state, a child's dependence on others to give drugs (and HIV-infected parents may have problems with remembering to take their own drugs), and adolescents' denial or fear of their infection, distrust of the medical establishment, and lack of family support.

[**Table 281-3.** Dosage and Administration of Antiretroviral Drugs for Children [a]]

**Monitoring:** Clinical and laboratory monitoring are important for identifying drug toxicity and therapeutic failure.

- Every 3 to 4 mo: Physical examination, CBC, serum chemistry values, including liver and kidney function tests, amylase and lipase (if taking drugs with pancreatic toxicity, eg, didanosine), HIV RNA viral load, and lymphocyte subsets

- Every 6 to 12 mo: Lipid profiles, and amylase and lipase (if not taking drugs with pancreatic toxicity)

**Vaccination:** Routine pediatric vaccination protocols (see p. 2718) are recommended for children with HIV infection, with several exceptions. The main exception is that live-virus vaccines and live-bacteria vaccines (eg, BCG) should be avoided or used only in certain circumstances (see Table 281-4). In addition, 1 to 2 mo after the last dose of the hepatitis B vaccine series, HIV-infected children should be tested to determine whether the level of antibodies to hepatitis B surface antigen (anti-HBs) is protective (≥ 10 mIU/mL), and children aged ≥ 2 yr should be given pneumococcal polysaccharide vaccine (PPSV) ≥ 2 mo after their last pneumococcal conjugate vaccine (PCV) dose, and a single

revaccination should be given after 5 yr. Certain postexposure treatment recommendations also differ.

Live oral poliovirus vaccine and live-attenuated influenza vaccine are not recommended.

The live measles-mumps-rubella (MMR) and varicella vaccines should not be given to children with AIDS or other manifestations of severe immunosuppression. However, the MMR and varicella vaccines (separately; not combined as MMRV vaccine, which has a higher titer of attenuated varicella virus, the safety of which has not been shown in this population) *can* be given to asymptomatic patients following the routine schedule and to symptomatic patients who are not severely immunocompromised (ie, not in category 3 [see Table 281-1], including having a CD4+ T-cell percentage of ≥ 15%); if possible, these vaccines should be given starting at age 12 mo in symptomatic patients to enhance the likelihood of an immune response, ie, before the immune system deteriorates. The 2nd dose of each may be given as soon as 4 wk later in an attempt to induce seroconversion as early as possible, although generally a 3-mo interval between varicella vaccine doses is preferred in noninfected children < 13 yr. If the risk of exposure to measles is increased, as during an outbreak, the measles vaccine should be given at an earlier age, such as 6 to 9 mo.

The live oral rotavirus vaccine may be given to HIV-exposed or HIV-infected infants according to the routine schedule. Safety and efficacy data are limited in symptomatic infants but experts feel that there is overall benefit to immunization, particularly in areas where rotavirus causes significant mortality.

The BCG vaccine is not recommended in the US, an area of low TB prevalence. However, elsewhere in the world, especially in developing countries where TB prevalence is high, the WHO recommends that BCG be given to all infants shortly after birth, unless they have symptoms of HIV infection or already have been confirmed to have HIV infection (eg, positive virologic assay). Some cases of disseminated BCG infection in severely immunocompromised AIDS patients have been reported.

Because children with symptomatic HIV infection generally have poor immunologic responses to vaccines, they should be considered susceptible when they are exposed to a vaccine-preventable disease (eg, measles, tetanus, varicella) regardless of their vaccination history. Such children should receive passive immunization with immune globulin. Immune globulin also should be given to any nonimmunized household member who is exposed to measles.

**Seronegative children living with a person with symptomatic HIV infection** should receive inactivated poliovirus vaccine rather than oral polio vaccine. Influenza (inactivated or live), MMR, varicella, and rotavirus vaccines may be given normally because these vaccine viruses are not commonly transmitted by the vaccinee. Adult household contacts should receive annual influenza vaccination (inactivated or live) to reduce the risk of transmitting influenza to the HIV-infected person.

### Prevention

For postexposure prevention, see p. 1455.

**Prevention of perinatal transmission:** Appropriate prenatal ARV therapy attempts to optimize maternal health, interrupt MTCT, and minimize in utero drug toxicity. In the US and other countries where ARV drugs and HIV testing are readily available, treatment with ARV drugs is standard for all HIV-infected pregnant women (see p. 1450). Rapid HIV testing of pregnant women who present in labor without documentation of their HIV serostatus may allow immediate institution of such measures.

HIV-infected pregnant women who have not received ARV drugs previously and who do not meet adult criteria (see p. 1450) for HAART are nevertheless recommended to initiate HAART, preferably including ZDV 300 mg po bid, beginning at 14 to 34 wk gestation. Pregnancy is not a contraindication to HAART regimens, although the use of efavirenz is generally contraindicated during the 1st trimester. This regimen is continued throughout the pregnancy. ZDV is given during labor 2 mg/kg IV for the first hour and then 1 mg/kg/h IV until delivery. ZDV 2 mg/kg po qid is given to the neonate for the first 6 wk of life. In the immediate postpartum period, a decision can be made whether to continue maternal therapy.

Most experts believe that HIV-infected women already receiving combination ARV therapy who become

pregnant should continue that therapy, even during the 1st trimester. An alternative is to stop all therapy until the beginning of the 2nd trimester and resume at that time.

[**Table 281-4.** Considerations for Use of Live Vaccines in Children with HIV Infection]

For HIV-infected pregnant women who present in labor and have had no prior therapy, clinicians have used ARV combinations, cesarean delivery, or both; the woman and her infant are given ZDV as described previously (ie, the woman receives drugs IV during labor and delivery; the infant receives drugs by mouth). Some authorities give additional antiretrovirals in this situation; an expert in pediatric or maternal HIV infection should be immediately consulted (see information at www.aidsinfo.nih.gov or www.nccc.ucsf.edu).

Although the final decision to accept ARV therapy remains with the pregnant woman, it should be stressed that the proven benefits of therapy far outweigh the theoretical risks of fetal toxicity.

**Breastfeeding** (or donating to milk banks) is contraindicated for HIV-infected women in the US and other countries where safe and affordable alternative sources of feeding are readily available. However, in countries where infectious diseases and undernutrition are major causes of early childhood mortality and safe, affordable infant formula is not available, the protection breastfeeding offers against the mortality risks of respiratory and GI infections may counterbalance the risk of HIV transmission. In these developing countries, the WHO recommends that mothers continue to breastfeed.

**Prevention of adolescent transmission:** Because adolescents are at special risk of HIV infection, they should receive education, have access to HIV testing, and know their serostatus. Education should include information about transmission, implications of infection, and strategies for prevention, including abstaining from high-risk behaviors and engaging in safe sex practices (eg, correct and consistent use of condoms [see p. 2587]) for those who are sexually active. Efforts should especially target adolescents at high risk of HIV infection, although all adolescents should receive risk-reduction education.

In most US states, informed consent is necessary for testing and the release of information regarding HIV serostatus. Decisions regarding disclosure of HIV status to a sex partner without the patient's consent should be based on the possibility of domestic violence to the patient after disclosure to the partner, likelihood that the partner is at risk, whether the partner has reasonable cause to suspect the risk and to take precautions, and presence of a legal requirement to withhold or disclose such information.

**Prevention of opportunistic infections:** Prophylactic drug treatment is recommended in certain HIV-infected children for prevention of *Pneumocystis* pneumonia and *M. avium* complex infections. Data are limited on the use of prophylaxis for opportunistic infection by other organisms, such as cytomegalovirus, fungi, and toxoplasma. Guidance on prophylaxis of these and other opportunistic infections is also available at www.aidsinfo.nih.gov.

**Prophylaxis against *Pneumocystis* pneumonia** is indicated for

- HIV-infected children > 6 yr of age with CD4+ count < 200 cells/μL or CD4+ percentage < 15%
- HIV-infected children 1 to 5 yr of age with CD4+ count < 500 cells/μL or CD4+ percentage < 15%
- HIV-infected infants < 12 mo of age regardless of CD4+ count or percentage (at 1 yr of age, need for prophylaxis is reassessed using CD4+ counts and percentages)
- Infants born to HIV-infected women (beginning at 4 to 6 wk of age), until HIV infection is either presumptively excluded (by documentation of 2 negative virologic test results, 1 at ≥ 2 wk of age and 1 at ≥ 4 wk of age) or definitively excluded (by documentation of 2 negative virologic test results, 1 at ≥ 1 mo of age and 1 at ≥ 4 mo of age). For these definitions of HIV exclusion to be valid, the infant must not be breastfeeding.

Once immune reconstitution with HAART occurs, discontinuation of *Pneumocystis* pneumonia prophylaxis may be considered for HIV-infected children who have received HAART for > 6 mo and whose CD4+

percentage and CD4+ count have remained higher than the previously described treatment thresholds for > 3 consecutive mo. Subsequently, the CD4+ percentage and count should be reevaluated at least every 3 mo, and prophylaxis should be reinstituted if the original criteria are reached.

The drug of choice for *Pneumocystis* prophylaxis at any age is trimethoprim/sulfamethoxazole (TMP/SMX) TMP 75 mg/SMX 375 mg/$m^2$ po bid on 3 consecutive days/wk (eg, Monday-Tuesday-Wednesday); alternative schedules include the same dose bid every day, the same dose bid on alternate days, or twice the dose (TMP 150 mg/SMX 750 mg/$m^2$) po once/day for 3 consecutive days/wk.

For patients ≥ 5 yr who cannot tolerate TMP/SMX, dapsone 2 mg/kg (not to exceed 100 mg) po once/day is an alternative, especially for those < 5 yr of age. Oral atovaquone given daily or aerosolized pentamidine (300 mg via specially designed inhaler) given once/mo is an additional alternative. IV pentamidine has also been used but is less effective and potentially more toxic.

**Prophylaxis against *Mycobacterium avium* complex** infection is indicated in

• Children ≥ 6 yr with CD4+ count < 50/µL

• Children 2 to 6 yr with CD4+ count < 75/µL

• Children 1 to 2 yr with CD4+ count < 500/µL

• Children < 1 yr with CD4+ count < 750/µL

Weekly azithromycin or daily clarithromycin is the drug of choice, and daily rifabutin is an alternative.

# Chapter 282. Rheumatic Fever

## Introduction

**Rheumatic fever is a nonsuppurative, acute inflammatory complication of group A streptococcal infection, causing combinations of arthritis, carditis, subcutaneous nodules, erythema marginatum, and chorea. Diagnosis is based on applying the Jones criteria to information gleaned from history, examination, and laboratory testing. Treatment includes aspirin or other NSAIDs, corticosteroids during severe carditis, and antimicrobials to eradicate residual streptococcal infection and prevent reinfection.**

A first episode of acute rheumatic fever (ARF) can occur at any age but occurs most often between 5 yr and 15 yr and is uncommon before 3 yr and after 21 yr. Therefore, testing for group A streptococcal (GAS) infection for primary prevention of rheumatic fever is usually not necessary in patients < 3 yr with pharyngitis.

Worldwide, incidence is 19/100,000 (range, 5 to 51/100,000), with lowest rates (< 10/100,000) in North America and Western Europe and highest rates (> 10/100,000) in Eastern Europe, the Middle East, Asia, Australia, and New Zealand. The attack rate (percentage of patients with untreated GAS pharyngitis who develop ARF) varies from 0.4 to 3.0%. Higher attack rates occur with certain streptococcal M protein serotypes and a stronger host immune response. In patients with a prior episode of ARF, the attack rate in untreated GAS pharyngitis approaches 50%, underscoring the importance of long-term antistreptococcal prophylaxis. Incidence has declined in most developed countries but remains high in less developed parts of the world. However, recurrent local outbreaks of ARF suggest that more rheumatogenic strains of streptococci are still present in the US. The prevalence of chronic rheumatic heart disease is uncertain because criteria are not standardized and autopsy is not done routinely.

### Pathophysiology

GAS infection is the etiologic precursor of ARF, but host and environmental factors are important. GAS M proteins share epitopes (antigenic-determinant sites that are recognized by antibodies) with proteins found in synovium, heart muscle, and heart valve, suggesting that molecular mimicry contributes to the arthritis, carditis, and valvular damage. Genetic host risk factors include the D8/17 B-cell antigen and certain class II histocompatibility antigens. Undernutrition, overcrowding, and lower socioeconomic status predispose to streptococcal infections and subsequent episodes of rheumatic fever.

The joints, heart, skin, and CNS are most often affected. Pathology varies by site.

**Joints:** Joint involvement manifests as non-specific inflammation in a synovial biopsy specimen, sometimes with small foci resembling Aschoff bodies (granulomatous collections of leukocytes, myocytes, and interstitial collagen).

**Heart:** Cardiac involvement manifests as carditis, typically affecting the heart from the inside out, ie, valves and endocardium, then myocardium, and finally pericardium. It is sometimes followed years later by chronic rheumatic heart disease, primarily manifested by valvular stenosis, but also sometimes by regurgitation, arrhythmias, and ventricular dysfunction. Aschoff bodies often develop in the myocardium and other parts of the heart. Fibrinous nonspecific pericarditis, sometimes with effusion, occurs only in patients with endocardial inflammation and usually subsides without permanent damage. Characteristic and potentially dangerous valve changes may occur. Acute interstitial valvulitis may cause valvular edema. Left untreated, valve thickening, fusion, and retraction or other destruction of leaflets and cusps may result, leading to stenosis or insufficiency. Similarly, chordae tendineae can shorten, thicken, or fuse, adding to regurgitation of damaged valves or causing regurgitation of an otherwise unaffected valve. Dilation of valve rings may also cause regurgitation. The mitral, aortic, tricuspid, and pulmonic valves are affected, in order of decreasing frequency. Regurgitation and stenosis are the usual effects on the mitral and tricuspid valves; the aortic valve generally becomes regurgitant initially and stenotic much later.

**Skin:** Subcutaneous nodules appear indistinguishable from those of RA, but biopsy shows features resembling Aschoff bodies. Erythema marginatum differs histologically from other skin lesions with similar

macroscopic appearance, eg, the rash of systemic juvenile idiopathic arthritis (JIA), Henoch-Schonlein purpura, erythema chronicum migrans, and erythema multiforme. Perivascular neutrophilic and mononuclear infiltrates of the dermis occur.

**CNS:** Sydenham's chorea, the form of chorea that occurs with ARF, manifests in the CNS as hyperperfusion and increased metabolism in the basal ganglia. Increased levels of antineuronal antibodies have also been shown.

**Symptoms and Signs**

An initial episode of symptoms occurs typically about 2 to 4 wk after the streptococcal infection. Manifestations typically involve some combination of the joints, heart, skin, and CNS.

**Joints: Migratory polyarthritis** is the most common manifestation, occurring in about 70% of children; it is often accompanied by fever. Occasionally monarthritis occurs. Joints become extremely painful and tender and may be red, hot, and swollen. Ankles, knees, elbows, and wrists are usually involved. Shoulders, hips, and small joints of the hands and feet also may be involved, but almost never alone. If vertebral joints are affected, another disorder should be suspected.

Arthralgia-like symptoms may be due to nonspecific myalgia or tenodynia in the periarticular zone; tenosynovitis may develop at the site of muscle insertions. Joint pain and fever usually subside within 2 wk and seldom last > 1 mo.

**Heart:** Carditis can occur alone or in combination with pericardial rub, murmurs, cardiac enlargement, or heart failure. In the first episode of ARF, carditis occurs in about 50%. Patients may have high fever, chest pain, or both. In about 50% of cases, cardiac damage (ie, valve dysfunction) occurs much later.

**Murmurs** are common and, although usually evident early, may not be heard at initial examination; in such cases, repeated examinations are recommended to determine the presence of carditis. The soft diastolic blow of aortic regurgitation and the presystolic murmur of mitral stenosis may be difficult to detect. Murmurs often persist indefinitely. If no worsening occurs during the next 2 to 3 wk, new manifestations of carditis seldom follow. ARF typically does not cause chronic, smoldering carditis. Scars left by acute valvular damage may contract and change, and secondary hemodynamic difficulties may develop in the myocardium without persistence of acute inflammation.

**Heart failure** caused by the combination of carditis and valvular dysfunction may cause dyspnea without rales, nausea and vomiting, a right upper quadrant or epigastric ache, and a hacking, nonproductive cough. Marked lethargy and fatigue may be early manifestations of heart failure.

**Skin:** Cutaneous and subcutaneous features are uncommon and almost never occur alone, usually developing in a patient who already has carditis, arthritis, or chorea.

**Subcutaneous nodules**, which occur most frequently on the extensor surfaces of large joints, usually coexist with arthritis and carditis. About 2% of children with ARF have nodules. Ordinarily, the nodules are painless and transitory and respond to treatment of joint or heart inflammation.

**Erythema marginatum** is a serpiginous, flat or slightly raised, nonscarring, and painless rash. About 2% of children have this rash. It sometimes lasts < 1 day. Its appearance is often delayed after the inciting streptococcal infection; it may appear with or after the other manifestations of rheumatic inflammation.

**CNS: Sydenham's chorea** occurs in about 10% of children. It may develop along with other manifestations but frequently arises after the other manifestations have subsided (often months after the acute streptococcal infection). Onset of chorea is typically insidious and may be preceded by inappropriate laughing or crying. Chorea consists of rapid and irregular jerking movements that may begin in the hands but often becomes generalized, involving the feet and face. Characteristic findings include fluctuating grip strength (milkmaid's grip), tongue darting (the tongue cannot protrude without darting in and out), facial grimacing, and explosive speech with or without tongue clucking. Associated motor symptoms include loss of fine motor control, and weakness and hypotonia (that can be severe enough to

be mistaken for paralysis).

Obsessive-compulsive behavior develops in many patients.

**Other:** Fever and other systemic manifestations such as anorexia and malaise can be prominent but are not specific. ARF can occasionally manifest as FUO until a more identifiable sign develops. Abdominal pain and anorexia can occur because of the hepatic involvement in heart failure or because of concomitant mesenteric adenitis. Because of the fever, elevated WBC count, and abdominal guarding, the situation may resemble acute appendicitis, particularly when other rheumatic manifestations are absent. Epistaxis occurs in about 4% of children with an initial episode and in 9% of those with a recurrence. Both abdominal pain and epistaxis were minor manifestations in earlier versions of the Jones criteria.

Prolonged episodes of ARF (> 8 mo) occur in about 5% of patients, with spontaneous recurrences of inflammation (clinical and laboratory manifestations) unrelated to intervening streptococcal infection or to cessation of anti-inflammatory therapy. Recurrences usually mimic the initial episode.

**Diagnosis**

• Jones criteria (for initial diagnosis)

• Testing for GAS (culture, rapid strep test, or antistreptolysin O and anti-DNase B titers)

• ECG

• ESR and C-reactive protein (CRP) level

Diagnosis of a first episode of ARF is based on the modified Jones criteria (see Table 282-1); 2 major criteria or 1 major and 2 minor criteria are required, along with evidence of preceding GAS infection. Sydenham's chorea alone (ie, without minor criteria) fulfills diagnostic criteria if other causes of movement disorder are ruled out. The Jones criteria should not be used to establish a recurrence.

A preceding streptococcal infection is suggested by a recent history of pharyngitis and is confirmed by a positive throat culture, an increase in the antistreptolysin O titer, or a positive rapid GAS antigen test. Recent scarlet fever is highly suggestive. Throat cultures and rapid antigen tests are often negative by the time ARF manifests, whereas titers of anti-streptolysin O and other antibodies typically are peaking. Only 80% of children with a prior infection have a significantly elevated antistreptolysin O titer; therefore, anti-DNase B antibody level should also be obtained.

Joint aspiration may be needed to exclude other causes of arthritis (eg, infection). The joint fluid is usually cloudy and yellow, with an elevated WBC count composed primarily of neutrophils; culture is negative. Complement levels are usually normal or slightly decreased, compared with decreased levels in other inflammatory arthritides.

ECG is done during the initial evaluation. An echocardiogram and a repeat ECG are done at the time of diagnosis. Serum cardiac marker levels are obtained; normal cardiac troponin I levels exclude prominent myocardial damage. ECG abnormalities such as PR prolongation do not correlate with other evidence of carditis. Only 35% of children with ARF have a prolonged PR interval. Other ECG abnormalities may be due to pericarditis, enlargement of ventricles or atria, or arrhythmias. Echocardiography can detect evidence of carditis in many patients. Chest x-rays are not routinely done but can detect cardiomegaly, a common manifestation of carditis in ARF. Biopsy of a subcutaneous nodule can aid in early diagnosis, especially when other major clinical manifestations are absent. Rheumatic carditis must be distinguished from congenital heart disease and endocardial fibroelastosis; echocardiography or coronary angiography can be used to verify difficult diagnoses.

[**Table 282-1.** Modified Jones Criteria for a First Episode of Acute Rheumatic Fever*]

ESR and serum CRP are sensitive but not specific. The ESR is often > 120 mm/h. CRP is often > 2 mg/dL; because it rises and falls faster than ESR, a normal CRP may confirm that inflammation is resolving in a patient with prolonged ESR elevation after acute symptoms have subsided. In the absence of carditis, ESR usually returns to normal within 3 mo. Evidence of acute inflammation, including ESR, usually subsides within 5 mo in uncomplicated carditis. The WBC count reaches 12,000 to 20,000/µL and may go higher with corticosteroid therapy.

The differential diagnosis includes JIA (especially systemic JIA and, less so, polyarticular JIA), Lyme disease, reactive arthritis, arthropathy of sickle cell disease, leukemia or other cancer, SLE, embolic bacterial endocarditis, serum sickness, Kawasaki disease, drug reactions, and gonococcal arthritis. These are frequently distinguished by history or specific laboratory tests. The absence of an antecedent GAS infection, the diurnal variation of the fever, evanescent skin rash, and prolonged symptomatic joint inflammation usually distinguish systemic JIA from ARF.

**Prognosis**

Prognosis depends mostly on the severity of the initial carditis. Patients with severe carditis during the first episode may have residual heart disease that is often worsened by the rheumatic fever recurrences to which they are particularly susceptible. Murmurs eventually disappear in about half of patients whose acute episodes were manifested by mild carditis without major cardiac enlargement or decompensation. Risk of recurrent inflammation is intermediate, between the low risk of those without carditis and the high risk of those with a history of severe carditis, but recurrences may cause or worsen permanent cardiac damage. Patients who did not have carditis are less likely to have recurrences and are unlikely to develop carditis if ARF recurs. Sydenham's chorea usually lasts several months and resolves completely in most patients, but about one third of patients have recurrences. All other manifestations subside without residual effects.

**Treatment**

• Aspirin or another NSAID

• Sometimes corticosteroids

• Antibiotics

The primary goals are suppression of inflammation and relief of acute symptoms, eradication of GAS infection, and prophylaxis against future infection to prevent recurrent heart disease.

Patients should generally limit their activities if symptomatic with arthritis, chorea, or heart failure. In the absence of carditis, no physical restrictions are needed after the initial episode subsides. In asymptomatic patients with carditis, strict bed rest has no proven value.

**Aspirin** controls fever and pain caused by arthritis and carditis. The dose is titrated upward until clinical effectiveness is attained or toxicity supervenes. The starting dose for children and adolescents is 15 mg/kg po qid. If not effective overnight, the dosage is increased to 22.5 mg/kg qid the next day and 30 mg/kg qid on the next. Salicylate toxicity is manifested by tinnitus, headache, or hyperpnea and may not appear until after 1 wk. Salicylate levels are measured only to manage toxicity and should not be done until the patient has been receiving aspirin for 5 days. Enteric-coated, buffered, or complex salicylate molecules provide no advantage. Other NSAIDs can be used. For example, naproxen 7.5 to 10 mg/kg po bid is as effective as aspirin.

If a therapeutic effect has not occurred after the 4th day, which is sometimes the case if carditis or arthritis is severe, NSAIDs should be abandoned in favor of a corticosteroid.

**Prednisone** 0.25 to 1 mg/kg po bid (or 0.125 to 0.5 mg/kg po qid) up to 60 mg/day is recommended. If inflammation is not suppressed after 2 days, an IV corticosteroid pulse of methylprednisolone succinate (30 mg/kg IV once/day, maximum 1 g/day, for 3 successive days) may be given. Oral corticosteroids are given until ESR has remained normal for 1 wk and then are tapered at the rate of 5 mg every 2 days. To

prevent worsening of inflammation during the corticosteroid taper, NSAIDs are begun simultaneously and continued until 2 wk after the corticosteroid has been stopped. Inflammatory markers such as ESR and CRP are used to monitor disease activity and response to treatment.

Recurrences of cardiac inflammation (indicated by fever or chest pain) may subside spontaneously, but NSAIDs or corticosteroids should be resumed if recurrent symptoms last longer than a few days or if heart failure is uncontrolled by standard management (eg, diuretics, ACE inhibitors, β-blockers, inotropic agents). In patients with prolonged, recurrent episodes of carditis, immunosuppressants may be effective. Although useful in the acute episode, NSAIDs and corticosteroids do not prevent or reduce long-term valve damage.

Although poststreptococcal inflammation is well developed by the time ARF is detected, antibiotics are used to eradicate any lingering organisms and to prevent reinfection. Appropriate regimens for the treatment of acute infection are described under Streptococcal and Enterococcal Infections on p. 1230.

**Antibiotic prophylaxis:** Antistreptococcal prophylaxis should be maintained continuously after the initial episode of ARF to prevent recurrences (see Table 282-2). Antibiotics taken orally are just as effective as those given by injection. With the oral route, painful injections are avoided, and clinic visits and observation for postinjection reactions are not needed. With the IM route, adherence difficulties of taking a pill once or twice daily are avoided. The IM regimen has been the standard against which other regimens are measured.

The optimal duration of antistreptococcal prophylaxis is uncertain. Children without carditis should receive prophylaxis for 5 yr or

[**Table 282-2.** Recommended Prophylaxis Against Recurrent Group a Streptococcal Infection]

up to age 21 (if the patient turns 21 before 5 yr of prophylaxis is completed). The American Academy of Pediatrics recommends that those with carditis without evidence of residual heart damage receive prophylaxis for 10 yr. Children with carditis and evidence of residual heart damage should receive prophylaxis for > 10 yr; many experts recommend that such patients continue prophylaxis indefinitely. Some experts believe prophylaxis should be life long in all patients with chorea and should continue in all patients who have close contact with young children because of their high rate of GAS carriage.

The American Heart Association no longer recommends that patients with known or suspected rheumatic valvular disease (*who are not currently taking prophylactic antibiotics*) take short-term antibiotic prophylaxis against bacterial endocarditis for dental or oral surgical procedures (see p. 2199).

## Poststreptococcal Reactive Arthritis

**Poststreptococcal reactive arthritis is development of arthritis after group A streptococcal infection in patients who do not meet the criteria for ARF.**

Poststreptococcal reactive arthritis may represent an attenuated variant of ARF. Compared with the arthritis of ARF, poststreptococcal reactive arthritis typically involves fewer joints, is less migratory but more protracted, and responds less to aspirin. It can be treated with other NSAIDs (eg, ibuprofen, naproxen, tolmetin). Although clinical practice for secondary prevention of cardiac involvement varies greatly, it is reasonable to give antistreptococcal prophylaxis for 1 yr and then to repeat the echocardiogram. If cardiac lesions are detected by echocardiogram, long-term prophylaxis is indicated.

# Chapter 283. Respiratory Disorders in Neonates, Infants, and Young Children

## Introduction

Symptoms and signs of respiratory distress vary and include nasal flaring; intercostal, subcostal, and suprasternal retractions; weak breathing, irregular breathing, or a combination; tachypnea and apneic spells; cyanosis, pallor, mottling, delayed capillary refill, or a combination; and hypotension. In neonates, symptoms and signs may be apparent immediately on delivery or develop minutes or hours afterward.

### Etiology

Respiratory distress in neonates and infants has multiple causes (see Table 283-1).

### Physiology

There are several significant differences in the physiology of the respiratory system in neonates and infants compared with that of older children and adults. These differences include

[**Table 283-1.** Causes of Respiratory Distress in Neonates and Infants]

• A more compliant collapsible chest wall

• More reliance on diaphragmatic excursions over intercostal muscles

• Collapsible extrathoracic airways

Also, infants' smaller airway caliber gives increased airway resistance, and absence of collateral ventilation increases tendency toward atelectasis. Yet, other principles of respiration are similar in adults and children.

### Evaluation

Evaluation starts with a thorough history and physical examination.

History in the neonate focuses on maternal and prenatal history, particularly gestational age, maternal infection or bleeding, meconium staining of amniotic fluid, and oligohydramnios or polyhydramnios.

Physical examination focuses on the heart and lungs. Chest wall asymmetry or sunken abdomen suggests diaphragmatic hernia. Asymmetric breath sounds suggest pneumothorax, pneumonia, or asthma. A displaced left apical impulse, heart murmur, or both suggest a congenital heart defect. Assessment of BP and femoral pulses may identify circulatory collapse with or without congenital defects. Poor capillary refill reflects circulatory compromise.

In both neonates and infants, it is important to assess oxygenation and response to $O_2$ therapy by pulse oximetry or blood gases. Chest x-ray also is recommended.

## Respiratory Support in Neonates and Infants

Initial stabilization maneuvers include mild tactile stimulation, head positioning, and suctioning of the mouth and nose followed as needed by

• Supplemental $O_2$

• Continuous positive airway pressure (CPAP)

• Bag and mask ventilation or mechanical ventilation

Neonates who cannot be oxygenated by any of these means may require a full cardiac evaluation to exclude congenital heart disease and treatment with high-frequency oscillatory ventilation, nitric oxide, extracorporeal membrane oxygenation, or a combination.

**Oxygen:** $O_2$ may be given using a nasal cannula, face mask, or $O_2$ hood, with $O_2$ concentration set to achieve a $PaO_2$ of 50 to 70 mm Hg in preterm infants and 50 to 80 mm Hg in term infants or an $O_2$ saturation of 84 to 90% in preterm infants and 92 to 96% in term infants. Lower $PaO_2$ in preterm infants provides almost full saturation of Hb, because fetal Hb has a higher affinity for $O_2$; maintaining higher $PaO_2$ increases the risk of retinopathy of prematurity. No matter how $O_2$ is delivered, it should be warmed (36 to 37° C) and humidified to prevent secretions from cooling and drying and to prevent bronchospasm. An umbilical artery catheter (UAC) is usually placed for sampling ABGs in neonates who require fraction of inspired $O_2$ ($FIO_2$) ≥ 40%. If a UAC cannot be placed, a percutaneous radial artery catheter can be used for continuous BP monitoring and blood sampling.

Neonates who are unresponsive to these maneuvers may require fluids to improve cardiac output and are candidates for CPAP ventilation or bag and mask ventilation (40 to 60 breaths/min). If the infant does not oxygenate with or requires prolonged bag-and-mask ventilation, endotracheal intubation with mechanical ventilation is indicated, although very immature neonates (eg, < 28 wk gestation or < 1000 g) are typically begun on ventilatory support immediately after delivery so that they can receive preventive surfactant therapy. Because bacterial sepsis is a common cause of respiratory distress in neonates, it is common practice to draw blood cultures and give antibiotics to neonates with high $O_2$ requirements pending culture results.

**Continuous positive airway pressure:** CPAP delivers $O_2$ at a positive pressure, usually 5 to 7 cm $H_2O$, which keeps alveoli open and improves oxygenation by reducing the amount of blood shunted through atelectatic areas while the infant breathes spontaneously. CPAP can be provided using nasal prongs and various apparatuses to provide the positive pressure; it also can be given using an endotracheal tube connected to a conventional ventilator with the rate set to zero. CPAP is indicated when $FIO_2$ ≥ 40% is required to maintain acceptable $PaO_2$ (50 to 70 mm Hg) in infants with respiratory disorders that are of limited duration (eg, diffuse atelectasis, mild respiratory distress syndrome, lung edema). In these infants, CPAP may preempt the need for positive pressure ventilation.

**Mechanical ventilation: Endotracheal tubes** are required for mechanical ventilation (see also p. 2273):

• Endotracheal tubes 2.5 mm in diameter (the smallest) typically used for infants < 1250 g

• 3 mm for infants 1250 to 2500 g

• 3.5 mm for infants > 2500 g

Intubation is safer if $O_2$ is insufflated into the infant's airway during the procedure. Orotracheal intubation is preferred. The tube should be inserted such that the

• 7-cm mark is at the lip for infants who weigh 1 kg

• 8-cm mark for 2 kg

• 9-cm mark for 3 kg

The endotracheal tube is properly placed when its tip can be palpated through the anterior tracheal wall at the suprasternal notch. It should be positioned about halfway between the clavicles and the carina on chest x-ray, coinciding roughly with vertebral level T2. If position or patency is in doubt, the tube should be removed and the infant should be supported by bag-and-mask ventilation until a new tube is inserted. Acute deterioration of the infant's condition (sudden changes in oxygenation, ABGs, BP, or perfusion)

should trigger suspicion of changes in the position of the tube, patency of the tube, or both.

**Ventilators** can be set to deliver fixed pressures or volumes; can provide assist control (AC, in which the ventilator is triggered to deliver a full breath with each patient inspiration) or intermittent mandatory ventilation (IMV, in which the ventilator delivers a set number of breaths within a time period, and patients can take spontaneous breaths in between without triggering the ventilator); and can be normal or high frequency (delivering 400 to 900 breaths/min). Optimal mode or type of ventilation depends on the infant's response. Volume ventilators are considered useful for larger infants with varying pulmonary compliance or resistance (eg, in bronchopulmonary dysplasia), because delivering a set volume of gas with each breath ensures adequate ventilation. AC mode is often used for treating less severe pulmonary disease and for decreasing ventilator dependence while providing a small increase in airway pressure or a small volume of gas with each spontaneous breath. High-frequency jet, oscillatory, and flow-interrupter ventilators are used in extremely premature infants (< 28 wk) and in some infants with air leaks, widespread atelectasis, or pulmonary edema.

**Initial ventilator settings** are estimated by judging the severity of respiratory impairment. Typical settings for an infant in moderate respiratory distress are $FIO_2$ = 40%; inspiratory time (IT) = 0.4 sec; expiratory time = 1.1 sec; IMV or AC rate = 40 breaths/min; peak inspiratory pressure (PIP) = 15 cm $H_2O$ for very low-birth-weight infants and up to 25 cm $H_2O$ for near-term infants; and positive end-expiratory pressure (PEEP) = 5 cm $H_2O$. These settings are adjusted based on the infant's oxygenation, chest wall movement, breath sounds, and respiratory efforts along with arterial or capillary blood gases.

- **$PaCO_2$** is lowered by increasing the minute ventilation through an increase in tidal volume (increasing PIP or decreasing PEEP) or an increase in rate.

- **$PaO_2$** is increased by increasing the $FIO_2$ or increasing the mean airway pressure (increasing PIP, PEEP, or rate or prolonging IT).

Patient-triggered ventilation often is used to synchronize the positive pressure ventilator breaths with the onset of the patient's own spontaneous respirations. This seems to shorten the time on a ventilator and may reduce barotrauma. A pressure-sensitive air-filled balloon attached to a pressure transducer (Graseby capsule) taped to the infant's abdomen just below the xiphoid process can detect the onset of diaphragmatic contraction, or a flow or temperature sensor placed at the endotracheal tube adapter can detect the onset of a spontaneous inhalation.

Ventilator pressures or volumes should be as low as possible to prevent barotrauma and bronchopulmonary dysplasia; an elevated $PaCO_2$ is acceptable as long as pH remains ≥ 7.25 (permissive hypercapnia). Likewise, a $PaO_2$ as low as 40 mm Hg is acceptable if BP is normal and metabolic acidosis is not present.

**Adjunctive treatments** used with mechanical ventilation in some patients include

- Paralytics

- Sedation

- Nitric oxide

Paralytics (eg, vecuronium or pancuronium bromide 0.03 to 0.1 mg/kg IV q 1 to 2 h prn [with pancuronium, a test dose of 0.02 mg/kg is recommended in neonates]) and sedatives (eg, fentanyl 1 to 4 µg/kg IV push q 2 to 4 h or midazolam 0.05 to 0.15 mg/kg IV over 5 min q 2 to 4 h) may facilitate endotracheal intubation and can help stabilize infants whose movements and spontaneous breathing prevent optimal ventilation. These drugs should be used selectively, however, because paralyzed infants may need greater ventilator support, which can increase barotrauma. Inhaled nitric oxide 5 to 20 ppm may be used for refractory hypoxemia when pulmonary vasoconstriction is a contributor to hypoxia (eg, in idiopathic pulmonary hypertension, pneumonia, or congenital diaphragmatic hernia) and may prevent the need for extracorporeal membrane oxygenation (see below).

**Weaning** from the ventilator can occur as respiratory status improves. The infant can be weaned by lowering

• $FIO_2$

• Inspiratory pressure

• Rate

Continuous-flow positive pressure ventilators permit the infant to breathe spontaneously against PEEP while the ventilator rate is progressively slowed. After the rate has been reduced to 10 breaths/min, the infant usually tolerates extubation. The final steps in ventilator weaning involve extubation, possibly support with nasal (or nasopharyngeal) CPAP, and, finally, use of a hood or nasal cannula to provide humidified $O_2$ or air.

Very-low-birth-weight infants may benefit from the addition of a methylxanthine (eg, aminophylline, theophylline, caffeine) during the weaning process. Methylxanthines are CNS-mediated respiratory stimulants that increase ventilatory effort and may reduce apneic and bradycardic episodes that may interfere with successful weaning. Caffeine is the preferred agent because it is better tolerated, easier to give, safer, and requires less monitoring. Corticosteroids, once used routinely for weaning and treatment of chronic lung disease, are no longer recommended in premature infants because risks (eg, impaired growth and neurodevelopmental delay) outweigh benefits. A possible exception is as a last resort in near-terminal illness, in which case parents should be fully informed of risks.

**Complications:** Mechanical ventilation complications more common among neonates include

• Pneumothorax

• Asphyxia from endotracheal tube obstruction

• Ulceration, erosion, or narrowing of airway structures due to adjacent pressure

• Bronchopulmonary dysplasia

**Extracorporeal membrane oxygenation (ECMO):** ECMO is a form of cardiopulmonary bypass used for infants who cannot be oxygenated adequately or ventilated with conventional ventilators. Eligibility criteria vary by center, but in general, infants should have reversible disease (eg, persistent pulmonary hypertension of the newborn, congenital diaphragmatic hernia, overwhelming pneumonia) and should have been on mechanical ventilation < 7 days. After systemic heparinization, blood is circulated through large-diameter catheters from the internal jugular vein into a membrane oxygenator, which serves as an artificial lung to remove $CO_2$ and add $O_2$. Oxygenated blood is then circulated back to the internal jugular vein (venovenous ECMO) or to the carotid artery (venoarterial ECMO). Venoarterial ECMO is used when both circulatory support and ventilatory support are needed (eg, in overwhelming sepsis). Flow rates can be adjusted to obtain desired $O_2$ saturation and BP. ECMO is contraindicated in infants < 34 wk, < 2 kg, or both because of the risk of intraventricular hemorrhage with systemic heparinization. Complications include thromboembolism, air embolization, neurologic (eg, stroke, seizures) and hematologic (eg, hemolysis, neutropenia, thrombocytopenia) problems, and cholestatic jaundice.

## Apnea of Prematurity

**Apnea of prematurity is defined as respiratory pauses > 20 sec or airflow interruption and respiratory pauses > 20 sec associated with bradycardia (< 80 beats/min), central cyanosis, or $O_2$ saturation < 85% in neonates born at < 37 wk gestation and with no underlying disorders causing apnea. Cause may be CNS immaturity (central) or airway obstruction. Diagnosis is by multichannel respiratory monitoring. Treatment is with respiratory stimulants for central apnea and head positioning for obstructive apnea. Prognosis is excellent; apnea resolves in most**

**neonates by 37 wk.**

About 25% of preterm infants have apnea of prematurity, which usually begins 2 to 3 days after birth and only rarely on the first day. Apnea that develops > 14 days after birth in an otherwise healthy infant signifies a serious illness other than apnea of prematurity (eg, sepsis). Risk increases with earlier gestational age.

**Pathophysiology**

Apnea of prematurity may be

• Central

• Obstructive

• A mixed pattern (most common)

**Central apnea** is caused by immaturity of medullary respiratory control centers; insufficient neural impulses from the respiratory centers in the medulla reach the respiratory muscles, and the infant stops breathing. Hypoxemia and hypercarbia stimulate respiratory efforts.

**Obstructive apnea** is caused by obstructed airflow, neck flexion causing opposition of hypopharyngeal soft tissues, nasal occlusion, or reflex laryngospasm.

Both types of apnea can cause hypoxemia, cyanosis, and bradycardia if the apnea is prolonged. Among infants dying of SIDS, 18% have a history of prematurity, but apnea of prematurity does not seem to be a precursor to SIDS.

**Diagnosis**

• Clinical evaluation

• Cardiorespiratory monitoring, physiologic parameter recordings

• Other causes (eg, hypoglycemia, sepsis, intracranial hemorrhage, gastroesophageal reflux disease [GERD]) ruled out

Although frequently attributable to immature respiratory control mechanisms, apnea of prematurity can be sign of major infectious, metabolic, thermoregulatory, respiratory, cardiac, GI, or CNS dysfunction. Careful history, physical assessment, and, when necessary, testing should be done before accepting prematurity as the cause of apnea.

Diagnosis of apnea usually is made by visual observation or by use of impedance-type cardiorespiratory monitors used continuously during assessment and ongoing care of preterm infants. Multichannel recordings of multiple physiologic parameters (eg, chest wall movement, airflow, $O_2$ saturation, heart rate, brain electric activity) taken for up to 24 h can be used as adjuncts for diagnosis and planning and monitoring treatment.

**Prognosis**

Most preterm infants stop having apneic spells by the time they reach about 37 wk gestation. Apnea may continue for weeks in infants born at extremely early gestational ages (eg, 23 to 27 wk). Death is rare.

**Treatment**

• Stimulation

• Treatment of underlying disorder

• Respiratory stimulants (eg, caffeine)

When apnea is noted, either by observation or monitor alarm, infants are stimulated, which may be all that is required; if breathing does not resume, bag-valve-mask or mouth-to-mouth-and-nose ventilation is provided (see p. 2272). For infants at home, the physician is contacted if apnea occurs but ceases after stimulation; if intervention beyond stimulation is required, the infant should be rehospitalized and evaluated.

Frequent or severe episodes should be quickly and thoroughly evaluated, and identifiable causes should be treated. If no infectious or other treatable underlying disorder is found, respiratory stimulants are indicated for treatment of frequent or severe episodes, characterized by hypoxemia, cyanosis, bradycardia, or a combination. Caffeine is the safest and most commonly used respiratory stimulant drug. It can be given as caffeine base (loading dose 10 mg/kg followed by a maintenance dose of 2.5 mg/kg po q 24 h) or caffeine citrate, a caffeine salt that is 50% caffeine (loading dose 20 mg/kg followed by a maintenance dose of 5 to 10 mg/kg q 24 h). Caffeine is preferred because of ease of administration, fewer adverse effects, larger therapeutic window and less need to monitor drug levels. Treatment continues until the infant is 34 to 35 wk gestation and free from apnea requiring physical intervention for at least 5 to 7 days. Monitoring continues until the infant is free of apnea requiring intervention for 5 to 10 days.

If apnea continues despite respiratory stimulants, the infant may be given continuous positive airway pressure starting at 5 to 8 cm $H_2O$ pressure. Intractable apneic spells require ventilator support. Discharge practices vary; some practitioners observe infants for 7 days after treatment has ended to ensure that apnea or bradycardia does not recur, whereas others discharge with caffeine if treatment seems effective.

### Prevention

Hospitalized high-risk infants who have not had clinically significant cardiopulmonary events (eg, apnea > 20 sec, apnea accompanied by central cyanosis, apnea associated with heart rate < 80 for > 5 sec) during continuous cardiorespiratory monitoring can be discharged home safely without a monitor. A home cardiorespiratory monitor may be prescribed to shorten the hospital stay for infants that are otherwise ready for discharge but are still having clinically significant cardiopulmonary events that reverse without intervention. Caffeine can be used as an adjunct to a home monitor to achieve this status. Parents should be taught how to properly use equipment, assess alarm situations, intervene (eg, CPR), and keep a log of events. Round-the-clock telephone support and triage as well as outpatient follow-up regarding the decision to stop using the monitor should be provided. Monitors that store event information are preferred.

Infants should sleep on their back. The infant's head should be kept in the midline, and the neck should be kept in the neutral position or slightly extended to prevent upper airway obstruction. All premature infants, especially those with apnea of prematurity, are at risk of apnea, bradycardia, and $O_2$ desaturation while in a car seat and should undergo a car seat challenge test before discharge.

## Bronchopulmonary Dysplasia

**Bronchopulmonary dysplasia (BPD) is chronic lung disease of the neonate that typically is caused by prolonged ventilation and is further defined by age of prematurity and extent of $O_2$ requirement.**

BPD is considered present when there is need for supplemental $O_2$ in premature infants who do not have other conditions requiring $O_2$ (eg, pneumonia, congenital heart disease).

### Etiology

BPD has a multifactorial etiology. Significant risk factors include

• Prolonged mechanical ventilation

• High concentrations of inspired $O_2$

• Infection

• Degree of prematurity

Additional risk factors include

• Pulmonary interstitial emphysema

• High peak inspiratory pressures

• Large end-tidal volumes

• Increased airway resistance

• Increased pulmonary artery pressures

• Male sex

The lungs of premature infants are more vulnerable to the inflammatory changes that result from mechanical ventilation. The development of normal lung architecture is interrupted; fewer and larger alveoli develop, and the interstitium is thickened.

**Diagnosis**

• National Institute of Child Health and Human Development (NICHD) criteria

• Characteristic x-ray findings

BPD typically is suspected when a ventilated infant is unable to wean from $O_2$ therapy, mechanical ventilation, or both. Infants typically develop worsening hypoxemia, hypercapnia, and increasing $O_2$ requirements. Additionally, when an infant cannot be weaned within the expected time, possible underlying disorders, including patent ductus arteriosus and nursery-acquired pneumonia, should be sought.

For diagnosis, the patient has to have required at least 28 days of > 21% $O_2$. Specific additional diagnostic criteria (see Table 283-2) have been developed by the NICHD.

Chest x-ray initially shows diffuse haziness due to accumulation of exudative fluid; appearance then becomes multicystic or sponge-like, with alternating areas of emphysema, pulmonary scarring, and atelectasis. Alveolar epithelium may slough, and macrophages, neutrophils, and inflammatory mediators may be found in the tracheal aspirate.

**Prognosis**

Prognosis varies with severity. Infants who still depend on mechanical ventilation at 36 wk gestation have a 20 to 30% mortality rate

[**Table 283-2.** National Institute of Child Health and Human Development Criteria for Diagnosis of Bronchopulmonary Dysplasia*]

in infancy. Infants with BPD have a 3- to 4-fold increased rate of growth failure and neurodevelopmental problems. For several years, infants are at increased risk of lower respiratory tract infections (particularly

viral pneumonia or bronchiolitis) and may quickly develop respiratory decompensation if pulmonary infection occurs. The threshold for hospitalization should be low if signs of a respiratory infection or respiratory distress develop.

**Treatment**

• Nutrition supplementation

• Fluid restriction

• Diuretics

• Inhaled bronchodilators

• $O_2$ supplementation as needed

• Respiratory syncytial virus (RSV) monoclonal antibody

Treatment is supportive and includes nutritional supplementation, fluid restriction, diuretics, and perhaps inhaled bronchodilators. Respiratory infections must be diagnosed early and treated aggressively. Weaning from mechanical ventilation and supplemental $O_2$ should be accomplished as early as possible.

Feedings should achieve an intake of 150 calories/kg/day; caloric requirements are increased because of the increased work of breathing and to aid lung healing and growth.

Because pulmonary congestion and edema may develop, daily fluid intake is often restricted to about 120 to 140 mL/kg/day. Diuretic therapy is sometimes used: chlorothiazide 10 to 20 mg/kg po bid plus spironolactone 1 to 3 mg/kg po once/day or split into twice-daily doses. Furosemide (1 to 2 mg/kg IV or IM or 1 to 4 mg/kg po q 12 to 24 h for neonates and q 8 h for older infants) may be used for short periods, but prolonged use causes hypercalciuria with resultant osteoporosis, fractures, and renal calculi. If long-term diuretic use is required, chlorothiazide is preferred because it has fewer adverse effects. Hydration and serum electrolytes should be monitored closely during diuretic therapy.

Weeks or months of additional ventilator support, supplemental $O_2$, or both may be required for advanced BPD. Ventilator pressures and fraction of inspired $O_2$ ($FIO_2$) should be reduced as rapidly as tolerated, but the infant should not be allowed to become hypoxemic. Arterial oxygenation should be continuously monitored with a pulse oximeter and maintained at ≥ 88% saturation. Respiratory acidosis may occur during ventilator weaning and treatment and is acceptable as long as the pH remains > 7.25 and the infant does not develop severe respiratory distress.

Passive immunoprophylaxis with palivizumab, a monoclonal antibody to RSV, decreases RSV-related hospitalizations and ICU stays but is costly and is indicated primarily in high-risk infants (see p. 1411 for indications). During RSV season (November through April), children are given 15 mg/kg IM q 30 days until 6 mo after treatment of the acute illness. Infants > 6 mo also should be vaccinated against influenza.

Systemic or inhaled corticosteroids are discouraged except as a last-resort therapy for established BPD with rapidly worsening pulmonary status and impending death. Informed parental consent is required.

**Prevention**

Practices for prevention of BPD include

• Use of antenatal corticosteroids

• Prophylactic use of exogenous surfactant in selected high-risk infants (eg, < 30 wk gestation)

• Early therapeutic continuous positive airway pressure

- Early use of surfactant for treatment of respiratory distress syndrome
- Prophylactic use of methylxanthines to assist successful early ventilator therapy withdrawal
- Permissive hypercarbia and hypoxemia to achieve low ventilator pressures, volumes, or both
- Prophylactic use of vitamin A (5000 units IM 3 times/wk for a total of 12 doses) for infants with birth weight < 1000 g
- Avoidance of large volumes of fluid
- Early aggressive management of patent ductus arterious

Inhaled nitric oxide seems to be promising and is under investigation.

## Meconium Aspiration Syndrome

**Intrapartum meconium aspiration can cause inflammatory pneumonitis and mechanical bronchial obstruction, causing a syndrome of respiratory distress. Findings include tachypnea, rales and rhonchi, and cyanosis or desaturation. Diagnosis is suspected when there is respiratory distress after delivery through meconium-tinged amniotic fluid and is confirmed by chest x-ray. Treatment is vigorous suction immediately on delivery before neonates take their first breath, followed by respiratory support as needed. Prognosis depends on the underlying physiologic stressors.**

### Etiology

Physiologic stress at the time of labor and delivery (eg, due to hypoxia caused by umbilical cord compression or placental insufficiency or caused by infection) may cause the fetus to pass meconium into the amniotic fluid before delivery; meconium passage is noted in about 10 to 15% of births. During delivery, perhaps 5% of neonates with meconium passage aspirate the meconium, triggering lung injury and respiratory distress, termed meconium aspiration syndrome. Postterm infants delivered through reduced amniotic fluid volume are at risk of more severe disease because the less dilute meconium is more likely to cause airway obstruction.

### Pathophysiology

The mechanisms by which aspiration induces the clinical syndrome probably include

- Nonspecific cytokine release
- Airway obstruction
- Surfactant inactivation
- Chemical pneumonitis

Underlying physiologic stressors also may contribute. If complete bronchial obstruction occurs, atelectasis results; partial blockage leads to air trapping on expiration, resulting in hyperexpansion of the lungs and possibly pulmonary air leak (see p. 2874) with pneumomediastinum or pneumothorax. Persistent pulmonary hypertension can be associated with meconium aspiration as a comorbid condition or because of continuing hypoxia (see p. 2873).

Neonates also may aspirate vernix caseosa, amniotic fluid, or blood of maternal or fetal origin during delivery, which can cause respiratory distress and signs of aspiration pneumonia on chest x-ray.

### Symptoms and Signs

Signs include tachypnea, nasal flaring, retractions, cyanosis or desaturation, rales, rhonchi, and greenish yellow staining of the umbilical cord, nail beds, or skin. Meconium staining may be visible in the oropharynx and (on intubation) in the larynx and trachea. Neonates with air trapping may have a barrel-shaped chest and also symptoms and signs of pneumothorax, pulmonary interstitial emphysema, and pneumomediastinum (see p. 2875).

**Diagnosis**

• Meconium passage

• Respiratory distress

• Characteristic x-ray findings

Diagnosis is suspected when a neonate shows respiratory distress in the setting of meconium-tinged amniotic fluid. Diagnosis is confirmed by chest x-ray showing hyperinflation with variable areas of atelectasis and flattening of the diaphragm. Initial x-ray findings can be confused with the findings of transient tachypnea of the newborn (see p. 2877). Fluid may be seen in the lung fissures or pleural spaces, and air may be seen in the soft tissues or mediastinum. Because meconium may enhance bacterial growth and meconium aspiration syndrome is difficult to distinguish from bacterial pneumonia, cultures of blood and tracheal aspirate also should be taken.

**Prognosis**

Prognosis is generally good, although it varies with the underlying physiologic stressors; overall mortality is slightly increased. Infants with meconium aspiration syndrome may be at greater risk of asthma in later life.

**Treatment**

• Suctioning at birth before the first breath

• Endotracheal intubation as needed

• Mechanical ventilation as needed

• Supplemental $O_2$ as needed

• IV antibiotics

Immediate treatment, indicated for all neonates delivered through meconium, is vigorous suctioning of the mouth and nasopharynx using a DeLee suction apparatus as soon as the head is delivered and before the neonate breathes and cries. If suction returns no meconium and the neonate appears vigorous, observation without further intervention is appropriate. If the neonate has labored or depressed respirations, poor muscle tone, or is bradycardic (< 100 beats/min), the trachea should be intubated with a 3.5- or 4.0-mm endotracheal tube. A meconium aspirator connected to a suction apparatus is attached directly to the endotracheal tube, which then serves as the suction catheter. Suction is maintained while the endotracheal tube is removed. Reintubation and continuous positive airway pressure are indicated for continued respiratory distress, followed by mechanical ventilation and admission to the neonatal ICU as needed. Because positive pressure ventilation enhances risk of pulmonary air-leak syndrome, regular evaluation (including physical examination and chest x-ray) is important to detect this complication, which should be sought immediately in any intubated neonate whose BP, perfusion, or $O_2$ saturation suddenly worsens. See p. 2874 for treatment of air-leak syndromes.

Additional treatments may include surfactant for mechanically ventilated neonates with high $O_2$ requirements, which can decrease the need for extracorporeal membrane oxygenation, and antibiotics

(usually ampicillin and an aminoglycoside). Inhaled nitric oxide in the range of 5 to 20 ppm and high-frequency ventilation are other therapies that are used if refractory hypoxemia develops; they also may decrease need for extracorporeal membrane oxygenation.

## Persistent Pulmonary Hypertension of the Newborn

**Persistent pulmonary hypertension of the newborn is the persistence of or reversion to pulmonary arteriolar constriction, causing a severe reduction in pulmonary blood flow and right-to-left shunting. Symptoms and signs include tachypnea, retractions, and severe cyanosis or desaturation unresponsive to $O_2$. Diagnosis is by history, examination, chest x-ray, and response to $O_2$. Treatment is with $O_2$; alkalinization; high-frequency ventilation; nitric oxide; pressors, inotropes, or both; and extracorporeal membrane oxygenation if other therapies fail.**

Persistent pulmonary hypertension of the newborn is a disorder of pulmonary vasculature that affects term or postterm infants.

### Etiology

The most common causes involve

- Perinatal asphyxia or hypoxia

A history of meconium staining of amniotic fluid or meconium in the trachea is common. Hypoxia triggers reversion to or persistence of intense pulmonary arteriolar constriction, a normal state in the fetus.

Additional causes include

- Premature ductus arteriosus or foramen ovale closure, which increases fetal pulmonary blood flow and may be triggered by maternal NSAID use
- Polycythemia, which obstructs blood flow
- Congenital diaphragmatic hernia, in which one lung is severely hypoplastic, forcing most of the pulmonary blood flow through the other lung
- Neonatal sepsis presumably because vasoconstrictive prostaglandins are produced by activation of the cyclooxygenase pathway by bacterial phospholipids

### Pathophysiology

Whatever the cause, elevated pressure in the pulmonary arteries causes abnormal smooth muscle development and hypertrophy in the walls of the small pulmonary arteries and arterioles and right-to-left shunting via the ductus arteriosus or a foramen ovale, resulting in intractable systemic hypoxemia. Both pulmonary and systemic resistances are high, which leads to an increased load on the heart. This load increase may result in right heart dilation, tricuspid insufficiency, and right heart failure.

### Symptoms and Signs

Symptoms and signs include tachypnea, retractions, and severe cyanosis or desaturation unresponsive to supplemental $O_2$. In infants with a right-to-left shunt via a patent ductus arteriosus, oxygenation is higher in the right brachial artery than in the descending aorta; thus cyanosis may be differential (ie, $O_2$ saturation in the lower extremities is ≥ 5% lower than in the right upper extremity).

### Diagnosis

- Cyanosis unresponsive to $O_2$ therapy

• Echocardiogram

• X-ray to identify underlying disorders

Diagnosis should be suspected in any near-term infant with arterial hypoxemia, cyanosis, or both, especially one with a suggestive history whose $O_2$ saturation does not improve with administration of 100% $O_2$. Diagnosis is confirmed by echocardiogram, which can confirm the presence of elevated pressures in the pulmonary artery and simultaneously can exclude congenital heart disease. On x-ray, lung fields may be normal or may show changes due to the underlying disorder (eg, meconium aspiration syndrome, neonatal pneumonia, congenital diaphragmatic hernia).

**Prognosis**

An oxygenation index (mean airway pressure [cm $H_2O$] × fraction of inspired $O_2$ [$FIO_2$] × 100/$PaO_2$) > 40 predicts mortality of > 50%. Overall mortality ranges from 10 to 80% and is directly related to the oxygenation index but also varies with the underlying disorder. However, many survivors (perhaps one third) exhibit developmental delay, hearing deficits, functional disabilities, or a combination. This rate of disability may be no different from that of other infants with severe illness.

**Treatment**

• $O_2$ to dilate pulmonary vasculature and improve oxygenation

• Mechanical ventilation support

• Use of nitric oxide considered

• Extracorporeal membrane oxygenation as needed

• Circulatory support

Treatment with $O_2$, which is a potent pulmonary vasodilator, is begun immediately to prevent disease progression. $O_2$ is delivered via bag and mask or mechanical ventilation; mechanical distention of alveoli aids vasodilation. $FIO_2$ should initially be 1 but can be titrated downward to maintain $PaO_2$ between 50 and 90 mm Hg to minimize lung injury. Once $PaO_2$ is stabilized, weaning can be attempted by reducing $FIO_2$ in decrements of 2 to 3%, then reducing ventilator pressures; changes should be gradual, because a large drop in $PaO_2$ can cause recurrent pulmonary artery vasoconstriction. High-frequency oscillatory ventilation expands and ventilates the lungs while minimizing barotrauma and should be considered for infants with underlying lung disease in whom atelectasis and ventilation/perfusion (V/Q) mismatch may exacerbate the hypoxemia of persistent pulmonary hypertension of the newborn.

Inhaled nitric oxide relaxes endothelial smooth muscle, dilating pulmonary arterioles, which increases pulmonary blood flow and rapidly improves oxygenation in as many as half of patients. Initial dose is 20 ppm, titrated downward by effect.

Extracorporeal membrane oxygenation (see p. 2868) may be used in newborns with severe hypoxic respiratory failure defined by an oxygenation index > 35 to 40 despite maximum respiratory support.

Normal fluid, electrolyte, glucose, and Ca levels must be maintained. Infants should be kept in a neutral thermal environment and treated with antibiotics for possible sepsis until culture results are known. Inotropes and pressors may be required as part of circulatory support.

## Pulmonary Air-Leak Syndromes

**Pulmonary air-leak syndromes involve dissection of air out of the normal pulmonary airspaces.**

Air-leak syndromes include pulmonary interstitial emphysema, pneumomediastinum, pneumothorax, pneumopericardium, pneumoperitoneum, and subcutaneous emphysema. Pneumothorax and pneumomediastinum occur in 1 to 2% of normal neonates, probably because large negative intrathoracic forces created when the neonate starts breathing occasionally disrupt alveolar epithelium, which allows air to move from the alveoli into extra-alveolar soft tissues or spaces.

Air leak is more common and severe among neonates with lung disease, who are at risk because of poor lung compliance and the need for high airway pressures (eg, in respiratory distress) or because of air trapping (eg, meconium aspiration syndrome), which leads to alveolar overdistention.

Many affected neonates are asymptomatic; diagnosis is suspected clinically or because of deterioration in $O_2$ status and is confirmed by x-ray. Treatment varies by type of air leak but in ventilated infants always involves lowering inspiratory pressures to lowest tolerated settings. High-frequency ventilators may be helpful but are of unproven benefit.

**Pulmonary interstitial emphysema:** Pulmonary interstitial emphysema is leakage of air from alveoli into the pulmonary interstitium, lymphatics, or subpleural space. It usually occurs in infants with poor lung compliance, such as those with respiratory distress syndrome who are being treated with mechanical ventilation, but it may occur spontaneously. One or both lungs may be involved, and pathology may be focal or generalized within each lung. If dissection of air is widespread, respiratory status may acutely worsen because lung compliance suddenly is reduced.

Chest x-ray shows a variable number of cystic or linear lucencies in the lung fields. Some lucencies are elongated; others appear as enlarged subpleural cysts ranging from a few millimeters to several centimeters in diameter.

Pulmonary interstitial emphysema may resolve dramatically over 1 or 2 days or persist on x-ray for weeks. Some infants with severe respiratory disease and pulmonary interstitial emphysema develop bronchopulmonary dysplasia (BPD—see p. 2870), and the cystic changes of long-standing pulmonary interstitial emphysema then merge into the x-ray picture of BPD.

Treatment is mainly supportive. If one lung is significantly more involved than the other, the infant may be laid down on the side of the lung with the more severe pulmonary interstitial emphysema; this will help to compress the lung with pulmonary interstitial emphysema, thereby decreasing air leakage and perhaps improving ventilation of the normal (elevated) lung. If one lung is very severely affected and the other is mildly affected or uninvolved, differential bronchial intubation and ventilation of the less-involved lung also may be attempted; total atelectasis of the non-intubated lung soon results. Because only one lung is now being ventilated, ventilator settings and fraction of inspired $O_2$ may need to be altered. After 24 to 48 h, the endotracheal tube is pulled back into the trachea, at which time the air leak may have stopped.

**Pneumomediastinum:** Pneumomediastinum is dissection of air into connective tissue of the mediastinum (see also p. 2001); the air may further dissect into the subcutaneous tissues of the neck and scalp. Pneumomediastinum usually causes no symptoms or signs, though subcutaneous air causes crepitus. Diagnosis is by x-ray; in an anteroposterior view, air may form a lucency around the heart, whereas on a lateral view, air lifts the lobes of the thymus away from the cardiac silhouette (spinnaker sail sign). No treatment is usually needed, and the condition resolves spontaneously.

**Pneumopericardium:** Pneumopericardium is dissection of air into the pericardial sac. It affects mechanically ventilated infants almost exclusively. Most cases are asymptomatic, but if sufficient air accumulates, it can cause cardiac tamponade (see p. 2201). Diagnosis is suspected if infants experience acute circulatory collapse and is confirmed by lucency around the heart on x-ray or by return of air on pericardiocentesis using an angiocatheter and syringe. Treatment is pericardiocentesis followed by surgical insertion of a pericardial tube.

**Pneumoperitoneum:** Pneumoperitoneum is dissection of air into the peritoneum. It is generally not clinically significant but must be distinguished from pneumoperitoneum due to a ruptured abdominal viscus, which is a surgical emergency. Diagnosis is made by abdominal x-ray and physical examination. Clinical symptoms that include abdominal rigidity, absent bowel sounds, and signs of sepsis suggest

abdominal viscus injury.

**Pneumothorax:** Pneumothorax is dissection of air into the pleural space; sufficient accumulation of air causes tension pneumothorax (see p. 2002). Although sometimes asymptomatic, pneumothorax typically causes worsening of tachypnea, grunting, and cyanosis. Breath sounds decrease, and the chest enlarges on the affected side. Tension pneumothorax causes cardiovascular collapse.

Diagnosis is suspected by deterioration of respiratory status, by transillumination of the chest with a fiberoptic probe, or both. Diagnosis is confirmed by chest x-ray or, in the case of tension pneumothorax, return of air during thoracentesis.

Most small pneumothoraces resolve spontaneously, but larger and tension pneumothoraces require evacuation of the air in the pleural cavity. In tension pneumothorax, a scalp vein needle or an angiocatheter and syringe can be used to temporarily evacuate free air from the pleural space. Definitive treatment is insertion of an 8 or 10 French chest tube attached to continuous suction. Follow-up auscultation, transillumination, and x-ray confirm that the tube is functioning properly.

## Respiratory Distress Syndrome

(Hyaline Membrane Disease)

**Respiratory distress syndrome (RDS) is caused by pulmonary surfactant deficiency in the lungs of neonates, most commonly in those born at < 37 wk gestation. Risk increases with degree of prematurity. Symptoms and signs include grunting respirations, use of accessory muscles, and nasal flaring appearing soon after birth. Diagnosis is clinical; prenatal risk can be assessed with tests of fetal lung maturity. Treatment is surfactant therapy and supportive care.**

### Etiology

Surfactant is not produced in adequate amounts until relatively late in gestation; thus, risk of RDS increases with greater prematurity. Other risk factors include multifetal pregnancies, maternal diabetes, and being male and white.

Risk decreases with fetal growth restriction, preeclampsia or eclampsia, maternal hypertension, prolonged rupture of membranes, and maternal corticosteroid use.

Rare cases are hereditary, caused by mutations in surfactant protein (SP-B and SP-C) and ATP-binding cassette transporter *A3* (*ABCA3*) genes.

### Pathophysiology

Pulmonary surfactant is a mixture of phospholipids and lipoproteins secreted by type II pneumocytes (see p. 2766). It diminishes the surface tension of the water film that lines alveoli, thereby decreasing the tendency of alveoli to collapse and the work required to inflate them.

With surfactant deficiency, the lungs become diffusely atelectatic, triggering inflammation and pulmonary edema. Because blood passing through the atelectatic portions of lung is not oxygenated (forming a right-to-left intrapulmonary shunt), the infant becomes hypoxemic. Lung compliance is decreased, thereby increasing the work of breathing. In severe cases, the diaphragm and intercostal muscles fatigue, and $CO_2$ retention and respiratory acidosis develop.

**Complications:** Complications of RDS include intraventricular hemorrhage, periventricular white matter injury, tension pneumothorax, bronchopulmonary dysplasia, sepsis, and neonatal death. Intracranial complications have been linked to hypoxemia, hypercarbia, hypotension, swings in arterial BP, and low cerebral perfusion (see also Intracranial Hemorrhage on p. 2773 and Hemorrhagic Shock and Encephalopathy Syndrome on p. 2934).

### Symptoms and Signs

Symptoms and signs include rapid, labored, grunting respirations appearing immediately or within a few hours after delivery, with suprasternal and substernal retractions and flaring of the nasal alae. As atelectasis and respiratory failure progress, symptoms worsen, with cyanosis, lethargy, irregular breathing, and apnea.

Neonates weighing < 1000 g may have lungs so stiff that they are unable to initiate or sustain respirations in the delivery room.

On examination, breath sounds are decreased. Peripheral pulses may be decreased with peripheral extremity edema and decreased urine output.

**Diagnosis**

• Clinical presentation

• ABG (hypoxemia and hypercapnia)

• Chest x-ray

• Blood, CSF, and tracheal aspirate cultures

Diagnosis is by clinical presentation, including recognition of risk factors; ABGs showing hypoxemia and hypercapnia; and chest x-ray. Chest x-ray shows diffuse atelectasis classically described as having a ground-glass appearance with visible air bronchograms; appearance correlates loosely with clinical severity.

Differential diagnosis includes group B streptococcal pneumonia and sepsis, transient tachypnea of the newborn, persistent pulmonary hypertension, aspiration, pulmonary edema, and congenital cardiopulmonary anomalies. Neonates typically require cultures of blood, CSF, and possibly tracheal aspirate. Clinical diagnosis of group B streptococcal pneumonia is extremely difficult; thus, antibiotics usually are started pending culture results.

RDS can be anticipated prenatally using tests of fetal lung maturity, which measure surfactant obtained by amniocentesis or collected from the vagina (if membranes have ruptured) and which can help determine the optimal timing of delivery. These are indicated for elective deliveries before 39 wk when fetal heart tones, human chorionic gonadotropin levels, and ultrasound measurements cannot confirm gestational age and for nonelective deliveries between 34 wk and 36 wk. Risk of RDS is low when lecithin/sphingomyelin ratio is > 2, phosphatidyl glycerol is present, foam stability index = 47, surfactant/albumin ratio (measured by fluorescence polarization) is > 55 mg/g, or a combination.

**Treatment**

• Surfactant

• Supplementary $O_2$ as needed

• Mechanical ventilation as needed

Prognosis with treatment is excellent; mortality is < 10%. With adequate ventilatory support alone, surfactant production eventually begins, and once production begins, RDS resolves within 4 or 5 days. However, in the meantime, severe hypoxemia can result in multiple organ failure and death.

Specific treatment is intratracheal surfactant therapy. This therapy requires endotracheal intubation, which also may be necessary to achieve adequate ventilation and oxygenation. Less premature infants (those > 1 kg) and those with lower $O_2$ requirements (fraction of inspired $O_2$ [$FIO_2$] < 40 to 50%) may respond well to supplemental $O_2$ alone or to treatment with nasal continuous positive airway pressure. A

treatment strategy of early (within 20 to 30 min after birth) surfactant therapy is associated with significant decrease in duration of mechanical ventilation, lesser incidence of air leak syndromes, and lower incidence of bronchopulmonary dysplasia.

Surfactant hastens recovery and decreases risk of pneumothorax, interstitial emphysema, intraventricular hemorrhage, bronchopulmonary dysplasia, and neonatal mortality in the hospital and at 1 yr. However, neonates who receive surfactant for established RDS have an increased risk of apnea of prematurity. Options for surfactant replacement include beractant (a lipid bovine lung extract supplemented with proteins B and C, colfosceril palmitate, palmitic acid, and tripalmitin) 100 mg/kg q 6 h prn up to 4 doses; poractant alfa (a modified porcine-derived minced lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins B and C) 200 mg/kg followed by up to 2 doses of 100 mg/kg 12 h apart prn; and calfactant (a calf lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins B and C) 105 mg/kg q 12 h up to 3 doses prn. Lung compliance can improve rapidly after therapy. The ventilator peak inspiratory pressure may need to be lowered rapidly to reduce risk of a pulmonary air leak. Other ventilator parameters (eg, $FIO_2$, rate) also may need to be reduced.

**Prevention**

When a fetus must be delivered between 24 wk and 34 wk, giving the mother 2 doses of betamethasone 12 mg IM 24 h apart or 4 doses of dexamethasone 6 mg IV or IM q 12 h at least 48 h before delivery induces fetal surfactant production and reduces the risk of RDS or decreases its severity. (See also Preterm Labor on p. 2683.)

Prophylactic intratracheal surfactant therapy given to neonates that are at high risk of developing RDS (infants < 30 wk completed gestation especially in absence of antenatal corticosteroid exposure) has been shown to decrease risk of neonatal death and certain forms of pulmonary morbidity (eg, pneumothorax).

## Transient Tachypnea of the Newborn

(Neonatal Wet Lung Syndrome)

**Transient tachypnea of the newborn is respiratory distress caused by delayed resorption of fetal lung fluid.**

Transient tachypnea of the newborn affects premature infants, term infants delivered by cesarean section, and infants born with respiratory depression, all of whom have delayed clearance of fetal lung fluid. (Mechanisms for normal resorption of fetal lung fluid are discussed on p. 2766.) For unknown reasons, maternal diabetes and asthma are also risk factors. The disorder can occur in preterm infants with respiratory distress syndrome and in term infants born through meconium-stained amniotic fluid.

Transient tachypnea of the newborn is suspected when the infant develops respiratory distress shortly after birth. Symptoms include tachypnea, intracostal and subcostal retractions, grunting, nasal flaring, and possible cyanosis.

Pneumonia and sepsis may have similar manifestations, so chest x-ray, CBC, and blood cultures usually are done. Chest x-ray shows hyperinflated lungs with streaky perihilar markings, giving the appearance of a shaggy heart border while the periphery of the lungs is clear. Fluid is often seen in the lung fissures. If initial findings are indeterminate or suggest infection, antibiotics (eg, ampicillin, gentamicin) are given while awaiting culture results.

Recovery usually occurs within 2 to 3 days. Treatment is supportive and involves giving $O_2$ by hood and monitoring ABGs or pulse oximetry. Rarely, extremely premature infants, those with neurologic depression at birth, or both require continuous positive airway pressure and occasionally even mechanical ventilation.

## Bacterial Tracheitis

(Pseudomembranous Croup)

**Bacterial tracheitis is bacterial infection of the trachea.**

Bacterial tracheitis is uncommon and can affect children of any age. *Staphylococcus aureus* and group A β-hemolytic streptococci are involved most frequently. Onset is acute and is characterized by respiratory stridor, high fever, and often copious purulent secretions. Rarely, bacterial tracheitis may develop as a complication of viral croup or endotracheal intubation. As in patients with epiglottitis, the child may have marked toxicity and respiratory distress that may progress rapidly and may require intubation.

Diagnosis is suspected clinically and can be confirmed by direct laryngoscopy, which reveals purulent secretions and inflammation in the subglottic area with a shaggy, purulent membrane or by lateral neck x-ray, which reveals subglottic narrowing that may be irregular as opposed to the symmetric tapering typical of croup.

Treatment in severe cases is the same as that of epiglottitis (see p. 476); whenever possible, endotracheal intubation should be done in controlled circumstances by a clinician skilled in managing a pediatric airway (see p. 2273). Initial antibiotics should cover *S. aureus* and streptococcal species; cefuroxime or an equivalent IV preparation may be appropriate empirically unless methicillin-resistant staphylococcus is prevalent in the community, in which case vancomycin should be used. Therapy for critically ill children should be guided by a consultant knowledgeable in local susceptibility patterns. Once definitive microbial diagnosis is made, coverage is narrowed and continued for ≥ 10 days.

Complications include bronchopneumonia, sepsis, and retropharyngeal cellulitis or abscess. Subglottic stenosis secondary to prolonged intubation is uncommon. Most children treated appropriately recover without sequelae.

## Bronchiolitis

**Bronchiolitis is an acute viral infection of the lower respiratory tract affecting infants < 24 mo and is characterized by respiratory distress, wheezing, and crackles. Diagnosis is suspected by history, including presentation during a known epidemic; the primary cause, respiratory syncytial virus, can be identified with a rapid assay. Treatment is supportive with $O_2$ and hydration. Prognosis is generally excellent, but some patients develop apnea or respiratory failure.**

Bronchiolitis often occurs in epidemics and mostly in children < 24 mo, with a peak incidence in infants < 6 mo. The annual incidence in the first year of life is about 11 cases/100 children. Most cases occur between November and April, with a peak incidence during January and February.

### Etiology

Most cases are caused by

• Respiratory syncytial virus (RSV)

• Parainfluenza 3 virus

Less frequent causes are influenza A and B, parainfluenza 1 and 2, metapneumovirus, and adenoviruses. Rhinoviruses, enteroviruses, measles virus, and *Mycoplasma pneumoniae* are uncommon causes.

### Pathophysiology

The virus spreads from the upper respiratory tract to the medium and small bronchi and bronchioles, causing epithelial necrosis and initiating an inflammatory response. The developing edema and exudate result in partial obstruction, which is most pronounced on expiration and leads to alveolar air trapping. Complete obstruction and absorption of the trapped air may lead to multiple areas of atelectasis.

### Symptoms and Signs

Typically, an affected infant has URI symptoms with progressively increasing respiratory distress characterized by tachypnea, retractions, and a wheezy or hacking cough. Young infants may present with recurrent apneic spells followed by more typical symptoms and signs over 24 to 48 h. Signs of distress may include circumoral cyanosis, deepening retractions, and audible wheezing. Fever is usually but not always present. Infants initially appear nontoxic and in no distress, despite tachypnea and retractions, but may become increasingly lethargic as the infection progresses. Hypoxemia is the rule in more severely affected infants. Dehydration may develop from vomiting and decreased oral intake. With fatigue, respirations may become more shallow and ineffective, leading to respiratory acidosis. Auscultation reveals wheezing, prolonged expiration, and, often, fine moist crackles. Many children have accompanying acute otitis media.

### Diagnosis

• Clinical presentation

• Pulse oximetry

• Chest x-ray as needed

• RSV antigen test from nasal swab or washing for seriously ill children

Diagnosis is suspected by history, examination, and occurrence of the illness as part of an epidemic. Symptoms similar to bronchiolitis can result from asthma, which is more likely in a child > 18 mo of age, especially if previous episodes of wheezing and a family history of asthma have been documented. Gastric reflux with aspiration of gastric contents also may cause the clinical picture of bronchiolitis; multiple episodes in an infant may be clues to this diagnosis. Foreign body aspiration occasionally causes wheezing and should be considered if the onset is sudden and not associated with manifestations of URI. Heart failure associated with a left-to-right shunt manifesting at age 2 to 3 mo also can be confused with bronchiolitis.

Patients suspected of having bronchiolitis should undergo pulse oximetry to evaluate oxygenation. No further testing is required for mild cases with normal $O_2$ levels, but in cases of hypoxemia, a chest x-ray supports the diagnosis, typically showing hyperinflated lungs, depressed diaphragm, and prominent hilar markings. Infiltrates may be present from atelectasis as well as RSV pneumonia, which is relatively common among infants with RSV bronchiolitis. RSV rapid antigen testing done on a nasal swab or washing is diagnostic but not generally necessary; it may be reserved for patients with illness severe enough to require hospitalization. Other laboratory testing is nonspecific; about two thirds of the children have WBC counts of 10,000 to 15,000/µL. Most have 50 to 75% lymphocytes.

### Prognosis

Prognosis is excellent. Most children recover in 3 to 5 days without sequelae, although wheezing and cough may continue for 2 to 4 wk. Mortality is < 1% when medical care is adequate. An increased incidence of asthma is suspected in children who have had bronchiolitis in early childhood, but the association is controversial and the incidence seems to decrease as children age.

### Treatment

• Supportive therapy

• $O_2$ supplementation as needed

• IV hydration as needed

Treatment is supportive, and most children can be managed at home with hydration and comfort

measures.

**Indications for hospitalization** include accelerating respiratory distress, ill appearance (eg, cyanosis, lethargy, fatigue), apnea by history, hypoxemia, and inadequate oral intake. Children with underlying disorders such as cardiac disease, immunodeficiency, or bronchopulmonary dysplasia, which put them at high risk of severe or complicated disease, also should be considered candidates for hospitalization.

In hospitalized children, 30 to 40% $O_2$ delivered by tent or face mask is usually sufficient to maintain $O_2$ saturation > 90%. Endotracheal intubation is indicated for severe recurrent apnea, hypoxemia unresponsive to $O_2$ therapy, or $CO_2$ retention or if the child cannot clear bronchial secretions.

Hydration may be maintained with frequent small feedings of clear liquids. For sicker children, fluids should be given IV initially, and the level of hydration should be monitored by urine output and specific gravity and by serum electrolyte determinations.

There is some evidence that systemic corticosteroids are beneficial when given very early in the course of the illness or in children with underlying corticosteroid-responsive conditions (eg, bronchopulmonary dysplasia, asthma), but benefit in most hospitalized infants is unproven.

Antibiotics should be withheld unless a secondary bacterial infection (a rare sequela) occurs. Bronchodilators are not uniformly effective, but a substantial subset of children may respond with short-term improvement. This is particularly true of infants who have wheezed previously. Hospital stays probably are not shortened.

Ribavirin, an antiviral drug active in vitro against RSV, influenza, and measles, is probably not effective clinically and is no longer recommended; it also is potentially toxic to hospital staff. RSV immune globulin has been tried but is probably ineffective.

Prevention of RSV infection by passive immunoprophylaxis with monoclonal antibody to RSV (palivizumab) decreases the frequency of hospitalization but is costly and is indicated primarily in high-risk infants (see p. 1411 for indications and dosage).

## Croup

(Laryngotracheobronchitis)

**Croup is acute inflammation of the upper and lower respiratory tracts most commonly caused by parainfluenza virus type 1 infection. It is characterized by a barking cough and inspiratory stridor. Diagnosis is usually obvious clinically but can be made by anteroposterior neck x-ray. Treatment is antipyretics, hydration, nebulized racemic epinephrine, and corticosteroids. Prognosis is excellent.**

Croup affects mainly children aged 6 mo to 3 yr.

### Etiology

The parainfluenza viruses, especially type 1, are the most common pathogens. Less common causes are respiratory syncytial virus (RSV) and influenza A and B viruses, followed by adenovirus, enterovirus, rhinovirus, measles virus, and *Mycoplasma pneumoniae*. Croup caused by influenza may be particularly severe and may occur in a broader age range of children.

Seasonal outbreaks are common. Cases caused by parainfluenza viruses tend to occur in the fall; those caused by RSV and influenza viruses tend to occur in the winter and spring. Spread is usually through the air or by contact with infected secretions.

### Pathophysiology

The infection causes inflammation of the larynx, trachea, bronchi, bronchioles, and lung parenchyma.

Obstruction caused by swelling and inflammatory exudates develops and becomes pronounced in the subglottic region. Obstruction increases the work of breathing; rarely, tiring results in hypercapnia. Atelectasis may occur concurrently if the bronchioles become obstructed.

### Symptoms and Signs

Croup is usually preceded by URI symptoms. A barking, often spasmodic, cough and hoarseness then occur, commonly at night; inspiratory stridor may be present as well. The child may awaken at night with respiratory distress, tachypnea, and retractions. In severe cases, cyanosis with increasingly shallow respirations may develop as the child tires.

The obvious respiratory distress and harsh inspiratory stridor are the most dramatic physical findings. Auscultation reveals prolonged inspiration and stridor. Rales also may be present, indicating lower airway involvement. Breath sounds may be diminished with atelectasis. Fever is present in about half of children. The child's condition may seem to have improved in the morning but worsens again at night.

Recurrent episodes are often called spasmodic croup. Allergy or airway reactivity may play a role in spasmodic croup, but the clinical manifestations cannot be differentiated from those of viral croup. Also, spasmodic croup usually is initiated by a viral infection.

### Diagnosis

• Clinical presentation (eg, barking cough, inspiratory stridor)

• Anteroposterior (AP) and lateral neck x-rays as needed

Diagnosis is usually obvious by the barking nature of the cough. Similar inspiratory stridor can result from epiglottitis, bacterial tracheitis, foreign body, diphtheria, and retropharyngeal abscess. Epiglottitis (see p. 475), retropharyngeal abscess (see p. 471), and bacterial tracheitis (see p. 2878) have a more rapid onset and cause a more toxic appearance, odynophagia, and fewer upper respiratory tract symptoms. A foreign body may cause respiratory distress and a typical croupy cough, but fever and a preceding URI are absent. Diphtheria is excluded by a history of adequate immunization and is confirmed by identification of the organism in viral cultures of scrapings from typical grayish diphtheritic membrane.

If the diagnosis is unclear, patients should have AP and lateral x-rays of the neck and chest; subepiglottic narrowing (steeple sign) seen on AP neck x-ray supports the diagnosis. Seriously ill patients, in whom epiglottitis is a concern, should be examined in the operating room by appropriate specialists able to establish an airway (see p. 476). Patients should have pulse oximetry, and those with respiratory distress should have ABG measurement.

### Treatment

• For outpatients, cool humidified air and possibly a single dose of oral corticosteroids

• For inpatients, humidified $O_2$, racemic epinephrine, and oral corticosteroids

The illness usually lasts 3 to 4 days and resolves spontaneously. A mildly ill child may be cared for at home with hydration and antipyretics. Keeping the child comfortable is important, because fatigue and crying can aggravate the condition. Humidification devices (eg, cold-steam vaporizers or humidifiers) may ameliorate upper airway drying and are frequently used at home by families but have not been shown to alter the course of the illness. The vast majority of children with croup recover completely.

Increasing or persistent respiratory distress, tachycardia, fatigue, cyanosis or hypoxemia, or dehydration indicates need for hospitalization. Pulse oximetry is helpful for assessing and monitoring severe cases. If $O_2$ saturation falls below 92%, humidified $O_2$ should be given, and ABGs should be measured to assess $CO_2$ retention. A 30 to 40% inspired $O_2$ concentration is usually adequate. $CO_2$ retention ($PaCO_2$ > 45 mm Hg) generally indicates fatigue and the need for endotracheal intubation, as does inability to maintain

oxygenation.

Nebulized racemic epinephrine 5 to 10 mg in 3 mL of saline q 2 h offers symptomatic relief and relieves fatigue. However, the effects are transient; the course of the illness, the underlying viral infection, and the $PaO_2$ are not altered by its use. Tachycardia and other adverse effects may occur.

High-dose dexamethasone 0.6 mg/kg IM or po once (maximum dose 10 mg) may benefit children early in the first 24 h of the disease. It can help prevent hospitalization or help the child who is hospitalized with moderate to severe croup. The viruses that most commonly cause croup do not usually predispose to secondary bacterial infection, and antibiotics are rarely indicated.

# Chapter 284. Cystic Fibrosis

## Introduction

**Cystic fibrosis (CF) is an inherited disease of the exocrine glands affecting primarily the GI and respiratory systems. It leads to chronic lung disease, exocrine pancreatic insufficiency, hepatobiliary disease, and abnormally high sweat electrolytes. Diagnosis is by sweat test or identification of 2 CF-causing mutations in patients with characteristic symptoms or a positive newborn screening test result. Treatment is supportive through aggressive multidisciplinary care.**

CF is the most common life-threatening genetic disease in the white population. In the US, it occurs in about 1/3,300 white births, 1/15,300 black births, and 1/32,000 Asian-American births. Because of improved treatment and life expectancy, 45% of patients are adults.

### Etiology

CF is carried as an autosomal recessive trait by about 3% of the white population. The responsible gene has been localized on the long arm of chromosome 7. It encodes a membrane-associated protein called the cystic fibrosis transmembrane conductance regulator (CFTR). The most common gene mutation, $\Delta F_{508}$, occurs in about 70% of CF alleles; > 1500 less common CFTR mutations have been identified. CFTR seems to be part of a cAMP-regulated Cl channel, regulating Cl and Na transport across epithelial membranes. A number of additional functions are considered likely. Disease manifests only in homozygotes. Heterozygotes may show subtle abnormalities of epithelial electrolyte transport but are clinically unaffected.

### Pathophysiology

Nearly all exocrine glands are affected in varying distribution and degree of severity. Glands may

- Become obstructed by viscid or solid eosinophilic material in the lumen (pancreas, intestinal glands, intrahepatic bile ducts, gallbladder, and submaxillary glands)

- Appear histologically abnormal and produce excessive secretions (tracheobronchial and Brunner's glands)

- Appear histologically normal but secrete excessive Na and Cl (sweat, parotid, and small salivary glands)

**Respiratory:** Although the lungs are generally histologically normal at birth, most patients develop pulmonary disease beginning in infancy or early childhood. Mucus plugging and chronic bacterial infection, accompanied by a pronounced inflammatory response, damage the airways, ultimately leading to bronchiectasis and respiratory insufficiency. The course is characterized by episodic exacerbations with infection and progressive decline in pulmonary function.

Pulmonary damage is probably initiated by diffuse obstruction in the small airways by abnormally thick mucus secretions. Bronchiolitis and mucopurulent plugging of the airways occur secondary to obstruction and infection. Airway changes are more common than parenchymal changes, and emphysema is not prominent. About 40% of patients have bronchial hyperreactivity that is responsive to bronchodilators; however, benefits of bronchodilator therapy may not persist into adulthood. Chronic hypoxemia results in muscular hypertrophy of the pulmonary arteries, pulmonary hypertension, and right ventricular hypertrophy. Much of the pulmonary damage may be caused by inflammation secondary to the release of proteases by neutrophils in the airways.

The lungs of most patients are colonized by pathogenic bacteria. Early in the course, *Staphylococcus aureus* is the most common pathogen, but as the disease progresses, *Pseudomonas aeruginosa* is most frequently isolated. A mucoid variant of *P. aeruginosa* is uniquely associated with CF. Colonization with *Burkholderia cepacia* occurs in about 3% of patients and may be associated with rapid pulmonary

deterioration.

**GI:** The pancreas, intestines, and hepatobiliary system are frequently affected. Exocrine pancreatic function is compromised in 85 to 95% of patients. Exceptions are a subset of patients who have certain mild CF mutations, in whom pancreatic function is unaffected. Patients with pancreatic insufficiency have malabsorption of fats (and fat-soluble vitamins) and protein. Duodenal fluid is abnormally viscid and shows absence or diminution of enzyme activity and decreased $HCO_3^-$ concentration; stool trypsin and chymotrypsin are absent or diminished. Endocrine pancreatic dysfunction is less common, but about 40% of older patients have abnormal glucose tolerance secondary to reduced and delayed insulin response, and about 17% develop diabetes.

Bile duct involvement with bile stasis and biliary plugging leads to asymptomatic hepatic fibrosis in 30% of patients. About 5 to 6% of patients progress to irreversible multi-nodular biliary cirrhosis with varices and portal hypertension, usually by 12 yr of age. Hepatocellular failure is a rare and late event. There is an increased incidence of cholelithiasis, which is usually asymptomatic.

Abnormally viscid intestinal secretions often cause meconium ileus in neonates (see p. 2801) and sometimes meconium plugging of the colon. Older children and adults also may develop intestinal obstruction.

Other GI problems include intussusception, rectal prolapse, periappendiceal abscess, pancreatitis, an increased risk of cancer of the hepatobiliary and GI tracts, gastroesophageal reflux, and esophagitis.

**Other:** Infertility occurs in 98% of adult men secondary to maldevelopment of the vas deferens or to other forms of obstructive azoospermia. In women, fertility is decreased secondary to viscid cervical secretions, although many women with CF have carried pregnancies to term. However, the incidence of maternal complications and preterm births is increased.

Other complications include osteopenia/osteoporosis, renal stones, iron deficiency anemia, and episodic arthralgias/arthritis.

### Symptoms and Signs

**Respiratory:** Fifty percent of patients not diagnosed through newborn screening present with pulmonary manifestations, often beginning in infancy. Recurrent or chronic infections manifested by cough and wheezing are common. Cough is the most troublesome complaint, often accompanied by sputum, gagging, vomiting, and disturbed sleep. Intercostal retractions, use of accessory muscles of respiration, a barrel-chest deformity, digital clubbing, and cyanosis occur with disease progression. Upper respiratory tract involvement includes nasal polyposis and chronic or recurrent sinusitis. Adolescents may have retarded growth, delayed onset of puberty, and a declining tolerance for exercise. Pulmonary complications in adolescents and adults include pneumothorax, infection with nontuberculous mycobacteria, hemoptysis, and right heart failure secondary to pulmonary hypertension.

**GI:** Meconium ileus due to obstruction of the ileum by viscid meconium may be the earliest sign and is present in 15 to 20% of affected neonates. It typically manifests with abdominal distention, vomiting, and failure to pass meconium. Some infants have intestinal perforation, with signs of peritonitis and shock. Infants with meconium plug syndrome have a delayed passage of meconium. They can have similar signs of obstruction or very mild and transient symptoms that go unnoticed. Older patients with CF can have partial bowel obstruction similar to what is seen in infancy. Distal intestinal obstruction syndrome (DIOS) can occur in 10 to 20% of adolescents and adults with CF.

In infants without meconium ileus, disease onset may be heralded by a delay in regaining birth weight and inadequate weight gain at 4 to 6 wk of age.

Occasionally, infants who are undernourished, especially if on hypoallergenic formula or soy formula, present with generalized edema secondary to protein malabsorption.

Pancreatic insufficiency is usually clinically apparent early in life and may be progressive. Manifestations include the frequent passage of bulky, foul-smelling, oily stools; abdominal protuberance; and poor growth pattern with decreased subcutaneous tissue and muscle mass despite a normal or voracious appetite. Clinical manifestations may occur secondary to deficiency of fat-soluble vitamins.

Rectal prolapse occurs in 20% of untreated infants and toddlers. Gastroesophageal reflux is relatively common among older children and adults.

**Other:** Excessive sweating in hot weather or with fever may lead to episodes of hypotonic dehydration and circulatory failure. In arid climates, infants may present with chronic metabolic alkalosis. Salt crystal formation and a salty taste on the skin are highly suggestive of CF.

**Diagnosis**

• Suggested by a positive prenatal or newborn screening, family history, or symptomatic presentation

• Confirmed by a sweat test showing elevated sweat Cl on ≥ 2 occasions

• Sometimes confirmed by genetic testing or in vivo ion transport abnormalities across nasal epithelium

People are suspected of having CF by prenatal or newborn screening, family history, or symptoms. In all cases, diagnosis needs to be confirmed by a quantitative pilocarpine iontophoresis sweat test.

**Sweat testing:** In this test, localized sweating is stimulated with pilocarpine, the amount of sweat is measured, and its Cl concentration is determined (see Table 284-1). The results are valid after 48 h of life, but an adequate sweat sample (> 75 mg on filter paper or > 15 µL in microbore tubing) may be difficult to obtain before 2 wk of age. False-negative results are rare but may occur in the presence of edema and hypoproteinemia or an inadequate quantity of sweat. False-positive results are usually due to technical error. Transient elevation of sweat Cl concentration can occur from psychosocial deprivation (eg, child abuse, neglect) and in patients with anorexia nervosa. Although the sweat Cl concentration increases slightly with age, the sweat test is valid at all ages. A positive sweat test result should be confirmed by a 2nd sweat test or by identification of 2 CF-causing mutations.

**Intermediate sweat test results:** A small subset of patients have a mild or partial CF phenotype and sweat Cl values that are persistently in the intermediate or even normal range. In addition, there are patients who have single organ manifestations such as pancreatitis, chronic sinusitis, or congenital bilateral absence of the vas deferens that may be due to partial CFTR protein dysfunction. In some of these patients, the diagnosis of CF can be confirmed by the identification of 2 CF-causing mutations. If 2 CF-causing mutations are not identified, ancillary evaluations such as pancreatic function testing and pancreatic imaging, high-resolution chest CT, pulmonary function testing, urogenital evaluation in males, and bronchoalveolar lavage including assessment of microbial flora may be useful. Additional potentially helpful tests include expanded CFTR genetic analysis and measurement of nasal transepithelial potential difference (based on the observation of increased Na reabsorption across epithelium that is relatively impermeable to Cl in patients with CF).

[**Table 284-1.** Sweat Cl Concentration Ranges]

**Pancreatic tests:** Pancreatic function should be assessed at the time of diagnosis, usually by measuring 72 h fecal fat excretion or the concentration of human pancreatic elastase in stool. This latter test is valid even in the presence of exogenous pancreatic enzymes. Infants who are initially pancreatic sufficient and who carry 2 severe mutations should have serial measurements to detect progression to pancreatic insufficiency.

**Respiratory assessment:** Chest x-rays are done at times of pulmonary deterioration or exacerbations and routinely every 1 to 2 yr. High-resolution CT may be helpful to more precisely define the extent of lung damage and to detect subtle airway abnormalities. Both may show hyperinflation and bronchial wall thickening as the earliest findings. Subsequent changes include areas of infiltrate, atelectasis, and hilar

adenopathy. With advanced disease, segmental or lobar atelectasis, cyst formation, bronchiectasis, and pulmonary artery and right ventricular enlargement occur. Branching, fingerlike opacifications that represent mucoid impaction of dilated bronchi are characteristic.

Sinus CT studies are indicated in patients with significant sinus symptoms or nasal polyps in whom endoscopic sinus surgery is being considered. These studies almost always show persistent opacification of the paranasal sinuses.

Pulmonary function tests are the best indicators of clinical status and should be done 2 to 4 times/yr. Pulmonary function can now be evaluated in infants by using a raised volume rapid thoracoabdominal compression technique. Pulmonary function tests indicate hypoxemia; reduction in forced vital capacity (FVC), forced expiratory volume in 1 sec ($FEV_1$), forced expiratory flow between 25% and 75% expired volume ($FEF_{25-75}$), and $FEV_1$/FVC ratio; and an increase in residual volume and the ratio of residual volume to total lung capacity. Fifty percent of patients have evidence of reversible airway obstruction as shown by improvement in pulmonary function after aerosol administration of a bronchodilator.

Oropharyngeal or sputum cultures should be done 2 to 4 times/yr, especially in patients not yet colonized with *P. aeruginosa*. Bronchoscopy/bronchoalveolar lavage is indicated when it is important to precisely define the patient's lower airway microbial flora (eg, to direct antibiotic selection).

**Newborn screening:** Newborn screening for CF is rapidly expanding in the US and should be universal by 2010. Screening is based on detecting an elevated concentration of immunoreactive trypsinogen (IRT) in the blood. There are two methods of confirming an elevated IRT level. In one method, a second IRT test is done, which, if also elevated, is followed by a sweat test. In the other method, an elevated IRT level is followed by CFTR mutation testing and, if 1 or 2 mutations are identified, then a sweat test is done. Both strategies have about 95% sensitivity.

**Carrier screening:** CF carrier screening is available in the US and is recommended for couples who are planning a pregnancy or seeking prenatal care. If both potential parents carry a CFTR mutation, prenatal screening of the fetus can be done by chorionic villus sampling or amniocentesis. Prenatal counseling in such cases is complicated by the wide phenotypic variability of CF and incomplete information on the clinical consequences of many of the CFTR mutations that are identified through screening.

### Prognosis

The course is largely determined by the degree of pulmonary involvement. Deterioration is inevitable, leading to debilitation and eventual death, usually due to a combination of respiratory failure and cor pulmonale. Prognosis has improved steadily over the past 5 decades, mainly because of aggressive treatment before the onset of irreversible pulmonary changes. Median survival in the US is to age 37 yr. Long-term survival is significantly better in patients without pancreatic insufficiency. Outcomes are also affected by CFTR mutation profile, modifier genes, airway microbiology, exposure to air pollutants (including tobacco smoke), and socioeconomic status. The $FEV_1$, adjusted for age and sex, is the best predictor of survival.

### Treatment

• Comprehensive, multidisciplinary support

• Antibiotics, aerosol drugs to thin airway secretions, and physical maneuvers to clear airway secretions

• Inhaled bronchodilators and sometimes corticosteroids for responders

• Pancreatic enzyme supplementation

Comprehensive and intensive therapy should be directed by an experienced physician working with a multidisciplinary team that includes other physicians, nurses, dieticians, physical and respiratory therapists, counselors, pharmacists, and social workers. The goals of therapy are maintenance of normal

nutritional status, prevention or aggressive treatment of pulmonary and other complications, encouragement of physical activity, and provision of psychosocial support. With appropriate support, most patients can make an age-appropriate adjustment at home and school. Despite myriad problems, the educational, occupational, and marital successes of patients are impressive.

**Respiratory:** Treatment of pulmonary problems centers on prevention of airway obstruction and prophylaxis against and control of pulmonary infection. Prophylaxis against pulmonary infections includes maintenance of pertussis, *Haemophilus influenzae*, varicella, *Streptococcus pneumoniae*, and measles immunity and annual influenza vaccination. In patients exposed to influenza, a neuraminidase inhibitor can be used prophylactically. Giving palivizumab to infants with CF for prevention of respiratory syncytial virus infection has been shown to be safe, but efficacy has not been documented.

Chest physical therapy consisting of postural drainage, percussion, vibration, and assisted coughing is recommended at the first indication of pulmonary involvement (see p. 1867). In older patients, alternative airway clearance techniques, such as active cycle of breathing, autogenic drainage, positive expiratory pressure devices, and mechanical vest therapy, may be effective.

For those with reversible airway obstruction, bronchodilators may be given by aerosol. Corticosteroids by aerosol usually are not effective. $O_2$ therapy is indicated for patients with severe pulmonary insufficiency and hypoxemia.

Mechanical ventilation is generally not indicated for chronic respiratory failure. Its use should be restricted to patients with good baseline status in whom acute reversible respiratory complications develop, in association with pulmonary surgery, or to patients in whom lung transplantation is imminent. Noninvasive positive pressure ventilation nasally or by face mask also can be beneficial. Oral expectorants are widely used, but few data support their efficacy. Cough suppressants should be discouraged. Long-term daily aerosol therapy with dornase alfa (recombinant human deoxyribonuclease) as well as 7% hypertonic saline has been shown to slow the rate of decline in pulmonary function and to decrease the frequency of severe respiratory tract exacerbations.

Pneumothorax can be treated with closed chest tube thoracostomy drainage. Open thoracotomy or thoracoscopy with resection of pleural blebs and sponge abrasion of the pleural surfaces is effective in treating recurrent pneumothoraces.

Massive or recurrent hemoptysis is treated by embolizing involved bronchial arteries.

Oral corticosteroids are indicated in infants with prolonged bronchiolitis and in patients with refractory bronchospasm, allergic bronchopulmonary aspergillosis, and inflammatory complications (eg, arthritis, vasculitis). Long-term use of alternate-day corticosteroid therapy can slow the decline in pulmonary function, but because of corticosteroid-related complications, it is not recommended for routine use. Patients receiving corticosteroids must be closely monitored for evidence of diabetes and linear growth retardation.

Ibuprofen, when given over several years at a dose sufficient to achieve a peak plasma concentration between 50 and 100 µg/mL, has been shown to slow the rate of decline in pulmonary function, especially in children 5 to 13 yr. The appropriate dose must be individualized based on pharmacokinetic studies.

**Antibiotics:** Antibiotics should be used in symptomatic patients according to culture and sensitivity testing. A penicillinase-resistant penicillin (eg, cloxacillin or dicloxacillin) or a cephalosporin (eg, cephalexin) is the drug of choice for staphylococci. Erythromycin, amoxicillin/clavulanate, ampicillin, tetracycline, linezolid, trimethoprim/sulfamethoxazole, or occasionally chloramphenicol may be used individually or in combination for protracted ambulatory therapy of pulmonary infection due to a variety of organisms. Fluoroquinolones are effective against sensitive strains of *P. aeruginosa* and have been used safely in young children.

For severe pulmonary exacerbations, especially in patients colonized with *P. aeruginosa*, parenteral antibiotic therapy is advised. Patients often require hospital admission, but carefully selected patients can safely receive the therapy at home. Combinations of an aminoglycoside (eg, tobramycin, gentamicin) and

an antipseudomonal penicillin are given IV. IV administration of cephalosporins and monobactams with antipseudomonal activity may also be useful. The usual starting dose of tobramycin or gentamicin is 2.5 to 3.5 mg/kg tid, but higher doses (3.5 to 4 mg/kg tid) may be required to achieve acceptable serum concentrations (peak level 8 to 10 µg/mL [11 to 17 µmol/L], trough value of < 2 µg/mL [< 4 µmol/L]). Alternatively, tobramycin can be given safely and effectively in one daily dose (10 to 12 mg/kg). Because of enhanced renal clearance, large doses of some penicillins may be required to achieve adequate serum levels. The goal of treating pulmonary infections should be to improve the patient's clinical status sufficiently so that continuous use of antibiotics is unnecessary. However, in patients who are colonized with *P. aeruginosa*, long-term use of alternate-month aerosol tobramycin therapy and oral azithromycin given 3 times/wk may be effective in improving or stabilizing pulmonary function and decreasing the frequency of pulmonary exacerbations.

In symptomatic patients who are chronically colonized with *P. aeruginosa*, the role of antibiotic therapy is to improve clinical parameters and possibly reduce the bacterial burden in the airways. Eradication of *Pseudomonas* is not usually possible. It has been shown, however, that early antibiotic treatment around the time of initial airway colonization with nonmucoid strains of *P. aeruginosa* may be effective in eradicating the organism for some period of time. Treatment strategies vary but usually consist of inhaled tobramycin or colistin often in association with an oral fluoroquinolone.

**GI:** Neonatal intestinal obstruction can sometimes be relieved by enemas containing a hyperosmolar or iso-osmolar radiopaque contrast material; otherwise, surgical enterostomy to flush out the viscid meconium in the intestinal lumen may be necessary. After the neonatal period, episodes of partial intestinal obstruction (distal intestinal obstruction syndrome) can be treated with enemas containing a hyperosmolar or iso-osmolar radiopaque contrast material or acetylcysteine, or by oral administration of a balanced intestinal lavage solution. A stool softener such as dioctyl sodium sulfosuccinate or lactulose may help prevent such episodes. Ursodeoxycholic acid, a hydrophilic bile acid, is often used in patients with liver disease caused by CF, but there is little evidence to support its efficacy.

**Pancreatic enzyme replacement** should be given with all meals and snacks. The most effective enzyme preparations contain pancrelipase in pH-sensitive, enteric-coated micro-spheres or microtablets. Infants are usually started at a dose of 2000 to 4000 IU lipase per 120 mL of formula or per breastfeeding session. After infancy, weight-based dosing is used starting at 1000 IU lipase/kg/meal for children < 4 yr and at 500 IU lipase/kg/meal for those > 4 yr. Usually, half the standard dose is given with snacks. Doses > 2500 IU lipase/kg/meal or > 10,000 IU lipase/kg/day should be avoided because high enzyme dosages have been associated with fibrosing colonopathy. In patients with high enzyme requirements, acid suppression with an $H_2$ blocker or proton pump inhibitor may improve enzyme effectiveness.

**Diet** therapy includes sufficient calories and protein to promote normal growth—30 to 50% more than the usual recommended dietary allowances may be required (see Table 1-4 on p. 5) as well as a normal-to-high total fat in-take to increase the caloric density of the diet; a water-miscible multivitamin supplement in double the recommended daily allowance; and salt supplementation during infancy and periods of thermal stress and increased sweating. Infants receiving broad-spectrum antibiotics and patients with liver disease and hemoptysis should be given supplemental vitamin K. Formulas containing protein hydrolysates and medium-chain triglycerides may be used instead of modified whole-milk formulas for infants with severe malabsorption. Glucose polymers and medium-chain triglyceride supplements can be used to increase caloric intake. In patients who fail to maintain adequate nutritional status, enteral supplementation via NGT, gastrostomy, or jejunostomy may restore normal growth and stabilize pulmonary function (see p. 20). The use of appetite stimulants to enhance growth may be helpful in some patients.

**Other:** Patients with symptomatic right heart failure should be treated with diuretics, salt restriction, and $O_2$.

**Surgery** may be indicated for localized bronchiectasis or atelectasis that cannot be treated effectively with drugs, nasal polyps, chronic sinusitis, bleeding from esophageal varices secondary to portal hypertension, gall-bladder disease, and intestinal obstruction due to a volvulus or an intussusception that cannot be medically reduced. Liver transplantation has been done successfully in patients with end-stage

liver disease. Bilateral cadaveric lung and live donor lobar transplantation has been done successfully in patients with advanced cardiopulmonary disease, as well as combined liver-lung transplantation for patients with end-stage liver and lung disease. Double lung transplantation for severe lung disease is becoming more routine and more successful with experience and improved techniques. About 60% of people are alive 5 yr after transplantation of both lungs, and their condition is much improved.

Gene therapy, in which normal CF genes are delivered directly to the airways, holds promise for treating CF. However, this therapy is only available in research trials. A number of new drugs to improve chloride channel function, delivered by mouth or aerosol, are under investigation.

**End-of-life care:** The patient and family deserve sensitive discussions of prognosis and preferences for care throughout the course of illness, especially as the patient's pulmonary reserves become increasingly limited. Most people facing the end of life with CF will be older adolescents or adults and will be appropriately responsible for their own choices. Thus, they must know what is in store and what can be done. One mark of respect for patients living with CF is to ensure that they are given the information and opportunity to make life choices, including having a substantial hand in determining how and when to accept dying. Often, discussion of transplantation is needed. In considering transplantation, patients need to weigh the merits of longer survival with a transplant against the uncertainty of getting a transplant and the ongoing (but different) illness of living with an organ transplant.

Deteriorating patients need to discuss the eventuality of dying. Patients and their families need to know that most often dying is actually gentle and not profoundly symptomatic. When appropriate, palliative care, including sufficient sedation, should be offered to ensure peaceful dying. A useful strategy for the patient to consider is to accept a time-limited trial of fully aggressive treatment when needed, but to agree in advance to parameters that indicate when to stop aggressive measures.

# Chapter 285. Endocrine Disorders in Children

## Introduction

(See also Hypopituitarism in Children Resulting in Short Stature on p. 767 and see p. 866 for diabetes in adults and children.)

Some endocrine disorders occur mostly in children (eg, precocious or delayed puberty); others occur in children and adults (eg, diabetes, thyroid disorders). Those that affect both adults and children may cause different symptoms in children.

## Congenital Goiter

**Congenital goiter is a diffuse or nodular enlargement of the thyroid gland present at birth. Thyroid hormone secretion may be decreased, increased, or normal. Diagnosis is by confirming thyroid size with ultrasonography. Treatment is thyroid hormone replacement when hypothyroidism is the cause. Surgery is indicated when breathing or swallowing is impaired.**

### Etiology

Congenital goiters may be caused by dyshormonogenesis (abnormal thyroid hormone production), transplacental passage of maternal antibodies, or transplacental passage of goitrogens. Some causes are hereditary.

**Dyshormonogenesis:** Genetic defects in thyroid hormone production result in increased levels of thyroid-stimulating hormone (TSH), which in turn can cause congenital goiter. There are 4 main types of dyshormonogenesis.

- Type 1 is caused by a defect in iodide transport secondary to altered synthesis of a cell surface protein necessary for transport.

- Type 2 is caused by one of several defects in thyroid iodination mechanisms. The enzyme peroxidase, necessary for iodine organification, may be absent (resulting in goitrous cretinism) or dysfunctional. Another defect may impair hydrogen peroxide generation. Children with Pendred's syndrome have mild hypothyroidism or euthyroidism, goiter, and sensorineural hearing loss due to an abnormal transport protein (pendrin) involved in iodine transport and cochlear function.

- Type 3 is caused by complete or partial deiodination defects of monoiodotyrosine and diiodotyrosine in thyroglobulin.

- Type 4 is caused by one of several defects in thyroglobulin synthesis, usually via X-linked inheritance and thus commonly occurs in boys. This condition does not cause clinical hypothyroidism. It is, however, characterized by a very low level of total serum thyroxine ($T_4$) but normal levels of free $T_4$ and TSH.

**Transplacental passage of maternal antibodies:** Women with an autoimmune thyroid disorder produce antibodies that may cross the placenta during the 3rd trimester. Depending on the disorder, the antibodies either block TSH receptors, causing hypothyroidism, or stimulate them, causing hyperthyroidism. Typically, in affected infants, the changes in hormone secretion and the associated goiter resolve spontaneously within 3 to 6 mo.

**Transplacental passage of goitrogens:** Goitrogens such as amiodarone or antithyroid drugs (eg, propylthiouracil, methimazole) can cross the placenta, sometimes causing hypothyroidism and rarely causing goiter.

### Symptoms and Signs

The most common manifestation is firm, nontender enlargement of the thyroid. Enlargement is most often diffuse but can be nodular. It may be noticeable at birth or detected later. In some patients, enlargement is not directly observable, but continued growth can cause deviation or compression of the trachea, compromising breathing and swallowing. Many children with goiters are euthyroid, but some present with hypothyroidism or hyperthyroidism.

### Diagnosis

If the diagnosis is suspected, thyroid size is typically assessed by ultrasonography. $T_4$ and TSH are measured.

### Treatment

Hypothyroidism is treated with thyroid hormone. Goiters that compromise breathing and swallowing can be treated surgically.

## Hypothyroidism

**Hypothyroidism is thyroid hormone deficiency. Symptoms in infants include poor feeding and growth failure; symptoms in older children and adolescents are similar to those of adults but also include growth failure, delayed puberty, or both. Diagnosis is by thyroid function testing (eg, serum thyroxine, thyroid-stimulating hormone). Treatment is thyroid hormone replacement.**

### Etiology

Hypothyroidism in infants and young children may be congenital or acquired.

**Congenital hypothyroidism** occurs in about 1/4000 live births. Most congenital cases are sporadic, but about 10 to 20% are inherited. The most frequent cause of congenital hypothyroidism is dysgenesis, either absence (agenesis) or underdevelopment (hypoplasia) of the thyroid gland. About 10% of congenital hypothyroidism results from dyshormonogenesis (abnormal thyroid hormone production), of which there are 4 types (see p. 2887). Rarely in the US but commonly in certain developing countries, hypothyroidism results from maternal iodine deficiency. Rarely, transplacental transfer of antibodies, goitrogens (eg, amiodarone), or antithyroid drugs (eg, propylthiouracil, methimazole) causes transient hypothyroidism.

**Acquired hypothyroidism** is typically caused by autoimmune thyroiditis (Hashimoto's thyroiditis) and occurs during later childhood and adolescence.

### Symptoms and Signs

Symptoms and signs in infants and young children differ from those in older children and adults. If iodine deficiency occurs very early during pregnancy, infants may present with endemic cretinism (a syndrome involving deaf-mutism), intellectual disability, and spasticity. Most other hypothyroid infants initially have few if any symptoms or signs. Symptoms that do occur may be subtle or develop slowly because some maternal thyroid hormone crosses the placenta. However, after the maternal thyroid hormone is metabolized, if the underlying cause of hypothyroidism persists and hypothyroidism remains undiagnosed or untreated, it usually slows CNS development moderately to severely and may be accompanied by low muscle tone, prolonged hyperbilirubinemia, umbilical hernia, respiratory distress, macroglossia, large fontanelles, poor feeding, and hoarse crying. Rarely, delayed diagnosis and treatment of severe hypothyroidism lead to intellectual disability and short stature.

Some symptoms and signs in older children and adolescents are similar to those of adults (eg, weight gain; constipation; coarse, dry hair; sallow, cool, or mottled coarse skin—see p. 781). Signs specific to children are growth retardation, delayed skeletal maturation, and usually delayed puberty.

### Diagnosis

• Routine neonatal screening

• Thyroid function tests

Routine neonatal screening detects hypothyroidism before clinical signs are evident. If screening is positive, confirmation is necessary with thyroid function tests, including measurement of serum thyroxine ($T_4$), free $T_4$, and thyroid-stimulating hormone (TSH). These tests are also done in older children and adolescents in whom hypothyroidism is suspected.

Severe congenital hypothyroidism, even when treated promptly, may still cause subtle developmental problems and sensorineural hearing loss. Hearing loss may be so mild that initial screening misses it, although it may still interfere with language acquisition. Retesting after infancy is advised to detect subtle hearing loss.

### Treatment

• Thyroid hormone replacement

Most cases of congenital hypothyroidism require lifelong thyroid hormone replacement. Treatment with L-thyroxine 10 to 15 µg/kg po once/day must be started immediately and be closely monitored. This dosage is intended to rapidly normalize serum $T_4$ and should then be adjusted to maintain the serum $T_4$ level between 10 and 15 µg/dL during infancy. After age 1 yr, the usual dosage is 5 to 6 µg/kg po once/day, titrated to maintain serum $T_4$ and TSH levels within the normal range for age. This dosing regimen is also used for acquired hypothyroidism in children and adolescents. In later childhood or adolescence, the starting dosage may be calculated as 100 µg/$m^2$ po once/day. In most treated infants, motor and intellectual development is normal. Thyroxine-binding globulin deficiency, detected by screening that relies primarily on $T_4$ measurement, does not require treatment because affected infants are euthyroid.

## Hyperthyroidism

**Hyperthyroidism is excessive thyroid hormone production. Diagnosis is by thyroid function testing (eg, free serum thyroxine, thyroid-stimulating hormone). Treatment is with propylthiouracil or methimazole.**

### Etiology

Hyperthyroidism is rare in infants but potentially life-threatening. It develops in fetuses of women with current or prior Graves' disease who have elevated titers of thyroid-stimulating immunoglobulins, which overstimulate thyroid hormone production by binding to thyroid-stimulating hormone (TSH) receptors in the thyroid gland. These antibodies cross the placenta and cause thyroid hyperfunction in the fetus (intrauterine Graves' disease), which can result in fetal death or premature birth. Because infants clear the antibodies after birth, neonatal Graves' disease is usually transient. However, because the clearance rate varies, duration of neonatal Graves' disease varies. In children and adolescents, Graves' disease is the usual cause of hyperthyroidism.

### Symptoms and Signs

Symptoms and signs in infants include irritability, feeding problems, hypertension, tachycardia, exophthalmos, goiter, frontal bossing, and microcephaly. Other early findings are failure to thrive, vomiting, and diarrhea. Affected infants almost always recover within 6 mo; the course is rarely longer. Persistent hyperthyroidism may result in craniosynostosis (premature fusion of the cranial sutures), impaired intellect, growth failure, short stature, and hyperactivity later in childhood. Mortality rate may reach 10 to 15%. In children and adolescents, acquired Graves' disease is characterized by diffuse goiter, thyrotoxicosis, and, rarely, infiltrative ophthalmopathy.

### Diagnosis

• Thyroid function tests

Diagnosis is suspected in infants whose mothers have Graves' disease and high titers of stimulatory antibodies (thyroid-stimulating immunoglobulins) and is confirmed by measuring free serum thyroxine ($T_4$) and TSH. Diagnosis in adolescents is similar to that in adults and also includes thyroid function tests.

**Treatment**

• Antithyroid drugs

• Radioactive sodium iodine

• Sometimes surgery

Infants are given an antithyroid drug (eg, propylthiouracil 1.7 to 3.3 mg/kg po tid, methimazole 0.17 to 0.33 mg/kg po tid), sometimes with a β-blocker (eg, propranolol 0.8 mg/kg po tid) to treat symptoms. Treatment must be monitored closely and stopped as soon as the disease has run its course (for treatment of Graves' disease during pregnancy, see p. 2650). For older children and adolescents, treatment is similar to that for adults (see p. 782) and includes antithyroid drugs, radioactive sodium iodine, and sometimes surgery.

## Congenital Adrenal Hyperplasia

(Adrenogenital Syndrome; Adrenal Virilism)

**Congenital adrenal hyperplasia is a group of genetic disorders, each characterized by inadequate synthesis of cortisol, aldosterone, or both. In the most common forms, accumulated hormone precursors are shunted into androgen production, causing androgen excess; in rarer forms, synthesis of androgens is also inadequate.**

In the various forms of congenital adrenal hyperplasia, production of cortisol (a glucocorticoid), aldosterone (a mineralocorticoid), or both is impaired because of an autosomal recessive genetic defect in one of the adrenal enzymes involved in synthesizing adrenal steroid hormones from cholesterol. The enzyme may be absent or deficient, completely or partially disabling synthesis of cortisol, aldosterone, or both. In the forms in which cortisol synthesis is absent or decreased, ACTH (corticotropin) release, normally suppressed by cortisol, is excessive. In the most common forms, 21-hydroxylase deficiency and 11β-hydroxylase deficiency, precursors proximal to the enzyme block accumulate and are shunted into adrenal androgens. The consequent excess androgen secretion causes varying degrees of virilization in external genitals of affected female fetuses; no defects are discernible in external genitals of male fetuses. In some less common forms affecting enzymes other than 21-hydroxylase and 11β-hydroxylase, the enzyme block impairs androgen synthesis (dehydoepiandrosterone [DHEAS] or androstenedione). As a result, virilization of male fetuses is inadequate, but no defect is discernible in female fetuses.

### 21-Hydroxylase Deficiency

**21-Hydroxylase (CYP21A2) deficiency causes defective conversion of adrenal precursors to cortisol and, in some cases, to aldosterone, resulting in virilization and sometimes severe hyponatremia and hyperkalemia. Diagnosis is by measurement of cortisol, its precursors, and adrenal androgens, sometimes after ACTH administration. Treatment is with a glucocorticoid plus, if needed, a mineralocorticoid and, for some female neonates with genital ambiguity, surgical reconstruction.**

21-Hydroxylase deficiency causes 90% of all cases of congenital adrenal hyperplasia. Incidence ranges from 1/10,000 to 1/15,000 live births. The deficiency completely or partially blocks conversion of adrenal precursors into cortisol and aldosterone, resulting in increased levels of progesterone, 17-hydroxyprogesterone, dehydroepiandrosterone (DHEA, a weak androgen that masculinizes affected female infants), and androstenedione. Plasma deoxycorticosterone, deoxycortisol, cortisol, and aldosterone levels are low or absent.

**Complete 21-hydroxylase deficiency**, the salt-wasting form, accounts for 70% of 21-hydroxylase deficiency cases. The salt-wasting form (sometimes called the classic form of congenital adrenal hyperplasia) is the most severe form of 21-hydroxylase deficiency; aldosterone is not secreted and salt is lost, leading to hyponatremia, hyperkalemia, and increased plasma renin activity.

**Partial 21-hydroxylase deficiency** causes a less severe, non-salt-losing form, in which aldosterone levels are normal or only slightly decreased.

### Symptoms and Signs

The salt-wasting form causes hyponatremia (sometimes severe), hyperkalemia, and hypotension as well as virilization. If undiagnosed and untreated, this form can lead to life-threatening adrenal crisis, with vomiting, diarrhea, hypoglycemia, hypovolemia, and shock.

Very young female infants with the salt-wasting form have ambiguous external genitals, with clitoral enlargement, fusion of the labia majora, and a urogenital sinus rather than distinct urethral and vaginal openings. Male infants typically have normal sexual development. When the enzyme deficiency is much milder, neonates have little or no virilization, but androgen excess manifests later with early appearance of pubic hair and increase in growth velocity in both sexes, clitoral enlargement in girls, and penile enlargement and earlier deepening of voice in boys.

In affected females, especially those with the salt-wasting form, reproductive function may be impaired as they reach adulthood; they may have labial fusion and anovulatory cycles or amenorrhea. Some males with the salt-wasting form are fertile as adults, but others have Leydig cell dysfunction, decreased testosterone, and impaired spermatogenesis. Most affected males with the non-salt-losing form, even if untreated, are fertile, but in some, spermatogenesis is impaired. Patients with the non-salt-losing form are normotensive.

### Diagnosis

• Blood tests

• Possibly ACTH stimulation test

• Possibly genotyping

Routine neonatal screening typically includes measuring serum levels of 17-hydroxyprogesterone. If levels are elevated, the diagnosis is confirmed by identifying low blood levels of deoxycortisol, cortisol, deoxycorticosterone, corticosterone, progesterone, and 17-hydroxyprogesterone and by identifying high blood levels of DHEA and androstenedione. Rarely, the diagnosis is uncertain, and levels of these hormones must be measured before and 60 min after ACTH is given (ACTH or cosyntropin stimulation test). In patients who develop symptoms later, ACTH stimulation testing may help, but genotyping may be required. In children with the salt-wasting form, deoxycorticosterone, corticosterone, and aldosterone levels are low, and renin levels are high. Levels of urinary metabolites of cortisol precursors (eg, pregnanetriol) and androgen precursors (eg, 17-ketosteroids) are also high but rarely necessary for the diagnosis.

**Prenatal screening** and diagnosis (and experimental treatment) are possible; *CYP21* genes are analyzed if risk is high (eg, the fetus has an affected sibling with the genetic defect). Carrier status (heterozygosity) can be determined in children and adults.

### Treatment

• Corticosteroid replacement

• Mineralocorticoid replacement (salt-wasting form)

• Possibly reconstructive surgery

For **adrenal crisis** in infants, urgent therapy with IV fluids is needed. Stress doses of hydrocortisone (100 mg/m$^2$/day) are given by continuous IV infusion; the dose is reduced over several weeks to a more physiologic replacement dose. Stress doses of hydrocortisone are also given to prevent adrenal crisis if the salt-wasting form is suspected.

Maintenance treatment is corticosteroids as replacement for deficient steroids (typically, oral hydrocortisone 5 to 8 mg/m$^2$ tid or prednisone 1.5 to 2 mg/m$^2$ bid). Dexamethasone is used only in postpubertal adolescents and adults. Cortisone acetate 18 to 36 mg/m$^2$ IM q 3 days may be used in infants when oral therapy is unreliable. Response to therapy is monitored in infants every 3 mo and in children aged > 12 mo every 3 to 4 mo. Overtreatment with a corticosteroid results in iatrogenic Cushing's disease, causing obesity, subnormal growth, and delayed skeletal maturation. Under-treatment results in inability to suppress ACTH with consequent hyperandrogenism, causing virilization and supranormal growth velocity in children and, eventually, premature termination of growth and short stature. Monitoring involves measuring serum 17-hydroxyprogesterone and DHEA or androstenedione, as well as assessing growth velocity and skeletal maturation each year.

Maintenance treatment for the salt-wasting form, in addition to corticosteroids, is miner-alocorticoid replacement for restoration of Na and K homeostasis. Oral fludrocortisone (usually 0.1 mg once/day, range 0.05 to 0.3 mg) is given if salt loss occurs. Infants often require supplemental oral salt for about 1 yr. Close monitoring during therapy is critical.

Affected female infants may require surgical reconstruction with reduction clitoroplasty and construction of a vaginal opening. Often, further surgery is required during adulthood. With appropriate care and attention to psychosexual issues, a normal sex life and fertility may be expected.

For prenatal treatment, a corticosteroid (usually dexamethasone) is given to the pregnant mother to suppress fetal pituitary secretion of ACTH and thus reduce or prevent masculinization of affected female fetuses. Treatment, which is experimental, must begin in the first several weeks of gestation.

### 11β-Hydroxylase Deficiency

**11β-Hydroxylase (CYP11B1) deficiency involves defective conversion of adrenal precursors to cortisol, resulting in virilization, hypernatremia, hypokalemia, and hypertension. Diagnosis is by measurement of cortisol, its precursors, and adrenal androgens and sometimes by measuring 11-deoxycortisol and 11-deoxycorticosterone after ACTH administration. Treatment is with a corticosteroid.**

11β-Hydroxylase deficiency causes about 5% of all cases of congenital adrenal hyperplasia. Conversion of 11-deoxycortisol to cortisol and 11-deoxycorticosterone to corticosterone is partially blocked, leading to increased levels of ACTH and overproduction of 11-deoxycortisol, 11-deoxycorticosterone (which has mineralocorticoid activity), and adrenal androgens.

#### Symptoms and Signs

Female neonates may present with genital ambiguity, including clitoral enlargement, labial fusion, and a urogenital sinus. Male neonates usually appear normal, but some present with penile enlargement. Some children present later, with sexual precocity or, in females, menstrual irregularities and hirsutism. Salt retention with hypernatremia, hypertension, and hypokalemic alkalosis may result from increased mineralocorticoid activity.

#### Diagnosis

Prenatal diagnosis is not available. Plasma levels in neonates are determined for 11-deoxycortisol, 11-deoxycorticosterone, adrenal androgens, and renin. Diagnosis is established by increased levels. If the diagnosis is uncertain, levels of 11-deoxycortisol and 11-deoxycorticosterone are measured before and 60

min after ACTH stimulation. In affected adolescents, basal plasma levels may be normal, so ACTH stimulation is recommended.

**Treatment**

• Corticosteroid replacement

• Possibly mineralocorticoid replacement

• Possibly reconstructive surgery

Treatment is cortisol replacement, typically with hydrocortisone 5 to 8 mg/$m^2$ tid, which reduces ACTH secretion and reduces levels of 11-deoxycorticosterone and adrenal androgens to normal. Mineralocorticoid replacement is usually not necessary for restoration of Na and K homeostasis but may be required in the neonate or during severe stress. Response to treatment should be monitored, typically by measuring serum 11-deoxycortisol, DHEA, and androstenedione and by assessing growth velocity and skeletal maturation. BP should be monitored in patients who presented with hypertension.

Affected female infants may require surgical reconstruction with reduction clitoroplasty and construction of a vaginal opening. Often, further surgery is required in adulthood, but with appropriate care and attention to psychosexual issues, a normal sex life and fertility may be expected.

## Male Hypogonadism

(See also p. 2340.)

**Male hypogonadism is decreased production of testosterone, sperm, or both or, rarely, decreased response to testosterone, resulting in delayed puberty, reproductive insufficiency, or both. Diagnosis is by measurement of serum testosterone, luteinizing hormone, and follicle-stimulating hormone and by stimulation tests with human chorionic gonadotropin or gonadotropin-releasing hormone. Treatment depends on the cause.**

**Classification**

There are 3 types of hypogonadism: primary, secondary, and a type caused by defective androgen action, primarily due to defective androgen receptor activity.

**Primary:** In primary (hypergonadotropic) hypogonadism, damage to the Leydig cells impairs testosterone production, damages the seminiferous tubules, or does both; oligospermia or azoospermia and elevated gonadotropins result. The most common cause is Klinefelter's syndrome; other causes are gonadal dysgenesis (rare), cryptorchidism, bilateral anorchia, Leydig cell aplasia, Noonan's syndrome, and myotonic dystrophy. Rare causes include orchitis due to mumps (which is becoming even rarer as immunization rates increase), testicular torsion, and trauma.

**Klinefelter's syndrome** is seminiferous tubule dysgenesis associated with the 47,XXY karyotype, in which an extra X chromosome is acquired through maternal or, to a lesser extent, paternal meiotic nondisjunction (see also p. 3005). The syndrome is usually identified at puberty, when inadequate sexual development is noted, or later, when infertility is investigated. Diagnosis is based on elevated gonadotropin levels and low to low-normal testosterone levels.

**Gonadal dysgenesis** occurs in hermaphroditism, which is rare.

In **cryptorchidism**, one or both testes are undescended (see p. 2987). Etiology is usually unknown. Sperm counts may be slightly low if one testis is undescended but are almost always very low if both are undescended.

In **bilateral anorchia (vanishing testes syndrome)**, the testes were presumably present but were

resorbed before or after birth. External genitals and wolffian structures are normal, but mullerian duct structures are lacking. Thus, testicular tissue must have been present during the first 12 wk of embryogenesis because testicular differentiation occurred and testosterone and mullerian-inhibiting factor were produced.

**Leydig cell aplasia** occurs when congenital absence of Leydig cells causes male pseudohermaphroditism with ambiguous external genitals. Although wolffian ducts develop to some extent, testosterone production is insufficient to induce normal male differentiation of the external genitals. Mullerian ducts are absent because of normal production of mullerian-inhibiting hormone by Sertoli cells. Gonadotropin levels are high with low testosterone levels.

**Noonan's syndrome** may occur sporadically or as an autosomal dominant disorder. Phenotypic abnormalities include hyperelasticity of the skin, hypertelorism, ptosis, low-set ears, short stature, shortened 4th metacarpals, high-arched palate, and primarily right-sided cardiovascular abnormalities (eg, pulmonic valve stenosis, atrial septal defect). Testes are often small or cryptorchid. Testosterone levels may be low with high gonadotropin levels.

**Defective androgen synthesis** is caused by enzyme defects that impair androgen synthesis, which may occur in any of the pathways leading from cholesterol to dihydrotestosterone. These congenital problems may occur in congenital adrenal hyperplasia when the same enzyme defect occurs in the adrenal glands and the testes, resulting in defective androgen activity and ambiguous external genitals (ie, male pseudohermaphroditism) of varying degrees.

**Secondary:** Causes of secondary hypogonadism include panhypopituitarism, hypothalamic pituitary tumors, isolated gonadotropin deficiency, Kallmann syndrome, Laurence-Moon syndrome, constitutional delay of puberty, isolated luteinizing hormone deficiency, Prader-Willi syndrome, and functional and acquired disorders of the CNS (eg, trauma, infection). Several acute disorders and chronic systemic disorders (eg, chronic renal insufficiency, anorexia nervosa) may lead to hypogonadotropic hypogonadism, which resolves after recovery from the underlying disorder. Relative hypogonadism is becoming more common among long-term survivors of childhood cancers treated with craniospinal irradiation. Chemotherapy with alkylating drugs may lead to testicular damage and relative hypogonadism.

**Panhypopituitarism** may occur congenitally or anatomically (eg, in septo-optic dysplasia or Dandy-Walker malformation), causing deficiency of hypothalamic-releasing factors or pituitary hormones. Acquired hypopituitarism may result from tumors, neoplasia, their treatment, vascular disorders, infiltrative disorders (eg, sarcoidosis, Langerhans' cell histiocytosis), infections (eg, encephalitis, meningitis), or trauma. Hypopituitarism in childhood may cause delayed growth, hypothyroidism, diabetes insipidus, hypoadrenalism, and lack of sexual development when puberty is expected. Hormone deficiencies, whether originating in the anterior or posterior pituitary, may be varied and multiple.

**Kallmann syndrome** is characterized by anosmia due to aplasia or hypoplasia of the olfactory lobes and by hypogonadism due to deficiency of hypothalamic gonadotropin-releasing hormone (GnRH). It occurs when fetal GnRH neurosecretory neurons do not migrate from the olfactory placode to the hypothalamus. The genetic defect is known; inheritance is usually X-linked. Other manifestations include microphallus, cryptorchidism, midline defects, and unilateral kidney agenesis.

**Laurence-Moon syndrome** is characterized by obesity, intellectual disability, retinitis pigmentosa, and polydactyly.

**Constitutional delay of puberty** is absence of pubertal development in boys ≥ 14 yr. Many have a family history of delayed sexual development in a parent or sibling. Most affected boys have some evidence of sexual maturation by age 18 yr or have a skeletal age of at least 12 yr (the average age at which testicular enlargement is first noted). Typically, stature is usually short during childhood, adolescence, or both but ultimately reaches normal range. Growth velocity is nearly normal, and growth pattern parallels the lower percentile curves of the growth chart; the pubertal growth spurt is delayed. When skeletal age is plotted on the growth curve, it essentially equals the percentile curve of the genetic target. Diagnosis is by exclusion of growth hormone deficiency, hypothyroidism, and hypogonadism

(whether primary or due to gonadotropin deficiency).

**Isolated luteinizing hormone (LH) deficiency (fertile eunuch syndrome)** is monotropic loss of LH secretion in boys; follicle-stimulating hormone (FSH) levels are normal. At puberty, growth of the testes is normal because most testicular volume consists of seminiferous tubules, which respond to FSH. Spermatogenesis may occur as tubular development proceeds. However, absence of LH results in Leydig cell atrophy and testosterone deficiency. Therefore, patients do not develop normal secondary sexual characteristics, but they continue to grow, reaching eunuchoidal proportions because the epiphyses do not close.

**Prader-Willi syndrome** is characterized by diminished fetal activity, muscular hypotonia, and failure to thrive during early childhood, obesity from early childhood, intellectual disability, and hypogonadotropic hypogonadism. The syndrome is caused by deletion or disruption of a gene or genes on the proximal long arm of paternal chromosome 15 or by uniparental disomy of maternal chromosome 15. Failure to thrive due to hypotonia and feeding difficulties during infancy usually resolves after age 6 to 12 mo. From 12 to 18 mo onward, uncontrollable hyperphagia causes excessive weight gain and psychologic problems; plethoric obesity becomes the most striking feature. Rapid weight gain continues into adulthood; stature remains short. Features include emotional lability, poor gross motor skills, facial abnormalities (eg, a narrow bitemporal dimension, almond-shaped eyes, a mouth with thin upper lips and down-turned corners), and skeletal abnormalities (eg, scoliosis, kyphosis, osteopenia). Hands and feet are small. Other features include cryptorchidism and a hypoplastic penis and scrotum.

### Symptoms and Signs

Clinical presentation depends on whether, when, and how testosterone and sperm production are affected. (For presentation in adulthood, see p. 2341.)

If androgen deficiency or defects in androgen activity occur during the 1st trimester (< 12 wk gestation), differentiation of internal wolffian ducts and external genitals is inadequate. Presentation may range from ambiguous external genitals (ie, male pseudohermaphroditism) to normal-appearing female external genitals. Androgen deficiency during the 2nd and 3rd trimesters may cause a microphallus and partially or completely undescended testes.

Androgen deficiency that develops early in childhood has few consequences, but if it occurs when puberty is expected, secondary sexual development is impaired. Such patients have poor muscle development, a high-pitched voice, inadequate phallic and testicular growth, a small scrotum, sparse pubic and axillary hair, and absent body hair. They may develop gynecomastia and grow to eunuchoidal body proportions (arm span exceeds height by 5 cm; pubic to floor length exceeds crown to pubic length by > 5 cm) because fusion of the epiphyses is delayed and long bone growth continues.

### Diagnosis

• Measurement of testosterone, LH, FSH

• Karyotyping (for primary hypogonadism)

Diagnosis is often suspected based on developmental abnormalities or delayed puberty but requires confirmation by testing, including measurement of testosterone, LH, and FSH. LH and FSH levels are more sensitive than testosterone levels, especially for detecting primary hypogonadism.

LH and FSH levels also help determine whether hypogonadism is primary or secondary:

• High levels, even with low-normal testosterone levels, indicate primary hypogonadism.

• Levels that are low or lower than expected for the testosterone level indicate secondary hypogonadism.

In boys with short stature, delayed pubertal development, low testosterone, and low FSH and LH levels may indicate constitutional delay. Elevated serum FSH levels with normal serum testosterone and LH

levels typically indicate impaired spermatogenesis but not impaired testosterone production. In primary hypogonadism, it is important to determine the karyotype to investigate for Klinefelter's syndrome.

Measurement of testosterone, FSH, and LH for diagnosis of hypogonadism requires an understanding of how the levels vary. Before puberty, serum testosterone levels are < 20 ng/dL (< 0.7 nmol/L) and in adulthood, levels are > 300 to 1200 mg/dL. Serum testosterone secretion is primarily circadian. In the 2nd half of puberty, levels are higher at night than during the latter part of the day. A single sample obtained in the morning can establish that circulating testosterone levels are normal. Because 98% of testosterone is bound to carrier proteins in serum (testosterone-binding globulin), alterations in these protein levels alter total testosterone levels. Measurement of total serum testosterone (protein bound and free) is usually the most accurate indicator of testosterone secretion.

For LH and FSH levels, 3 blood samples should be taken at 20-min intervals. This approach maximizes the likelihood of detecting LH pulsations, which occur at 90- to 120-min intervals. Serum LH and FSH levels are usually < 5 mIU/mL before puberty and fluctuate between 5 and 20 mIU/mL during the 2nd half of puberty and into adulthood.

The human chorionic gonadotropin (hCG) stimulation test is done to assess the presence and secretory ability of testicular tissue; hCG 100 IU/kg is given to children. hCG stimulates Leydig cells, as does LH, with which it shares a structural subunit, and stimulates testicular production of testosterone. Testosterone levels should double after 3 to 4 days.

The GnRH stimulation test is done in boys to distinguish between hypothalamic dysfunction and pituitary dysfunction as the cause of hypogonadotropic hypogonadism. GnRH 2.5 µg/kg or leuprolide acetate 500 µg is rapidly injected IV. The injection directly stimulates the pituitary to secrete LH and FSH, which are measured every 20 to 30 min for 2 h. Throughout childhood and into early puberty, response to GnRH is predominantly an increase in FSH with little or no increase in LH. During puberty, LH and FSH respond more or less equally (by doubling or tripling). An inadequate to absent increase in FSH and LH may indicate hypopituitarism.

**Treatment**

• Surgery as needed

• Hormone replacement

Cryptorchidism is corrected early to obviate concerns about cancer developing in later adulthood and to prevent testicular torsion (see p. 2987).

For secondary hypogonadism, any underlying pituitary or hypothalamic disorder is treated. Overall, the goal is to provide androgen replacement starting with a low dose and progressively increasing the dose over 18 to 24 mo.

Adolescents with androgen deficiency should be given long-acting injectable testosterone enanthate or cypionate 50 mg q 2 to 4 wk; the dose is increased up to 200 mg over 18 to 24 mo. A transdermal patch or gel may be used instead.

Treatment of Kallmann syndrome with hCG can correct cryptorchidism and establish fertility. Pulsatile GnRH therapy given subcutaneously by a portable pump leads to endogenous sex hormone secretion, progressive virilization, and even fertility.

In isolated LH deficiency, testosterone, via conversion to estrogen by aromatase, induces normal epiphyseal closure.

## Delayed Puberty

**Delayed puberty is absence of sexual maturation at the expected time.**

Delayed puberty may result from constitutional delay (see p. 2893), which often occurs in adolescents with a family history of delayed growth. Prepubertal growth velocity is normal, but skeletal maturation and adolescent growth spurt are delayed; sexual maturation is delayed but normal. Other causes include Turner's syndrome in girls, Klinefelter's syndrome in boys, CNS disorders (eg, pituitary tumors that reduce gonadotropin secretion), certain chronic disorders (eg, diabetes mellitus, inflammatory bowel disorders, renal disorders, cystic fibrosis), and excess physical activity, especially in girls.

In girls, delayed puberty is diagnosed if no breast development occurs by age 13, if no pubic hair appears by age 14, if > 5 yr elapse between the beginning of breast growth and menarche, or if menstruation does not occur by age 16. In boys, delayed puberty is diagnosed if no testicular enlargement occurs by age 14, if no pubic hair appears by age 15, or if > 5 yr elapse between initial and complete growth of the genitals. Short stature may indicate delayed puberty in either sex. Although many children seem to be starting puberty earlier than in past years, there are no indications that the criteria for delayed puberty should change.

Constitutional delay of puberty is more prevalent in boys. Girls with severe pubertal delay should be investigated for primary amenorrhea (see p. 2501). If boys show no sign of pubertal development or of skeletal maturation beyond 11 to 12 yr by age 15, they may be given a 4- to 8-mo course of IM testosterone enanthate 50 mg once/mo. These low doses induce puberty with some degree of virilization and do not jeopardize adult height potential.

## Precocious Puberty

**Precocious puberty is onset of sexual maturation before age 8 in girls or age 9 in boys. Diagnosis is by comparison with population standards, x-rays of the left hand and wrist to assess skeletal maturation and check for accelerated bone growth, and measurement of serum levels of gonadotropins and gonadal and adrenal steroids. Treatment depends on the cause.**

The definition of precocious puberty depends on reliable population standards for onset of puberty (ie, when pubertal milestones occur); because onset seems to be occurring earlier in the US, these standards are being reevaluated. Almost 8 to 10% of white girls, almost 30% of black girls, and an intermediate percentage of Hispanic girls reach early puberty at age 8. The lower limit of normal puberty may be 7 yr for white girls and 6 yr for black girls. The mean age for early breast development is about 10 yr for white girls and 9 yr for black girls (range 8 to 13 yr). The mean age for pubic hair growth is 9 to 10.5 yr for both groups. These findings imply that guidelines for evaluating disorders that cause precocious puberty can be interpreted more leniently if children are otherwise healthy and are not at risk of not reaching their full adult height potential.

In girls, the first pubertal milestone is typically breast development (thelarche), followed soon after by appearance of pubic hair (pubarche) and axillary hair and later by the first menstrual period (menarche). In boys, the first pubertal milestone is typically testicular growth, followed by penile growth and appearance of pubic and axillary hair. In both sexes, appearance of pubic and axillary hair is called adrenarche.

Precocious puberty can be divided into 2 types:

• Gonadotropin-releasing hormone (GnRH)-dependent

• GnRH-independent

GnRH-dependent precocious puberty is 5 to 10 times more frequent in girls; in boys, GnRH-dependent and GnRH-independent precocious puberty occur with similar frequency. In GnRH-dependent precocious puberty, the hypothalamic-pituitary axis is activated, resulting in enlargement and maturation of the gonads, development of secondary sexual characteristics, and oogenesis or spermatogenesis. In GnRH-independent precocious puberty, secondary sexual characteristics result from high circulating levels of estrogens or androgens, without activation of the hypothalamic-pituitary axis.

Precocious puberty may also be classified by whether gonadarche or adrenarche occurs. In girls,

gonadarche includes breast development, change in body habitus, growth of the uterus, and eventually menarche. In boys, gonadarche includes testicular enlargement; phallic growth; the initial appearance of pubic, facial, and axillary hair; adult body odor; and facial skin oiliness or acne. Adrenarche for both girls and boys involves the development of body hair, body odor, and acne.

Premature appearance of only one specific pubertal milestone is generally considered a benign variant of development. Examples are precocious appearance of pubic and axillary hair before age 8 in girls and age 9 in boys, and precocious onset of breast development before age 8 in girls.

### Etiology

**GnRH-dependent precocious puberty:** In most affected girls ≥ 4 yr, a specific cause cannot be identified. However, many girls < 4 yr have a CNS lesion. Most (60%) affected boys have an identifiable underlying lesion. Such lesions include intracranial tumors, especially of the hypothalamus (hamartoma, rarely craniopharyngioma) or pineal gland region (teratoma, pinealoma). Neurofibromatosis and a few other rare disorders have also been linked to precocious puberty.

**GnRH-independent precocious puberty:** Follicular ovarian cysts cause most cases; other causes include granulosatheca cell tumors, adrenal enzyme defects, and McCune-Albright syndrome (a triad of follicular cysts, polyostotic fibrous dysplasia, and cafe-au-lait spots). Causes of GnRH-independent precocious puberty in boys include certain enzyme defects, familial male gonadotropin-independent precocity (due to an activating mutation of the gene for luteinizing hormone [LH] receptors), testosterone-producing testicular tumors, and occasionally McCune-Albright syndrome.

Rarely in girls and boys, puberty results from pituitary adenomas (hamartomas) that secrete gonadotropins.

### Symptoms and Signs

In girls, breasts develop, and pubic hair, axillary hair, or both appear. Girls may begin to menstruate. In boys, facial, axillary, and pubic hair appears and the penis grows, with or without enlargement of testes. Body odor, acne, and behavior changes may develop in either sex. Height gain is initially rapid in both sexes, but premature closure of the epiphyses results in short adult stature. Ovarian or testicular enlargement occurs in precocious puberty but is usually absent in isolated precocious adrenarche.

### Diagnosis

• Bone age x-rays

• Serum hormone measurement

• Possibly pelvic ultrasonography and brain MRI or CT

Diagnosis is clinical. X-rays of the left hand and wrist are done to check for accelerated skeletal maturation as a result of sex hormone effect. Unless history and examination suggest an abnormality, no further evaluation is required for children with pubertal milestones that are within 1 yr of population standards. Girls and boys with precocious adrenarche and girls with precocious thelarche also do not require further evaluation as long as x-rays confirm that skeletal maturation is not accelerated.

When further evaluation is necessary, the following serum hormones may be measured: β-human chorionic gonadotropin, estradiol, testosterone, dehydroepiandrosterone, 17-hydroxyprogesterone, LH, follicle-stimulating hormone (FSH), and prolactin. Pelvic and adrenal ultrasonography and MRI or CT of the brain may be done.

A GnRH stimulation test (see p. 2894) confirms a diagnosis of GnRH-independent precocious puberty when gonadotropin responses to exogenous GnRH are prepubertal in boys or girls with no tumor or other obvious cause of early sexual development. If the response is pubertal, CNS lesions must be excluded.

**Treatment**

• GnRH agonist therapy (GnRH-dependant precocious puberty)

• Androgen or estrogen antagonist therapy (GnRH-independent precocious puberty)

• Tumor excision as needed

If pubertal milestones are within 1 yr of population standards, reassurance and regular reexamination are sufficient. Treatment is not needed for premature adrenarche or thelarche, but regular reexamination is warranted to check for later development of precocious puberty. For GnRH-dependent precocious puberty, pituitary LH and FSH secretion can be suppressed until normal puberty begins with the GnRH agonist leuprolide acetate 0.2 to 0.3 mg/kg (minimum, 7.5 mg) IM q 4 wk. Responses to treatment must be monitored, and drug dosages modified accordingly.

In girls with McCune-Albright syndrome, testolactone, an aromatase inhibitor, reduces serum estradiol and effectively treats affected girls; alternatively, tamoxifen, an estrogen antagonist, may be beneficial.

If GnRH-independent precocious puberty in boys is due to familial male gonadotropin-independent precocity or McCune-Albright syndrome, androgen antagonists (eg, spironolactone) ameliorate the effects of excess androgen. The antifungal drug ketoconazole reduces testosterone in boys with familial male gonadotropin-independent precocity.

If GnRH-independent precocious puberty is due to a hormone-producing tumor (eg, granulosatheca cell tumors in girls, testicular tumors in boys), the tumor should be excised. However, girls require extended follow-up to check for recurrence in the contralateral ovary.

# Chapter 286. Neurologic Disorders in Children

## Introduction

Related topics are discussed elsewhere in THE MANUAL: see Chs. 176, 180, and 298 and p. 2830.

## Cerebral Palsy Syndromes

**Cerebral palsy (CP) refers to nonprogressive syndromes characterized by impaired voluntary movement or posture and resulting from prenatal developmental malformations or perinatal or postnatal CNS damage. Syndromes manifest before age 5 yr. Diagnosis is clinical. Treatment may include physical and occupational therapy, braces, drug therapy or botulinum toxin injections, orthopedic surgery, intrathecal baclofen, or, in certain cases, dorsal rhizotomy.**

CP is a group of syndromes that causes non-progressive spasticity, ataxia, or involuntary movements; it is not a specific disorder or single syndrome. CP syndromes occur in 0.1 to 0.2% of children and affect up to 15% of premature infants.

### Etiology

Etiology is multifactorial, and a specific cause is often hard to establish. Prematurity, in utero disorders, neonatal encephalopathy, and kernicterus often contribute. Perinatal factors (eg, perinatal asphyxia, stroke, CNS infections) probably cause 15 to 20% of cases. Spastic diplegia after premature birth, spastic quadriparesis after perinatal asphyxia, and athetoid and dystonic forms after perinatal asphyxia or kernicterus are examples of types of CP. CNS trauma or a severe systemic disorder (eg, stroke, meningitis, sepsis, dehydration) during early childhood may also cause a CP syndrome.

### Symptoms and Signs

Before a specific syndrome develops, symptoms include lagging motor development and often persistent infantile reflex patterns, hyperreflexia, and altered muscle tone.

**Categories:** Syndromes are categorized mainly as one of the following, depending on which parts of the CNS are malformed or damaged:

- **Spastic syndromes** occur in > 70% of cases. Spasticity is a state of resistance to passive range of motion; resistance increases with increasing speed of that motion. It is due to upper motor neuron involvement and may mildly or severely affect motor function. These syndromes may cause hemiplegia, quadriplegia, diplegia, or paraplegia. Usually, deep tendon reflexes in affected limbs are increased, muscles are hypertonic, and voluntary movements are weak and poorly coordinated. Joint contractures develop, and joints may become misaligned. A scissors gait and toe walking are typical. In mild cases, impairment may occur only during certain activities (eg, running). Corticobulbar impairment of oral, lingual, and palatal movement, with consequent dysarthria or dysphagia, commonly occurs with quadriplegia.

- **Athetoid or dyskinetic syndromes** occur in about 20% of cases and result from basal ganglia involvement. The syndromes are defined by slow, writhing, involuntary movements of the proximal extremities and trunk (athetoid movements), often activated by attempts at voluntary movement or by excitement. Abrupt, jerky, distal (choreic) movements may also occur. Movements increase with emotional tension and disappear during sleep. Dysarthria occurs and is often severe.

- **Ataxic syndromes** occur in < 5% of cases and result from involvement of the cerebellum or its pathways. Weakness, incoordination, and intention tremor cause unsteadiness, a wide-based gait, and difficulty with rapid or fine movements.

- **Mixed syndromes** are common—most often with spasticity and athetosis.

**Associated findings:** About 25% of patients, most often those with spasticity, have other manifestations.

Strabismus and other visual defects may occur. Children with athetosis due to kernicterus commonly have nerve deafness and upward gaze paralysis. Many children with spastic hemiplegia or paraplegia have normal intelligence; children with spastic quadriplegia and mixed syndromes may have severe intellectual disability.

**Diagnosis**

• Cranial MRI

If CP is suspected, cranial MRI is done; it can detect abnormalities in most cases.

CP can rarely be confirmed during early infancy, and the specific syndrome often cannot be characterized until age 2 yr. High-risk children (eg, those with evidence of asphyxia, stroke, periventricular abnormalities seen on cranial ultrasonography in premature infants, jaundice, meningitis, neonatal seizures, hypertonia, hypotonia, or reflex suppression) should be followed closely.

CP should be differentiated from progressive hereditary neurologic disorders and disorders requiring surgical or other specific neurologic treatments. Ataxic forms are particularly hard to distinguish, and in many children with ataxia, a progressive cerebellar degenerative disorder is ultimately identified as the cause. Athetosis, self-mutilation, and hyperuricemia in boys indicate Lesch-Nyhan syndrome (see p. 3024). Cutaneous or ocular abnormalities may indicate tuberous sclerosis, neurofibromatosis, ataxia-telangiectasia, von Hippel-Lindau disease, or Sturge-Weber syndrome. Infantile spinal muscular atrophy and muscular dystrophies associated with hypotonia and hyporeflexia usually lack signs of cerebral disease. Adrenoleukodystrophy begins later in childhood, but other leukodystrophies begin earlier and may be mistaken for CP at first.

Laboratory tests can exclude certain progressive storage disorders that involve the motor system (eg, Tay-Sachs disease, metachromatic leukodystrophy, mucopolysaccharidoses). Other progressive disorders (eg, infantile neuroaxonal dystrophy) may be suggested by nerve conduction studies and electromyography but must be diagnosed clinically or pathologically. Children with pronounced intellectual disability and symmetric motor abnormalities should be evaluated for amino acid and other metabolic abnormalities (see p. 3009).

**Prognosis**

Most children survive to adulthood. Severe limitations in sucking and swallowing, which may require feeding by gastrostomy tube, decrease likelihood of survival. The goal is for children to develop maximal independence within the limits of their motor and associated deficits. With appropriate management, many children, especially those with spastic paraplegia or hemiplegia, can lead near-normal lives.

**Treatment**

• Physical and occupational therapy

• Braces, drugs, or surgery to treat spasticity

• Assistive devices

Physical therapy and occupational therapy for stretching, strengthening, and facilitating good movement patterns are usually used first. Bracing, drug therapy, and surgery are used to treat spasticity. Botulinum toxin may be injected into muscles to decrease their uneven pull at joints and to prevent fixed contractures. Drugs such as baclofen, benzodiazepines (eg, diazepam), tizanidine, and sometimes dantrolene may diminish spasticity. Intrathecal baclofen (via subcutaneous pump and catheter) is the most effective treatment for severe spasticity. Orthopedic surgery (eg, muscle-tendon release) may help reduce restricted joint motion or misalignment. Selective dorsal rhizotomy may help a few children if spasticity affects primarily the legs and if cognitive abilities are good.

When intellectual and physical limitations are not severe, children should attend mainstream schools.

However, some children require varying degrees of lifelong supervision and assistance. Speech training or other forms of facilitated communication may be required. Even severely affected children can benefit from training in activities of daily living (eg, washing, dressing, feeding), which increases their independence and self-esteem and greatly reduces the burden for family members or other caregivers. Assistive devices may increase mobility and communication, help maintain range of motion, and help children and their caregivers with activities of daily living.

Parents of a child with chronic limitations need assistance and guidance in understanding the child's status and potential and in dealing with their own feelings of guilt, anger, denial, and sadness (see p. 2755). Such children reach their maximal potential only with stable, sensible parental care and the assistance of public and private agencies (eg, community health agencies, vocational rehabilitation organizations, lay health organizations such as the United Cerebral Palsy Association).

## Febrile Seizures

**Febrile seizures are diagnosed in children < 6 yr with body temperature > 38° C and no previous afebrile seizures when no cause can be identified. Diagnosis is clinical after exclusion of other causes. Treatment of seizures lasting < 15 min is supportive. Seizures lasting ≥ 15 min are treated with IV lorazepam and, if persistent, IV fosphenytoin, phenobarbital, valproate, or levetiracetam. Maintenance drug therapy is usually not indicated.**

Febrile seizures occur in about 2 to 5% of children < 6 yr; most occur at age 6 to 36 mo. Febrile seizures may be simple or complex:

- Simple febrile seizures last < 15 min and have no focal features, and if they occur in a series, total duration is < 30 min.

- Complex febrile seizures last 15 min and have focal features or postictal paresis, or occur in a series with a total duration of > 30 min.

Most (> 90%) febrile seizures are simple.

Febrile seizures occur during bacterial or viral infections. They sometimes occur after certain vaccinations such as measles, mumps, and rubella. Genetic and familial factors may increase susceptibility to febrile seizures. Monozygotic twins have a much higher concordance rate than dizygotic twins. Several genes associated with febrile seizures have been identified.

### Symptoms and Signs

Often, febrile seizures occur during the initial rapid rise in body temperature, and most develop within 24 h of fever onset. Typically, seizures are generalized; most are clonic, but some manifest as periods of atonic or tonic posturing.

### Diagnosis

- Exclusion of other causes

Seizures are diagnosed as febrile after exclusion of other causes. A fever may trigger seizures in children with previous afebrile seizures; such events are not termed "febrile seizures" because such children have already shown a tendency to have seizures.

Tests to exclude other disorders are determined clinically:

- CSF analysis to rule out meningitis and encephalitis if children are < 6 mo, have meningeal signs or signs of CNS depression, or have seizures after several days of febrile illness

- Serum glucose, Na, Ca, Mg, and P and liver and kidney function tests to rule out metabolic disorders if the history includes recent vomiting, diarrhea, or impaired fluid intake; if there are signs of dehydration

or edema; or if a complex febrile seizure occurs

- Cranial CT or MRI if examination detects focal features or if there are signs of increased intracranial pressure

- Consideration of EEG if febrile seizures are complex or recurrent

EEG typically does not identify specific abnormalities or help predict recurrent seizures; it is not recommended after an initial simple febrile seizure in children with a normal neurologic examination.

### Prognosis

Overall recurrence rate is about 35%. Risk of recurrence is higher if children are < 1 yr when the initial seizure occurs or have 1st-degree relatives who have had febrile seizures. Risk of developing an afebrile seizure disorder after experiencing febrile seizures is about 2 to 5%, unless children have additional risk factors (eg, complex febrile seizures, family history of seizures, developmental delay), which increase risk up to 10%.

### Treatment

- Supportive therapy if seizures last < 15 min

- Drugs and sometimes intubation if seizures last ≥ 15 min

Treatment is supportive if seizures last < 15 min.

Seizures lasting ≥ 15 min require drugs to end them, with careful monitoring of circulatory and respiratory status. Intubation may be necessary if response is not immediate and the seizure persists.

Drug therapy is usually IV, with a short-acting benzodiazepine (eg, lorazepam 0.05 to 0.1 mg/kg IV over 2 to 5 min repeated q 5 to 10 min for up to 3 doses). Fosphenytoin 15 to 20 mg PE (phenytoin equivalents)/kg may be given over 15 min if the seizure persists. In children 2 to 5 yr, diazepam rectal gel 0.5 mg/kg may be given once and repeated in 4 to 12 h if lorazepam cannot be given IV. Phenobarbital, valproate, or levetiracetam can also be used to treat a persistent seizure.

Maintenance drug therapy to prevent recurrent febrile seizures or development of afebrile seizures is usually not indicated unless multiple or prolonged episodes have occurred.

## Infantile Spasms

**Infantile spasms (salaam seizures) are seizures characterized by sudden flexion of the arms, forward flexion of the trunk, extension of the legs, and hypsarrhythmia on EEG.**

Infantile spasms last a few seconds and can recur many times a day. They usually manifest in children < 1 yr; peak incidence is 2 to 3 yr. Seizures may resolve spontaneously by about age 5 yr but can be replaced by other types of seizures.

Pathophysiology is unknown; however, infantile spasms may reflect abnormal interactions between the cortex and brain stem and within the hypothalamic-pituitary-adrenal axis. An immature CNS may also be a factor.

Malformations of the brain and disorders that damage the brain before a few months of age can cause infantile spasms; tuberous sclerosis is a common cause (see p. 2905). The cause may be idiopathic.

### Symptoms and Signs

Spasms begin with a sudden, rapid, tonic contraction of the trunk and limbs, sometimes for several seconds. Spasms range from subtle head nodding to contraction of the whole body. They involve flexion,

extension, or, more often, both (mixed). The spasms usually occur in clusters, often several dozens, in close succession; they occur typically after children wake up and occasionally during sleep.

Developmental defects (eg, in intellect) are usually present. In the first stages of the disorder, developmental regression can occur (eg, children may lose the ability to sit up or roll over).

Rate of premature death rate ranges from 5 to 31%; death often occurs before age 10 yr and is related to the etiology of the infantile spasms.

**Diagnosis**

• Neuroimaging

• Waking and sleep EEG

• Laboratory testing as clinically indicated

Symptoms suggest the diagnosis. Physical and neurologic examinations are done, but often no pathognomonic findings are identified except in tuberous sclerosis.

Waking and sleep EEG is done to check for specific abnormalities. Typically, the interictal pattern is hypsarrhythmic (chaotic, high-voltage polymorphic delta and theta waves with superimposed multifocal spike discharges). Multiple variations (eg, focal or asymmetric hypsarrhythmia) are possible. The ictal pattern varies. Usually, electrical activity is markedly attenuated diffusely.

Tests to determine the cause may include

• Laboratory tests (eg, CBC with differential, serum glucose, electrolytes, BUN, creatinine, Na, Ca, Mg, and P, liver function tests) if a metabolic disorder is suspected

• CSF analysis

• Neuroimaging (MRI)

**Treatment**

Infantile spasms are difficult to treat, and the optimal regimen is controversial. ACTH 20 to 60 units IM once/day may be used but has become very hard to obtain. Corticosteroids for 8 to 10 wk can also be effective. Many anticonvulsants are ineffective; valproate is preferred, followed by clonazepam. Nitrazepam, topiramate, zonisamide, or vigabatrin may help.

A ketogenic diet may help but is difficult to maintain.

In some patients, focal cortical resection can eliminate seizures.

## Neonatal Seizure Disorders

(See also Ch. 176.)

**Neonatal seizures are abnormal electrical discharges in the CNS of neonates and usually manifest as stereotyped muscular activity or autonomic changes. Diagnosis is confirmed by EEG; testing for causes is indicated. Treatment depends on the cause.**

Seizures occur in up to 1.4% of term infants and 20% of premature infants. Seizures may be related to a serious neonatal problem and require immediate evaluation. Most neonatal seizures are focal, probably because generalization of electrical activity is impeded in neonates by lack of myelination and incomplete formation of dendrites and synapses in the brain.

Some neonates undergoing EEG to assess seizures or other symptoms of encephalopathy (eg, hypoactivity, decreased responsiveness) are found to have clinically silent seizures (epileptiform electrical activity during an EEG but without any visible seizure activity). Occasionally, clinically silent electrical activity is continuous and persists for > 20 min; at that point, it is defined as electrical status epilepticus.

**Etiology**

The abnormal CNS electrical discharge may be caused by a

- Primary intracranial process (eg, meningitis, ischemic stroke, encephalitis, intracranial hemorrhage, tumor, malformation)

- Systemic problem (eg, hypoxia-ischemia, hypoglycemia, hypocalcemia, hyponatremia, other disorders of metabolism)

Seizures resulting from an intracranial process usually cannot be differentiated from seizures resulting from a systemic problem by their clinical features (eg, focal vs generalized).

**Hypoxia-ischemia,** the most common cause of neonatal seizures, may occur before, during, or after delivery. Such seizures may be severe and difficult to treat, but they tend to abate after about 3 to 4 days.

**Ischemic stroke** is more likely to occur in neonates with polycythemia, with thrombophilia due to a genetic disorder, or with severe hypotension but may occur in neonates without any risk factors. Stroke occurs typically in the middle cerebral artery distribution or, if associated with hypotension, in watershed zones. Seizures resulting from stroke tend to be focal and may cause apnea.

**Infections** such as meningitis and sepsis may cause seizures; in such cases, seizures are usually accompanied by other symptoms and signs. Group B streptococci and gram-negative bacteria are common causes of such infections in neonates. Encephalitis due to cytomegalovirus, herpes simplex virus, rubella virus, *Treponema pallidum*, or *Toxoplasma gondii* can also cause seizures.

**Hypoglycemia** is common among neonates whose mothers have diabetes, who are small for gestational age, or who have hypoxiaischemia or other stresses. Seizures due to hypoglycemia tend to be focal and variable. Prolonged or recurrent hypoglycemia may permanently affect the CNS.

**Intracranial hemorrhage,** including subarachnoid, intracerebral, and intraventricular hemorrhage, may cause seizures. Intraventricular hemorrhage, which occurs in premature infants, results from bleeding in the germinal matrix (an area that is adjacent to the ventricles and that gives rise to neurons and glial cells during development).

**Hypernatremia** or **hyponatremia** may cause seizures. Hypernatremia can result from accidental oral or IV NaCl overload. Hyponatremia can result from dilution (when too much water is given po or IV) or may follow Na loss in stool or urine.

**Hypocalcemia** (serum Ca level < 7.5 mg/dL [< 1.87 mmol/L]) is usually accompanied by a serum P level of > 3 mg/dL (> 0.95 mmol/L) and can be asymptomatic. Risk factors for hypocalcemia include prematurity and a difficult birth.

**Hypomagnesemia** is a rare cause of seizures, which may occur when the serum Mg level is < 1.4 mEq/L (< 0.7 mmol/L). Hypomagnesemia often occurs with hypocalcemia and should be considered in neonates with hypocalcemia if seizures continue after adequate Ca therapy.

**Inborn errors of metabolism** (eg, amino or organic aciduria) can cause neonatal seizures. Rarely, pyridoxine deficiency or dependency causes seizures; it is readily treated.

Other causes include CNS malformations. Maternal substance abuse (eg, cocaine, heroin, diazepam) is an increasingly common problem; seizures can accompany acute withdrawal after birth. Neonatal seizures may be familial; some have genetic causes.

### Symptoms and Signs

Neonatal seizures are usually focal and may be difficult to recognize. Common manifestations include migratory clonic jerks of extremities, alternating hemiseizures, and primitive subcortical seizures (which cause respiratory arrest, chewing movements, persistent eye deviations or nystagmoid movements, and episodic changes in muscle tone). Generalized tonic-clonic seizures are uncommon.

Clinically silent electrical seizure activity is often present after a hypoxic-ischemic insult (including perinatal asphyxia or stroke) and in neonates with CNS infections, especially after initial seizure treatment, which is more likely to stop clinical manifestations than electrical seizure activity.

### Diagnosis

• EEG

• Laboratory testing (eg, CSF analysis, electrolytes) as clinically indicated

• Usually cranial imaging

Evaluation begins with a detailed family history and a physical examination. EEG (waking and sleep) is essential, especially when it is difficult to determine whether the neonate is having seizures; EEG is also helpful for monitoring response to treatment. EEG should capture periods of active and quiet sleep and thus may require ≥ 2 h of recording. A normal EEG with expected variation during sleep stages is a good prognostic sign; an EEG with diffuse severe abnormalities (eg, suppressed voltage or burst suppression pattern) is a poor one.

Other tests should include pulse oximetry; measurement of serum glucose, Na, K, Cl, $HCO_3$, Ca, and Mg; and lumbar puncture for CSF analysis (cell count and differential, glucose, protein) and culture. Urine and blood cultures are obtained. The need for other metabolic tests (eg, arterial pH, blood gases, serum bilirubin, urine amino or organic acids) or tests for commonly abused drugs (passed to the neonate transplacentally or by breast-feeding) depends on the clinical situation.

Most infants should have cranial CT because it can detect intracranial bleeding and some brain malformations. Cranial ultrasonography may detect intraventricular bleeding but not subarachnoid bleeding; it may be preferred as a bedside test for very sick infants who cannot be moved to radiology. Diffusion-weighted MRI and magnetic resonance spectroscopy may detect ischemic tissue within a few hours but cannot be done until infants are stable.

Jitteriness (alternating contraction and relaxation of opposing muscles in the extremities) must be distinguished from true seizure activity. Jitteriness is usually stimulus-induced and can be stopped by holding the extremity still. Seizures occur spontaneously, and motor activity is felt even when the extremity is held still.

### Prognosis

Prognosis depends on the etiology. About 50% of neonates with seizures due to hypoxiaischemia develop normally. Most neonates with seizures due to subarachnoid hemorrhage, hypocalcemia, or hyponatremia do well. Those with severe intraventricular hemorrhage have a high morbidity rate. For idiopathic seizures or seizures due to malformations, earlier onset is associated with higher morbidity and mortality rates.

Whether neonatal seizures cause damage beyond that caused by the underlying disorder is unknown, although there is concern that the metabolic stress of prolonged nerve cell firing during lengthy seizures may cause additional brain damage. When caused by hypoxia-ischemia, stroke, or infection, neonates may have a series of seizures, but seizures typically abate after about 3 to 4 days; they may recur months to years later if brain damage has occurred. Seizures due to other conditions may be more persistent during the neonatal period.

**Treatment**

• Treatment of cause

• Anticonvulsants

Treatment focuses primarily on the underlying disorder and secondarily on seizures.

For low serum glucose, 10% dextrose 2 mL/kg IV is given, and the serum glucose level is monitored; additional infusions are given as needed.

For hypocalcemia, 10% Ca gluconate 1 mL/kg IV (9 mg/kg of elemental Ca) is given; this dosage can be repeated for persistent hypocalcemic seizures. Rate of Ca gluconate infusion should not exceed 0.5 mL/min (50 mg/min); continuous cardiac monitoring is necessary during the infusion. Extravasation should be avoided because skin may slough.

For hypomagnesemia, 0.2 mL/kg of a 50% Mg sulfate solution is given IM.

Bacterial infections are treated with antibiotics; herpes encephalitis is treated with acyclovir.

Anticonvulsants are used unless seizures stop quickly after correction of reversible disorders such as hypoglycemia, hypocalcemia, hypomagnesemia, hyponatremia, or hypernatremia. Phenobarbital is the drug of choice; a loading dose of 15 to 20 mg/kg IV is given. If seizures continue, 5 to 10 mg/kg can be given q 15 to 30 min until seizures cease or until a maximum of 30 mg/kg is given. Maintenance therapy may be started about 12 h later at 1.5 to 2 mg/kg bid and increased to 2.5 mg/kg bid based on clinical or EEG response or serum drug levels. Phenobarbital is continued IV, especially if seizures are frequent or prolonged. When seizures are controlled, phenobarbital can be given orally. Therapeutic serum levels of phenobarbital are 15 to 40 µg/mL (65 to 170 µmol/L).

If a 2nd drug is needed, fosphenytoin or phenytoin is used. The loading dose is 20 mg PE (phenytoin equivalents)/kg IV. It is given over 40 min to avoid hypotension or arrhythmias. A maintenance dose is then started at 2 to 3 mg/kg q 12 h and adjusted based on clinical response or serum levels. Therapeutic serum levels for phenytoin are 10 to 20 µg/mL (40 to 80 µmol/L). Appropriate duration of therapy with any drug is not known.

Lorazepam 0.1 mg/kg IV may be used for resistant seizures and repeated at 5- to 10-min intervals, up to 3 doses in any 8-h period.

Some of the newer anticonvulsants are being investigated for treatment of neonatal seizures.

Neonates given IV anticonvulsants are closely observed; overmedication may result in respiratory depression.

## Tourette's Syndrome

(Gilles de la Tourette's Syndrome)

**Tourette's syndrome is a hereditary tic disorder that begins during childhood. Symptoms include simple, complex, and vocal tics. Diagnosis is clinical. Treatment may include clonidine and antipsychotics.**

Tourette's syndrome is probably autosomal dominant with variable penetrance; the specific genetic abnormality is unknown. Male:female ratio is 3:1. Simple transient tics, chronic tic disorder, and Tourette's syndrome form a continuum or spectrum.

### Symptoms and Signs

The movement disorder may begin with simple tics (eg, facial grimacing, head jerking, blinking, sniffing)

that progress to multiple complex tics, including respiratory and vocal ones (eg, loud, irritating vocalizations; snorting). Vocal tics may begin as grunting or barking noises and evolve into compulsive utterances that are often loud or shrill. Patients may voluntarily suppress tics for seconds or minutes. Coprolalia (involuntary scatologic or obscene utterances) occurs in a few patients. Severe tics and coprolalia are physically and socially disabling. Echolalia (immediate repetition of one's own or another person's words or phrases) is common. In most children, tics tend to wane during the teenage years.

Comorbid disorders (eg, attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, learning disabilities, anxiety) and poor socialization are common and may be more problematic and more likely to need intervention than the tics.

**Diagnosis**

• Clinical evaluation

Diagnosis is clinical. To differentiate Tourette's syndrome from transient tics, physicians may have to monitor patients over time.

**Treatment**

• Clonidine

• Sometimes antipsychotics

Treatment to suppress tics is recommended only if they are significantly interfering with the children's activities or self-image; treatment does not alter the natural history of the disorder. Clonidine 0.05 to 0.1 mg po tid or qid is effective in some patients. Adverse effects of fatigue may limit dosage; hypotension is uncommon.

Antipsychotics (eg, risperidone 0.25 to 1.5 mg po bid, haloperidol 0.5 to 2 mg po bid or tid, pimozide 1 to 2 mg po bid, olanzapine 2.5 to 5 mg once/day) may be required. The lowest dose required to make tics tolerable is used; doses are tapered as tics wane. Adverse effects of dysphoria, parkinsonism, akathisia, and tardive dyskinesia may limit use of anti-psychotics; using lower daytime doses and higher bedtime doses may decrease adverse effects.

# Chapter 287. Neurocutaneous Syndromes

## Introduction

Neurocutaneous syndromes (eg, neurofibromatosis, Sturge-Weber syndrome, tuberous sclerosis, von Hippel-Lindau disease) are neurologic syndromes with cutaneous manifestations. These disorders frequently also cause eye lesions, brain malformations, seizures, and intellectual disability.

## Neurofibromatosis

**Neurofibromatosis is an autosomal dominant disorder that causes tumors to develop along the course of peripheral nerves and that occasionally results in marked soft-tissue or bone deformities. Diagnosis is clinical. There is no specific treatment, but tumors can be removed surgically.**

Neurofibromatosis has 2 types. Type 1 (von Recklinghausen's disease) is most prevalent, causing neurologic, cutaneous, and sometimes soft-tissue or bone manifestations. Type 2 accounts for 10% of cases, manifesting primarily as congenital bilateral acoustic neuromas. The gene for type 1 is located on band 17q11.2, and that for type 2 is located on band 22q11.

Neurofibromas (benign tumors consisting of Schwann cells and neural fibroblasts) may be peripheral or central.

**Peripheral neurofibromas** can develop anywhere along the course of peripheral nerves. Most appear during adolescence. There are 4 forms:

- Cutaneous neurofibromas are soft and fleshy.
- Subcutaneous neurofibromas are firm and nodular.
- Nodular plexiform neurofibromas may involve spinal nerve roots, typically growing through an intervertebral foramen to cause intraspinal and extraspinal masses (dumb-bell tumor). The intraspinal part may compress the spinal cord.
- Diffuse plexiform neurofibromas (subcutaneous nodules or amorphous overgrowth of underlying bone or Schwann cells) can be disfiguring and may cause deficits distal to the neurofibroma. These neurofibromas can become malignant.

**Central (cranial nerve) neurofibromas** have 2 forms:

- Optic gliomas: These may cause progressive blindness. They may occur in both types 1 and 2.
- Acoustic neuromas (vestibular schwannomas): These may cause dizziness, ataxia, deafness, and tinnitus. They occur in type 2.

### Symptoms and Signs

**Type 1:** Most patients are asymptomatic. Some present with neurologic symptoms or bone deformities. In > 90%, characteristic skin lesions (see Plate 72) are apparent at birth or develop during infancy. Lesions are medium-brown (cafe-au-lait), freckle-like macules, distributed most commonly over the trunk, pelvis, and flexor creases of elbows and knees. During late childhood, flesh-colored cutaneous tumors of various sizes and shapes appear, ranging in number from several to thousands. Rarely, plexiform neurofibromas develop, causing an irregularly thickened, distorted structure with grotesque deformities.

Neurologic symptoms vary, depending on location and number of neurofibromas. Bone abnormalities include

- Fibrous dysplasia
- Subperiosteal bone cysts
- Vertebral scalloping
- Scoliosis
- Thinning of the long-bone cortex
- Pseudarthrosis
- Absence of the greater wing of the sphenoid bone (posterior orbital wall), with consequent pulsating exophthalmos

An optic glioma and Lisch nodules (iris hamartomas) occur in some patients. Changes in arterial walls may lead to Moyamoya disease or intracranial artery aneurysms. Some children have learning problems and slightly larger heads.

**Type 2:** Bilateral acoustic neuromas develop and become symptomatic during childhood or early adulthood. They cause hearing loss, unsteadiness, and sometimes headache or facial weakness. Bilateral 8th cranial (vestibulocochlear) nerve masses may be present. Family members may have gliomas, meningiomas, or schwannomas.

### Diagnosis

- Clinical evaluation
- CT or MRI

Most patients with type 1 are identified during routine examination, examination for cosmetic complaints, or evaluation of a positive family history. Diagnosis is clinical (see Table 287-1). CT or MRI is done in patients with neurologic symptoms or signs on presentation and in those with other examination findings that suggest neurofibromatosis. Neuroimaging may detect 8th cranial nerve masses in type 2; MRI may show focal density changes in type 1.

Genetic testing exists but is not routinely available.

### Treatment

- Possibly surgery or irradiation

No general treatment is available. Neurofibromas that cause severe symptoms may require surgical removal or irradiation, although surgery may obliterate function of the involved nerve.

Genetic counseling is advisable. If either parent has neurofibromatosis, risk to subsequent offspring is 50%; if neither has it, risk for subsequent children is unclear because new mutations are common.

## Sturge-Weber Syndrome

**Sturge-Weber syndrome is a rare congenital vascular disorder characterized by a facial port-wine stain, a leptomeningeal angioma, and neurologic complications (eg, seizures, focal neurologic deficits, intellectual disability).**

Sturge-Weber syndrome causes a port-wine stain typically on the forehead and upper eyelid in the distribution of the 1st or 2nd division of the trigeminal nerve. A leptomeningeal angioma occurs in 90% of patients when the port-wine stain involves upper and lower eyelids on one side but only in 10 to 20% when only one eyelid is affected. Neurologic complications include seizures, focal neurologic deficits (eg,

hemiparesis), and intellectual disability. The disorder can also cause glaucoma and vascular malformations, which may increase risk of vascular events (eg, stroke,

[Table 287-1. Diagnosing Neurofibromatosis]

thrombosis, venous occlusion, infarction). It is not inherited; etiology is unclear.

**Types:** There are 3 types:

• Type I: Port-wine stain and brain angiomas

• Type II: Port-wine stain but no brain angiomas

• Type III: Brain angioma but no port-wine stain

### Symptoms and Signs

The port-wine stain can vary in size and color, ranging from light pink to deep purple.

Seizures occur in about 75 to 90% of patients and typically start by age 1 yr. Seizures are usually focal but can become generalized. Hemiparesis of the side opposite the port-wine stain occurs in 25 to 50% of patients. About 50% of patients have intellectual disability, and more have some kind of learning difficulty. Development may be delayed.

Glaucoma may be present at birth or develop later. The eyeball may enlarge and bulge out of its socket (buphthalmos).

### Diagnosis

Diagnosis is suggested by a characteristic port-wine stain. CT and MRI are used to check for a leptomeningeal angioma. Neurologic examination is done to check for neurologic complications.

### Treatment

Treatment focuses on symptoms. Anticonvulsants and drugs to treat glaucoma are used. Low-dose aspirin is often given to help prevent strokes. Selective photothermolysis can lighten the port-wine stain.

## Tuberous Sclerosis

**Tuberous sclerosis (TS) is a dominantly inherited genetic disorder in which tumors (usually hamartomas) develop in multiple organs.**

Children with TS or TS complex have tumors in multiple organs, including the heart, eyes, kidneys, lungs, and skin. Many children have kidney tumors, usually angiomyolipomas, which can cause hypertension and cystic kidney disease. Renal carcinoma can also occur. Some children also have cardiac rhabdomyomas. Brain tubers (gyral enlargements) and tumors, usually astrocytomas, can occur.

In families with several affected members, up to 4 separate gene sites have been identified. If either parent has the disorder, children have a 50% risk of having it. However, new mutations account for most new cases.

### Symptoms and Signs

Affected children may have seizures, intellectual disability, autism, learning disorders, or behavioral problems. Infants may present with a type of seizure called infantile spasms (see p. 2899). Retinal patches are common and may be visible with funduscopy.

Skin findings include

• Initially pale, ash leaf-shaped macules, which develop during infancy or early childhood

• Angiofibromas of the face (adenoma sebaceum), which develop during later childhood

• Congenital shagreen patches (raised lesions resembling an orange peel), usually on the back

• Subcutaneous nodules

• Cafe-au-lait spots

• Subungual fibromas, which can develop any time during childhood or early adulthood

**Diagnosis**

• Imaging of affected organs

• Genetic testing

Cardiac or cranial manifestations may be visible on prenatal ultrasonography. MRI or ultrasonography of the affected organs is necessary for confirmation.

Specific genetic testing is available.

**Prognosis**

Prognosis depends on symptom severity. Infants with mild symptoms generally do well and live long, productive lives; infants with severe symptoms may have serious disabilities. Regardless of severity, most children show continued developmental progress. Occasionally, neurologic degeneration may occur and requires investigation.

**Treatment**

Treatment is symptomatic:

• **For seizures:** Anticonvulsants or even brain surgery

• **For skin lesions:** Dermabrasion or laser techniques

• **For neurobehavioral problems:** Behavior management techniques or drugs

• **For hypertension caused by renal problems:** Antihypertensives or surgery to remove growing tumors

• **For developmental delays:** Special schooling or occupational therapy

Genetic counseling is indicated for adolescents and adults of childbearing age.

## Von Hippel-Lindau Disease

**Von Hippel-Lindau disease (VHL) is a rare hereditary neurocutaneous disorder characterized by tumors in multiple organs.**

VHL most commonly causes cerebellar hemangioblastomas and retinal angiomas. Tumors, including pheochromocytomas and cysts (renal, hepatic, or pancreatic), can occur in other organs; risk of developing renal cell carcinoma increases with age and by age 60 may be as high as 70%. Manifestations typically appear between ages 10 and 30 but can appear earlier.

The disorder is inherited as an autosomal dominant trait with variable penetrance. The *VHL* gene is located on the short arm of chromosome 3.

**Symptoms and Signs**

Symptoms depend on the size and location of the tumors. Symptoms may include headaches, dizziness, weakness, impaired vision, and high BP.

Retinal angiomas, detected by direct ophthalmoscopy, appear as a dilated artery leading from the disk to a peripheral tumor with an engorged vein. These angiomas are usually asymptomatic, but if they are centrally located and enlarge, they can result in substantial loss of vision. These tumors increase risk of retinal detachment, macular edema, and glaucoma.

Untreated, VHL can result in blindness, brain damage, or death. Death usually results from complications of cerebellar hemangioblastomas or renal cell carcinoma.

**Diagnosis**

The disorder is diagnosed when typical tumors are detected and one of the following criteria is met:

• More than one tumor in the brain or eye

• Single tumor in the brain or eye and one elsewhere in the body

• Family history of VHL and presence of a tumor

If one cerebellar hemangioblastoma, retinal angioma, or pheochromocytoma is detected, clinicians should look for other tumors.

Genetic testing is done to check for an abnormal *VHL* gene in at-risk family members. If an abnormal gene is detected, family members are monitored for tumors for the rest of their life.

**Treatment**

• Surgery or sometimes radiation therapy

• For retinal angiomas, laser coagulation or cryotherapy

• Regular monitoring

Treatment often involves surgical removal of the tumor before it becomes harmful. Some tumors can be treated with focused high-dose radiation. Typically, retinal angiomas are treated with laser coagulation or cryotherapy to preserve vision.

Patients should be monitored regularly for progression of the disorder. Appropriate monitoring and treatment can improve prognosis.

# Chapter 288. Bone and Connective Tissue Disorders in Children

## Introduction

Many bone disorders, particularly those affecting the lower extremities (eg, Osgood-Schlatter disease), result from the dramatic changes that occur in a growing child's musculoskeletal system. These disorders may resolve or worsen with continued growth. Other bone disorders may be inherited (eg, achondroplasia) or acquired (eg, Legg-Calve-Perthes disease).

There are over 200 disorders that involve connective tissue. Certain disorders are characterized by overactivity of the immune system with resulting inflammation and systemic damage to the tissues (eg, SLE [see p. 305] and juvenile idiopathic arthritis [formerly known as juvenile RA—see p. 339]). Other disorders involve biochemical abnormalities or structural defects of the connective tissue. Some of these disorders are inherited, and some are of unknown etiology.

## Cutis Laxa

**Cutis laxa (CL) is characterized by lax skin hanging in loose folds. Diagnosis is clinical. There is no specific treatment, but plastic surgery is sometimes done.**

CL may be inherited or acquired. There are 4 hereditary forms: autosomal dominant, X-linked recessive, and 2 autosomal recessive. The autosomal recessive forms tend to be more common. One of the recessive forms causes potentially lethal cardiovascular, respiratory, and GI complications. The other inherited forms are relatively benign.

Rarely, infants can acquire CL after a febrile illness or after exposure to a specific drug (eg, hypersensitivity reaction to penicillin, fetal exposure to penicillamine). In children or adolescents, CL usually develops after a severe illness involving fever, polyserositis, or erythema multiforme. In adults, it may develop insidiously. The underlying defect is unknown, but fragmented elastin is present in all forms.

### Pathophysiology

CL is caused by abnormal elastin metabolism that results in reduced elasticity of the skin. The precise cause is unknown. Several factors, such as copper deficiency, elastin quantity and morphology, and elastases and elastase inhibitors, are implicated in the abnormal elastin degradation.

### Symptoms and Signs

In hereditary forms, dermal laxity may be present at birth or develop later; it occurs wherever the skin is normally loose and hanging in folds, most obviously on the face. Affected children have mournful or Churchillian facies and a hooked nose. The benign autosomal recessive form also causes developmental retardation and joint laxity. GI tract hernias and diverticula are common. If the disorder is severe, progressive pulmonary emphysema may precipitate cor pulmonale. Bronchiectasis, heart failure, and aortic aneurysms can also occur.

### Diagnosis

Diagnosis is clinical. There are no specific laboratory findings; however, a skin biopsy may be done. Certain tests (eg, echocardiography, chest x-ray) may be done to check for associated conditions (eg, emphysema, cardiomegaly, heart failure). Typical CL can be distinguished from Ehlers-Danlos syndrome because dermal fragility and articular hypermobility are absent. Other disorders sometimes cause localized areas of loose skin. In Turner's syndrome, lax skinfolds at the base of an affected girl's neck tighten and resemble webbing as she ages. In neurofibromatosis, unilateral pendular plexiform neuromas occasionally develop, but their configuration and texture distinguish them from CL.

### Treatment

There is no specific treatment. Plastic surgery considerably improves appearance in patients with

hereditary CL but is less successful in those with acquired CL. Healing is usually uncomplicated, but dermal laxity may recur. Extracutaneous complications are treated appropriately.

## Ehlers-Danlos Syndrome

**Ehlers-Danlos syndrome is a hereditary collagen disorder characterized by articular hypermobility, dermal hyperelasticity, and widespread tissue fragility. Diagnosis is clinical. Treatment is supportive.**

Inheritance is usually autosomal dominant, but Ehlers-Danlos syndrome is heterogeneous. Different gene mutations affect the amount, structure, or assembly of different collagens. Mutations can exist in the genes that encode collagens (eg, type I, III, or V) or collagen-modifying enzymes (eg, lysyl hydroxylase, a collagen cleaving protease). The 6 major types are classic, hypermobility, vascular, kyphoscoliosis, arthrochalasis, and dermatosparaxis. There are also several rare or hard-to-classify types.

### Symptoms and Signs

Symptoms and signs vary widely. Predominant symptoms include hypermobile joints, abnormal scar formation and wound healing, fragile vessels, and velvety, hyperextensible skin. Skin can be stretched several centimeters but returns to normal when released. Wide papyraceous scars often overlie bony prominences, particularly elbows, knees, and shins; scarring is less severe in the hypermobility type. Molluscoid pseudotumors (fleshy outgrowths) frequently form on top of scars or at pressure points. Extent of joint hypermobility varies but may be marked in the arthrochalasis, classic, and hypermobility types. Bleeding tendency is rare, although the vascular type is characterized by vascular rupture and bruising. Subcutaneous calcified spherules may be palpated or seen on x-ray studies.

**Complications:** Minor trauma may cause wide gaping wounds but little bleeding; surgical wound closure may be difficult because sutures tend to tear out of the fragile tissue. Surgical complications occur because of deep tissue fragility. Sclera may be fragile, leading to perforation of the globe in the kyphoscoliosis type.

Bland synovial effusions, sprains, and dislocations occur frequently. Spinal kyphoscoliosis occurs in 25% of patients (especially those with the kyphoscoliosis type), thoracic deformity in 20%, and talipes equinovarum in 5%. About 90% of affected adults have pes planus (flat feet). Congenital hip dislocation occurs in 1% (the arthrochalasis type is characterized by bilateral congenital hip dislocation).

GI hernias and diverticula are common. Rarely, portions of the GI tract spontaneously hemorrhage and perforate, and dissecting aortic aneurysm and large arteries spontaneously rupture. Valvular prolapse is a common complication in the most severe type (vascular type). In pregnant women, tissue extensibility may cause premature birth, cervical incompetence, and possibly uterine rupture; if the fetus is affected, fetal membrane is fragile, sometimes resulting in early rupture. Maternal tissue fragility may complicate episiotomy or cesarean delivery. Antenatal, perinatal, and postnatal bleeding may occur. Other potentially serious complications include arteriovenous fistula, ruptured viscus, and pneumothorax or pneumohemothorax.

### Diagnosis

Diagnosis is largely clinical, and specialized genetic and biochemical tests are available at some research centers for some types. Ultra-structural examination of skin biopsy can help in diagnosing the classic, hypermobility, and vascular types. Echocardiography is done to check for heart disorders (eg, valvular prolapse, arterial aneurysm) that are associated with some of the types.

### Prognosis

Life span is usually normal with most types. Potentially lethal complications occur in certain types (eg, arterial rupture in the vascular type).

### Treatment

There is no specific treatment. Trauma should be minimized. Protective clothing and padding may help. If surgery is done, hemostasis must be meticulous. Wounds are carefully sutured, and tissue tension is avoided. Obstetric supervision during pregnancy and delivery is mandatory. Genetic counseling should be provided.

## Marfan Syndrome

**Marfan syndrome consists of connective tissue anomalies resulting in ocular, skeletal, and cardiovascular abnormalities (eg, dilation of ascending aorta, which can lead to aortic dissection). Diagnosis is clinical. Treatment may include prophylactic β-blockers to slow dilation of the ascending aorta and prophylactic aortic surgery.**

Inheritance is autosomal dominant. The basic molecular defect results from mutations in the gene encoding the glycoprotein fibrillin-1 (*FBN1*), which is the main component of microfibrils and helps anchor cells to the extracellular matrix. The principal structural defect involves the cardiovascular, musculoskeletal, and ocular systems. The pulmonary system and CNS are also affected. There are many different manifestations of the genetic mutation that causes Marfan syndrome; however, it is typically recognized by the constellation of long limbs, aortic root dilation, and dislocated lenses.

### Symptoms and Signs

**Cardiovascular system:** Findings include valvular prolapse and aortic aneurysm. A diastolic murmur may be heard over the aortic valve. Those with mitral valve prolapse may have a systolic click and a late systolic murmur or, in severe cases, a holosystolic murmur. Most severe complications result from pathologic changes in the aortic root and ascending aorta. The aortic media is affected preferentially in areas subject to the greatest hemodynamic stress. The aorta progressively dilates or acutely dissects, beginning in the coronary sinuses, sometimes before age 10 yr. The aortic root dilates in 50% of children and in 60 to 80% of adults and can cause aortic regurgitation. Bacterial endocarditis may develop. Redundant cusps and chordae tendineae may lead to mitral valve prolapse or regurgitation.

**Musculoskeletal system:** Severity varies greatly. Patients are taller than average for age and family; arm span exceeds height. Arachnodactyly (disproportionately long, thin digits) is noticeable, often by the thumb sign (the distal phalanx of the thumb protrudes beyond the edge of the clenched fist). Sternum deformity—pectus carinatum (outward displacement) or pectus excavatum (inward displacement)—is common, as are joint hyperextensibility, genu recurvatum (backward curvature of the legs at the knees), pes planus (flat feet), kyphoscoliosis, and diaphragmatic and inguinal hernias. Subcutaneous fat usually is sparse. The palate is often high-arched.

[
Table 288-1. Diagnostic Criteria for Marfan Syndrome (Ghent Nosology)]

**Ocular system:** Findings include ectopia lentis (subluxation or upward dislocation of the lens) and iridodonesis (tremulousness of the iris). The margin of the dislocated lens can often be seen through the undilated pupil. High-grade myopia may be present, and spontaneous retinal detachment sometimes occurs.

**Pulmonary system:** Cystic lung disease and recurrent spontaneous pneumothorax may occur. These disorders can cause pain and shortness of breath.

**CNS:** Dural ectasia is a common finding and most frequently occurs in the lumbosacral spine. It is widening of the dural sac surrounding the spinal cord and may cause headache, lower back pain, or neurologic deficits manifested by bowel or bladder weakness.

### Diagnosis

• Clinical criteria

• Echocardiography/MRI (measurement of the aortic root, detection of valve prolapse)

• Slit-lamp examination (lens abnormalities)

• X-rays of skeletal system (hand, spine, pelvis, chest, foot, and skull for characteristic abnormalities)

• MRI (dural ectasia)

Diagnosis can be difficult because many patients have few typical symptoms and signs and no specific histologic or biochemical changes. Considering this variability, diagnostic criteria are based on constellations of clinical findings and family and genetic history (see Table 288-1). Nonetheless, diagnosis is uncertain in many partial cases of Marfan syndrome. Homocystinuria can partially mimic Marfan syndrome but can be differentiated by detecting homocystine in the urine. Prenatal diagnosis by linkage analysis of the *FBN1* gene mutation is hampered by poor genotype/phenotype correlation. Standard imaging of the skeletal, cardiovascular, and ocular systems is done to detect any clinically relevant structural abnormalities and to provide information contributing to the diagnostic criteria (eg, echocardiography to identify aortic root enlargement). In addition to the criteria established within organ systems, family history (1st-degree relative with Marfan syndrome) and genetic history (presence of the *FBN1* mutation known to cause Marfan syndrome) are considered major criteria.

**Prognosis**

Advancements in therapy and regular monitoring have improved quality of life and reduced mortality. Median life expectancy increased from 48 yr in 1972 to 72 yr as of 1992. However, life expectancy is still reduced for the average patient, primarily because of the cardiac and vascular complications. This decreased life expectancy can take an emotional toll on an adolescent and the family.

**Treatment**

• Induction of precocious puberty in tall girls

• β-Blockers

• Elective aortic repair and valve repair

• Bacterial endocarditis prophylaxis

• Bracing and surgery for scoliosis

Treatment focuses on prevention and treatment of complications. For very tall girls, inducing precocious puberty by age 10 with estrogens and progesterone may reduce potential adult height. All patients should routinely be given β-blockers (eg, atenolol, propranolol) to help prevent cardiovascular complications. These drugs lower myocardial contractility and pulse pressure and reduce progression of aortic root dilation and risk of dissection. Prophylactic surgery is offered if aortic diameter is > 5 cm (less in children). Pregnant women are at especially high risk of aortic complications; elective aortic repair before conception should be discussed. Severe valve regurgitation is also surgically repaired. Bacterial endocarditis prophylaxis before certain invasive procedures (see p. 2199) is not indicated except in patients who have prosthetic valves or who previously had infective endocarditis (see Tables 215-3 and 215-4). Scoliosis is managed with bracing as long as possible, but surgical intervention is encouraged in patients with curves of 40 to 50°.

Cardiovascular, skeletal, and ocular findings should be reevaluated annually. Appropriate genetic counseling is indicated.

## Nail-Patella Syndrome

(Osteo-Onychodysplasia; Arthro-Onychodysplasia; Onycho-Osteodysplasia)

**Nail-patella syndrome is a rare inherited disorder of mesenchymal tissue characterized by abnormalities of bones, joints, fingernails and toenails, and kidneys.**

Nail-patella syndrome is an autosomal dominant disorder caused by a mutation in the gene for the transcription factor *LMX1B*, which plays an important role in vertebrate limb and kidney development.

There is bilateral hypoplasia or absence of the patella, subluxation of the radial head at the elbows, and bilateral accessory iliac horns. Fingernails and toenails are absent or hypoplastic, with pitting and ridges.

Renal dysfunction occurs in up to 50% of patients due to focal segmental glomerular deposits of IgM and C3. Proteinuria is the most common manifestation, but about 30% of people with renal involvement slowly progress to renal failure.

Diagnosis is suggested clinically; sometimes renal biopsy is indicated, which is diagnostic. *LMX1B* mutation analysis is possible, including for prenatal diagnosis, but the type of mutation does not usually predict clinical severity.

There is no specific treatment, but when indicated, kidney transplantation has been successful without evidence of recurrent disease in the graft.

## Osteogenesis Imperfecta

**Osteogenesis imperfecta (OI) is a hereditary collagen disorder causing diffuse abnormal fragility of bone and is sometimes accompanied by sensorineural hearing loss, blue sclerae, dentinogenesis imperfecta, and joint hypermobility.**

There are 4 main types of OI; types I and IV are autosomal dominant, whereas types II and III are autosomal recessive. Other types are rare.

### Symptoms and Signs

Hearing loss is present in 50 to 65% of all patients with OI and may occur in any of the 4 types.

**Type I** is the mildest. Symptoms and signs in some patients are limited to blue sclerae (due to a deficiency in connective tissue, allowing the underlying vessels to show through) and musculoskeletal pain due to joint hypermobility. Recurrent fractures in childhood are possible.

**Type II** (neonatal lethal type or OI congenita) is the most severe and is lethal. Multiple congenital fractures result in shortened extremities. Sclerae are blue. The skull is soft and, when palpated, feels like a bag of bones. Because the skull is soft, trauma during delivery may cause intracranial hemorrhage and stillbirth, or neonates may die suddenly during the first few days or weeks of life.

**Type III** is the most severe nonlethal form of OI. Patients with type III have short stature, spinal curvature, and multiple, recurrent fractures. Macrocephaly with triangular facies and pectal deformities are common. Scleral hue varies.

**Type IV** is intermediate in severity. Survival rate is high. Bones fracture easily in childhood before adolescence. Sclera are typically normal in color. Height is moderate-short stature. Accurate diagnosis is important because these patients may benefit from treatment.

### Diagnosis

Diagnosis is usually clinical, but there are no standardized criteria. Analysis of type I pro-collagen (a structural component of bones, ligaments, and tendons) from cultured fibro-blasts (from a skin biopsy) or sequence analysis of the *COL1A1* and *COL1A2* genes can be used when clinical diagnosis is unclear. Severe OI can be detected in utero by level II ultrasonography.

**Treatment**

• Growth hormone

• Bisphosphonates

Growth hormone helps growth-responsive children (types I and IV). There is limited experience with the use of IV bisphosphonates (eg, pamidronate 0.5 to 3 mg/kg once/day for 3 days, repeated as needed q 4 to 6 mo) with children, but they can increase bone density and decrease bone pain and fracture frequency. Preliminary studies suggest that oral alendronate (1 mg/kg, 20 mg maximum) is also effective. Orthopedic surgery, physical therapy, and occupational therapy help prevent fractures and improve function. Cochlear implantation is indicated in selected cases of hearing loss.

## Pseudoxanthoma Elasticum

**Pseudoxanthoma elasticum is a rare genetic disorder characterized by calcification of the elastic fibers of the skin, retina, and cardiovascular system.**

Pseudoxanthoma elasticum is caused by mutations in the *ABCC6* gene that are inherited in both autosomal dominant and recessive forms. The *ABCC6* gene product is a trans-membrane transporter protein that probably plays roles in cellular detoxification. Characteristic cutaneous papular lesions begin in childhood and are primarily of cosmetic concern. They appear as small yellowish papules that typically occur on the neck and axillae and flexural surfaces. Elastic tissues become calcified and fragmented, leading to disruption of the involved organ systems. Ocular involvement includes angioid streaks of the retina, retinal hemorrhages, and gradual vision loss. Cardiovascular manifestations can include intermittent claudication, premature atherosclerosis with subsequent hypertension, angina, and MI. Fragility of vessels can lead to GI hemorrhage and small vessel bleeding with subsequent anemia.

Diagnosis is based on clinical and histologic findings. Laboratory and imaging studies are done for associated conditions (eg, CBC, echocardiography, head CT).

Treatment of retinal angioid streaks with intravitreal injections of the angiogenesis-blocking antibody bevacizumab shows promise. Otherwise, there is no specific treatment, and the aim is to prevent complications. People should avoid drugs that may cause stomach or intestinal bleeding, such as aspirin, other NSAIDs, and anticoagulants. People with pseudoxanthoma elasticum should avoid contact sports because of the risk of injury to the eye. Complications may limit life span.

## Congenital Hypophosphatasia

**Congenital hypophosphatasia is absence or low levels of serum alkaline phosphatase due to mutations in the gene encoding tissue nonspecific alkaline phosphatase.**

Because serum alkaline phosphatase is absent or decreased, $Ca^{++}$ is not diffusely deposited in bones, causing low bone density and hypercalcemia. Vomiting, inability to gain weight, and enlargement of the epiphyses (similar to that in rickets) usually occur. Patients who survive infancy have bony deformities and short stature, but mental development is normal. No treatment is effective, but infusions of alkaline phosphatase and bone marrow transplantation have limited roles. NSAIDs reduce bone pain.

## Idiopathic Scoliosis

**Idiopathic scoliosis is lateral curvature of the spine.**

Idiopathic scoliosis is the most common form of scoliosis and is present in 2 to 4% of children aged 10 to 16 yr. Boys and girls are equally affected; however, it is 10 times more likely to progress and require treatment in girls.

**Symptoms and Signs**

Scoliosis may first be suspected when one shoulder seems higher than the other or when clothes do not hang straight, but it is often detected during routine physical examination. Other findings include asymmetry in shoulder height, apparent leg-length discrepancy, and asymmetry of the chest wall. Patients may initially report fatigue in the lumbar region after prolonged sitting or standing. Muscular backaches in areas of strain (eg, in the lumbosacral angle) may follow.

**Diagnosis**

• X-ray of the spine

The curve is most pronounced when patients bend forward. Most curves are convex to the right in the thoracic area and to the left in the lumbar area, so that the right shoulder is higher than the left. X-ray examination should include standing anteroposterior and lateral views of the spine.

The greater the curve, the greater the likelihood that it will progress after the skeleton matures. Curves > 10° are considered significant. Prognosis depends on site and severity of the curve and age at symptom onset. Significant intervention is required in < 10% of patients.

**Treatment**

• Physical therapy and bracing

• Sometimes surgery

Prompt referral to an orthopedist is indicated when progression is of concern or the curve is significant. Likelihood of progression is greatest around puberty for boys and girls. Moderate curves (20 to 40°) are treated conservatively (eg, physical therapy and bracing) to prevent further deformity. Severe curves (> 40°) can often be ameliorated surgically (eg, spinal fusion with rod placement). Scoliosis and its treatment often interfere with an adolescent's self-image and self-esteem. Counseling or psychotherapy may be needed.

## Chondromalacia Patellae

(Patellofemoral Syndrome)

**Chondromalacia patellae is softening of the cartilage underneath the patella.**

Chondromalacia patellae often causes generalized knee pain, without swelling, especially when climbing or descending stairs, playing sports that exert an axial load on the knees, or sitting for a long time. This disorder probably results from angular or rotational changes in the leg that unbalance elements of the quadriceps and cause patellar misalignment during movement.

Acute pain due to chondromalacia patellae is treated by applying ice and taking analgesics. Children with chondromalacia patellae should avoid pain-causing activities (typically, those that involve bending the knee) for several days. Persistent or recurrent pain due to chondromalacia patellae may be relieved by arthroscopic smoothing of the patella's undersurface.

## Osteochondrodysplasias

(Genetic Skeletal Dysplasias)

**Osteochondrodysplasias involve abnormal bone or cartilage growth, leading to skeletal maldevelopment, often short-limbed dwarfism. Diagnosis is by physical examination, x-rays, and, in some cases, genetic testing. Treatment is surgical.**

The basic genetic defects have been identified in most of the osteochondrodysplasias. The mutations typically cause perturbation of function in proteins involved in growth and development of connective tissue, bone, or cartilage (see

Table 288-2).

Dwarfism is markedly short stature (adult height < 4 ft 10 in) frequently associated with disproportionate growth of the trunk and extremities. Achondroplasia is the most common and best-known type of short-limbed dwarfism, but there are many other distinct types, which differ widely in genetic background, course, and prognosis (see Table 288-2). Lethal short-limbed dwarfism (thanatophoric dysplasia, caused by mutations in the same gene as achondroplasia) causes severe chest wall deformities and respiratory failure in neonates, resulting in death.

**Diagnosis**

Characteristic x-ray changes may be diagnostic. A whole-body x-ray of every affected neonate, even if stillborn, should be taken because diagnostic precision is essential for predicting prognosis. Prenatal diagnosis by fetoscopy or ultrasonography is possible in some cases (eg, when fetal limb shortening is severe). Standard laboratory tests do not help, but molecular diagnosis is feasible for chondrodysplasias with known molecular defects.

**Treatment**

In achondroplasia, treatment with human growth hormone is generally not effective. An increase in adult height may be achieved by surgical limb lengthening. In this and other nonlethal osteochondrodysplasias, surgery (eg, hip replacement) can help improve joint function. Hypoplasia of the odontoid process can predispose to subluxation of the 1st and 2nd cervical vertebrae and compression of the spinal cord. Therefore, the odontoid process should be evaluated preoperatively, and if it is abnormal, the patient's head should be carefully supported when hyperextended for endotracheal intubation during anesthesia.

Because the inheritance pattern in most types is known, genetic counseling can be effective. Organizations such as Little People of America (www.lpaonline.org) provide resources for affected people and act as advocates on their behalf. Similar societies are active in other countries.

## Osteochondroses

**Osteochondroses are noninflammatory, noninfectious derangements of bony growth at various ossification centers. These derangements occur during the period of greatest developmental activity and affect the epiphyses.**

Etiology is unknown, and inheritance is complex. Osteochondroses differ in their anatomic distribution, course, and prognosis; they typically cause pain and have important orthopedic implications. Rare osteochondroses and the involved bones include Freiberg's disease (head of 2nd metatarsal), Panner's disease (capitulum), and Blount disease (proximal tibia). Sever's disease is a more common osteochondrosis.

**Infrapatellar Tendinitis**

(Jumper's Knee; Sinding-Larsen-Johansson Syndrome)

**Infrapatellar tendinitis is an osteochondrosis that is an overuse injury to the patellar tendon at the attachment to the lower pole of the patella.**

Knee pain with infrapatellar tendon tenderness in physically active children is caused by an overuse syndrome that usually occurs in figure skaters and basketball or volleyball players. It typically affects children 10 to 13 yr. Pain is the most exaggerated when straightening the knee against force (eg, climbing stairs, jumping, doing knee bends). Etiology is thought to be trauma due to excessive traction by the patellar tendon at its site of origin, leading to microavulsion fractures. History and physical examination are usually sufficient for diagnosis; however, MRI can show the extent of the injury.

Pain is treated with modification of activities, NSAIDs, and physical therapy. Persistent pain may be treated with surgical repair; however, this is usually not necessary.

### Kohler's Bone Disease

**Kohler's bone disease is osteochondrosis of the tarsal navicular bone.**

Kohler's bone disease usually affects children aged 3 to 5 yr (more commonly boys) and is

[Table 288-2. Types of Osteochondrodysplastic Dwarfism]

unilateral. The foot becomes swollen and painful; tenderness is maximal over the medial longitudinal arch. Weight bearing and walking increase discomfort, and gait is disturbed. On x-ray, the navicular bone is initially flattened and sclerotic and later becomes fragmented, before reossification. X-rays comparing the affected side with the unaffected side help assess progression.

The course is chronic, but the disease rarely persists ≥ 2 yr. Rest, pain relief, and avoiding excessive weight bearing are required. The condition usually resolves spontaneously with no long-term sequelae. In acute cases, a few weeks of wearing a below-knee walking plaster cast, well molded under the longitudinal arch, may help.

### Legg-Calve-Perthes Disease

**Legg-Calve-Perthes disease is idiopathic aseptic necrosis of the femoral capital epiphysis.**

Legg-Calve-Perthes disease has a maximum incidence at age 5 to 10 yr, is more common among boys, and is usually unilateral. About 10% of cases are familial. Characteristic symptoms are pain in the hip joint and gait disturbance; onset is gradual, and progression is slow. Joint movements are limited, and thigh muscles may become wasted.

#### Diagnosis

Diagnosis is suspected based on symptoms. Bone scan or MRI should be done to confirm the diagnosis. X-rays initially may not be useful, because they can be normal or show minimal flattening. Later x-rays can show fragmentation of the femoral head, which contains areas of lucency and sclerosis.

In bilateral or familial cases, a skeletal survey to exclude hereditary skeletal disorders, particularly multiple epiphyseal dysplasia, is mandatory because prognosis and optimal management differ. Hypothyroidism, sickle cell anemia, and trauma must also be excluded.

#### Treatment

Orthopedic treatment includes prolonged bed rest, mobile traction, slings, and abduction plaster casts and splints to contain the femoral head. Some experts advocate subtrochanteric osteotomy with internal fixation and early ambulation. The bisphosphonate alendronate is effective in treating avascular necrosis of the femur in adults. Therefore, bisphosphonates may prove useful in the nonsurgical treatment of Legg-Calve-Perthes disease.

Without treatment, the course is usually prolonged but self-limited (usually 2 to 3 yr). When the disease eventually becomes quiescent, residual distortion of the femoral head and acetabulum predisposes to secondary degenerative osteoarthritis. With treatment, sequelae are less severe.

### Osgood-Schlatter Disease

**Osgood-Schlatter disease is osteochondrosis of the tibial tubercle.**

Osgood-Schlatter disease occurs between ages 10 yr and 15 yr and is usually unilateral. Although the disease is more common among boys, this status is changing as girls become more active in sports programs. Etiology is thought to be trauma due to excessive traction by the patellar tendon on its immature epiphyseal insertion, leading to microavulsion fractures. Characteristic symptoms are pain,

swelling, and tenderness over the tibial tubercle at the patellar tendon insertion. There is no systemic disturbance.

**Diagnosis**

Diagnosis is by examination. Lateral knee x-rays show fragmentation of the tibial tubercle. However, x-rays are not needed unless pain and swelling extend beyond the area over the tibial tubercle or unless pain is accompanied by redness and warmth. In such cases, x-rays are useful to rule out injuries or acute inflammatory conditions.

**Treatment**

Resolution is usually spontaneous within weeks or months. Usually, taking analgesics and avoiding excessive exercise, especially deep knee bending, are the only necessary measures. Complete avoidance of sports is unnecessary. Rarely, immobilization in plaster, intralesional injection of hydrocortisone, surgical removal of loose bodies (eg, ossicles, avulsed fragments of bone), drilling, and grafting are required.

**Scheuermann's Disease**

**Scheuermann's disease causes localized changes in vertebral bodies, leading to backache and kyphosis.**

Scheuermann's disease manifests in adolescence and is slightly more common among boys. It probably represents a group of diseases with similar symptoms, but etiology and pathogenesis are uncertain. It may result from osteochondritis of the upper and lower cartilaginous vertebral end plates or trauma. Some cases are familial.

Most patients present with a round-shouldered posture and they may have persistent low-grade backache. Some have an appearance similar to people with Marfan syndrome; trunk and limb length are disproportionate. Normal thoracic kyphosis is increased diffusely or locally.

**Diagnosis**

Some cases are recognized during routine screening for spinal deformity at school. Lateral spinal x-rays confirm the diagnosis by showing anterior wedging of the vertebral bodies, usually in the lower thoracic and upper lumbar regions. Later, the end plates become irregular and sclerotic. Spinal misalignment is predominantly kyphotic but is sometimes partly scoliotic. In atypical cases, generalized skeletal dysplasia must be excluded by x-ray skeletal survey, and spinal TB must be excluded by CT or MRI.

**Treatment**

The course is mild but long, often lasting several years (although duration varies greatly). Trivial spinal misalignment often persists after the disorder has become quiescent.

Mild, nonprogressive disease can be treated by reducing weight-bearing stress and by avoiding strenuous activity. Occasionally, when kyphosis is more severe, a spinal brace or rest with recumbency on a rigid bed is indicated. Rarely, progressive cases require surgical stabilization and correction of misalignment.

## Osteopetroses

(Marble Bones)

**Osteopetroses are characterized by increased bone density and skeletal modeling abnormalities.**

Osteopetroses can be categorized based on whether sclerosis or defective skeletal modeling

predominates. Some types are comparatively benign; others are progressive and fatal. Bony overgrowth sometimes severely distorts the face. Malocclusion of the teeth may require specialized orthodontic measures. Surgical decompression may be required to relieve elevated intracranial pressure or to release a trapped facial or auditory nerve.

**Craniotubular Dysplasias**

**Craniotubular dysplasias involve minor osteosclerosis with normal skeletal modeling.**

**Metaphyseal dysplasia (Pyle's disease):** This rare, autosomal recessive disorder is often confused semantically with craniometaphyseal dysplasia. Affected people are clinically normal, apart from genu valgum, although scoliosis and bone fragility occasionally occur. The diagnosis is usually made when x-rays are done for an unrelated reason. X-ray changes are striking. Long bones are undermodeled, and bony cortices are generally thin. Tubular leg bones have gross Erlenmeyer flask flaring, particularly in the distal femur. Pelvic bones and thoracic cage are expanded. However, the skull is essentially spared.

**Craniometaphyseal dysplasia:** In this autosomal dominant disorder, paranasal bossing develops during infancy, and progressive expansion and thickening of the skull and mandible distort the jaw and face. The encroaching bone entraps cranial nerves, causing dysfunction. Malocclusion of the teeth may be troublesome; partial sinus obliteration predisposes to recurrent nasorespiratory infection. Height and general health are normal, but progressive elevation of intracranial pressure is a rare, serious complication.

X-ray changes are age-related and usually evident by age 5 yr. Sclerosis is the main feature in the skull. Long bones have widened metaphyses, appearing club-shaped, particularly at the distal femur. However, these changes are much less severe than those in Pyle's disease. The spine and pelvis are unaffected.

**Frontometaphyseal dysplasia:** This disorder has distinct autosomal dominant and X-linked forms; it becomes evident during early childhood. The supraorbital ridge is prominent, resembling a knight's visor. The mandible is hypoplastic with anterior constriction; dental anomalies are common. Deafness develops during adulthood because sclerosis narrows the internal acoustic foramina and middle ear. Long leg bones are moderately bowed. Progressive contractures in the digits may simulate RA. Height and general health are normal.

On x-ray examination, bony overgrowth of the frontal region is obvious; patchy sclerosis is seen in the cranial vault. Vertebral bodies are dysplastic but not sclerotic. Iliac crests are abruptly flared, and pelvic inlet is distorted. Femoral capital epiphyses are flattened, with expansion of the femoral heads and coxa valga (hip deformity). Finger bones are undermodeled, with erosion and loss of joint space. Corrective surgery is indicated for severely disfiguring deformities or those causing orthopedic problems.

**Craniotubular Hyperostoses**

**Craniotubular hyperostoses are bony overgrowths that alter contour and increase skeletal density.**

**Endosteal hyperostosis (van Buchem's syndrome):** This disorder is usually autosomal recessive. Overgrowth and distortion of the mandible and brow become evident during mid-childhood. Subsequently, cranial nerves become entrapped, leading to facial palsy and deafness. Life span is not compromised, stature is normal, and bones are not fragile. X-rays show widening and sclerosis of the calvaria, cranial base, and mandible. Diaphyseal endosteum in the tubular bones is thickened. Surgical decompression of entrapped nerves may be helpful.

**Sclerosteosis:** This autosomal recessive disorder is most common among Afrikaners of South Africa. Overgrowth and sclerosis of the skeleton, particularly of the skull, develop during early childhood. Height and weight are often excessive. Initial symptoms and signs may include deafness and facial palsy due to cranial nerve entrapment. Distortion of facies, apparent by age 10 yr, eventually becomes severe. Cutaneous or bony syndactyly of the 2nd and 3rd fingers distinguishes sclerosteosis from other forms of craniotubular hyperostoses. Predominant x-ray features are gross widening and sclerosis of the calvaria

and mandible. Vertebral bodies are spared, although their pedicles are dense. Pelvic bones are sclerotic but have normal contours. Long bones have sclerosed, hyperostotic cortices and undermodeled shafts. Surgery to relieve intracranial pressure may help.

**Diaphyseal dysplasia (Camurati-Engelmann disease):** This autosomal dominant disorder manifests during mid-childhood with muscular pain, weakness, and wasting, typically in the legs. These symptoms usually resolve by age 30. Cranial nerve compression and elevated intracranial pressure occur occasionally. Some patients are severely handicapped; others are virtually asymptomatic. The predominant x-ray feature is marked thickening of the periosteal and medullary surfaces of the diaphyseal cortices of the long bones, but findings vary. Medullary canals and external bone contours are irregular. The extremities and axial skeleton usually are spared. Rarely, the skull is involved, with calvarial widening and basal sclerosis. Corticosteroids may help relieve bone pain and improve muscle strength.

**Osteosclerosis**

**Osteosclerosis is abnormal hardening of bone that involves increased skeletal density with little disturbance of modeling.**

**Osteopetrosis with delayed manifestations (Albers-Schonberg disease):** This type of osteopetrosis is autosomal dominant, benign, and delayed (tarda), manifesting during childhood, adolescence, or young adulthood. The defective *CLCN7* gene encodes a chloride channel that is apparently important in osteoclast function. This type is relatively common and has a wide geographic and ethnic distribution. Affected people may be asymptomatic; general health is usually unimpaired. However, facial palsy, deafness, and anemia (due to bone marrow compromise or hypersplenism) may occur.

The skeleton usually is radiologically normal at birth. However, bone sclerosis becomes increasingly apparent as children age, and diagnosis is typically based on x-rays done for unrelated reasons. Bony involvement is widespread but patchy. The calvaria is dense, and sinuses may be obliterated. Sclerosis of the vertebral end plate causes the characteristic rugby-shirt appearance (horizontal banding). Bone marrow can be compromised by bony overgrowth, leading to pancytopenia. Extramedullary hematopoiesis may occur, resulting in hepatosplenomegaly. Some patients require transfusion or splenectomy to treat anemia.

**Osteopetrosis with precocious manifestations:** This type of osteopetrosis is autosomal recessive, malignant, and congenital, manifesting during infancy. It is uncommon, frequently lethal, and often due to a mutation in the osteoclast-associated gene *TCIRG1*. Bony overgrowth causes marrow dysfunction. Initial symptoms include failure to thrive, spontaneous bruising, abnormal bleeding, and anemia. Palsies of the 2nd, 3rd, and 7th cranial nerves and hepatosplenomegaly occur later. Death due to bone marrow failure (anemia, overwhelming infection, or hemorrhage) usually occurs in the first year of life.

General increased bone density is the predominant feature on x-rays. Penetrated x-rays of long bones show transverse bands in the metaphyseal regions and longitudinal striations in the shafts. As the disorder progresses, the ends of the long bones, particularly the proximal humerus and distal femur, become flask-shaped. Characteristic endobones (bone within a bone) form in the vertebrae, pelvis, and tubular bones. The skull becomes thickened, and the spine has a rugby-shirt appearance.

Bone marrow transplantation with HLA-identical sibling grafts has had excellent results. However, prognosis is poor with HLA-mismatched grafts. Prednisone, calcitriol, and interferon-γ are effective in some cases.

**Osteopetrosis with renal tubular acidosis:** This type of osteopetrosis is autosomal recessive. It causes weakness, stunted stature, and failure to thrive. Bones appear dense on x-rays, and cerebral calcifications are seen; renal tubular acidosis (RTA) is present, and RBC carbonic anhydrase activity is decreased. The genetic defect involves mutations of the gene encoding carbonic anhydrase II. Bone marrow transplantation cures the osteopetrosis but has no effect on the RTA. Maintenance therapy consists of bicarbonate and electrolyte supplementation to correct renal losses.

**Pyknodysostosis:** This autosomal recessive disorder is caused by loss of function mutations in the gene encoding cathepsin K, an osteoclast-derived protease important in degradation of extracellular matrix. Short stature becomes evident in early childhood; adult height is ≤ 150 cm (5 ft). Other manifestations include an enlarged skull, short and broad hands and feet, and dystrophic nails. Blue sclerae (due to a deficiency in connective tissue, allowing the underlying vessels to show through) are usually recognized during infancy. Affected people resemble each other closely; they have a small face, a receding chin, and carious, misplaced teeth. The cranium bulges, and the anterior fontanelle remains patent. Terminal phalanges are short, and fingernails are dysplastic. Pathologic fractures are a complication.

Bone sclerosis appears on x-rays during childhood, but neither bone striations nor endobones are seen. Facial bones and paranasal sinuses are hypoplastic, and the mandibular angle is obtuse. Clavicles may be gracile, and their lateral portions may be underdeveloped; distal phalanges are rudimentary. Plastic surgery has been used to correct severe deformities of the face and jaw.

## Slipped Capital Femoral Epiphysis

**Slipped capital femoral epiphysis (SCFE) is movement of the femoral neck upward and forward on the femoral epiphysis.**

SCFE usually occurs in early adolescence and preferentially affects boys. Obesity is a significant risk factor. Genetic factors also contribute. SCFE is bilateral in one fifth of patients, and unilateral SCFE becomes bilateral in up to two thirds of patients. The exact cause is unknown but probably relates to weakening of the physis (growth plate), which can result from trauma, hormonal changes, inflammation, or increased shearing forces due to obesity.

### Symptoms and Signs

Onset is usually insidious, and symptoms are associated with stage of slippage. The first symptom may be hip stiffness that abates with rest; it is followed by a limp, then hip pain that radiates down the anteromedial thigh to the knee. Up to 15% of patients present with knee or thigh pain, and the true problem (hip) may be missed until slippage worsens. Early hip examination may detect neither pain nor limitation of movement. In more advanced stages, findings may include pain during movement of the affected hip, with limited flexion, abduction, and medial rotation; knee pain without specific knee abnormalities; and a limp. The affected leg is externally rotated. If blood supply to the area is compromised, avascular necrosis and collapse of the epiphysis may occur.

### Diagnosis

Because treatment of advanced slippage is difficult, early diagnosis is vital. Anteroposterior and frog-leg lateral x-rays of both hips are taken. X-rays show widening of the epiphyseal line or apparent posterior and inferior displacement of the femoral head. Ultrasonography and MRI are also useful, especially if x-rays are normal.

### Treatment

SCFE usually progresses; it requires surgery as soon as it is diagnosed. Patients should not bear weight on the affected leg until SCFE has been ruled out or treated. Surgical treatment consists of screw fixation through the physis.

# Chapter 289. Eye Defects and Conditions in Children

## Introduction

Defects and conditions can affect any part of the eye. They often affect vision, and some can result in blindness if not adequately treated. Other defects and conditions that affect vision during childhood are discussed elsewhere in THE MANUAL (see Chs. 63, 64, and 181).

## Amblyopia

**Amblyopia is functional reduction in visual acuity of an eye caused by disuse during visual development. Blindness can occur in the affected eye if amblyopia is not detected and treated before age 8 yr. Diagnosis is based on detecting a difference in visual acuity between the two eyes. Treatment depends on the cause.**

Amblyopia affects about 2 to 3% of children and almost always develops before age 2.

The brain must simultaneously receive a clear, focused, properly aligned, overlapping image from each eye for the visual system to develop properly. This development takes place mainly in the first 3 yr of life but is not complete until about 8 yr of age. Amblyopia results when there is persistent interference with the image from one eye but not the other. The visual cortex suppresses the image from the affected eye. If suppression persists long enough, vision loss can be permanent.

### Etiology

There are 3 causes. Strabismus (see p. 2920) can cause amblyopia because misalignment of the eyes results in different retinal images being sent to the visual cortex. Because the visual pathways are developed in adults, presentation of 2 different images results in diplopia rather than suppression of one image.

Similarly, anisometropia (inequality of refraction in the 2 eyes, most often resulting from astigmatism, myopia, or hyperopia) results in different focus of the retinal images, with the image from the eye with the greater refractive error being less well focused.

Obstruction of the visual axis at some point between the surface of the eye and the retina (eg, by a cataract) interferes with or completely prevents formation of a retinal image in the affected eye.

### Symptoms and Signs

Children rarely complain of unilateral vision loss, although they may squint or cover one eye. Very young children either do not notice or are unable to express awareness that their vision differs in one eye compared with the other. Some older children may report impaired vision in the affected eye or exhibit poor depth perception. When strabismus is the cause, deviation of gaze may be noticeable to others. A cataract causing occlusion of the visual axis may go unnoticed.

### Diagnosis

• Early screening

• Photoscreening

• Additional testing (eg, cover test, cover-uncover test, refraction, ophthalmoscopy, slit lamp)

Screening for amblyopia (and strabismus) is recommended for all children before starting school, optimally around age 3 yr. Photoscreening is one approach for screening very young children and children with learning and developmental disorders who are unable to undergo subjective testing. Photoscreening involves use of a camera to record images of pupillary reflexes during fixation on a visual target and red reflexes in response to light; the images are then compared for symmetry. Screening in

older children consists of acuity testing with figures (eg, tumbling E figures, Allen cards, HOTV figures or characters) or Snellen eye charts.

Identifying the underlying cause requires additional testing. Strabismus can be confirmed with the cover test or the cover-uncover test (see p. 2922). Ophthalmologists can confirm anisometropia by doing a refraction on each eye. Obstruction of the visual axis can be confirmed by ophthalmoscopy or slit lamp examination.

**Prognosis and Treatment**

• Eyeglasses or contact lenses

• Cataract removal

• Patching

Amblyopia may become irreversible if not diagnosed and treated before age 8, at which time the visual system has matured. Most children identified and treated before age 5 have some vision improvement. Earlier treatment increases the likelihood of complete vision recovery. Recurrence (recidivism) is possible in certain cases until the visual system matures. Some patients have a small decrease in visual acuity of a line or two even after visual maturity has occurred.

Treatment should be directed by an ophthalmologist. Any underlying causes must be treated (eg, eyeglasses or contact lenses to correct refractive error, removal of a cataract). Use of the amblyopic eye is then encouraged by patching the better eye or by administering atropine drops into the better eye to provide a visual advantage to the amblyopic eye. Adherence to treatment is better with drop therapy. Maintenance treatment for prevention of recurrences may be recommended after improvement has stabilized, until a child is about 8 to 10.

## Congenital Cataract

(Infantile Cataract)

**Congenital cataract is a lens opacity that is present at birth or shortly after birth.**

Congenital cataracts may be sporadic, or they may be caused by chromosomal anomalies, metabolic disease (eg, galactosemia), or intrauterine infection (eg, rubella) or other maternal disease during pregnancy. Cataracts may be located in the center of the lens (nuclear), or they may involve the lens material underneath the anterior or posterior lens capsule (subcapsular or cortical). They may be unilateral or bilateral. They may not be noticed unless the red reflex is checked or unless ophthalmoscopy is done at birth. As with other cataracts, the lens opacity obscures vision. Cataracts may obscure the view of the optic disk and vessels and should always be evaluated by an ophthalmologist.

Removal of a cataract within 17 wk after birth permits the development of vision and cortical visual pathways. Cataracts are removed by aspirating them through a small incision. In many children, an intraocular lens may be implanted. Postoperative visual correction with eyeglasses, contact lenses, or both is usually required to achieve the best outcome.

After a unilateral cataract is removed, the quality of the image in the treated eye is inferior to that of the other eye (assuming the other eye is normal). Because the better eye is preferred, the brain suppresses the poorer-quality image, and amblyopia (see p. 2919) develops. Thus, effective amblyopia therapy is necessary for the treated eye to develop normal sight. Some children are unable to attain good visual acuity because of accompanying structural defects. In contrast, children with bilateral cataract removal in which image quality is similar in both eyes more frequently develop equal vision in both eyes.

Some cataracts are partial (posterior lenticonus) and opacify during the 1st decade of life. Eyes with partial cataracts have a better visual outcome.

## Primary Infantile Glaucoma

(Infantile Glaucoma; Congenital Glaucoma; Buphthalmos)

**Primary infantile glaucoma is a rare developmental defect in the iridocorneal filtration angle of the anterior chamber that prevents aqueous fluid from properly draining from the eye. This obstruction can cause increases in the intraocular pressure, which if untreated can damage the optic nerve.**

The disorder occurs in infants and young children and may be unilateral (40%) or bilateral (60%). Intraocular pressure increases above the normal range (10 to 22 mm Hg). Glaucoma can also occur in infants after trauma or intraocular surgery (eg, cataract extraction). Glaucoma associated with aniridia or Lowe syndrome or Sturge-Weber syndrome is called secondary glaucoma.

The eye becomes enlarged because the collagen of the sclera and cornea can stretch from the increased intraocular pressure. The large-diameter (> 12 mm) cornea is thinned and sometimes cloudy. The infant may have tearing and photophobia. If untreated, corneal clouding progresses, the optic nerve is damaged (as evidenced clinically by optic nerve cupping), and blindness may occur. Early surgical intervention (eg, goniotomy, trabeculotomy, trabeculectomy) is the mainstay of treatment.

## Strabismus

**Strabismus is misalignment of the eyes, which causes deviation from the parallelism of normal gaze. Diagnosis is clinical, including observation of the corneal light reflex and use of a cover test. Treatment may include correction of visual impairment with patching and corrective lenses, alignment by corrective lenses, and surgical repair.**

Strabismus occurs in about 3% of children. Although most strabismus is caused by refractive errors or muscle imbalance, rare causes include retinoblastoma or other serious ocular defects and neurologic disease. Left untreated, about 50% of children with strabismus have some visual loss due to amblyopia (see p. 2919).

Several varieties of strabismus have been described, based on direction of deviation, specific conditions under which deviation occurs, and whether deviation is constant or intermittent. Description of these varieties requires the definition of several terms.

The prefix "eso" refers to nasal deviations, and the prefix "exo" refers to temporal deviations. The prefix "hyper" refers to upward deviations, and the prefix "hypo" refers to downward deviations (see Fig. 289-1). Manifest deviations, detectable with both eyes open so that vision is binocular, are designated as tropia. Tropia can be constant or intermittent and may involve one eye or both eyes. Latent deviation, detectable only when one eye is covered so that vision is monocular, is designated as phoria. The deviation in phoria is latent because the brain, using the extraocular muscles, corrects the minor misalignment. Deviations that are the same (amplitude or degree of misalignment remains the same) in all gaze directions are designated as comitant, whereas deviations that vary (amplitude or degree of misalignment changes) depending on gaze direction are referred to as incomitant.

### Etiology

Strabismus may be congenital (the term infantile is preferred because detection of strabismus at birth is uncommon, and infantile permits inclusion of varieties that develop within the first 6 mo of life) or acquired (includes those that develop after 6 mo).

Risk factors for infantile strabismus include family history (1st- or 2nd-degree relative), genetic disorders (Down syndrome and Crouzon syndrome), prenatal drug exposure (including alcohol), prematurity or low birth weight, congenital eye defects, and cerebral palsy.

Acquired strabismus can develop acutely or gradually. Causes of acquired strabismus include tumors (eg, retinoblastoma), head trauma, neurologic conditions (eg, cerebral palsy; spina bifida; palsy of the 3rd,

4th, or 5th cranial nerve), viral infections (eg, encephalitis, meningitis), and acquired eye defects. Specific causes vary depending on the type of deviation.

Esotropia is commonly infantile. Infantile esotropia is considered idiopathic, although an anomaly of fusion is the suspected cause. Accommodative esotropia, a common variety of acquired esotropia, develops between 2 yr and 4 yr of age and is associated with hyperopia. Sensory esotropia occurs when severe visual loss (due to conditions such as cataracts, optic nerve anomalies, or tumors) interferes with the brain's effort to maintain ocular alignment.

Esotropia can be paralytic, so designated because the cause is a 6th (abducens) cranial nerve palsy, but it is an uncommon cause. Esotropia can also be a component of a syndrome. Duane's syndrome (congenital absence of the abducens nucleus with anomalous innervation of the lateral rectus extraocular muscle by the 3rd [oculomotor] cranial nerve) and Mobius' syndrome (anomalies of multiple cranial nerves) are specific examples.

[Fig. 289-1. Ocular deviations in strabismus.]

Exotropia may be intermittent and idiopathic. Less often, exotropia is constant and paralytic, as with 3rd (oculomotor) cranial nerve palsy.

Hypertropia can be paralytic, caused by 4th (trochlear) cranial nerve palsy that occurs congenitally or after head trauma or, less commonly, as a result of 3rd cranial nerve palsy.

Hypotropia can be restrictive, caused by mechanical restriction of full movement of the globe rather than neurologic interference with eye movement. For example, restrictive hypotropia can result from a blowout fracture of the orbit floor or walls. Less commonly, restrictive hypotropia can be caused by Graves' ophthalmopathy (thyroid eye disease). Third cranial nerve palsy and Brown syndrome (congenital or acquired tightness and restriction of the superior oblique muscle tendon) are other uncommon causes.

**Symptoms and Signs**

Unless severe, phorias rarely cause symptoms.

Tropias sometimes result in symptoms. For example, torticollis may develop to compensate for the brain's difficulty in fusing images from misaligned eyes and to reduce diplopia. Some children with tropias have normal and equal visual acuity. However, amblyopia frequently develops with tropias; it is due to cortical suppression of the image in the deviating eye to avoid confusion and diplopia.

**Diagnosis**

• Physical and neurologic examinations at well-child checkups

• Tests (eg, corneal light reflex, alternate cover, cover-uncover)

• Prisms

Strabismus can be detected during well-child checkups. History should include questions about family history of amblyopia or strabismus and, if family or caregivers have noticed deviation of gaze, questions about when the deviation began, when or how often it is present, and whether there is a preference for using one eye for fixation. Physical examination should include an assessment of visual acuity, pupil reactivity, and the extent of extraocular movements. Neurologic examination, particularly of the cranial nerves, is important.

The corneal light reflex test is a good screening test, but it is not very sensitive for detecting small deviations. The child looks at a light and the light reflection (reflex) from the pupil is observed; normally, the reflex appears symmetric (ie, in the same location on each pupil). The light reflex for an exotropic eye is nasal to the pupillary center, whereas the reflex for an esotropic eye is temporal to the pupillary center. Vision screening machines operated by trained personnel are being introduced to identify children at risk.

When performing the alternate cover test, the child is asked to fixate on an object. One eye is then covered while the other is observed for movement. No movement should be detected if the eyes are properly aligned, but strabismus is present if the unoccluded eye shifts to establish fixation once the other eye, which had fixed on the object, is occluded. The test is then repeated on the other eye.

In a variation of the cover test, called the cover-uncover test, the child is asked to fix on an object while the examiner alternately covers and uncovers one eye and then the other, back and forth. An eye with a latent strabismus shifts position when it is uncovered. In exotropia, the eye that was covered turns *in* to fixate; in esotropia, it turns *out* to fixate. Tropia can be quantified by using prisms positioned such that the deviating eye need not move to fixate. The power of the prism used to prevent deviation quantifies the tropia and provides a measurement of the magnitude of misalignment of the visual axes. The unit of measurement used by ophthalmologists is the prism diopter. One prism diopter is a deviation of the visual axes of 1 cm at 1 m.

Strabismus should be distinguished from pseudostrabismus, which is the appearance of esotropia in a child with good visual acuity in both eyes but a wide nasal bridge or broad epicanthal folds that obscure much of the white sclera nasally when looking laterally. The light reflex and cover tests are normal in a child with pseudostrabismus.

**Prognosis and Treatment**

• Patching

• Contact lenses or eyeglasses

• Topical agents

• Eye exercises

• Surgical repair to align eyes

Strabismus should not be ignored on the assumption that it will be outgrown. Permanent vision loss can occur if strabismus and its attendant amblyopia are not treated before age 4 to 6 yr. As a result, all children should have formal vision screening in the preschool years.

Treatment aims to equalize vision and then align the eyes. Children with amblyopia require patching or penalization of the normal eye; improved vision offers a better prognosis for development of binocular vision and for stability if surgery is done. Patching is not, however, a treatment for strabismus. Eyeglasses or contact lenses are sometimes used if the amount of refractive error is significant enough to interfere with fusion, especially in children with accommodative esotropia. Topical miotic agents, such as echothiophate iodide 0.125%, may facilitate accommodation in children with accommodative esotropia. Orthoptic eye exercises can help correct intermittent exotropia with convergence insufficiency.

Surgical repair is generally done when non-surgical methods are unsuccessful in aligning the eyes satisfactorily. Surgical repair consists of loosening (recession) and tightening (resection) procedures, most often involving the rectus muscles. Surgical repair is typically done in an outpatient setting. Rates for successful realignment can exceed 80%. The most common complications are overcorrection or undercorrection and recurrence of the strabismus later in life. Rare complications include infection, excessive bleeding, and vision loss.

# Chapter 290. Incontinence in Children

## Urinary Incontinence

(Enuresis)

Urinary incontinence is defined as involuntary voiding of urine ≥ 2 times/mo during the day or night. Daytime incontinence (diurnal enuresis) is usually not diagnosed until age 5 or 6. Nighttime incontinence (nocturnal enuresis, or bed-wetting) is usually not diagnosed until age 7. Before this time, nocturnal enuresis is typically referred to as nighttime wetting. These age limits are based on children who are developing typically and so may not be applicable to children with developmental delay. Both nocturnal and diurnal enuresis are symptoms—not diagnoses—and necessitate consideration of an underlying cause.

The age at which children attain urinary continence varies, but > 90% are continent during the day by age 5. Nighttime continence takes longer to achieve. Nocturnal enuresis affects about 30% of children at age 4, 10% at age 7, 3% at age 12, and 1% at age 18. About 0.5% of adults continue to have nocturnal wetting episodes. Nocturnal enuresis is more common among boys and when there is a family history.

In primary enuresis, children have never achieved urinary continence for ≥ 6 mo. In secondary enuresis, children have developed incontinence after a period of at least 6 mo of urinary control. An organic cause is more likely in secondary enuresis. Even when there is no organic cause, appropriate treatment and parental education are essential because of the physical and psychologic impact of urine accidents.

### Pathophysiology

Bladder function has a storage phase and a voiding phase. Abnormalities in either phase can cause primary or secondary enuresis.

In the **storage phase**, the bladder acts as a reservoir for urine. Storage capacity is affected by bladder size and compliance. Storage capacity increases as children grow. Compliance can be decreased by repeated infections or by outlet obstruction, with resulting bladder muscle hypertrophy.

In the **voiding phase**, bladder contraction synchronizes with the opening of the bladder neck and the external urinary sphincter. If there is dysfunction in the coordination or sequence of voiding, enuresis can occur. There are multiple reasons for dysfunction. One example is bladder irritation, which can lead to irregular contractions of the bladder and asynchrony of the voiding sequence, resulting in enuresis. Bladder irritation can result from a UTI or from anything that presses on the bladder (eg, a dilated rectum caused by constipation).

### Etiology

Urinary incontinence in children has different causes and treatments than urinary incontinence in adults. Although some abnormalities cause both nocturnal and diurnal enuresis, etiology can vary depending on whether enuresis is nocturnal (see Table 290-1) or diurnal (see Table 290-2), as well as primary or secondary. Most primary enuresis is nocturnal and not due to an organic disorder. Nocturnal enuresis can be divided into monosymptomatic (occurring only during sleep) and complex (other abnormalities are present, such as urgency or diurnal enuresis).

**Nocturnal enuresis:** Organic disorders account for about 30% of cases and are more common in complex compared to monosymptomatic enuresis. The remaining majority are of unclear etiology but are thought to be due to a combination of factors, including

- Maturational delay
- Functionally small bladder capacity (the bladder is not actually small but contracts before it is completely full)

- Increased nighttime urine volume
- Difficulties in arousal from sleep
- Family history (if one parent had nocturnal enuresis, there is a 30% chance offspring will have it, increasing to 70% if both parents were affected)

The factors contributing to organic causes of nocturnal enuresis include

- Conditions that increase urine volume (eg, diabetes mellitus, diabetes insipidus, renal failure, excessive water intake, sickle cell disease and sometimes sickle trait [hyposthenuria])
- Conditions that increase bladder irritability (eg, UTI, pressure on the bladder by the rectum and sigmoid colon [caused by constipation])
- Structural abnormalities (eg, ectopic ureter, which can cause both nocturnal and diurnal enuresis)

[Table 290-1. Some Factors Contributing to Nocturnal Enuresis]

- Abnormal sphincter weakness (eg, spinal cord abnormalities, which can cause both nocturnal and diurnal enuresis)

**Diurnal enuresis:** Common causes include

- Bladder irritability
- Relative weakness of the detrusor muscle (making it difficult to inhibit incontinence)
- Constipation, urethrovaginal reflux, or vaginal voiding: girls who use an incorrect position during voiding or have redundant skin folds may have reflux of urine into the vagina, which subsequently leaks out on standing
- Structural abnormalities (eg, ectopic ureter)
- Abnormal sphincter weakness (eg, spinal cord abnormality, tethered cord)

**Evaluation**

Evaluation should always include assessment for constipation (which can be a contributing factor to both nocturnal and diurnal enuresis).

**History: History of present illness** inquires about onset of symptoms (ie, primary vs secondary), timing of symptoms (eg, at night, during the day, only after voiding), and whether symptoms are continuous (ie, constant dribbling) or intermittent. Recording a voiding schedule, including timing, frequency, and volume of voids, can be helpful. Important associated symptoms include polydipsia, dysuria, urgency, frequency, dribbling, and straining. Position during voiding and strength of urine steam should be noted. To prevent leakage,

[Table 290-2. Some Organic Causes of Diurnal Enuresis]

children with enuresis may cross their legs or use other postures, which increase their risk of UTIs.

**Review of systems** should seek symptoms suggesting a cause, including frequency and consistency of stools (constipation); fever, abdominal pain, dysuria, and hematuria (UTI); perianal itching and vaginitis (pinworm infection); polyuria and polydipsia (diabetes insipidus or diabetes mellitus); and snoring or breathing pauses during sleep (sleep apnea). Children should be screened for the possibility of sexual abuse, which, although an uncommon cause, is too important to miss.

**Past medical history** should identify known possible causes, including perinatal insults or birth defects (eg, spina bifida), neurologic disorders, renal disorders, and history of UTIs. Any current or previous treatments for enuresis and how they were actually instituted should be noted, as well as a list of current drugs.

Developmental history should note developmental delay or other developmental disorders related to voiding dysfunction (eg, attention-deficit/hyperactivity disorder, which increases the likelihood of enuresis).

Family history should note the presence of nocturnal enuresis and any urologic disorders.

Social history should note any stressors occurring near the onset of symptoms, including difficulties at school, with friends, or at home; although enuresis is not a psychologic disorder, a brief period of wetting may occur during stress.

Clinicians also should ask about the impact of enuresis on the child because it also affects treatment decisions.

**Physical examination:** Examination begins with review of vital signs for fever (UTI), signs of weight loss (diabetes), and hypertension (renal disorder). Examination of the head and neck should note enlarged tonsils, mouth breathing, or poor growth (sleep apnea). Abdominal examination should note any masses consistent with stool or a full bladder.

In girls, genital examination should note any labial adhesions, scarring, or lesions suspicious of sexual abuse. An ectopic ureteral orifice is often difficult to see but should be sought. In boys, examination should check for meatal irritation or any lesions on the glans or around the rectum. In either sex, perianal excoriations can suggest pinworms.

The spine should be examined for any midline defects (eg, deep sacral dimple, sacral hair patch). A complete neurologic evaluation is essential and should specifically target lower-extremity strength, sensation and deep tendon reflexes, sacral reflexes (eg, anal wink), and, in boys, cremasteric reflex to identify possible spinal dysraphism. A rectal examination may be useful to detect constipation or decreased rectal tone.

**Red flags:** Findings of particular concern are

• Signs or concerns of sexual abuse

• Excessive thirst, polyuria, and weight loss

• Prolonged primary diurnal enuresis (beyond age 6 yr)

• Any neurologic signs, especially in the lower extremities

• Physical signs of spinal disruption

**Interpretation of findings:** Usually, primary **nocturnal enuresis** occurs in children with an otherwise unremarkable history and examination and probably represents maturational delay. A small percentage of children have a treatable medical disorder; sometimes findings suggest possible causes (see Table 290-1).

In **diurnal enuresis**, dysfunctional voiding is suggested by intermittent enuresis preceded by a sense of urgency, a history of being distracted by play, or a combination. Enuresis after urination (due to lack of total bladder emptying) can also be part of the history.

Enuresis caused by a UTI is likely a discrete episode rather than a chronic, intermittent problem and may be accompanied by typical symptoms (eg, urgency, frequency, pain on urination); however, other causes

of enuresis can result in secondary UTI.

Constipation should be considered in the absence of other findings in children who have hard stools and difficulty with elimination (and sometimes palpable stool on examination).

Sleep apnea should be considered with a history of excessive daytime sleepiness and disrupted sleep. Rectal itching (especially at night), vaginitis, urethritis, or a combination can be an indication of pinworms. Excessive thirst, diurnal and nocturnal enuresis, and weight loss suggest a possible organic cause (eg, diabetes mellitus). Stress or sexual abuse can be difficult to ascertain but should be considered.

**Testing:** Diagnosis is often apparent after history and physical examination. Urinalysis is appropriate for both sexes, often with addition of urine culture for girls. Further testing is useful mainly when history, physical examination, or both suggest an organic cause (see Tables 290-1 and 290-2).

**Treatment**

The most important part of treatment is family education about the cause and clinical course of enuresis. Education helps decrease the negative psychologic impact of urine accidents and results in increased adherence with treatment.

Treatment should be targeted toward any cause that is identified; however, frequently no cause is found. In such cases, the following treatments may be useful.

**Nocturnal enuresis:** The most effective long-term strategy is a bed-wetting alarm. Although labor intensive, the success rate can be as high as 70% when children are motivated to end the enuresis, and the family is able to adhere. It can take up to 4 mo of nightly use for complete resolution of symptoms. It is essential to avoid punitive approaches because these undermine treatment and lead only to poor self-esteem.

Drugs such as desmopressin (DDAVP) and imipramine (see Table 290-3) can decrease nighttime wetting episodes; however, results are not sustained in most patients when the treatment is stopped. DDAVP is preferable to imipramine because of the rare potential of sudden death with imipramine use.

**Diurnal enuresis:** It is important to treat any underlying constipation. Information from the voiding diary can help identify opportunities for intervention. General measures may include

- Urgency containment exercises: Children are directed to go to the bathroom as soon as they feel the urge to urinate. They then hold the urine as long as they can and, when they can hold it no longer, start to urinate and then stop and start the urine stream. This exercise strengthens the sphincter and gives children confidence that they can make it to the bathroom before they have an accident.

- Gradual lengthening of voiding intervals (if detrusor instability or dysfunctional voiding is suspected)

- Changes in behaviors (eg, delayed urination) through positive reinforcement and scheduled urination: Children are reminded to urinate by a clock that vibrates or sounds an alarm (preferable to having a parent in the reminder role).

- Use of correct voiding methods to discourage retention of urine in the vagina (eg, sitting facing backward on the toilet or with the knees wide apart)

For labial adhesions, a conjugated estrogen cream may also be used.

Drug treatment (see Table 290-3) is sometimes helpful but is not typically first-line therapy. Anticholinergic drugs may benefit patients with diurnal enuresis due to voiding dysfunction when behavioral therapy or physiotherapy is unsuccessful. Drugs for nocturnal enuresis may be useful in decreasing nighttime wetting episodes and are sometimes useful to encourage dryness during overnight events such as sleepovers.

### Key Points

• Primary urinary incontinence most frequently manifests as nocturnal enuresis.

• Constipation should be considered as a contributing source.

• Most nocturnal enuresis abates with maturation (15%/yr resolve with no intervention), but at least 0.5% of adults have nighttime wetting episodes.

• Organic causes of enuresis are infrequent but should be considered.

[Table 290-3. Drugs Used for Enuresis in Children*]

• Alarms are the most effective treatment for nocturnal enuresis.

• Other treatments include behavioral interventions and sometimes drugs.

• Parental education is essential to the child's outcome and well-being.

## Stool Incontinence

(Encopresis)

**Stool incontinence is the voluntary or involuntary passage of stool in inappropriate places in children > 4 yr (or developmental equivalent) who do not have an organic defect or illness with the exception of constipation.**

Encopresis is a common childhood problem; it occurs in about 3 to 4% of 4-yr-old children and decreases in frequency with age.

### Etiology

Encopresis is most commonly caused by constipation in children with behavioral and physical predisposing factors. It rarely occurs without retention or constipation, but when it does, other organic processes (eg, Hirschsprung's disease, celiac disease) or psychologic problems should be considered.

### Pathophysiology

Stool retention and constipation result in dilation of the rectum and sigmoid colon, which leads to changes in the reactivity of muscles and nerves of the bowel wall. These changes decrease the efficacy of bowel excretory function and lead to further retention. As stool remains in the bowel, water is absorbed, which hardens the stool, making passage more difficult and painful. Softer, looser stool may then leak around the hardened stool bolus, resulting in overflow. Both leakage and ineffective bowel control result in stool accidents.

### Diagnosis

Any organic process that results in constipation (see p. 2726) can result in encopresis and so should be considered. For most routine cases of encopresis, a thorough history and physical examination can help identify any physical cause. However, if further concerns arise, additional diagnostic tests (eg, abdominal x-rays, rarely rectal wall biopsy, and even more rarely bowel motility studies—see p. 2980) can be considered.

### Treatment

• Education and demystification (for parents and child)

• Relief of stool impaction

• Maintenance (eg, behavioral and dietary interventions, laxative therapy)

• Slow withdrawal of laxatives with continued behavioral and dietary intervention (see Table 268-14)

Any underlying disorders are treated. If there is no specific underlying pathology, symptoms are addressed. Initial treatment involves educating the parents and child about the physiology of encopresis, removing blame from the child, and diffusing the emotional reactions of those involved. Next the goal is to relieve any stool impaction.

Stool impaction can be relieved by a variety of regimens and drugs (see p. 2731); choice depends on the age of the child and other factors. A combination of polyethylene glycol (PEG) with electrolytes plus a stimulant laxative (eg, bisacodyl or senna), or a sequence of Na phosphate enemas plus a 2-wk regimen of oral drugs (eg, bisacodyl tablets) and suppositories are often used.

After evacuation, a follow-up visit should be held to assess whether the evacuation has been successful, make sure soiling has resolved, and establish a maintenance plan. This plan includes encouragement of maintenance of regular bowel movements (usually via ongoing laxative management) and behavioral interventions to encourage stool evacuation. There are many options for maintenance laxative therapy (see Table 268-14), but PEG without electrolytes is used most often, typically 1 to 2 doses of 17 g/day titrated to effect. At times a stimulant laxative may also be continued on the weekends to encourage extra evacuation of stool.

Behavioral strategies include structured toilet sitting times (eg, having children sit on the toilet for 5 to 10 min after each meal to take advantage of the gastrocolic reflex). If children have accidents during certain times of the day, they also should sit immediately prior to those times. Small rewards are often useful incentives. For example, giving children stickers to place on a chart each time they sit (even if there is no stool production) can increase adherence to a plan. Often a stepwise program is used in which children receive small tokens (eg, stickers) for sitting and larger rewards for consistent adherence. Rewards may need to be changed over time to maintain children's interest in the plan. In the maintenance phase, regular toilet sitting sessions still are needed to encourage evacuation of stool before the sensation is felt. This strategy decreases the likelihood of stool retention and allows the rectum to return to its normal size. During the maintenance phase, parent and child education about toilet sitting is instrumental to the success of the regimen.

Regular follow-up visits are necessary for ongoing guidance and support. Bowel retraining is a long process that may take months to years and includes slow withdrawal of laxatives once symptoms resolve and continued encouragement of toilet sitting.

Encopresis can recur in times of stress or transition, so family members must be prepared for this possibility. Success rates are affected by physical and psychosocial factors, but 1-yr cure rates are about 30 to 50% and 5-yr cure rates are about 48 to 75%. The mainstay of treatment is family education, bowel cleanout and maintenance, and ongoing support.

# Chapter 291. Miscellaneous Disorders in Infants and Children

## Apparent Life-Threatening Event

**An apparent life-threatening event (ALTE) is the sudden appearance of certain alarming symptoms (eg, apnea, change in color or muscle tone, coughing, gagging), typically in children < 1 yr. Causes may be digestive, neurologic, respiratory, cardiac, or metabolic. Treatment is aimed at specific causes when identified.**

An ALTE is not a diagnosis but a group of symptoms that occur acutely in young children.

### Etiology

The most common causes include

• Gastroesophageal reflux disease

• Neurologic disorders (eg, seizures, meningitis, brain tumors, abnormal brainstem neuro-regulation of cardiorespiratory control)

• Infection

Less common causes include

• Cardiac disorders

• Metabolic disorders

• Upper airway obstruction

Causes may be genetic or acquired. About 50% of cases are considered idiopathic. If an

[
Table 291-1. Diagnostic Tests for Causes of Apparent Life-Threatening Event (ALTE)]

infant is under the care of one person and has repeated episodes with no clear etiology, child abuse should be considered.

### Symptoms and Signs

An ALTE usually is characterized by an unexpected, acute change in an infant's breathing that alarms the parent or caretaker. Features of an event include some or all of the following:

• Apneic episode

• Color change

• Change in muscle tone

• Choking or gagging

### Diagnosis

Evaluation initially involves a thorough history, including

• Observations by the caregiver who witnessed the event (including description of changes in breathing, color, muscle tone, and eyes; noises made; and length of episode)

• Interventions taken (eg, gentle stimulation, mouth-to-mouth breathing, CPR)

• Prenatal (maternal) and current family use of drugs, tobacco, and alcohol

• Information about the infant's birth (eg, gestational age, perinatal complications)

• Feeding habits (whether gagging, coughing, vomiting, or poor weight gain has occurred)

• Developmental history (eg, milestones)

• Prior history of ALTE or recent trauma

• Family history of ALTE, early deaths, or possible causative disorders

Physical examination is done to check for obvious malformations, neurologic abnormalities (eg, posturing, inappropriate head lag), and signs of infection or trauma (particularly including retinal hemorrhage on funduscopy).

Laboratory and imaging tests (see Table 291-1) are done to check for possible causes. Some are routinely done, and others are done based only on history and physical examination findings.

### Prognosis

Prognosis depends on the cause of ALTE. That is, risk of death is higher if the cause is a serious neurologic disorder. The relationship of ALTE to SIDS is unclear. About 4 to 10% of infants who die of SIDS have a history of ALTE, and the risk of SIDS is higher if an infant has had 2 or more ALTEs. Also, infants who have had an ALTE share many of the same characteristics with infants who die of SIDS. However, incidence of ALTE, unlike that of SIDS, has not decreased in response to the Back to Sleep campaign.

There seem to be no long-term effects on development.

### Treatment

The cause, if identified, is treated. If infants have required resuscitation or if evaluation has detected any abnormalities, they are hospitalized for evaluation and monitoring that includes respiratory and cardiac monitoring and some of the tests listed in Table 291-1 as indicated.

Parents and caregivers should be trained in CPR for infants and in safe infant care. Home monitoring devices may be considered depending on risk of recurrent episodes. Monitors should be equipped with event recorders and used for a predetermined period of time. Parents should be taught how to use the monitor and be advised that home monitoring has not been shown to reduce the mortality rate. Also, exposure to tobacco smoke must be eliminated.

## Failure to Thrive

**Failure to thrive (FTT) is weight consistently below the 3rd to 5th percentile for age, progressive decrease in weight to below the 3rd to 5th percentile, or a decrease in the percentile rank of 2 major growth parameters in a short period. The cause may be an identified medical condition or may be related to environmental factors. Both types relate to inadequate nutrition. Treatment aims to restore proper nutrition.**

### Etiology

The physiologic basis for FTT of any etiology is inadequate nutrition and is divided into

• Organic FTT

• Nonorganic FTT

**Organic FTT:** Growth failure is due to an acute or chronic disorder that interferes with nutrient intake, absorption, metabolism, or excretion or that increases energy requirements (see Table 291-2). Illness of any organ system can be a cause.

**Nonorganic FTT:** Up to 80% of children with growth failure do not have an apparent growth-inhibiting (organic) disorder; growth failure occurs because of environmental neglect (eg, lack of food), stimulus deprivation, or both.

Lack of food may be due to

• Impoverishment

• Poor understanding of feeding techniques

• Improperly prepared formula (eg, overdiluting formula to stretch it because of financial difficulties)

• Inadequate supply of breast milk (eg, because the mother is under stress, exhausted, or poorly nourished)

Nonorganic FTT is often a complex of disordered interaction between a child and caregiver. In some cases, the psychologic basis of nonorganic FTT seems similar to that of hospitalism, a syndrome observed in infants who have depression secondary to stimulus deprivation. The unstimulated child becomes depressed, apathetic, and ultimately anorexic. Stimulation may be lacking because the caregiver

• Is depressed or apathetic

• Has poor parenting skills

• Is anxious about or unfulfilled by the caregiving role

• Feels hostile toward the child

• Is responding to real or perceived external stresses (eg, demands of other children in large or chaotic families, marital dysfunction, a significant loss, financial difficulties)

Poor caregiving does not fully account for all cases of nonorganic FTT. The child's temperament, capacities, and responses help shape caregiver nurturance patterns. Common scenarios involve parent-child mismatches, in which the child's demands, although not pathologic, cannot be adequately met by the

[**Table 291-2.** Some Causes of Organic Failure to Thrive]

parents, who might, however, do well with a child who has different needs or even with the same child under different circumstances.

**Mixed FTT:** In mixed FTT, organic and nonorganic causes can overlap; children with organic disorders also have disturbed environments or dysfunctional parental interactions. Likewise, those with severe undernutrition caused by nonorganic FTT can develop organic medical problems.

**Diagnosis**

• Frequent weight monitoring

• Thorough medical, family, and social history

• Diet history

• Laboratory testing

Children with organic FTT may present at any age depending on the underlying disorder. Most children with nonorganic FTT manifest growth failure before age 1 yr and many by age 6 mo. Age should be plotted against weight, height, and head size. Until premature infants reach 2 yr, age should be corrected for gestation.

Weight is the most sensitive indicator of nutritional status. Reduced linear growth usually indicates more severe, prolonged undernutrition. Because the brain is preferentially spared in protein-energy undernutrition (see p. 14), reduced growth in head circumference occurs late and indicates very severe or longstanding undernutrition.

Usually, when growth failure is noted, a history (including diet history—see Table 291-3) is obtained, diet counseling is provided, and the child's weight is monitored frequently. A child who does not gain weight satisfactorily in spite of outpatient assessment and intervention usually is admitted to the hospital so that all necessary observations can be made and diagnostic tests can be done quickly. Without historic or physical evidence of a specific underlying etiology for growth failure, no single clinical feature or test can reliably distinguish organic from nonorganic FTT. Because nonorganic FTT is not a diagnosis of exclusion, the physician should search simultaneously for an underlying physical problem and for personal, family, and child-family characteristics that support a psychosocial etiology. Optimally, evaluation is multidisciplinary, involving a physician, a nurse, a social worker, a nutritionist, an expert in child development, and often a psychiatrist or psychologist. The child's feeding behaviors with health care practitioners and with the parents must be observed, whether the setting is inpatient or outpatient.

Engaging the parents as co-investigators is essential. It helps foster their self-esteem and avoids blaming those who may already feel frustrated or guilty because of a perceived inability to nurture their child. The family should be encouraged to visit as often and as long as possible. Staff members should make them feel welcome, support their attempts to feed the child, and provide toys and ideas that promote parent-child play and other interactions. Staff members should avoid any comments implying parental inadequacy, irresponsibility, or other fault as the cause of FTT. However, parental adequacy and sense of responsibility should be evaluated. Suspected neglect or abuse must be reported to social services, but in many instances, referral for preventive services that are targeted to meet the family's needs for support and education (eg, additional food stamps, more accessible child care, parenting classes) is more appropriate.

During hospitalization, the child's interaction with people in the environment is closely observed, and evidence of self-stimulatory behaviors (eg, rocking, head banging) is noted. Some children with nonorganic FTT have been described as hypervigilant and wary

[**Table 291-3.** Essentials of the History for Failure to Thrive]

of close contact with people, preferring interactions with inanimate objects if they interact at all. Although nonorganic FTT is more consistent with neglectful than abusive parenting, the child should be examined closely for evidence of abuse (see p. 3062). A screening test of developmental level should be done and, if indicated, followed with more sophisticated assessment.

**Testing:** Extensive laboratory testing is usually nonproductive. If a thorough history or physical examination does not indicate a particular cause, most experts recommend limiting screening tests to

• CBC with differential

• ESR

• BUN or serum creatinine level

• Urinalysis (including ability to concentrate and acidify) and culture

• Stool for pH, reducing substances, odor, color, consistency, and fat content

Depending on prevalence of specific disorders in the community, blood lead level, HIV, or TB testing may be warranted.

Other tests that are sometimes appropriate include electrolyte concentrations if the child has a history of significant vomiting or diarrhea; a thyroxine level if growth in height is more severely affected than growth in weight; and a sweat test if the child has a history of recurrent upper or lower respiratory tract disease, a salty taste when kissed, a ravenous appetite, foul-smelling bulky stools, hepatomegaly, or a family history of cystic fibrosis. Investigation for infectious diseases should be reserved for children with evidence of infection (eg, fever, vomiting, cough, diarrhea). Radiologic investigation should be reserved for children with evidence of anatomic or functional pathology (eg, pyloric stenosis, gastroesophageal reflux).

**Prognosis**

Prognosis with organic FTT depends on the cause. With nonorganic FTT, the majority of children age > 1 yr achieve a stable weight above the 3rd percentile. Children who develop FTT before age 1 yr are at high risk of cognitive delay, especially verbal and math skills. Children diagnosed at age < 6 mo, when the rate of postnatal brain growth is maximal, are at highest risk. General behavioral problems, identified by teachers or mental health practitioners, occur in about 50% of children. Problems specifically related to eating (eg, pickiness, slowness) or elimination tend to occur in a similar proportion of children, usually those with other behavioral or personality disturbances.

**Treatment**

• Sufficient nutrition

• Treatment of underlying disorder

• Long-term social support

Treatment aims to provide sufficient health and environmental resources to promote satisfactory growth. A nutritious diet containing adequate calories for catch-up growth (about 150% of normal caloric requirement) and individualized medical and social supports are usually necessary. Ability to gain weight in the hospital does not always differentiate infants with nonorganic FTT from those with organic FTT; all children grow when given sufficient nutrition. However, some children with nonorganic FTT lose weight in the hospital, highlighting the complexity of this condition.

For children with organic or mixed FTT, the underlying disorder should be treated quickly. For children with apparent nonorganic FTT or mixed FTT, management includes provision of education and emotional support to correct problems interfering with the parent-child relationship. Because long-term social support or psychiatric treatment is often required, the evaluation team may be able only to define the family's needs, provide initial instruction and support, and institute appropriate referrals to community agencies. The parents should understand why the referrals are being made and, if options exist, should participate in decisions concerning which agencies will be involved. If the child is hospitalized in a tertiary care center, the referring physician should be consulted regarding local agencies and the level of expertise available in the community.

A predischarge planning conference involving hospital-based personnel, representatives from the community agencies that will provide follow-up services, and the child's primary physician is ideal. Areas of responsibility and lines of accountability must be clearly defined, preferably in writing, and distributed to everyone involved. The parents should be invited to a summary session after the conference so that they can meet the community workers, ask questions, and arrange follow-up appointments.

In some cases, the child must be placed in foster care. If the child is expected to eventually return to the

biologic parents, parenting skill training and psychologic counseling must be provided for them. Their child's progress must be monitored scrupulously. Return to the biologic parents should be based on the parents' demonstrated ability to care for the child adequately, not only on the passage of time.

## Hemorrhagic Shock and Encephalopathy Syndrome

**Hemorrhagic shock and encephalopathy syndrome (HSES) is an extremely rare disease characterized by acute onset of severe shock, coagulopathy, encephalopathy, and hepatic and renal dysfunction in previously healthy children, resulting in death or catastrophic neurologic outcome.**

HSES occurs predominantly in infants aged 3 to 8 mo (median age, 5 mo) but has been reported in a 15 yr old. HSES resembles heatstroke, with extremely high temperature and multiple organ dysfunction, but the cause is unknown. Overwrapping of infants who have febrile illness has been suggested, but evidence is slim. Other theories include a reaction to intestinal or environmental toxins, pancreatic release of trypsin, or an unidentified virus or bacterium. Diffuse cerebral edema with herniation and focal hemorrhages and infarcts in the cerebral cortex and other organs are common. The lungs and myocardium are not primarily involved.

### Symptoms and Signs

A prodrome of fever, upper respiratory tract symptoms, or vomiting and diarrhea occurs in most patients. The major features are an acute onset of encephalopathy, cerebral edema (manifested as seizures, coma, and hypotonia), and severe shock (ie, hypotension and poor perfusion). Other common features include hyperpyrexia (up to 43.9° C rectally), bloody or watery diarrhea, disseminated intravascular coagulation (DIC), myoglobinuria, and rhabdomyolysis.

### Diagnosis

• Laboratory testing

Similar symptoms can result from sepsis, Reye's syndrome, and hemolytic-uremic syndrome. Patients require laboratory evaluation, including blood and urine culture, ABG, CBC, electrolytes, BUN, creatinine, PT/PTT, and liver function tests. Multiple abnormalities include metabolic acidosis, elevated liver transaminases, acute renal failure, thrombocytopenia, falling Hct, leukocytosis, hypoglycemia, and hyperkalemia. Bacteriologic and viral cultures are negative. Diagnosis is by exclusion.

### Prognosis

In all cases, > 60% of patients died, and ≥ 70% of survivors had severe neurologic sequelae.

### Treatment

• Supportive measures

Treatment is entirely supportive. Infusions of large volumes of isotonic solutions and blood products (fresh frozen plasma, albumin, whole blood, packed RBCs) along with inotropic support (eg, dopamine, epinephrine) are necessary to maintain circulation. Marked temperature elevation (eg, > 39° C) requires external cooling (see p. 3266). Increased intracranial pressure caused by cerebral edema requires intubation and hyperventilation. DIC often progresses despite use of fresh frozen plasma.

## Kawasaki Disease

**Kawasaki disease (KD) is a vasculitis, sometimes involving the coronary arteries, that tends to occur in infants and children between ages 1 yr and 8 yr. It is characterized by prolonged fever, exanthem, conjunctivitis, mucous membrane inflammation, and lymphadenopathy. Coronary artery aneurysms may develop and rupture or cause MI. Diagnosis is by clinical criteria; once the disease is diagnosed, echocardiography is done. Treatment is aspirin and IV immune**

**globulin. Coronary thrombosis may require fibrinolysis or percutaneous interventions.**

KD is a vasculitis of medium-sized arteries, most significantly the coronary arteries, which are involved in about 20% of untreated patients. Early manifestations include acute myocarditis with heart failure, arrhythmias, endocarditis, and pericarditis. Coronary artery aneurysms may subsequently form. Giant coronary artery aneurysms (> 8 mm internal diameter on echocardiography), though rare, have the greatest risk of causing cardiac tamponade, thrombosis, or infarction. KD is the leading cause of acquired heart disease in children. Extravascular tissue also may become inflamed, including the upper respiratory tract, pancreas, biliary tract, and kidneys.

### Etiology

The etiology is unknown, but the epidemiology and clinical presentation suggest an infection or an abnormal immunologic response to an infection in genetically predisposed children. Children of Japanese descent have a particularly high incidence, but KD occurs worldwide. In the US, 3000 to 5000 cases occur annually. The male:female ratio is about 1.5:1. Eighty percent of patients are < 5 yr (peak, 18 to 24 mo). Cases in adolescents, adults, and infants < 4 mo are rare. Cases occur year-round, but most often in spring or winter. Clusters have been reported in communities without clear evidence of person-to-person spread. About 2% of patients have recurrences, typically months to years later.

### Symptoms and Signs

The illness tends to progress in stages, beginning with fever lasting at least 5 days, usually remittent and > 39° C, associated with irritability, occasional lethargy, or intermittent colicky abdominal pain. Usually within a day or two of fever onset, bilateral bulbar conjunctival injection appears without exudate. Within 5 days, a polymorphous, erythematous macular rash appears, primarily over the trunk, often with accentuation in the perineal region. The rash may be urticarial, morbilliform, erythema multiforme, or scarlatiniform. It is accompanied by injected pharynx; reddened, dry, fissured lips; and a red strawberry tongue (see Plate 74). During the first week, pallor of the proximal portion of the fingernails or toenails (leukonychia partialis) may occur. Erythema or a purple-red discoloration and variable edema of the palms and soles usually appear on about the 3rd to 5th day. Although edema may be slight, it is often tense, hard, and nonpitting. Periungual, palmar, and plantar and perineal desquamation begins on about the 10th day. The superficial layer of the skin sometimes comes off in large casts, revealing new normal skin. Tender, nonsuppurative cervical lymphadenopathy (≥ 1 node ≥ 1.5 cm in diameter) is present throughout the course in about 50% of patients. The illness may last from 2 to 12 wk or longer. Incomplete or atypical cases can occur, especially in younger infants, who have higher risk of developing coronary artery disease. These findings manifest in about 90% of patients.

Other less specific findings indicate involvement of many systems. Arthritis or arthralgias (mainly involving large joints) occur in about 33% of patients. Other clinical features include urethritis, aseptic meningitis, hepatitis, otitis, vomiting, diarrhea, hydrops of the gallbladder, and anterior uveitis.

Cardiac manifestations usually begin in the subacute phase of the syndrome about 1 to 4 wk after onset as the rash, fever, and other early acute clinical symptoms begin to subside.

### Diagnosis

- Clinical criteria
- Laboratory testing (CBC, ESR, antinuclear antibody [ANA], rheumatoid factor [RF], throat and blood cultures)
- Serial ECG and echocardiography

Diagnosis is by clinical criteria (see Table 291-4). Similar symptoms can result from scarlet fever, staphylococcal exfoliative syndromes, measles, drug reactions, and juvenile idiopathic arthritis; less common mimics are leptospirosis and

Rocky Mountain spotted fever.

Laboratory tests are not diagnostic but may be done to exclude other disorders. Patients generally undergo CBC, ANA, RF, ESR, and throat and blood cultures. Leukocytosis, often with a marked increase in immature cells, is common acutely. Other hematologic findings include a mild normocytic anemia, thrombocytosis (≥ 450,000/µL) in the 2nd or 3rd wk of illness, and elevated ESR or C-reactive protein. ANA, RF, and cultures are negative. Other abnormalities, depending on the organ systems involved, include sterile pyuria, elevated liver enzymes, proteinuria, and CSF pleocytosis.

Consultation with a pediatric cardiologist is important. At diagnosis, ECG and echocardiography are done; because abnormalities may not appear until later, these tests are repeated 2 to 3 wk, 6 to 8 wk, and perhaps 6 to 12 mo after onset. ECG may show arrhythmias, decreased voltage, or left ventricular hypertrophy. Echocardiography should detect coronary artery aneurysms, valvular regurgitation, pericarditis, or myocarditis. Coronary arteriography occasionally is useful in patients with aneurysms and abnormal stress test results.

[**Table 291-4.** Criteria for Diagnosis of Kawasaki Disease]

**Prognosis**

Without therapy, mortality may approach 1%, usually occurring within 6 wk of onset. With adequate therapy, the mortality rate in the US is 0.17%. Long duration of fever increases cardiac risk. Deaths most commonly result from cardiac complications and can be sudden and unpredictable: > 50% occur within 1 mo of onset, 75% within 2 mo, and 95% within 6 mo but may occur as long as 10 yr later. Effective therapy reduces acute symptoms and, more importantly, the incidence of coronary artery aneurysms from 20% to < 5%. In the absence of coronary artery disease, the prognosis for complete recovery is excellent. About two thirds of coronary aneurysms regress within 1 yr, although it is unknown whether residual coronary stenosis remains. Giant coronary aneurysms are less likely to regress and require more intensive follow-up and therapy.

**Treatment**

• High-dose immune globulin IV (IGIV)

• High-dose aspirin

Children should be treated by or in close consultation with an experienced pediatric cardiologist, pediatric infectious disease specialist, or both. Therapy is started as soon as possible, optimally within the first 10 days of illness, with a combination of high-dose IGIV (single dose of 2 g/kg given over 10 to 12 h) and oral high-dose aspirin 20 to 25 mg/kg po qid. The aspirin dose is reduced to 3 to 5 mg/kg once/day after the child has been afebrile for 4 to 5 days; some authorities prefer to continue high-dose aspirin until the 14th day of illness. Aspirin metabolism is erratic during acute KD, which partially explains the high dose requirements. Some authorities monitor serum aspirin levels during high-dose therapy, especially if therapy is given for 14 days.

Most patients have a brisk response over the first 24 h of therapy. A small fraction continues to be ill with fever for several days and requires repeated dosing with IGIV. An alternative regimen, which may lead to slightly slower resolution of symptoms but may benefit those with cardiac dysfunction who could not tolerate the volume of a 2 g/kg IGIV infusion, is IGIV 400 mg/kg once/day for 4 days (again in combination with high-dose aspirin). The efficacy of IGIV/aspirin therapy when begun > 10 days after onset of illness is unknown, but therapy should still be considered.

After the child's symptoms have abated for 4 to 5 days, aspirin 3 to 5 mg/kg/day is continued for at least 8 wk after onset until repeated echocardiographic testing is completed. If there are no coronary artery aneurysms and signs of inflammation are absent (shown by normalization of ESR and platelets), aspirin may be stopped. Because of its antithrombotic effect, aspirin is continued indefinitely for children with coronary artery abnormalities. Children with giant coronary aneurysms may require additional anticoagulant therapy (eg, warfarin, dipyridamole).

Children who receive IGIV therapy may have a lower response rate to live viral vaccines. Thus, measles-mumps-rubella vaccine should generally be delayed for 11 mo after IGIV therapy, and varicella vaccine should be delayed for ≥ 11 mo. If the risk of measles exposure is high, vaccination should proceed, but revaccination (or serologic testing) should be done 11 mo later.

A small risk of Reye's syndrome exists in children receiving long-term aspirin therapy during outbreaks of influenza or varicella; thus, annual influenza vaccination is indicated for children (≥ 6 mo of age) receiving long-term aspirin therapy. Further, parents of children receiving aspirin should be instructed to contact their child's physician promptly if the child is exposed to or develops symptoms of influenza or varicella. Temporary interruption of aspirin may be considered (with substitution of dipyridamole for children with documented aneurysms).

## Progeria

(Hutchinson-Gilford syndrome)

**Progeria is a rare syndrome of accelerated aging that manifests early in childhood and causes premature death.**

Progeria is caused by a sporadic mutation in the *LMNA* gene that codes for a protein (lamin A) that provides the molecular scaffolding of cell nuclei. The defective protein leads to nuclear instability from cell division and early death of every body cell.

Symptoms and signs develop within 2 yr and include

• Growth failure

• Craniofacial abnormalities (eg, craniofacial disproportion, micrognathia, beaked nose)

• Physical changes of aging (eg, wrinkled skin, balding)

Diagnosis is usually obvious by appearance but must be distinguished from segmental progerias (eg, acrogeria, metageria) and other causes of growth failure. Median age at death is 12 yr; cause is coronary artery and cerebrovascular disease. Of note is that other problems associated with normal aging (eg, increased cancer risk, degenerative arthritis) are not present. There is no known treatment.

**Other progeroid syndromes:** Premature aging is a feature of other rare progeroid syndromes, including Werner's syndrome (premature aging after puberty with hair thinning and development of conditions of old age [eg, cataracts, diabetes, osteoporosis, atherosclerosis]) and Rothmund-Thomson syndrome (premature aging with increased susceptibility to cancer). Both are caused by gene mutations leading to defective RecQ DNA helicases, which normally repair DNA. Cockayne's syndrome is an autosomal recessive disease caused by mutation in the *ERCC8* gene, which is important in DNA excision repair. Clinical features include severe growth failure, cachectic appearance, retinopathy, hypertension, renal failure, skin photosensitivity, and intellectual disability. Neonatal progeroid (Wiedemann-Rautenstrauch) syndrome is a recessively inherited syndrome of aging causing death by 2 yr. Other syndromes (eg, Down, Ehlers-Danlos) occasionally have progeroid features.

## Reye's Syndrome

**Reye's syndrome is a rare form of acute encephalopathy and fatty infiltration of the liver that tends to follow some acute viral infections, particularly when salicylates are used. Diagnosis is clinical. Treatment is supportive.**

The cause of Reye's syndrome is unknown, but many cases seem to follow infection with influenza A or B or varicella. Using salicylates during such illness increases the risk by as much as 35-fold. This finding has led to a marked decrease in salicylate use in the US since the mid-1980s (except when specifically indicated, such as in juvenile idiopathic arthritis and Kawasaki disease) and a corresponding decrease in

the incidence of Reye's syndrome from several hundred annual cases to < 20. The syndrome occurs almost exclusively in children < 18 yr. In the US, most cases occur in late fall and winter.

The disease affects mitochondrial function, causing disturbance in fatty acid and carnitine metabolism. Pathophysiology is similar to a number of inherited metabolic disorders.

**Symptoms and Signs**

The disease varies greatly in severity but is characteristically biphasic. Initial viral symptoms (URI or sometimes chickenpox) are followed in 5 to 7 days by pernicious nausea and vomiting and a sudden change in mental status. The changes in mental status may vary from a mild amnesia and lethargy to intermittent episodes of disorientation and agitation, which can progress rapidly to deepening stages of coma manifested by

- Progressive unresponsiveness
- Decorticate and decerebrate posturing
- Seizures
- Flaccidity
- Fixed dilated pupils
- Respiratory arrest

Focal neurologic findings usually are not present. Hepatomegaly occurs in about 40% of cases, but jaundice is absent.

**Complications:** Complications include

- Electrolyte and fluid disturbances
- Increased intracranial pressure (ICP)
- Diabetes insipidus
- Syndrome of inappropriate ADH secretion
- Hypotension
- Arrhythmias
- Bleeding diatheses (especially GI)
- Pancreatitis
- Respiratory insufficiency
- Hyperammonemia
- Aspiration pneumonia
- Poor temperature regulation

**Diagnosis**

- Clinical findings in association with laboratory testing

• Liver biopsy

Reye's syndrome should be suspected in any child exhibiting the acute onset of an encephalopathy (without known heavy metal or toxin exposure) and pernicious vomiting associated with hepatic dysfunction. Liver biopsy provides the definitive diagnosis, showing microvesicular, fatty changes, and is especially useful in sporadic cases and in children < 2 yr. The diagnosis may also be made when the typical clinical findings and history are associated with the following laboratory findings: increased liver transaminases (AST, ALT > 3 times normal), normal bilirubin, increased blood ammonia level, and prolonged PT. CSF examination usually shows increased pressure, < 8 to 10 WBCs/µL, and normal protein levels; the CSF glutamine level may be elevated. Hypoglycemia and hypoglycorrhachia occur in 15% of cases, especially in children < 4 yr; they should be screened for metabolic disease. The condition is staged from I to V according to severity.

Signs of metabolic derangement include elevated serum amino acid levels, acid-base disturbances (usually with hyperventilation, mixed respiratory alkalosis-metabolic acidosis), osmolar changes, hypernatremia, hypokalemia, and hypophosphatemia.

**Differential diagnosis:** The differential diagnosis of coma and liver dysfunction includes sepsis or hyperthermia (especially in infants); potentially treatable inborn abnormalities of urea synthesis (eg, ornithine transcarbamylase deficiency) or fatty acid oxidation (eg, systemic carnitine deficiency, medium chain acyl-CoA dehydrogenase deficiency); phosphorus or carbon tetrachloride intoxication; acute encephalopathy caused by salicylism, other drugs (eg, valproate), or poisons; viral encephalitis or meningoencephalitis; and acute hepatitis. Illnesses such as idiopathic steatosis of pregnancy and tetracycline liver toxicity may show similar light microscopic findings.

### Prognosis

Outcome is related to the duration of cerebral dysfunction, severity and rate of progression of coma, severity of increased ICP, and degree of blood ammonia elevation. Progression from stage I to higher stages is likely when the initial blood ammonia level is > 100 µg/dL (> 60 µmol/L) and the PT is ≥ 3 sec longer than that of the control. In fatal cases, the mean time from hospitalization to death is 4 days. Fatality rates average 21% but range from < 2% among patients in stage I to > 80% among patients in stage IV or V. Prognosis for survivors usually is good, and recurrences are rare. However, the incidence of neurologic sequelae (eg, intellectual disability, seizure disorders, cranial nerve palsies, motor dysfunction) is as high as 30% among survivors who developed seizures or decerebrate posturing during illness.

### Treatment

• Support measures

Treatment is supportive, with particular attention paid to control of ICP and blood glucose, because glycogen depletion is common. Treatment of elevated ICP includes intubation, hyperventilation, fluid restriction of 1500 mL/$m^2$/day, elevating the head of the bed, and osmotic diuretics. Infusion of 10 or 15% dextrose is common to maintain euglycemia. Coagulopathy may require fresh frozen plasma or vitamin K. Other treatments (eg, exchange transfusion, hemodialysis, barbiturate-induced deep coma) have not been proved effective but are sometimes used.

## Sudden Infant Death Syndrome

**Sudden infant death syndrome (SIDS) is the sudden and unexpected death of an infant or young child between 2 wk and 1 yr of age in which an examination of the death scene, thorough postmortem examination, and clinical history fail to show cause.**

SIDS is the most common cause of death of infants between 2 wk and 1 yr of age, accounting for 35 to 55% of all deaths in this age group. The rate of SIDS occurrence is 0.5/1000 births in the US; there are racial and ethnic disparities (African American and Native American children have twice the average risk

of SIDS). Peak incidence is between the 2nd and 4th mo of life. Almost all SIDS deaths occur when the infant is thought to be sleeping.

### Etiology

The cause is unknown, although it is most likely due to dysfunction of neural cardiorespiratory control mechanisms. The dysfunction may be intermittent or transient, and multiple mechanisms are probably involved. Fewer than 5% of infants with SIDS have episodes of prolonged apnea before their death, so the overlap between the SIDS population and infants with recurrent prolonged apnea is very small.

**Risk factors:** The association between a prone (on stomach) sleeping position and an increased risk of SIDS has been documented strongly. Other risk factors (see Table 291-5) include old or unsafe cribs, soft bedding (eg, lamb's wool), waterbed mattresses, smoking in the home, and an overheated environment. Siblings of infants who die of SIDS are 5 times more likely to die of SIDS; it is not clear whether this is related to genetics or environment.

Many risk factors for SIDS apply to non-SIDS infant deaths as well.

### Diagnosis

The diagnosis, while largely one of exclusion, cannot be made without an adequate autopsy to rule out other causes of sudden, unexpected death (eg, intracranial hemorrhage, meningitis, myocarditis).

[**Table 291-5.** Risk Factors for Sudden Infant Death Syndrome]

### Management

Parents who have lost a child to SIDS are grief-stricken and unprepared for the tragedy. Because no definitive cause can be found for their child's death, they usually have excessive guilt feelings, which may be aggravated by investigations conducted by police, social workers, or others. Family members require support not only during the days immediately after the infant's death but for at least several months to help them with their grief and dispel guilt feelings. Such support includes, whenever possible, an immediate home visit to observe the circumstances in which SIDS occurred and to inform and counsel the parents concerning the cause of death.

Autopsy should be done quickly. As soon as the preliminary results are known (usually within 12 h) they should be communicated to the parents. Some clinicians advise a series of home or office visits over the first month to continue the earlier discussions, answer questions, and give the family the final (microscopic) autopsy results. At the last meeting, it is appropriate to discuss the parents' adjustment to their loss, especially their attitude toward having other children. Much of the counseling and support can be complemented by specially trained nurses or by lay people who have themselves experienced the tragedy of and adjustment to SIDS (visit www.sids.org for more information and resources).

### Prevention

The American Academy of Pediatrics recommends that infants be placed supine (on their back) for sleep unless other medical conditions prevent this. The incidence of SIDS increases with overheating (eg, clothing, blankets, hot room) and in cold weather. Thus, every effort should be made to avoid an overly hot or an overly cold environment, to avoid over-wrapping the infant, and to remove soft bedding, such as sheepskin, pillows, stuffed toys/animals, and comforters, from the crib. Mothers should avoid smoking during pregnancy, and infants should not be exposed to smoke. Parents should not have the infant sleep in their bed. There is no evidence that home apnea monitors reduce the incidence of SIDS and therefore are not suggested for prevention.

# Chapter 292. Pediatric Cancers

## Introduction

Overall, childhood cancer is relatively rare, with fewer than 11,000 cases and about 1,500 deaths annually among children aged 0 to 14 yr. In comparison, there are 1.4 million cases and 565,000 deaths annually among adults. However, cancer is the 2nd leading cause of death among children, following only injuries.

Childhood cancers include many that also occur in adults. Leukemia (see p. 1004) is by far the most common, representing about 33% of childhood cancers, brain tumors represent about 21%, lymphomas (see p. 1016) about 8%, and certain bone cancers (osteosarcoma and Ewing sarcoma—see p. 407) about 4%. Cancers that are exclusive to children include neuroblastoma (7% of cases), Wilms' tumor (5%), rhabdomyosarcoma (3 to 4%), and retinoblastoma (3%).

Children who survive cancer have more years than adults to develop long-term consequences of chemotherapy and radiation therapy, which include

• Infertility

• Poor growth

• Cardiac damage

• Development of second cancers (in 3 to 12% of survivors)

Consensus guidelines on screening for and management of long-term consequences are available from the Children's Oncology Group at www.survivorshipguidelines.org/.

Because of the severe consequences and complexity of treatment, children with cancer are best treated in centers with expertise in childhood cancers.

The impact of being diagnosed with cancer and the intensity of the treatment are overwhelming to the child and family. Maintaining a sense of normalcy for the child is difficult, especially given the need for frequent hospitalizations and outpatient visits and potentially painful procedures. Overwhelming stress is typical, as parents struggle to continue to work, be attentive to siblings, and still attend to the many needs of the child with cancer. The situation is even more difficult when the child is being treated at a specialty center far from home.

## Brain Tumors

**Brain tumors are the most common solid cancer in children < 15 yr and are the 2nd leading cause of death due to cancer. Diagnosis is typically by imaging (usually MRI) and biopsy. Treatment may include surgical resection, chemotherapy, and radiation therapy.**

Entry into a clinical trial should be considered for all children with a brain tumor. Optimal treatment requires a multidisciplinary team of oncologists who have experience treating brain tumors in children. Because radiation therapy for brain tumors is technically demanding, children should be sent to centers that have experience in this area if possible.

### Astrocytomas

Astrocytomas range from low-grade indolent tumors (the most prevalent) to malignant high-grade tumors. As a group, astrocytomas are the most common brain tumor in children, representing about 40% of tumors. Most cases occur between ages 5 yr and 9 yr. These tumors can occur anywhere in the brain or spinal cord, but are most common in the cerebellum.

#### Symptoms and Signs

Most patients have symptoms consistent with increased intracranial pressure (eg, morning headaches, vomiting, lethargy). Location of the tumor determines other symptoms and signs; for example:

- **Cerebellum:** Weakness, tremor, and ataxia
- **Visual pathway:** Visual loss, proptosis, or nystagmus
- **Spinal cord:** Pain, weakness, and gait disturbance

**Diagnosis**

Contrast-enhanced MRI is the imaging test of choice for diagnosing the tumor, determining extent of disease, and detecting recurrence. Contrast-enhanced CT can also be used, although it is less specific and less sensitive. Biopsy is needed for determining tumor type and grade. These tumors are typically classified as low-grade (eg, juvenile pilocytic astrocytoma), intermediate-grade, or high-grade (eg, glioblastoma).

**Treatment**

Treatment depends on location and grade of tumor. As a general rule, the lower the grade, the less intensive the therapy and the better the outcome.

- **Low-grade:** Surgical resection is the primary treatment. Radiation therapy is reserved for children who are > 10 yr and whose tumors cannot be completely excised. For children < 10 yr with incompletely excised tumors, chemotherapy is used instead because radiation therapy may cause long-term cognitive impairment. Most children with low-grade astrocytomas are cured.
- **Intermediate-grade:** These tumors are somewhere between low-grade and high-grade lesions. If they are closer to high-grade tumors, they are treated more aggressively (radiation and chemotherapy); if they appear more like low-grade tumors, they are treated with surgery alone or surgery followed by radiation (older children) or chemotherapy (younger children).
- **High-grade:** These tumors are treated with a combination of surgery (unless location precludes it), radiation therapy, and chemotherapy. Prognosis is poor; overall survival is only 20-30%.

**Ependymomas**

Ependymomas are the 3rd most common CNS tumor in children (after astrocytomas and medulloblastomas), representing 10% of pediatric brain tumors. Mean age at diagnosis is 6 yr; however, about 30% of ependymomas occur in children < 3 yr.

Ependymomas are derived from the ependymal lining of the ventricular system. Up to 70% of ependymomas occur in the posterior fossa; both high-grade and low-grade tumors in the posterior fossae tend to spread locally to the brain stem.

Initial symptoms are typically related to increased intracranial pressure. Infants may present with developmental delay and irritability. Changes in mood, personality, or concentration may occur. Seizures, balance and gait disturbances, or symptoms of spinal cord compression (eg, back pain, loss of bladder and bowel control) may occur.

Diagnosis is based on MRI and biopsy.

The tumor is surgically removed, followed by MRI to check for residual tumor. Radiation therapy, chemotherapy, or both are then required.

Overall 5-yr survival rate is about 50% but depends partly on age:

- < 1 yr: 25%
- 1 to 4 yr: 46%
- ≥ 5 yr: 70%

Survival rate also depends on how much of the tumor can be removed (51 to 80% with total or near-total removal vs 0 to 26% with < 90% removal). Children who survive are at risk of neurologic deficits.

**Medulloblastoma**

Medulloblastoma is the most common malignant posterior fossa tumor in children and represents about 20% of all pediatric CNS cancers. It most commonly occurs in children aged 5 to 7 yr but can occur throughout adolescence. It is more common among boys. Medulloblastoma is a type of primitive neuroectodermal tumor (PNET).

Etiology is unclear, but medulloblastoma may occur with certain syndromes (eg, Gorlin syndrome, Turcot syndrome).

Patients present most commonly with vomiting, headache, nausea, visual changes (eg, double vision), and unsteady walking or clumsiness.

MRI with gadolinium contrast is the imaging test of choice for initial detection. Biopsy confirms diagnosis. Once the diagnosis is established, MRI of the entire spine along with lumbar puncture and sampling of the CSF are done to assess for spread of tumor into the spinal canal.

Treatment includes surgery, radiation, and chemotherapy. Children under the age of 3 may be effectively treated with chemotherapy alone. Combination therapy typically provides the best long-term survival.

Prognosis depends on the extent, histology, and biologic (eg, histologic, cytogenetic, molecular) parameters of the tumor and patient age:

- > 3 yr: Likelihood of 5-yr disease-free survival is 50 to 60% if the tumor is high-risk (disseminated) and 80% if the tumor is average-risk (no dissemination).
- ≤ 3 yr: Prognosis is more problematic, in part because up to 40% have disseminated disease at diagnosis. Children who survive are at risk of severe long-term neurocognitive deficits (eg, in memory, verbal learning, and executive function).

## Neuroblastoma

**Neuroblastoma is a cancer arising in the adrenal gland or less often from the extra-adrenal sympathetic chain, including the retroperitoneum, chest, and neck. Diagnosis is based on biopsy. Treatment may include surgical resection, chemotherapy, radiation therapy, and high-dose chemotherapy with stem cell transplantation.**

Neuroblastoma is the most common cancer among infants. Almost 90% of neuroblastomas occur in children < 5 yr. Neuroblastoma can result from numerous different cytogenetic abnormalities on several chromosomes; in 1 to 2%, abnormalities appear to be inherited. Some markers (eg, N-*myc* oncogene, hyperdiploidy, histopathology) correlate with progression and prognosis.

Neuroblastomas may begin in the abdomen (about 65%), thorax (15 to 20%), neck, pelvis, or other sites. Neuroblastoma occurs very rarely as a primary CNS cancer.

Most neuroblastomas produce catecholamines, which can be detected as elevated levels of urinary catecholamine breakdown products. Ganglioneuroma is a fully differentiated, benign variant of neuroblastoma.

About 40 to 50% of children have localized or regional disease at diagnosis; 50 to 60% have metastases at diagnosis. Neuroblastoma may metastasize to bone marrow, bone, liver, lymph nodes, or, less commonly, skin or brain.

### Symptoms and Signs

Symptoms and signs depend on the site of the primary cancer and pattern of disease spread. The most common symptoms are abdominal pain, discomfort, and a sense of fullness due to an abdominal mass.

Certain symptoms may result from metastases. These include bone pain due to widespread bone metastases, periorbital ecchymosis and proptosis due to retrobulbar metastasis, and abdominal distention and respiratory problems due to liver metastases, especially in infants. Occasionally, pallor due to anemia and petechiae due to thrombocytopenia occur in children with bone marrow metastases.

Children occasionally present with focal neurologic deficits or paralysis due to direct extension of the cancer into the spinal canal. They may also present with paraneoplastic syndromes (see p. 1054), such as cerebellar ataxia, opsoclonus-myoclonus, watery diarrhea, or hypertension.

### Diagnosis

- CT
- Biopsy
- Sometimes bone marrow aspirate or core biopsy plus measurement of urinary catecholamine intermediates

Routine prenatal ultrasonography occasionally detects neuroblastoma. Patients presenting with abdominal symptoms or a mass require CT. Diagnosis is then confirmed by biopsy of any identified mass. Alternatively, diagnosis can be confirmed by finding characteristic cancer cells in a bone marrow aspirate or core biopsy plus elevated urinary catecholamine intermediates. Urinary vanillylmandelic acid (VMA), homovanillic acid (HVA), or both are elevated in ≥ 90% of patients. A 24-h urine collection can be used, although a spot urine test is usually sufficient. Neuroblastomas must be differentiated from Wilms' tumor, other renal masses, rhabdomyosarcoma, hepatoblastoma, lymphoma, and tumors of genital origin.

The following should be done to evaluate for metastases:

- Bone marrow aspirates and core biopsies from multiple sites (typically, both iliac crests)
- Skeletal survey
- Bone scan or $^{131}$I-metaiodobenzylguanidine (MBIG) scan
- Abdominal, pelvis, and chest CT or MRI

Cranial imaging with CT or MRI is indicated if symptoms or signs suggest brain metastases.

When the cancer is resected, a portion should be analyzed for DNA index (a quantitative measure of chromosome content) and amplification of the N-*myc* oncogene to determine prognosis and intensity of therapy. Risk categorization is complex, but generally classified as

- **Low:** Age < 1 yr, no amplification of the N-*myc* oncogene, and lower-stage (localized) disease
- **Intermediate:** Regional spread but no amplification of the N-*myc* oncogene
- **High:** Age ≥ 1 yr plus metastatic disease, amplification of the N-*myc* oncogene, or both

### Prognosis

Prognosis is better for children with low-risk disease.

### Treatment

• Surgical resection

• Chemotherapy

• Sometimes stem cell transplantation

• Sometimes radiation therapy

Surgical resection is important for low-risk and intermediate-risk disease. Chemotherapy (typical drugs include vincristine, cyclophosphamide, doxorubicin, cisplatin, carboplatin, ifosfamide, and etoposide) is usually necessary for children with intermediate-risk disease. High-dose chemotherapy with stem cell transplantation and *cis*-retinoic acid are frequently used for children with high-risk disease. Radiation therapy is sometimes needed for children with intermediate-risk or high-risk disease or for inoperable tumors.

## Retinoblastoma

**Retinoblastoma is a cancer arising from the immature retina. Symptoms and signs commonly include leukocoria (a white reflex in the pupil), strabismus, and, less often, inflammation and impaired vision. Diagnosis is based on ophthalmoscopic examination and ultrasonography, CT, or MRI. Treatment of small cancers and bilateral disease may include photocoagulation, cryotherapy, and radiation therapy. Treatment of larger cancers is enucleation. Chemotherapy is sometimes used to reduce cancer volume and to treat cancers that have spread beyond the eye.**

Retinoblastoma occurs in 1/15,000 to 1/30,000 live births and represents about 3% of childhood cancers. It is usually diagnosed in children < 2 yr; < 5% of cases are diagnosed in those > 5 yr. The cancer may be hereditary. About 25% of patients have bilateral disease, which is always heritable. Another 15% of patients have heritable unilateral disease, and the remaining 60% have nonhereditary unilateral disease.

The pathogenesis of inheritance appears to involve mutational deactivation of both alleles of a retinoblastoma suppressor gene located on chromosome 13q14. In the hereditary form, a germline mutation alters one allele in all cells, and a later somatic mutation alters the other allele in the retinal cells (the 2nd hit in this 2-hit model), resulting in the cancer. The nonhereditary form probably involves somatic mutation of both alleles in a retinal cell.

### Symptoms and Signs

Patients typically present with leukocoria (a white reflex in the pupil, sometimes referred to as cat's-eye pupil—see Plate 73) or strabismus. Much less often, patients present with inflammation of the eye or impaired vision. Rarely, the cancer has already spread, via the optic nerve or the choroid or hematogenously, resulting in an orbital or soft-tissue mass, headache, anorexia, or vomiting.

When the diagnosis is suspected, both fundi must be closely examined by indirect ophthalmoscopy with the pupils widely dilated and the child under general anesthesia. The cancers appear as single or multiple gray-white elevations in the retina; cancer seeds may be visible in the vitreous.

### Diagnosis

• Orbital ultrasonography, CT, or MRI

• Sometimes bone scan, bone marrow aspirate and biopsy, and lumbar puncture

Diagnosis is usually confirmed by orbital ultrasonography or CT. In almost all cancers, calcification can be detected by CT. However, if the optic nerve appears abnormal during ophthalmoscopy, MRI is better for finding cancer extension into the optic nerve or choroid. Whenever extraocular spread is suspected, testing should include a bone scan, a bone marrow aspirate and biopsy, and lumbar puncture.

Children who have a parent or sibling with a history of retinoblastoma should be evaluated by an ophthalmologist shortly after birth and then every 4 mo until age 4 yr. Patients with retinoblastoma require molecular genetic testing, and if a germline mutation is identified, parents should also be tested for the same mutation. If subsequent offspring of parents have the germline mutation, the same genetic testing and regular ophthalmologic examination are required. Recombinant DNA probes may be useful for detecting asymptomatic carriers.

**Prognosis**

If the cancer is treated when it is intraocular, > 90% of patients can be cured. Prognosis for patients with metastatic disease is poor.

In patients with hereditary retinoblastoma, incidence of 2nd cancers is increased; about 50% arise within the irradiated area. These cancers can include sarcomas and malignant melanoma. Within 30 yr of diagnosis, 70% develop a 2nd cancer.

**Treatment**

Unilateral retinoblastoma is managed by enucleation with removal of as much of the optic nerve as possible.

For patients with bilateral cancer, vision can usually be preserved. Options include bilateral photocoagulation or unilateral enucleation and photocoagulation, cryotherapy, and irradiation of the other eye. Radiation therapy is by external beam or, for very small cancers, brachytherapy (attachment of a radioactive plaque to the eye wall near the cancer).

Systemic chemotherapy, such as carboplatin plus etoposide, or cyclophosphamide plus vincristine, may be helpful to reduce the size of large cancers or to treat cancer that has disseminated beyond the eye. However, chemotherapy alone can seldom cure this cancer.

Ophthalmologic reexamination of both eyes and retreatment, if necessary, are required at 2-mo to 4-mo intervals.

## Rhabdomyosarcoma

**Rhabdomyosarcoma is a cancer arising from embryonal mesenchymal cells that have potential to differentiate into skeletal muscle cells. It can arise from almost any type of muscle tissue in any location, resulting in highly variable clinical manifestations. Cancers are typically detected by CT or MRI, and diagnosis is confirmed by biopsy. Treatment involves surgery, radiation therapy, and chemotherapy.**

Rhabdomyosarcoma is the 3rd most common extra-CNS solid cancer in children (after Wilms' tumor and neuroblastoma). Nonetheless, it accounts for only 3 to 4% of all childhood cancers. Incidence of rhabdomyosarcoma in children is 4.3/million/yr. Two thirds of cancers are diagnosed in children < 7 yr. The disease is more common among whites than blacks (largely because frequency is lower in black girls) and is slightly more common among boys than girls.

**Histology:** There are 2 major histologic subtypes:

• Embryonal: Characterized by loss of heterozygosity on chromosome 11p15.5

• Alveolar: Associated with a translocation involving *PAX3* or *PAX7*, regulators of transcription during neuromuscular development (chromosome 2;13 or 1;13 translocation)

**Location:** Although rhabdomyosarcoma can occur almost anywhere in the body, the cancer has predilection for several sites:

• Head and neck region, usually in the orbit or nasopharyngeal passages: 35 to 40%, most common among school-aged children

• GU system, usually in the bladder, prostate, or vagina: 25%, usually occurring in infants and toddlers

• Extremities: 20%, most common among adolescents

Fewer than 25% of children present with metastatic disease.

**Symptoms and Signs**

Children do not typically have systemic symptoms such as fever, night sweats, or weight loss. Usually, children present with a firm, palpable mass or with organ dysfunction due to impingement on the organ by the cancer.

**Orbital and nasopharyngeal cancers** may cause tearing, eye pain, or proptosis. Nasopharyngeal cavity cancers may cause nasal congestion, a change in voice, or mucopurulent discharge.

**GU cancers** cause abdominal pain, a palpable abdominal mass, difficulty urinating, and hematuria.

**Extremity cancers** appear as firm, indiscrete masses anywhere on the arms or legs. Metastases occur frequently, especially in the lungs, bone marrow, and lymph nodes, and usually do not cause symptoms.

**Diagnosis**

• CT or MRI

• Biopsy or excision

Masses are evaluated by CT, although head and neck lesions are often better defined by MRI. Diagnosis is confirmed by biopsy or excision of the mass. The standard metastatic evaluation includes chest CT, a bone scan, and bone marrow aspiration and biopsy.

**Prognosis**

Prognosis is based on

• Cancer location (eg, prognosis is better with head and GU cancers)

• Extent of resection

• Presence of metastasis

• Age (more favorable in younger children)

• Histology (embryonal histology is associated with a better outcome than alveolar histology)

Combinations of these prognostic factors place children at low, intermediate, or high risk. Treatment intensifies with each risk category, and overall survival ranges from > 90% in children with low-risk disease to < 50% in children with high-risk disease.

**Treatment**

• Surgery and chemotherapy

• Sometimes radiation therapy

Treatment consists of surgery, chemotherapy, and sometimes radiation therapy. Complete excision of the primary cancer is recommended when it can be done safely. Because the cancer is so sensitive to chemotherapy and radiation therapy, aggressive resection is discouraged if it may result in organ damage or dysfunction.

Children in all risk categories are treated with chemotherapy; the most commonly used drugs are vincristine, actinomycin D, cyclophosphamide, doxorubicin, ifosfamide, and etoposide. Topotecan and irinotecan are newer drugs that have activity against this cancer; they are being investigated in some frontline treatment regimens.

Radiation therapy is generally reserved for children with residual cancer after surgery and for children with intermediate-risk or high-risk disease.

## Wilms' Tumor

(Nephroblastoma)

**Wilms' tumor is an embryonal cancer of the kidney composed of blastemal, stromal, and epithelial elements. Genetic abnormalities have been implicated in the pathogenesis, but familial inheritance accounts for only 1 to 2% of cases. Diagnosis is by ultrasonography and abdominal CT and is confirmed by biopsy. Treatment may include surgical resection, chemotherapy, and radiation therapy.**

Wilms' tumor usually manifests in children < 5 yr but occasionally in older children and rarely in adults. Wilms' tumor accounts for about 6% of cancers in children < 15 yr. Bilateral synchronous tumors occur in about 5% of patients; bilateral disease is more common among very young children, especially girls.

A chromosomal deletion of *WT1*, the Wilms' tumor suppressor gene, has been identified in some cases. Other associated genetic abnormalities include deletion of *WT2* (a 2nd Wilms' tumor suppressor gene), deletion of chromosome 16, and duplication of chromosome 12.

About 10% of cases manifest with other congenital abnormalities, especially GU abnormalities, but also commonly hemihypertrophy (asymmetry of the body). WAGR syndrome is the combination of Wilms' tumor (with *WT1* deletion), aniridia, GU malformations (eg, renal hypoplasia, cystic disease, hypospadias, cryptorchidism), and mental retardation (intellectual disability).

### Symptoms and Signs

The most frequent finding is a painless, palpable abdominal mass. Less frequent findings include abdominal pain, hematuria, fever, anorexia, nausea, and vomiting. Hematuria (occurring in 15 to 20%) indicates invasion of the collecting system. Hypertension may occur if compression of the renal pedicle or renal parenchyma causes ischemia.

### Diagnosis

• Abdominal ultrasonography and CT

• Biopsy

Abdominal ultrasonography determines whether the mass is cystic or solid and whether the renal vein or vena cava is involved. Abdominal CT is needed to determine the extent of the tumor and check for spread to regional lymph nodes, the contralateral kidney, or liver. The diagnosis is confirmed by biopsy of the mass. Renal arteriography, vena cavography, retrograde urography, or excretory urography is seldom

required. Chest CT is recommended to detect metastatic pulmonary involvement at initial diagnosis.

**Prognosis**

Prognosis depends on

• Histology (favorable or unfavorable)

• Stage at diagnosis

• Patient's age (younger is better)

The outcome for children with Wilms' tumor is excellent. Cure rates for lower-stage disease (localized to the kidney) range from 85% to 95%. Even children with more advanced disease fare well; cure rates range from 60% (unfavorable histology) to 90% (favorable histology).

The cancer may recur, typically within 2 yr of diagnosis. Cure is possible in children with recurrent cancer. Outcome after recurrence is better for children who present initially with lower-stage disease, whose tumors recur at a site that has not been irradiated, who relapse > 1 yr after presentation, and who receive less intensive treatment initially.

**Treatment**

• Surgery and chemotherapy

• Sometimes radiation therapy

The National Wilms' Tumor Study Group has established staging criteria and guidelines for treatment. Prompt surgical exploration of potentially resectable lesions is indicated, with examination of the contralateral kidney. If the cancer is unilateral and limited to the kidney or if extension is minimal, complete resection by nephrectomy is done, followed by treatment with vincristine and actinomycin D. If a unilateral cancer has spread extensively or if the disease is bilateral, chemotherapy with actinomycin D and vincristine, with or without radiation therapy, is used. Children with more advanced disease also receive doxorubicin. Other frequently used drugs include cyclophosphamide, ifosfamide, and etoposide.

Children with very large nonresectable tumors or bilateral tumors are candidates for chemotherapy followed by reevaluation and possibly resection.

# Chapter 293. Congenital Cardiovascular Anomalies

## Introduction

(See also Ch. 214.)

Congenital anomalies of the heart and blood vessels arise during the first 10 wk of embryonic development and are present at birth. The incidence is 1/120 live births; estimated risk is 2 to 3% in children with an affected 1st-degree relative.

### Etiology

About 5% of patients have a chromosomal abnormality (eg, trisomy 13, 18, or 21; Turner's syndrome); other anomalies may be part of a genetic syndrome (eg, Holt-Oram, Noonan's, Williams, 22q11 deletion). Other possible causes are maternal illnesses (eg, diabetes mellitus, SLE, rubella), environmental exposure (eg, to thalidomide, isotretinoin, lithium [Ebstein's anomaly], or alcohol [fetal alcohol syndrome]), or a combination. Usually, no specific cause is identified.

### Pathophysiology

Congenital heart anomalies are classified (see Table 293-1) as

• Cyanotic

• Acyanotic (left-to-right shunts or obstructive lesions)

The physiologic consequences of congenital heart anomalies vary greatly, ranging from an asymptomatic heart murmur or abnormal pulses to severe cyanosis and heart failure (HF).

**Left-to-right shunts:** Oxygenated blood from the left heart (left atrium or left ventricle) or the aorta shunts to the right heart (right atrium or right ventricle) or the pulmonary artery through an abnormal opening between

[**Table 293-1.** Classification of Congenital Heart Anomalies*]

the 2 sides. Blood flows from left to right initially because systemic pressure and vascular resistance are higher than pulmonary artery pressure and resistance. The additional blood flow to the right side increases pulmonary blood flow and pulmonary artery pressure to a varying degree. The greater the increase, the more severe the symptoms; a small left-to-right shunt is usually asymptomatic.

High-pressure shunts (those at the ventricular or great artery level) become apparent several days to a few weeks after birth; low-pressure shunts (atrial septal defects) become apparent considerably later. If untreated, elevated pulmonary artery pressure may lead to Eisenmenger's syndrome (see p. 2966). Large left-to-right shunts (eg, large ventricular septal defect [VSD], patent ductus arteriosus [PDA]) cause volume overload, which may lead to HF and during infancy often results in failure to thrive. A large left-to-right shunt also decreases lung compliance, leading to frequent lower respiratory tract infections.

**Obstructive lesions:** Blood flow is obstructed without shunting, causing a pressure gradient across the obstruction. The resulting pressure overload proximal to the obstruction may cause ventricular hypertrophy and HF. The principal manifestation is a heart murmur, which results from turbulent flow through the obstructed (stenotic) point. Examples are congenital aortic stenosis, which accounts for 3 to 6% of congenital heart anomalies, and congenital pulmonary stenosis, which accounts for 8 to 12% (for both, see Ch. 214).

**Cyanotic heart anomalies:** Varying amounts of deoxygenated venous blood are shunted to the left heart (right-to-left shunt), reducing systemic arterial $O_2$ saturation. If there is > 5 g/dL of deoxygenated

Hb, cyanosis results. Detection of cyanosis may be delayed in infants with dark pigmentation. Complications of persistent cyanosis include polycythemia, clubbing, thromboembolism (including stroke), bleeding disorders, brain abscess, and hyperuricemia. Hypercyanotic spells frequently occur in infants with tetralogy of Fallot (see p. 2958).

Depending on the anomaly, pulmonary blood flow may be increased (often resulting in HF in addition to cyanosis), normal, or reduced, resulting in cyanosis of variable severity. Heart murmurs are variably audible and are not specific.

**Heart failure:** Some congenital heart anomalies (eg, bicuspid aortic valve, mild aortic stenosis) do not significantly alter hemodynamics. Others cause pressure or volume overload, sometimes causing HF. HF occurs when cardiac output is insufficient to meet the body's metabolic needs or when the heart cannot adequately handle venous return, causing pulmonary congestion (in left ventricular failure), edema primarily in dependent tissues and abdominal viscera (in right ventricular failure), or both (see p. 2118). HF in infants and children has many causes other than congenital heart anomalies (see Table 293-2).

### Symptoms and Signs

Manifestations of the various heart anomalies are limited to several common ones:

- Murmurs
- Cyanosis
- HF

Less commonly, chest pain, diminished or nonpalpable pulses, circulatory shock, and arrhythmias are present.

**Murmurs:** Most left-to-right shunts and obstructive lesions cause systolic murmurs. Systolic murmurs and thrills are most prominent at the surface closest to their point of origin, making location diagnostically helpful. Increased flow across the pulmonary or aortic valve causes a midsystolic (ejection systolic) murmur. Regurgitant flow through an atrioventricular valve or flow across a VSD causes a holosystolic (pansystolic) murmur, possibly obscuring heart sounds as its intensity increases.

PDA causes a continuous murmur that is uninterrupted by the 2nd heart sound ($S_2$) because blood flows through the ductus during systole and diastole. This murmur is 2-toned, having a different sound during systole (when driven by higher pressure) than during diastole.

**Cyanosis:** This manifestation is characterized by bluish discoloration of mucous membranes or nail beds, clubbing of nail beds, or pulse oximetry < 93 to 95%.

**Heart failure:** In infants, symptoms or signs of HF include

- Tachycardia
- Tachypnea
- Dyspnea with feeding
- Diaphoresis
- Restlessness
- Irritability

Dyspnea with feeding causes inadequate intake and poor growth, which may be worsened by increased

metabolic demands in HF and frequent respiratory tract infections. Hepatomegaly is common. However, in contrast to adults and older children, most infants do not have distended neck veins and dependent edema, although they occasionally have edema

[**Table 293-2.** Common Causes of Heart Failure in Children]

in the periorbital area. Findings in older children with HF are similar to those in adults (see p. 2123).

**Other manifestations:** In neonates, circulatory shock may be the first manifestation of certain anomalies (eg, hypoplastic left heart syndrome, critical aortic stenosis, interrupted aortic arch, coarctation of the aorta). Neonates appear extremely ill and have cold extremities, diminished pulses, low BP, and reduced response to stimuli.

Chest pain may be manifested by unexplained irritability in infants with a coronary artery anomaly. In older children and adolescents, chest pain due to a cardiac etiology is usually associated with exertion and may be caused by severe aortic stenosis, pulmonic stenosis, or Eisenmenger's syndrome.

### Diagnosis

• Pulse oximetry, ECG, and chest x-ray

• Echocardiography

• Sometimes cardiac MRI or CT angiography, cardiac catheterization with angiocardiography

Diagnosis is suggested by the presence of heart murmurs, abnormal pulses, cyanosis, or HF. Cyanosis is usually noticed during the first few months of life. Cyanosis due to heart defects should be distinguished from that due to other disorders (eg, various respiratory disorders, CNS depression, hypothermia, hypoglycemia, hypocalcemia, sepsis, methemoglobinemia). Pulse oximetry, ECG, and chest x-ray are required. Echocardiography usually confirms the diagnosis.

Cardiac MRI or CT angiography may clarify important anatomic details. Cardiac catheterization with angiocardiography is occasionally needed to confirm the diagnosis or to assess severity of the anomaly; it is done more often for therapeutic purposes.

### Treatment

• Medical treatment of HF (eg, with $O_2$, diuretics, ACE inhibitors, digoxin, and salt restriction)

• Surgical repair of anomalies amenable to correction

After medical stabilization of acute HF symptoms or cyanosis, most children require surgical or transcatheter repair; the exceptions are certain VSDs that are likely to become smaller or close with time. Transcatheter procedures include balloon atrial septostomy for palliation of severely cyanotic neonates with transposition of the great arteries, balloon dilation of severe aortic or pulmonary valve stenosis, and transcatheter closure of cardiac shunts (most often atrial septal defect and PDA).

**Heart failure in neonates:** Acute, severe HF or cyanosis in the first week of life is a medical emergency. Secure vascular access should be established, preferably via an umbilical venous catheter. For HF, diuretics, inotropic drugs, and drugs to reduce afterload are given. The diuretic furosemide or ethacrynic acid is given as an initial bolus of 1 mg/kg IV and titrated based on urine output. The inotropic drug dopamine or dobutamine is given as an IV infusion of 5 to 15 µg/kg/min. Milrinone or, less frequently, nitroprusside is given to reduce afterload. Milrinone is given as a loading dose of 50 to 75 µg/kg IV over 10 to 60 min followed by an infusion of 0.5 µg/kg/min. Nitroprusside is started at 0.3 to 0.5 µg/kg/min and titrated to desired effect (usual maintenance dose is about 3 µg/kg/min).

Once a congenital cardiac lesion is suspected as the cause of the HF or cyanosis, an IV infusion of prostaglandins should be started (eg, prostaglandin $E_1$ 0.05 to 0.1 µg/kg/min) and titrated to the lowest

dose that maintains patency of the ductus arteriosus. Keeping the ductus open is important because most cardiac lesions manifesting at this age are ductal-dependent either for systemic blood flow (eg, hypoplastic left heart syndrome, critical aortic stenosis, coarctation of the aorta) or for pulmonary blood flow (cyanotic lesions such as pulmonary atresia or severe tetralogy of Fallot).

Mechanical ventilation is often necessary; $O_2$ should be given judiciously or even withheld because $O_2$ can decrease pulmonary vascular resistance, which is harmful to infants with certain defects (eg, hypoplastic left heart syndrome).

**Heart failure in older infants and children:** Standard approaches to acute and chronic heart failure, similar to those in adults, are used. These approaches may include a diuretic (eg, furosemide 0.5 to 1.0 mg/kg IV or 1 to 3 mg/kg po q 8 to 24 h, titrated upward as needed), an ACE inhibitor (eg, captopril 0.1 to 0.3 mg/kg po tid), digoxin (dose varies by age; see Table 293-3), and salt restriction. A potassium-sparing diuretic (spironolactone 1 mg/kg po once/day or bid, titrated up to 2 mg/kg/dose if needed) may be useful, particularly if high-dose furosemide is required.

A croupette, mask, or nasal prongs with adequate fractional inspired $O_2$ ($FIO_2$) should be given to prevent cyanosis and alleviate respiratory distress; when possible, $FIO_2$ should be kept < 40% to prevent pulmonary epithelial damage. A cardiac chair position may benefit small infants and children; this position reduces upward pressure into the thorax exerted by abdominal organs and thus reduces work required for breathing.

Because HF increases metabolic demands and makes feeding more difficult, enhanced caloric content feedings are recommended; these feedings increase calories supplied and do so with less risk of volume overload. Some children require nasogastric or gastrostomy feedings to maintain growth. If these measures do not result in weight gain, surgical repair of the anomaly is indicated.

[**Table 293-3.** Oral Digoxin Dosage in Children*]

**Endocarditis prophylaxis:** Current guidelines of the American Heart Association for prevention of endocarditis (see p. 2199) state that antibiotic prophylaxis is required for children with congenital heart disease (CHD) who have the following:

• Unrepaired cyanotic CHD (including children with palliative shunts and conduits)

• Completely repaired CHD during the first 6 mo after surgery if prosthetic material or a device was used

• Repaired CHD with residual defects at or adjacent to the site of a prosthetic patch or prosthetic device

## Atrial Septal Defect

(Ostium Secundum Defect)

**An atrial septal defect (ASD) is an opening in the interatrial septum, causing a left-to-right shunt and volume overload of the right atrium and right ventricle. Children are rarely symptomatic, but long-term complications after age 20 yr include pulmonary hypertension, heart failure, and atrial arrhythmias. Adults and, rarely, adolescents may present with exercise intolerance, dyspnea, fatigue, and atrial arrhythmias. A soft midsystolic murmur at the upper left sternal border with a prominently split 2nd heart sound ($S_2$) is common. Diagnosis is by echocardiography. Treatment is transcatheter or surgical repair.**

ASDs account for about 6 to 10% of cases of congenital heart disease. Most cases are isolated and sporadic, but some are part of a genetic syndrome (eg, mutations of chromosome 5, Holt-Oram syndrome).

**Classification:** ASDs can be classified by location:

- Ostium secundum (defect in the fossa ovalis—in the center [or middle] part of the atrial septum)
- Sinus venosus (defect in the posterior aspect of the septum, near the superior vena cava or inferior vena cava and frequently associated with anomalous return of the right upper or lower pulmonary veins to the right atrium or vena cava)
- Ostium primum (defect in the anteroinferior aspect of the septum, a form of atrioventricular septal [endocardial cushion] defect—see p. 2953).

**Pathophysiology**

To understand hemodynamic changes seen in ASD (and other anomalies), see Fig. 293-1 for normal hemodynamic data.

In ASD, shunting is left to right initially (see Fig. 293-2). Some small ASDs, often just a stretched patent foramen ovale, close spontaneously during the first few years of life. Persistent moderate-to-large ASDs result in large shunts, leading to right atrial and right ventricular volume overload and, over a number of years, pulmonary artery hypertension, elevated pulmonary vascular resistance, and right ventricular hypertrophy. Atrial fibrillation may also occur later. Ultimately, the increase in the pulmonary artery pressure and vascular resistance may result in a bidirectional atrial shunt with cyanosis during adulthood (Eisenmenger's reaction).

**Symptoms and Signs**

Most small ASDs are asymptomatic. Larger shunts may cause exercise intolerance, dyspnea during exertion, fatigue, and atrial arrhythmias with palpitations. Passage of microemboli from the venous circulation across the ASD (paradoxical embolization), often associated with arrhythmias, may lead to cerebral or systemic thromboembolic disorders. Rarely, when an ASD is undiagnosed or untreated, Eisenmenger's syndrome develops.

[**Fig. 293-1.** Normal circulation with representative right and left cardiac pressures (in mm Hg).]

Auscultation typically reveals a grade 2 to 3/6 midsystolic (ejection systolic) murmur and a widely split, fixed $S_2$ at the upper left sternal border in children. A large left-to-right atrial shunt may produce a low-pitched diastolic murmur (due to increased tricuspid flow) at the left lower sternal border. These findings may be absent in infants, even those who have a large defect. A prominent right ventricular cardiac impulse, manifested as a parasternal heave or lift, may be present.

**Diagnosis**

- Chest x-ray and ECG
- Echocardiography

Diagnosis is suggested by cardiac examination, chest x-ray, and ECG and is confirmed by 2-dimensional echocardiography with color flow and Doppler studies.

With a significant shunt, ECG may show right axis deviation, right ventricular hypertrophy, or right bundle branch block (with rSR´ pattern in $V_1$). Chest x-ray shows cardiomegaly with dilation of the right atrium and right ventricle, a prominent main pulmonary artery segment, and increased pulmonary vascular markings.

Cardiac catheterization is not usually necessary unless a transcatheter intervention is planned.

**Treatment**

- Observation, transcatheter closure, or surgical repair

Most small ostium secundum ASDs (< 3 mm) close spontaneously; many defects between 3 mm and 8 mm close spontaneously by age 18 mo. However, ostium primum and sinus venosus ASDs do not close spontaneously.

Asymptomatic children with a small shunt require only observation and periodic echocardiography. Although these children are theoretically at risk of paradoxical systemic embolization, it is not standard practice to close a small, hemodynamically insignificant defect.

Children with moderate to large defects (eg, pulmonary flow:systemic flow ratio > 1.5:1, or definite evidence of right ventricular volume

[Fig. 293-2. Atrial septal defect.]

overload on echocardiography) should have the ASD closed, typically between ages 2 to 6 yr.

Transcatheter closure with various devices (eg, Amplatzer® or Gore HELEX® septal occluder) is preferred when appropriate anatomic characteristics, such as adequate rims of septal tissue and distance from vital structures (eg, aortic root, pulmonary veins, tricuspid annulus), are present. Otherwise, surgical repair is indicated. Sinus venosus and ostium primum (atrioventricular septal type) defects are not amenable to device closure. If ASDs are repaired during childhood, perioperative mortality rate approaches 0, and long-term survival rates approach those of the general population. Before repair, children with large shunts and heart failure should be treated with diuretics, digoxin, and ACE inhibitors.

Endocarditis prophylaxis is not needed preoperatively and is required only for the first 6 mo after repair or if there is a residual defect adjacent to a surgical patch.

## Ventricular Septal Defect

**A ventricular septal defect (VSD) is an opening in the interventricular septum, causing a shunt between ventricles. Large defects result in a significant left-to-right shunt and cause dyspnea with feeding and poor growth during infancy. A loud, harsh, holosystolic murmur at the lower left sternal border is common. Recurrent respiratory infections and heart failure may develop. Diagnosis is by echocardiography. Defects may close spontaneously during infancy or require surgical repair.**

VSD (see
Fig. 293-3) is the 2nd most common congenital heart anomaly after bicuspid aortic valve, accounting for 20% of all defects. It can occur alone or with other congenital anomalies (eg, tetralogy of Fallot, complete atrioventricular septal defects, transposition of the great arteries).

**Classification:** VSDs are classified by location:

- Perimembranous
- Trabecular muscular
- Subpulmonary outlet (supracristal or doubly committed subarterial)
- Inlet

Perimembranous defects (70 to 80%) are defects in the membranous septum adjacent to the tricuspid valve and they extend into a variable amount of surrounding muscular tissue; the most common type of this defect occurs immediately below the aortic valve.

[Fig. 293-3. Ventricular septal defect.]

Trabecular muscular defects (5 to 20%) are completely surrounded by muscular tissue and may occur anywhere in the septum.

Subpulmonary outlet defects (5 to 7% in the US; about 30% in Far Eastern countries) occur in the ventricular septum immediately under the pulmonary valve. These defects are often referred to as supracristal or doubly committed subarterial defects and are frequently associated with aortic leaflet prolapse into the defect, causing aortic regurgitation.

Inlet defects (5 to 8%) are bordered superiorly by the tricuspid annulus and are located posterior to the membranous septum. These defects are sometimes referred to as atrioventricular septal-type defects.

**Pathophysiology**

The magnitude of the shunt depends on defect size and downstream resistance (ie, pulmonary outflow tract obstruction and pulmonary vascular resistance); larger defects result in a large left-to-right shunt. Assuming there is no pulmonic stenosis, over time, a large shunt causes pulmonary artery hypertension, elevated pulmonary artery vascular resistance, right ventricular pressure overload, and right ventricular hypertrophy. Ultimately, the increased pulmonary vascular resistance causes shunt direction to reverse (from the right to the left ventricle), leading to Eisenmenger's syndrome (see p. 2966).

Small defects cause a relatively small left-to-right shunt, and pulmonary artery pressure is normal. Heart failure (HF), pulmonary hypertension, and Eisenmenger's syndrome do not develop.

**Symptoms and Signs**

Symptoms depend on defect size and magnitude of the left-to-right shunt. Children with a small VSD are typically asymptomatic and grow and develop normally. In those with a larger defect, symptoms of HF (eg, respiratory distress, poor weight gain, fatigue after feeding) appear at age 4 to 6 wk when pulmonary vascular resistance falls. Frequent lower respiratory tract infections may occur. Eventually, untreated patients may develop symptoms of Eisenmenger's syndrome.

Auscultatory findings vary with the size of the defect. Small VSDs typically produce murmurs ranging from a grade 1 to 2/6 high-pitched, short systolic murmur (due to tiny defects that actually close during late systole) to a grade 3 to 4/6 holosystolic murmur (with or without thrill) at the lower left sternal border; this murmur is audible shortly after birth. The precordium is not hyperactive, and the 2nd heart sound ($S_2$) is normally split and has normal intensity.

Moderate to large VSDs produce a loud holosystolic murmur that is present by age 2 to 3 wk; $S_2$ is usually narrowly split with an accentuated pulmonary component. An apical diastolic rumble (due to increased flow through the mitral valve) and findings of HF (eg, tachypnea, dyspnea with feeding, failure to thrive, gallop, crackles, hepatomegaly) may be present. With large defects allowing equalization of left ventricular and right ventricular pressures, the systolic murmur is often attenuated.

**Diagnosis**

• Chest x-ray and ECG

• Echocardiography

Diagnosis is suggested by clinical examination, supported by chest x-ray and ECG, and established by echocardiography.

If the VSD is large, chest x-ray shows cardiomegaly and increased pulmonary vascular markings. ECG shows right ventricular hypertrophy or combined ventricular hypertrophy and, occasionally, left atrial enlargement. ECG and chest x-ray are typically normal if the VSD is small.

Two-dimensional echocardiography with color flow and Doppler studies establishes the diagnosis and can provide important anatomic and hemodynamic information, including the defect's location and size and right ventricular pressure. Cardiac catheterization is rarely necessary.

**Treatment**

• For HF, medical therapy (eg, diuretics, digoxin, ACE inhibitors)

• Sometimes surgical repair

Small VSDs, particularly muscular septal defects, often close spontaneously during the first few years of life. A small defect that remains open does not require medical or surgical therapy.

Larger defects are less likely to close spontaneously. Diuretics, digoxin, and ACE inhibitors are indicated before surgery if HF develops. If infants do not respond to medical treatment or have poor growth, surgical repair may be done during the first few months of life. Even in asymptomatic children, a large shunt (pulmonary flow:systemic flow ratio ≥ 2:1) that persists after 2 to 4 yr requires surgical repair. Current surgical mortality rate is < 2%. Surgical complications may include residual ventricular shunt, right bundle branch block, and complete heart block.

Endocarditis prophylaxis is not needed preoperatively and is required only for the first 6 mo after repair or if there is a residual defect adjacent to a surgical patch.

## Atrioventricular Septal Defect

(Atrioventricular Canal Defect; Endocardial Cushion Defect; Persistent Ostium Primum)

**Atrioventricular (AV) septal defect consists of primum type atrial septal defect with AV valve malformation, with or without a ventricular septal defect. These defects result from maldevelopment of the endocardial cushions. Defects may be asymptomatic if small. If large, they may cause heart failure with dyspnea with feeding, poor growth, tachypnea, diaphoresis, or arrhythmias. Heart murmurs are common. Diagnosis is by echocardiography. Treatment is surgical repair for all but the smallest defects.**

AV septal defect accounts for about 5% of congenital heart anomalies. The defect may be complete or partial; 30% of patients with the complete form have Down syndrome. AV septal defect is also common among patients with asplenia or polysplenia (heterotaxy) syndromes.

**Complete AV septal defect:** Complete AV septal defect (see Fig. 293-4) consists of a large ostium primum atrial septal defect (ASD) in the anteroinferior aspect of the septum, an inlet ventricular septal defect (VSD), and a common AV valve orifice. A left-to-right shunt occurs at the atrial and ventricular levels; AV valve regurgitation may be significant, sometimes causing a direct left ventricle-to-right atrial shunt. These abnormalities result in enlargement of all 4 cardiac chambers. Hemodynamic findings are similar to those of a large VSD. Over time, the increase in pulmonary blood flow, pulmonary artery pressure, and pulmonary vascular resistance may lead to reversal of shunt direction with cyanosis and Eisenmenger's syndrome (see p. 2966).

**Partial AV septal defect:** A partial defect consists of an ostium primum ASD, partitioning of the common AV valve into 2 separate AV orifices, and a cleft in the mitral valve (left AV orifice). The ventricular septum is intact, or there may be a small VSD. Hemodynamic abnormalities are similar to those of ostium secundum ASD with the additional finding of variable degrees of mitral regurgitation.

[**Fig. 293-4.** Atrioventricular septal defect (complete form).]

### Symptoms and Signs

Complete AV septal defect with a large left-to-right shunt causes signs of heart failure (HF—eg, tachypnea, dyspnea with feeding, poor weight gain, diaphoresis) by age 4 to 6 wk. Pulmonary vascular obstructive disease (Eisenmenger's syndrome) is usually a late complication but may occur earlier, especially in children with Down syndrome.

Partial AV septal defects are asymptomatic during childhood if mitral regurgitation is mild or absent. However, symptoms (eg, exercise intolerance, fatigue, palpitations) may develop during adolescence or

early adulthood. Infants with moderate or severe mitral regurgitation often have signs of HF.

Physical examination in children with complete AV septal defects shows an active precordium due to volume and pressure overload of the right ventricle; a single, loud 2nd heart sound ($S_2$) due to pulmonary hypertension; a grade 3 to 4/6 systolic murmur; and sometimes a diastolic murmur at the apex and low left sternal border. Most children with a partial defect have wide splitting of the $S_2$ and a midsystolic (eg, ejection systolic) murmur audible at the upper left sternal border. A mid-diastolic rumble may be present at the lower left sternal border when the atrial shunt is large. A cleft in the left AV valve results in a blowing apical systolic murmur of mitral regurgitation. Thus, cardiac findings in children with the partial form are the same as those described for secundum ASD (see p. 2950); if mitral regurgitation coexists, there will also be a high-pitched holosystolic murmur at the apex.

**Diagnosis**

• Chest x-ray and ECG

• Echocardiography

Diagnosis is suggested by clinical examination, supported by chest x-ray and ECG, and established by 2-dimensional echocardiography with color flow and Doppler studies.

Chest x-ray shows cardiomegaly with right atrial enlargement, biventricular enlargement, a prominent main pulmonary artery segment, and increased pulmonary vascular markings.

ECG shows a superiorly directed QRS axis (eg, left axis deviation or northwest axis), frequent 1st-degree AV block, left or right ventricular hypertrophy or both, and occasional right atrial enlargement and right bundle branch block.

Two-dimensional echocardiography with color flow and Doppler studies establishes the diagnosis and can provide important anatomic and hemodynamic information. Cardiac catheterization is not usually necessary unless hemodynamics must be further characterized before surgical repair.

**Treatment**

• Surgical repair

• For HF, medical therapy (eg, diuretics, digoxin, ACE inhibitors) before surgery

Complete AV septal defect should be repaired by age 2 to 4 mo, because most infants have HF and failure to thrive. However, even if infants are growing well without significant symptoms, repair should be done before 6 mo to prevent development of pulmonary vascular disease, especially in infants with Down syndrome. In patients with 2 adequately sized ventricles and no additional defects, the large central defect (combination of the primum ASD and inlet VSD) is closed and the common AV valve is reconstructed into 2 separate valves. For a single-stage complete repair, mortality rate was 5 to 10% in older series but more recently was as low as 3 to 4%. Surgical complications include complete heart block (3%) and mitral regurgitation. Pulmonary artery banding is no longer recommended unless associated abnormalities make complete repair in a small infant high risk. For asymptomatic patients with a partial defect, elective surgery is done at age 1 to 3 yr. Surgical mortality rate should be very low.

For patients with large shunts and HF, diuretics, digoxin, and ACE inhibitors are indicated before surgery.

Endocarditis prophylaxis is not needed preoperatively and is required only for the first 6 mo after repair or if there is a residual defect adjacent to a surgical patch.

## Patent Ductus Arteriosus

**Patent ductus arteriosus (PDA) is a persistence of the fetal connection (ductus arteriosus) between the aorta and pulmonary artery after birth, resulting in a left-to-right shunt. Symptoms**

**may include failure to thrive, poor feeding, tachycardia, and tachypnea. A continuous murmur at the upper left sternal border is common. Diagnosis is by echocardiography. Administration of indomethacin with or without fluid restriction may be tried in premature infants with a significant shunt, but this therapy is not effective in term infants or older children with PDA. If the connection persists, surgical or catheter-based correction is indicated.**

PDA accounts for 5 to 10% of congenital heart anomalies; the male:female ratio is 1:3. PDA is very common among premature infants (in 45% with birth weight < 1750 g; in about 80% with birth weight < 1200 g). A significant PDA causes heart failure (HF) in 15% of premature infants with birth weight < 1750 g and in 40 to 50% of infants with birth weight < 1500 g.

### Pathophysiology

The ductus arteriosus is a normal connection between the pulmonary artery and aorta; it is necessary for proper fetal circulation. At birth, the rise in $PaO_2$ and decline in prostaglandin concentration cause closure of the ductus arteriosus, typically beginning within the first 10 to 15 h of life. If this normal process does not occur, PDA results (see Fig. 293-5).

Physiologic consequences depend on ductal size. A small ductus rarely causes symptoms. A large ductus causes a large left-to-right shunt. Over time, a large shunt results in pulmonary artery hypertension and elevated pulmonary vascular resistance, ultimately leading to Eisenmenger's syndrome (see p. 2966).

### Symptoms and Signs

Clinical presentation depends on PDA size and gestational age at delivery. Infants and children with a small PDA are generally asymptomatic; infants with a large PDA present with signs

[**Fig. 293-5.** Patent ductus arteriosus.]

of HF (eg, failure to thrive, poor feeding, tachypnea, dyspnea with feeding, tachycardia). Premature infants may present with respiratory distress, apnea, worsening mechanical ventilation requirements, or other serious complications (eg, necrotizing enterocolitis). Signs of HF occur earlier in premature infants than in full-term infants and may be more severe. A large ductal shunt in a premature infant often is a major contributor to the severity of the lung disease of prematurity.

Most children with a small PDA have normal heart sounds and peripheral pulses. A grade 1 to 3/6 continuous murmur is heard best in the upper left sternal border. The murmur extends from systole to beyond the 2nd heart sound ($S_2$) into diastole and typically has a different pitch in systole and diastole.

Full-term infants with a significant PDA shunt have full or bounding peripheral pulses with a wide pulse pressure. A grade 1 to 4/6 continuous murmur is characteristic. If the murmur is loud, it has a "machinery-sounding" quality. An apical diastolic rumble (due to high flow across the mitral valve) or gallop rhythm may be audible if there is a large left-to-right shunt or HF develops.

Premature infants with a significant shunt have bounding pulses and a hyperdynamic precordium. A heart murmur occurs in the pulmonary area; the murmur may be continuous, systolic with a short diastolic component, or only systolic, depending on the pulmonary artery pressure. Some infants have no audible heart murmur.

### Diagnosis

• Chest x-ray and ECG

• Echocardiography

Diagnosis is suggested by clinical examination, supported by chest x-ray and ECG, and established by 2-dimensional echocardiography with color flow and Doppler studies.

Chest x-ray and ECG are typically normal if the PDA is small. If the shunt is significant, chest x-ray shows prominence of the left atrium, left ventricle, and ascending aorta and increased pulmonary vascular markings; ECG may show left ventricular hypertrophy. Cardiac catheterization is not necessary unless used for therapy.

**Treatment**

• Prostaglandin synthesis inhibitor therapy (eg, indomethacin, ibuprofen)

• Sometimes transcatheter occlusion devices or surgical repair

[
Table 293-4. Indomethacin Dosing Guidelines (mg/kg)]

In **premature infants** with compromised respiratory status, the PDA can sometimes be closed by using a prostaglandin synthesis inhibitor (eg, indomethacin [see Table 293-4 for doses] IV q 12 h for 3 doses or ibuprofen 10 mg/kg po followed by 2 doses of 5 mg/kg at 24-h intervals) with or without fluid restriction. If this treatment is ineffective, surgical ligation is indicated.

In **full-term infants**, indomethacin is usually ineffective. Transcatheter closure has become the treatment of choice in children > 1 yr; a variety of catheter-delivered occlusion devices are available (eg, coils, Amplatzer® duct occluder). In infants < 1 yr or who have certain anatomic varieties of the ductus, surgical division and ligation may be preferred over the transcatheter approach. For a PDA with a shunt large enough to cause symptoms of HF or pulmonary hypertension, closure should be done after medical stabilization. For a persistent PDA without HF or pulmonary hypertension, closure can be done electively any time after 1 yr. Outcomes after PDA closure are excellent.

Endocarditis prophylaxis is not needed preoperatively and is required only for the first 6 mo after closure or if there is a residual defect adjacent to a transcatheter-placed device or surgical material.

## Coarctation of the Aorta

**Coarctation of the aorta is a localized narrowing of the aortic lumen that results in upper-extremity hypertension, left ventricular hypertrophy, and malperfusion of the abdominal organs and lower extremities. Symptoms vary with the anomaly's severity and range from headache, chest pain, cold extremities, fatigue, and leg claudication to fulminant heart failure and shock. A soft bruit may be heard over the coarctation site. Diagnosis is by echocardiography or by CT or MR angiography. Treatment is balloon angioplasty with stent placement, or surgical correction.**

Coarctation of the aorta accounts for 6 to 8% of congenital heart anomalies. It occurs in 10 to 20% of patients with Turner's syndrome. The male:female ratio is 2:1.

**Pathophysiology**

Coarctation of the aorta usually occurs at the proximal thoracic aorta just beyond the left subclavian artery. It rarely involves the abdominal aorta. Coarctation may occur alone or with various other congenital anomalies (eg, bicuspid aortic valve, ventricular septal defect, aortic stenosis, patent ductus arteriosus, mitral valve disorders, intracerebral aneurysms).

Physiologic consequences include left ventricular pressure overload, left ventricular hypertrophy, hypertension in the upper part of the body including the brain, and malperfusion of the abdominal organs and lower extremities. Malperfusion of the intestines increases the risk of sepsis due to enteric organisms.

Untreated coarctation may result in left ventricular failure, rupture of the aorta, intracranial hemorrhage, hypertensive encephalopathy, and hypertensive cardiovascular disease during adulthood.

**Symptoms and Signs**

If coarctation is significant, circulatory shock with renal insufficiency (oliguria or anuria) and metabolic acidosis may develop in the first 7 to 10 days of life and may mimic findings of other systemic disorders such as sepsis.

Less severe coarctation may be asymptomatic during infancy. Subtle symptoms (eg, headache; chest pain, fatigue, and leg claudication during physical activities) may be present as children age. Hypertension is often present, but heart failure (HF) rarely develops after the neonatal period. Rarely, intracerebral aneurysms rupture, resulting in subarachnoid or intracerebral hemorrhage.

Typical physical examination findings include hypertension in the upper extremities, diminished or delayed femoral pulses, and low or unobtainable arterial BP in the lower extremities. A grade 2 to 3/6 ejection systolic murmur is often present at the upper left sternal border, left axilla, and sometimes most prominently in the left interscapular area. An apical ejection click is present if a bicuspid aortic valve is also present. Dilated intercostal collateral arteries may cause a continuous murmur in the intercostal spaces. Affected females may have Turner's syndrome, a congenital disorder causing lymphedema of the feet, webbed neck, squarely shaped chest, cubitus valgus, and widely spaced nipples.

**Diagnosis**

• Chest x-ray and ECG

• Echocardiography or CT or MR angiography

Diagnosis is suggested by clinical examination (including BP measurement in all 4 extremities), supported by chest x-ray and ECG, and established by 2-dimensional echocardiography with color flow and Doppler studies or with CT or MR angiography.

Chest x-ray shows coarctation as a "3" sign in the upper left mediastinal shadow. Heart size is normal unless HF supervenes. Dilated intercostal collateral arteries may erode the 3rd to 8th ribs, causing rib notching, but this is seldom seen before age 5 yr.

ECG usually shows left ventricular hypertrophy but may be normal. In neonates and small infants, ECG usually shows right ventricular hypertrophy rather than left ventricular hypertrophy.

**Treatment**

• For symptomatic neonates, prostaglandin $E_1$ infusion

• For hypertension, β-blockers

• Surgical correction or balloon angioplasty (sometimes with stent placement)

Symptomatic neonates require cardio-pulmonary stabilization with infusion of prostaglandin $E_1$ (0.05 to 0.10 µg/kg/min—may titrate up to 0.4 µg/kg/min then back down to lowest effective dose) to reopen the constricted ductus arteriosus. Opening the ductus and its aortic ampulla provides some relief of the aortic obstruction and allows pulmonary artery blood to increase perfusion of the descending aorta through the ductus, improving systemic perfusion and reversing metabolic acidosis. IV cardioactive drugs (eg, milrinone, dopamine, dobutamine), diuretics, and $O_2$ are used to treat HF.

In nonemergent situations, patients with hypertension may be treated with β-blockers; ACE inhibitors may adversely affect renal function. After repair of the coarctation, hypertension may persist or develop years after repair and can be treated with β-blockers, ACE inhibitors, angiotensin II receptor blockers, or Ca channel blockers.

The preferred definitive treatment is controversial. Some centers prefer balloon angioplasty with or

without stent placement, but most prefer surgical correction and reserve the balloon procedure for recoarctation after surgical correction or for primary treatment of discrete coarctation in older children or adolescents. Initial success rate after balloon angioplasty is 80 to 90%; subsequent catheterization can dilate the stent as children grow.

Surgical options include resection and end-to-end anastomosis, patch aortoplasty, and left subclavian flap aortoplasty. In severe coarctation manifesting early in life, the transverse aorta and isthmus are often hypoplastic, and this region of the aorta may need to be surgically enlarged. Choice of surgical technique depends on anatomy and center preference. Surgical mortality rate is < 5% for symptomatic infants and < 1% for older children. Residual coarctation is common (6 to 33%). Rarely, paraplegia results from cross-clamping of the aorta during surgery.

Endocarditis prophylaxis is not needed preoperatively and is required only for the first 6 mo after repair or if there is a residual defect adjacent to a surgical patch.

## Tetralogy of Fallot

**Tetralogy of Fallot consists of 4 features: a large ventricular septal defect, right ventricular outflow tract and pulmonary valve obstruction, right ventricular hypertrophy, and over-riding of the aorta. Symptoms include cyanosis, dyspnea with feeding, poor growth, and tet spells (sudden, potentially lethal episodes of severe cyanosis). A harsh systolic murmur at the left upper sternal border with a single 2nd heart sound ($S_2$) is common. Diagnosis is by echocardiography or cardiac catheterization. Definitive treatment is surgical repair.**

Tetralogy of Fallot (see Fig. 293-6) accounts for 7 to 10% of congenital heart anomalies. Associated anomalies include right aortic arch (25%), abnormal coronary artery anatomy (5%), stenosis of the pulmonary artery branches, presence of aorticopulmonary collateral vessels, patent ductus arteriosus, complete atrioventricular septal defect, atrial septal defect, additional muscular ventricular septal defects (VSDs), and aortic valve regurgitation.

### Pathophysiology

The VSD is typically large; thus, systolic pressures in the right and left ventricles (and in the aorta) are the same. Pathophysiology depends on the degree of right ventricular outflow obstruction. A mild obstruction may result in a left-to-right shunt through the VSD; a severe obstruction causes a right-to-left shunt, resulting in low systemic arterial saturation (cyanosis) that is unresponsive to supplemental $O_2$.

In some children with tetralogy of Fallot, most often those several months up to 2 yr of age, sudden episodes of profound cyanosis and hypoxia (tet spell) may occur, which may be lethal. A spell may be triggered by any event that slightly decreases $O_2$ saturation (eg, crying, defecating) or that suddenly decreases systemic vascular resistance (eg, playing, kicking legs when awakening) or by sudden onset of tachycardia or hypovolemia. The mechanism of a tet spell remains uncertain, but several factors are probably important in causing an increase in right to left shunting and a fall in arterial saturation. Factors include an increase in right ventricular outflow tract obstruction and a decrease in systemic resistance—a vicious circle caused by the initial fall in arterial $PO_2$, which stimulates the respiratory center and causes hyperpnea and increased adrenergic tone. The increased circulating catecholamines then stimulate increased contractility, which increases outflow tract obstruction.

[Fig. 293-6. Tetralogy of Fallot.]

### Symptoms and Signs

Neonates with severe right ventricular outflow obstruction (or atresia) have severe cyanosis and dyspnea with feeding with poor weight gain. But those with mild obstruction may not have cyanosis at rest.

**Tet spells** may be precipitated by activity and are characterized by paroxysms of hyperpnea (rapid and

deep respirations), irritability and prolonged crying, increasing cyanosis, and decreasing intensity of the heart murmur. The spells occur most often in young infants; peak incidence is age 2 to 4 mo. A severe spell may lead to limpness, seizures, and occasionally death. During play, some toddlers may intermittently squat, a position that increases systemic vascular resistance and aortic pressure, which decreases right to left ventricular shunting and thus raises arterial $O_2$ saturation.

Auscultation detects a harsh grade 3 to 5/6 systolic ejection murmur at the left mid and upper sternal border. The murmur in tetralogy is always due to the pulmonary stenosis; the VSD is silent because it is large and has no pressure gradient. The 2nd heart sound ($S_2$) is often single because the pulmonary component is markedly reduced. A prominent right ventricular impulse and a systolic thrill may be present.

**Diagnosis**

• Chest x-ray and ECG

• Echocardiography

Diagnosis is suggested by history and clinical examination, supported by chest x-ray and ECG, and established by 2-dimensional echocardiography with color flow and Doppler studies. Chest x-ray shows a boot-shaped heart with a concave main pulmonary artery segment and diminished pulmonary vascular markings. A right aortic arch is present in 25%. ECG shows right ventricular hypertrophy and may also show right atrial hypertrophy. Cardiac catheterization is rarely needed, unless there is suspicion of a coronary anomaly that might affect the surgical approach (eg, anterior descending arising from the right coronary artery) that cannot be clarified with echocardiography.

**Treatment**

• For symptomatic neonates, prostaglandin $E_1$ infusion

• For tet spells, positioning, calming, $O_2$, and sometimes drugs

• Surgical repair

Neonates with severe cyanosis may be palliated with an infusion of prostaglandin $E_1$ (0.05 to 0.1 µg/kg/min IV) to open the ductus arteriosus.

**Tet spells:** Tet spells are treated by placing infants in a knee-chest position (older children usually squat spontaneously and do not develop tet spells), establishing a calm environment, and giving $O_2$. If the spell persists, options (roughly in order of preference) include morphine 0.1 to 0.2 mg/kg IV or IM, IV fluids for volume expansion, $NaHCO_3$ 1 mEq/kg IV, and propranolol starting at 0.02 to 0.05 mg/kg, titrated up to 0.1 to 0.2 mg/kg IV if needed for effect. If these measures do not control the spell, systemic BP can be increased with ketamine 0.5 to 3 mg/kg IV or 2 to 3 mg/kg IM (ketamine also has a beneficial sedating effect) or phenylephrine starting at 5 µg/kg and titrating up to 20 µg/kg IV for effect. Ultimately, if the preceding steps do not relieve the spell or if the infant is rapidly deteriorating, intubation with muscle paralysis and general anesthesia may be necessary. Propranolol 0.25 to 1 mg/kg po q 6 h may prevent recurrences, but most experts feel that even one significant spell indicates the need for expeditious surgical repair.

**Definitive management:** Complete repair consists of patch closure of the VSD, widening of the right ventricular outflow tract with muscle resection and pulmonary valvuloplasty, and a limited patch across the pulmonic annulus or main pulmonary artery if necessary. Surgery is usually done electively at age 3 to 6 mo but can be done at any time if symptoms are present.

In neonates and very small infants with complex anatomy, initial palliation may be preferred to complete repair; the usual procedure is a modified Blalock-Taussig shunt, in which the subclavian artery is connected to the ipsilateral pulmonary artery with a synthetic graft.

Perioperative mortality rate for complete repair is < 5% for uncomplicated tetralogy of Fallot. For untreated patients, survival rates are 55% at 5 yr and 30% at 10 yr.

Endocarditis prophylaxis is recommended preoperatively but is required only for the first 6 mo after repair unless there is a residual defect adjacent to a surgical patch or prosthetic material.

## Transposition of the Great Arteries

**Transposition of the great arteries (TGA) occurs when the aorta arises directly from the right ventricle and the pulmonary artery arises from the left ventricle, resulting in independent, parallel pulmonary and systemic circulations; oxygenated blood cannot reach the body except through openings connecting the right and left sides (eg, patent foramen ovale, ventricular septal defect [VSD]). Symptoms are primarily severe neonatal cyanosis and occasionally heart failure, if there is an associated VSD. Heart sounds and murmurs vary depending on the presence of associated congenital anomalies. Diagnosis is by echocardiography. Definitive treatment is surgical repair.**

TGA (see Fig. 293-7) accounts for 5 to 7% of congenital heart anomalies. About 30 to 40% of patients have a VSD; 5% have subpulmonary stenosis.

### Pathophysiology

Systemic and pulmonary circulations are completely separated. After returning to the right heart, desaturated systemic venous blood is pumped into the systemic circulation without being oxygenated in the lungs; oxygenated blood entering the left heart goes back to the lungs rather than to the rest of the body. This anomaly is not compatible with life unless desaturated and oxygenated blood can mix through openings at one or more levels (eg, atrial, ventricular, or great artery level).

[**Fig. 293-7.** Transposition of the great arteries.]

### Symptoms and Signs

Severe cyanosis occurs within hours of birth, progressing rapidly to metabolic acidosis secondary to poor tissue oxygenation. Patients with a large VSD, a patent ductus arteriosus, or both are less cyanotic, but symptoms and signs of heart failure (eg, tachypnea, dyspnea, tachycardia, diaphoresis, inability to gain weight) may develop during the first 3 to 6 wk of life.

Except for generalized cyanosis, physical examination is usually unremarkable. Heart murmurs may be absent unless associated anomalies are present. The 2nd heart sound ($S_2$) is single and loud.

### Diagnosis

• Chest x-ray and ECG

• Echocardiography

Diagnosis is suspected clinically, supported by chest x-ray and ECG, and established by 2-dimensional echocardiography with color flow and Doppler studies.

On chest x-ray, the cardiac shadow may have the classic egg-on-a-string appearance with a narrow upper mediastinum. ECG shows right ventricular hypertrophy but may be normal for a neonate.

Cardiac catheterization is not usually necessary for diagnosis but may be done to enlarge the atrial communication.

### Treatment

• Prostaglandin $E_1$ ($PGE_1$) infusion

• Sometimes balloon atrial septostomy

• Surgical repair

Unless arterial $O_2$ saturation is only mildly decreased and the atrial communication is adequate, a $PGE_1$ infusion (0.05 to 0.1 µg/kg/min IV) is used to open and maintain patency of the ductus arteriosus; this infusion increases pulmonary blood flow, which promotes left to right atrial shunting, leading to improved systemic oxygenation. Metabolic acidosis is corrected via infusion of $NaHCO_3$. Pulmonary edema and respiratory failure may require intubation and mechanical ventilation.

For severely hypoxemic neonates who do not immediately respond to $PGE_1$ or who have a very restrictive foramen ovale, cardiac catheterization and balloon atrial septostomy (Rashkind's procedure) can immediately improve systemic arterial $O_2$ saturation. A balloon-tipped catheter is advanced into the left atrium through the patent foramen ovale. The balloon is inflated with diluted radiopaque dye and abruptly withdrawn to the right atrium to enlarge the opening in the atrial septum. As an alternative to taking the neonate to the catheterization laboratory, the septostomy procedure can be done at the bedside under echocardiographic guidance.

Definitive repair is the arterial switch (Jatene) operation, typically done during the first week of life. The proximal portions of the great arteries are transected, the coronary arteries are transplanted to the native pulmonary root (which will become the neoaortic root), and the aorta is connected to the left ventricle and the pulmonary artery is connected to the right ventricle. Survival rate after surgery is > 95%. An associated VSD should be closed at the time of primary repair unless it is small and hemodynamically insignificant. Pulmonic stenosis is problematic unless it can be addressed surgically at the time of the arterial switch procedure.

Endocarditis prophylaxis is recommended preoperatively but is required only for the first 6 mo after repair unless there is a residual defect adjacent to a surgical patch or prosthetic material.

## Tricuspid Atresia

**Tricuspid atresia is absence of the tricuspid valve accompanied by a hypoplastic right ventricle. Associated anomalies are common and include atrial septal defect, ventricular septal defect, patent ductus arteriosus, and transposition of the great arteries. Symptoms include cyanosis and those of heart failure. The 2nd heart sound ($S_2$) is single, and murmurs depend on the presence of associated anomalies. Diagnosis is by echocardiography or cardiac catheterization. Definitive treatment is surgical repair.**

Tricuspid atresia accounts for 1 to 3% of congenital heart anomalies. The most common type (sometimes referred to as classic tricuspid atresia) includes a ventricular septal defect (VSD) and pulmonary stenosis, which results in decreased pulmonary blood flow, elevated right atrial pressure, and an obligatory right-to-left shunt at the atrial level through a stretched patent foramen ovale or an atrial septal defect (ASD), causing cyanosis (see Fig. 293-8). In 12 to 25% of cases, the great arteries are transposed with a VSD and a normal pulmonary valve, with unrestricted pulmonary blood flow coming directly from the left ventricle, typically resulting in heart failure (HF) and pulmonary hypertension.

### Symptoms and Signs

Infants with decreased pulmonary blood flow usually have mild to moderate cyanosis at birth, which increases, sometimes dramatically, over the first several months of life. Infants with increased pulmonary blood flow usually show signs of HF (eg, tachypnea, dyspnea with feeding, poor weight gain, diaphoresis) by age 4 to 6 wk.

[**Fig. 293-8.** Tricuspid atresia.]

Physical examination usually detects a single 2nd heart sound ($S_2$) and a grade 2 to 3/6 holosystolic or early systolic murmur of a VSD at the lower left sternal border. A systolic ejection murmur of pulmonary stenosis or a continuous murmur of patent ductus arteriosus may be present in the upper left sternal border. A systolic thrill is rarely palpable. An apical diastolic rumble may be audible if pulmonary blood flow is markedly increased. Cyanosis, when present for > 6 mo, may result in clubbing.

**Diagnosis**

• Chest x-ray and ECG

• Echocardiography

• Usually cardiac catheterization

Diagnosis is suspected clinically, supported by chest x-ray and ECG, and established by 2-dimensional echocardiography with color flow and Doppler studies.

In the most common form, chest x-ray shows normal or slightly increased heart size, right atrial enlargement, and decreased pulmonary vascular markings. Occasionally, the cardiac silhouette resembles that of tetralogy of Fallot (with a boot-shaped heart and concave pulmonary artery segment). Pulmonary vascular markings may be increased and cardiomegaly may be present in infants with associated transposition of the great arteries. ECG characteristically shows left axis deviation (between 0° and -90°) and left ventricular hypertrophy. Left axis deviation is not usually present if there is associated transposition of the great arteries. Right atrial or combined atrial enlargement is also common.

Cardiac catheterization may be necessary before the first palliative procedure to define hemodynamics and pulmonary artery anatomy unless echocardiography or other modalities clearly show the pulmonary vascular anatomy and confidently predict normal pulmonary artery pressures.

**Treatment**

• For severely cyanotic neonates, prostaglandin $E_1$ infusion

• Sometimes balloon atrial septostomy

• Staged surgical repair

Most neonates with tricuspid atresia, although cyanotic, are well compensated in the first several weeks of life. In severely cyanotic neonates, prostaglandin $E_1$ (beginning at 0.05 to 0.1 µg/kg/min IV) is infused to prevent closure of the ductus arteriosus or to reopen the constricted ductus before cardiac catheterization or surgical repair.

Although not usually required, balloon atrial septostomy (Rashkind's procedure) may be done as part of the initial catheterization to decompress the right atrium and facilitate unrestricted right-to-left atrial shunting when the interatrial communication is inadequate. Some infants with transposition of the great arteries and signs of HF require medical treatment (eg, diuretics, digoxin, ACE inhibitors—see p. 2949).

Definitive repair requires staged operations. If intervention is needed within the first 4 to 8 wk of life, a modified Blalock-Taussig shunt (connection of a systemic and a pulmonary artery by a Gore-Tex tube) is done. Otherwise, if the infant remains stable with good growth, the first procedure would be a bidirectional Glenn shunt (anastomosis between the superior vena cava and right pulmonary artery) at 3 to 6 mo, then a modified Fontan procedure is done by 2 yr. The Fontan procedure involves diverting the inferior vena cava flow directly to the pulmonary artery, usually by an extracardiac conduit, completely bypassing the right atrium. The proximal pulmonary root is ligated, which prevents anterograde flow across the pulmonary outflow tract, and an adequate interatrial opening is created, if not already present, to allow equalization of right and left atrial pressures and free communication between these chambers.

Because the systemic venous and conduit pressure must be at least 3 to 5 mm Hg greater than the left atrial pressure to provide an adequate transpulmonary pressure gradient for pulmonary blood flow, a fenestration (small opening) is frequently made between the conduit and the right atrium. Right-to-left shunting from the conduit to the atria and left ventricle allows decompression of the systemic venous pressure and improvement in cardiac output, albeit at the expense of mild arterial desaturation. This approach has increased early survival rates to > 90%, 5-yr survival rates to > 80%, and 10-yr survival rates to > 70%.

Endocarditis prophylaxis is recommended preoperatively but is required only for the first 6 mo after repair unless there is a residual defect adjacent to a surgical patch or prosthetic material.

## Hypoplastic Left Heart Syndrome

**Hypoplastic left heart syndrome consists of hypoplasia of the left ventricle and ascending aorta, maldevelopment and hypoplasia of the aortic and mitral valves (frequently aortic atresia is present), an atrial septal defect, and a large patent ductus arteriosus. Unless normal closure of the patent ductus arteriosus is prevented with prostaglandin infusion, cardiogenic shock and death ensue. A loud, single 2nd heart sound ($S_2$) and nonspecific systolic murmur are common. Diagnosis is by emergency echocardiography. Definitive treatment is staged surgical correction or heart transplantation.**

Hypoplastic left heart syndrome accounts for 2% of congenital heart anomalies. Because the mitral valve, left ventricle, and aortic valve are hypoplastic (often with aortic atresia), oxygenated blood coming into the left atrium from the lungs is diverted across the atrial communication into the right heart, where it mixes with desaturated systemic venous return (see Fig. 293-9). This relatively desaturated blood exits the right ventricle through the pulmonary artery to the lungs and through the

[**Fig. 293-9.** Hypoplastic left heart.]

ductus arteriosus to the systemic circulation. Systemic blood flow is maintained only through the right-to-left ductal shunt; thus immediate survival depends on patency of the ductus arteriosus.

### Symptoms and Signs

Symptoms appear when the ductus arteriosus begins to close during the first 24 to 48 h of life. Subsequently, the clinical picture of cardiogenic shock (eg, tachypnea, dyspnea, weak pulse, pallor, cyanosis, hypothermia, metabolic acidosis, lethargy, oliguria or anuria) rapidly develops. When systemic circulation is compromised, coronary and cerebral perfusion may be reduced, leading to symptoms of myocardial or cerebral ischemia. If the ductus arteriosus is not reopened, death rapidly ensues.

Physical examination shows a very active precordium with a marked parasternal lift associated with very poor peripheral perfusion, cool extremities, bluish gray skin color, and absent or barely palpable pulses. The 2nd heart sound ($S_2$) is loud and single. Occasionally, a soft, nonspecific systolic murmur is present. Severe metabolic acidosis out of proportion to the $PO_2$ and $PCO_2$ is characteristic.

### Diagnosis

• Chest x-ray and ECG

• Echocardiography

Diagnosis is suspected clinically and confirmed by emergency echocardiography with color flow and Doppler studies. Cardiac catheterization is rarely required.

Chest x-ray shows cardiomegaly and pulmonary venous congestion or pulmonary edema. ECG shows right ventricular hypertrophy.

**Treatment**

• Prostaglandin $E_1$ ($PGE_1$) infusion

• Staged surgical repair

• Sometimes heart transplantation

All affected infants should be stabilized immediately in a neonatal ICU. Vascular access should be established, usually via an umbilical venous catheter; then $PGE_1$ (beginning at 0.05 to 0.1 µg/kg/min IV) is infused to prevent closure of the ductus arteriosus or to reopen a constricted ductus. Neonates usually require intubation and mechanical ventilation. Metabolic acidosis is corrected via infusion of $NaHCO_3$. Severely ill neonates with cardiogenic shock may require inotropic drugs (eg, milrinone) and diuretics to improve cardiac function and control volume status. It is critical to keep pulmonary vascular resistance relatively high and systemic vascular resistance low in order to prevent marked pulmonary overcirculation at the expense of systemic perfusion. These resistance ranges are maintained by avoiding hyperoxia, alkalosis, and hypocarbia, all of which may lead to pulmonary vasodilation. Because $O_2$ is one of the most potent pulmonary vasodilators, infants are ventilated with room air or even hypoxic mixtures to aim for systemic saturations of 70 to 80%. If the infant requires mechanical ventilation, $PCO_2$ can be controlled in the high normal or mildly elevated range. Systemic vascular resistance is managed by avoiding, or minimizing, the use of vasoconstricting drugs (eg, epinephrine or high-dose dopamine). Milrinone may be beneficial because it can cause systemic vasodilation.

Survival ultimately requires staged procedures that enable the right ventricle to function as the systemic ventricle. Stage 1, done during the first week of life, is the Norwood procedure. The main pulmonary artery is divided, the distal stump is closed with a patch, and the ductus arteriosus is ligated. Then, a right-sided modified Blalock-Taussig shunt (see p. 2959) or right ventricular-pulmonary artery conduit (Sano modification) is done; the atrial septum is enlarged, and the proximal pulmonary artery and hypoplastic aorta are connected with an aortic or pulmonary artery allograft to create a neoaorta. Stage 2, done at 3 to 6 mo of age, consists of a bidirectional Glenn operation (end-to-side connection of the superior vena cava to the right pulmonary artery). The 3rd stage, done at 18 to 36 mo, is a modified Fontan procedure (see p. 2962). Survival rate is 75% for stage 1, 95% for stage 2, and 90% for stage 3. Overall survival rate is 70% at 5 yr after surgical correction. Many survivors have neurodevelopmental disabilities, which may be due to preexisting developmental abnormalities of the CNS or to overt or occult CNS hypoperfusion or thromboemboli occurring during the multistage procedures.

In some centers, heart transplantation is the procedure of choice; however, $PGE_1$ infusion must be continued along with careful management of pulmonary and systemic vascular resistance until a donor heart is available. Because availability of donor hearts is very limited, about 20% of infants die while waiting for one. The 5-yr survival rates after transplantation and after multistage surgery are similar. After heart transplantation, immunosuppressants are required. These drugs make patients more susceptible to infections and cause pathologic changes in the coronary arteries of the transplanted heart in > 50% of patients over a 5-yr period. The only known treatment for allograft coronary artery disease is retransplantation.

Endocarditis prophylaxis is recommended preoperatively but is required only for the first 6 mo after repair unless there is a residual defect adjacent to a surgical patch or prosthetic material.

## Total Anomalous Pulmonary Venous Return

**In total anomalous pulmonary venous return, the pulmonary veins do not connect to the left atrium. Instead, the entire pulmonary venous return enters the systemic venous circulation through a variety of connections. If there is no obstruction to pulmonary venous return, cyanosis is mild and heart failure develops within the first 2 to 4 wk of life. Severe obstruction of the pulmonary venous return may occur, resulting in severe neonatal cyanosis, pulmonary edema, and pulmonary hypertension. Diagnosis is by echocardiography. Surgical repair is**

**required.**

Total anomalous pulmonary venous return (see Fig. 293-10) accounts for 1 to 2% of congenital heart anomalies. The clinical manifestation depends on the connection between the pulmonary venous confluence and the right side of the circulation. The most common types include

• Return via an ascending left vertical vein that drains to the innominate vein

• A descending vein that drains infradiaphragmatically to the portal circulation

• Connection of the confluence to the coronary sinus

The infradiaphragmatic drainage type is invariably severely obstructed, leading to dramatic pulmonary edema and cyanosis unresponsive to $O_2$. The other 2 types do not typically involve obstruction and lead to heart failure (HF) and mild cyanosis in the first month of life.

**Symptoms and Signs**

Neonates with obstructed pulmonary venous return present with severe pulmonary hypertension, pulmonary edema, and cyanosis. Physical examination usually shows a parasternal

[**Fig. 293-10.** Total anomalous pulmonary venous return.]

lift and a single, loud 2nd heart sound ($S_2$), with no significant murmur.

If pulmonary venous return is not obstructed, symptoms of HF are prominent and physical examination detects a hyperdynamic precordium, a loud and split $S_2$, and a grade 2 to 3/6 systolic ejection murmur audible along the left sternal border. A mid-diastolic tricuspid flow murmur may be audible at the lower left sternal border.

**Diagnosis**

• Chest x-ray and ECG

• Echocardiography

Diagnosis is suspected by chest x-ray and established by 2-dimensional echocardiography with color flow and Doppler studies. Cardiac catheterization is rarely necessary; occasionally, cardiac MRI or CT angiography may need to be done to better delineate the anatomy of pulmonary venous return.

Chest x-ray shows a small heart and severe diffuse pulmonary edema when there is pulmonary venous obstruction; otherwise, there is cardiomegaly with increased pulmonary vascular markings. ECG shows right axis deviation, right ventricular hypertrophy, and occasionally right atrial enlargement.

**Treatment**

• Surgical repair

• Medical treatment of HF (eg, diuretics, digoxin, ACE inhibitors) before surgery

Neonates with infradiaphragmatic return with obstruction require emergent surgical repair. In older infants, HF should be treated, followed by surgical repair as soon as the infant is stabilized.

Surgical repair consists of creating a wide anastomosis between the pulmonary venous confluence and the posterior wall of the left atrium, along with ligation of the vein decompressing the confluence into the systemic venous circulation. The repair is different for return to the coronary sinus, in which case the

coronary sinus is unroofed into the left atrium and its opening to the right atrium is closed.

Endocarditis prophylaxis is recommended preoperatively but is required only for the first 6 mo after repair unless there is a residual defect adjacent to a surgical patch or prosthetic material.

## Persistent Truncus Arteriosus

**Persistent truncus arteriosus occurs when, during fetal development, the primitive truncus does not divide into the pulmonary artery and aorta, resulting in a single, large, arterial trunk that overlies a large, malaligned, perimembranous ventricular septal defect. Consequently, a mixture of oxygenated and deoxygenated blood enters systemic, pulmonary, and coronary circulations. Symptoms include cyanosis and heart failure, with poor feeding, diaphoresis, and tachypnea. A normal 1st heart sound ($S_1$) and a loud, single 2nd heart sound ($S_2$) are common; murmurs may vary. Diagnosis is by echocardiography or cardiac catheterization. Medical treatment for heart failure is typically followed by early surgical repair.**

Persistent truncus arteriosus (see Fig. 293-11) accounts for 1 to 2% of congenital heart anomalies. About 35% of patients have 22q11 deletion syndrome, which includes DiGeorge syndrome and velocardiofacial syndromes.

**Classification:** There are 3 types.

- Type I: The main pulmonary artery arises from the truncus and then divides into the right and left pulmonary arteries.
- Type II: The right and left pulmonary arteries arise separately (but adjacent to each other) from the posterior aspect of the truncus.
- Type III: The right and left pulmonary arteries arise from the lateral aspects of the truncal root reasonably distant from each other.

[**Fig. 293-11.** Truncus arteriosus.]

Previously, a type IV was defined, in which arteries supplying blood to the lungs arose from the descending aorta. However, this anomaly is now placed in the category of tetralogy of Fallot with pulmonary atresia.

Other anomalies (eg, truncal valve insufficiency, right aortic arch, interrupted aortic arch, coronary artery anomalies, atrioventricular septal defect) may be present and may contribute to the high surgical mortality rate.

Physiologic consequences of truncus arteriosus include mild cyanosis, significant pulmonary overcirculation, and heart failure (HF).

### Symptoms and Signs

Infants usually present with mild cyanosis and symptoms and signs of HF (eg, tachypnea, poor feeding, diaphoresis) in the first few weeks of life. Physical examination may detect a hyperdynamic precordium, increased pulse pressure with bounding pulses, a loud and single 2nd heart sound ($S_2$), and an ejection click. A grade 2 to 4/6 systolic murmur is audible along the left sternal border. A mid-diastolic mitral flow murmur may be audible at the apex when pulmonary blood flow is increased. With truncal valve insufficiency, a high-pitched diastolic decrescendo murmur is audible over the mid left sternal border.

### Diagnosis

- Chest x-ray and ECG
- Echocardiography

• Occasionally cardiac catheterization, cardiac MRI, or CT angiography

Diagnosis is suspected clinically, supported by chest x-ray and ECG, and established by 2-dimensional echocardiography with color flow and Doppler studies. Cardiac catheterization is occasionally necessary to delineate associated anomalies before surgery, but cardiac MRI or CT angiography may supplant the need for catheterization.

Chest x-ray shows varying degrees of cardiomegaly with increased pulmonary vascular markings, right aortic arch (in about 30%), and relatively high position of pulmonary arteries. ECG commonly shows combined ventricular hypertrophy. Substantial pulmonary overcirculation may produce evidence of left atrial enlargement.

**Treatment**

• Surgical repair

• Medical treatment of HF (eg, diuretics, digoxin, ACE inhibitors) before surgery

HF is treated vigorously with diuretics, digoxin, and ACE inhibitors, followed by early surgical repair. Prostaglandin infusion is not beneficial.

Surgical management consists of complete repair. The ventricular septal defect is closed so that the left ventricle ejects into the truncal root. A conduit with or without a valve is placed between the right ventricle and the confluence of the pulmonary arteries. Surgical mortality rates have decreased to as low as 10% in recent years. Because the conduit is placed during early infancy, its size becomes inadequate as children grow, and the conduit must be revised during childhood.

Endocarditis prophylaxis is recommended preoperatively but is required only for the first 6 mo after repair unless there is a residual defect adjacent to a surgical patch or prosthetic material.

## Eisenmenger's Syndrome

(Pulmonary Vascular Obstructive Disease)

**Eisenmenger's syndrome is a complication of uncorrected congenital heart anomalies that cause left-to-right shunting. Increased pulmonary resistance may develop over time, reversing left-to-right shunting to right-to-left shunting. Deoxygenated blood enters the systemic circulation, causing symptoms of hypoxia. Murmurs and heart sounds depend on the underlying anomaly. Diagnosis is by echocardiography or cardiac catheterization. Treatment is generally supportive, but heart and lung transplantation may be an option when symptoms are severe. Endocarditis prophylaxis is recommended.**

Congenital heart anomalies that, if untreated, result in Eisenmenger's syndrome include

• Ventricular septal defect

• Atrioventricular canal defect

• Atrial septal defect

• Patent ductus arteriosus

• Persistent truncus arteriosus

• Transposition of the great arteries

In the US, the incidence has markedly decreased because of early diagnosis and definitive repair of the

causative anomaly.

Right-to-left shunting due to Eisenmenger's syndrome results in cyanosis and its complications. Systemic desaturation leads to clubbing of fingers and toes, secondary polycythemia, hyperviscosity, hemoptysis, CNS events (eg, brain abscess or cerebrovascular accident), and sequelae of increased RBC turnover (eg, hyperuricemia causing gout, hyperbilirubinemia causing cholelithiasis, iron deficiency with or without anemia).

**Symptoms and Signs**

Symptoms usually do not occur until age 20 to 40 yr; they include cyanosis, syncope, dyspnea during exertion, fatigue, chest pain, palpitations, atrial and ventricular arrhythmias, and rarely right heart failure (eg, hepatomegaly, peripheral edema, jugular venous distention).

Hemoptysis is a late symptom. Signs of cerebral embolic phenomena, brain abscess, or endocarditis may develop.

Secondary polycythemia commonly causes symptoms (eg, transient ischemic attacks with slurred speech or other neurologic symptoms, visual problems, headaches, increased fatigue, signs of thromboembolism). Abdominal pain may result from cholelithiasis.

Physical examination detects central cyanosis and digital clubbing. Rarely, signs of right ventricular failure (see p. 2947) may be present. A holosystolic murmur of tricuspid regurgitation may be present at the lower left sternal border. An early diastolic, decrescendo, high-pitched murmur of pulmonary insufficiency may be audible along the left sternal border. A loud, single 2nd heart sound ($S_2$) is a constant finding; an ejection click is common. Scoliosis is present in about one third of patients.

**Diagnosis**

• Chest x-ray and ECG

• Echocardiography or cardiac catheterization

Diagnosis is suspected by history of uncorrected cardiac anomalies, supported by chest x-ray and ECG, and established by 2-dimensional echocardiography with color flow and Doppler studies or cardiac catheterization.

Laboratory testing shows polycythemia with Hct > 55%. Increased RBC turnover may be reflected as an iron deficiency state (eg, microcythemia), hyperuricemia, and hyperbilirubinemia.

Chest x-ray usually shows prominent central pulmonary arteries, peripheral pulmonary vessel pruning, and right heart enlargement. ECG shows right ventricular hypertrophy, right axis deviation, and, occasionally, right atrial enlargement.

**Treatment**

• Drugs to lower pulmonary artery pressure (eg, prostacyclin antagonists, endothelin antagonists, nitric oxide enhancers)

• Supportive therapy

• Heart and lung transplantation

Ideally, corrective operations should have been done earlier to prevent Eisenmenger's syndrome. There is no specific treatment once the syndrome develops, other than heart and lung transplantation, but drugs that may lower pulmonary artery pressure are being studied. They include prostacyclin antagonists (eg, treprostinil, epoprostenol), endothelin antagonists (eg, bosentan), and nitric oxide enhancers (eg, sildenafil).

Supportive treatment includes avoidance of conditions that may exacerbate the syndrome (eg, pregnancy, volume depletion, isometric exercise, high altitudes) and use of supplemental $O_2$. Symptomatic polycythemia can be treated by cautious phlebotomy to lower Hct to 55 to 65% plus simultaneous volume replacement with normal saline. However, compensated and asymptomatic polycythemia does not require phlebotomy, regardless of Hct; phlebotomy eventually leads to iron deficiency and does not change the natural history. Hyperuricemia can be treated with allopurinol 300 mg po once/day. Anticoagulation therapy with warfarin is potentially harmful and its use should be individualized, but aspirin 81 mg po once/day is indicated to prevent thrombotic complications.

Life expectancy depends on type and severity of the underlying congenital anomaly and ranges from 20 to 50 yr; median age at death is 37 yr. However, low exercise tolerance and secondary complications severely limit quality of life.

Heart and lung transplantation may be an option but is reserved for patients with severe symptoms and unacceptable quality of life. Long-term survival after transplantation is not promising.

All patients should be given endocarditis prophylaxis (see Table 215-4 on p. 2200) before dental or surgical procedures that are likely to cause bacteremia.

### Other Less Common Congenital Cardiac Anomalies

Less frequent structural congenital cardiac anomalies include the following:

- Single ventricle with or without pulmonary stenosis
- Pulmonary atresia with an intact ventricular septum
- Double outlet right ventricle
- Ebstein's anomaly
- Congenitally corrected transposition

**Single ventricle spectrum:** These anomalies include any complex lesion with only one functional ventricle and include hypoplastic right ventricle (RV) and left ventricle (LV) and, less commonly, a true undifferentiated single ventricular chamber. Surgical management involves ensuring adequate pulmonary blood flow via a systemic-to-pulmonary artery anastomosis (eg, modified Blalock-Taussig shunt [see p. 2959]) for patients with decreased pulmonary blood flow or protecting the pulmonary vascular bed via pulmonary artery banding if pulmonary overcirculation exists. Later, the Fontan procedure (see p. 2962) can be used as definitive treatment to make the functioning single ventricle solely a systemic ventricle.

**Pulmonary atresia with intact septum:** This anomaly is most frequently associated with a hypoplastic RV and follows the same treatment algorithm as tricuspid atresia (see p. 2961).

**Double outlet right ventricle:** This anomaly is associated with a very wide spectrum of anatomy and physiology depending on the size and location of the ventricular septal defect (VSD), as well as the presence and degree of pulmonic stenosis. In the most common variety with a subaortic VSD, a complete repair is possible with closure of the VSD in such a way as to direct LV outflow to the aorta.

**Ebstein's anomaly:** This anomaly consists of variable apical displacement and dysplasia of the septal and inferior leaflets of the tricuspid valve with dysplasia, but normal origin, of the anterior leaflet as well. These abnormalities displace the effective valve orifice downward, resulting in compromise of the function of the RV with an atrialized portion that is proximal to the valve opening. This anomaly has been associated with maternal use of lithium during pregnancy. Associated abnormalities include atrial septal defect, pulmonic stenosis, and Wolff-Parkinson-White syndrome.

There is a remarkably wide spectrum of presentation, ranging from severely cyanotic newborns to

cardiomegaly with mild cyanosis in childhood to a previously asymptomatic adult presenting with atrial arrhythmias or reentry supraventricular tachycardia. The onset of symptoms depends on the degree of tricuspid valve anatomic and functional derangement and presence of accessory pathways (eg, Wolff-Parkinson-White syndrome). When symptoms result from a severely dysfunctional tricuspid valve, surgical repair or replacement should be considered.

**Congenitally corrected transposition:** This anomaly is relatively rare and accounts for about 0.5% of congenital cardiac anomalies. The normal embryologic looping of the fetal heart tube is reversed, resulting in atrioventricular and ventriculoarterial discordance. The result is the right atrium connects to a right-sided morphologic LV and the left atrium connects to a left-sided morphologic RV. In almost all cases, the morphologic LV connects to the pulmonary artery and the morphologic RV connects to the aorta. The circulation is thus physiologically "corrected," but associated anomalies are invariably present, including VSD, pulmonic stenosis, Ebstein's anomaly of the tricuspid valve, congenital atrioventricular block, mesocardia or dextrocardia, and heterotaxy syndromes. These anomalies result in a wide range of clinical manifestations. As patients reach adulthood, a common concern is development of dysfunction of the morphologic RV, which serves as the systemic ventricle. This dysfunction may be subclinical or manifest as severe cardiomyopathy and heart failure, leading to consideration of heart transplantation.

Rare nonstructural cardiac anomalies include

• Congenital complete heart block

• Congenital metabolic errors leading to cardiomyopathy

See p. 2176 for prolonged QT syndrome and other genetic arrhythmia syndromes with risks of severe and possibly fatal ventricular arrhythmias.

# Chapter 294. Congenital Craniofacial and Musculoskeletal Abnormalities

## Introduction

Many craniofacial and musculoskeletal abnormalities occur only at a single, specific site. They may be a deformity (alteration in shape due to unusual pressure and malpositioning [eg, clubfoot]) or a malformation (an error in normal organ or tissue development [eg, anencephaly]). Both deformities and malformations affect function. Some abnormalities (eg, arthrogryposis multiplex congenita) affect multiple sites.

## Arthrogryposis Multiplex Congenita

(Multiple Congenital Contractures)

**Arthrogryposis multiplex congenita (AMC) refers to a variety of conditions that involve congenital limitation of joint movement. Intelligence is relatively normal except when the arthrogryposis is caused by a disorder or syndrome that also affects intelligence.**

There are two major types of AMC:

• **Amyoplasia (classic arthrogryposis):** Multiple symmetric contractures occur in the limbs.

• **Distal arthrogryposis:** The hands and feet are involved, but the large joints are spared.

### Etiology

Any condition that impairs in utero movement for > 3 wk can result in AMC. Causes may involve

• Physical limitation of movement (eg, due to uterine malformations, multiple gestations, or oligohydramnios)

• Maternal disorders (eg, multiple sclerosis, impaired uterine vascularity)

• Fetal disorders (eg, neuropathies; myopathies, including muscular dystrophies; connective tissue abnormalities; impaired fetal vascularity; anterior horn cell disease)

More than 35 specific genetic disorders (eg, spinal muscular atrophy type I, trisomy 18) have been linked to AMC.

### Symptoms and Signs

Deformities are prominent at birth. AMC is not progressive; however, the condition that causes it (eg, muscular dystrophy) may be. Affected joints are contracted in flexion or extension. In classic AMC, shoulders are sloped, adducted, and internally rotated; the elbows are extended; and the wrists and digits are flexed. Hips may be dislocated and are usually slightly flexed. Knees are extended; feet are often in the equinovarus position. Leg muscles are usually hypoplastic, and limbs tend to be tubular and featureless. Soft-tissue webbing sometimes occurs over ventral aspects of the flexed joints. The spine may be scoliotic. Except for slenderness of the long bones, the skeleton appears normal on x-rays. Physical disabilities may be severe. As noted, some children may have primary CNS dysfunction, but intelligence is usually unimpaired.

Endotracheal intubation during surgery may be difficult because children have small immobile jaws. Other abnormalities that rarely accompany arthrogryposis include microcephaly, cleft palate, cryptorchidism, and cardiac and urinary tract abnormalities.

### Diagnosis

• Clinical evaluation

• Testing for cause

Evaluation should include a thorough assessment for associated abnormalities. Electromyography and muscle biopsy are useful to diagnose neuropathic and myopathic disorders. In classic AMC, muscle biopsy typically shows amyoplasia, with fatty and fibrous replacement of tissues.

**Treatment**

• Joint manipulation and casting

• Sometimes surgical procedures

Early orthopedic and physical therapy evaluations are indicated. Joint manipulation and casting during the first few months of life may produce considerable improvement. Orthotics may help. Surgery may be needed later to align the angle of ankylosis, but mobility is rarely enhanced. Muscle transfers (eg, surgically moving the triceps so that it can flex the elbow) may improve function. Many children do remarkably well; two thirds are ambulatory after treatment.

## Congenital Amputations

Congenital amputations are missing or incomplete limbs at birth. Mechanism can involve primary intrauterine growth inhibition or secondary intrauterine destruction of normal embryonic tissues. Etiology is often unclear, but teratogenic agents (eg, thalidomide) and amniotic bands, which are loose strands of amnion that entangle or fuse with fetal tissue, are known causes.

Limb deficiencies can be

• Transverse

• Longitudinal

In **transverse deficiencies**, all elements beyond a certain level are absent, and the limb resembles an amputation stump. Amniotic bands are the most common cause; the degree of deficiency varies based on the location of the band.

**Longitudinal deficiencies** involve specific maldevelopments (eg, complete or partial absence of the radius, fibula, or tibia). They may result from syndromes or associations such as VACTERL (*v*ertebral anomalies, *a*nal atresia, *c*ardiac malformations, *t*racheo*e*sophageal fistula, *r*enal anomalies and *r*adial aplasia, and *l*imb anomalies).

Infants with transverse or longitudinal limb deficiencies may also have hypoplastic or bifid bones, synostoses, duplications, dislocations, or other bony defects; eg, in proximal femoral focal deficiency, the proximal femur and acetabulum do not develop. One or more limbs may be affected, and the type of defect may be different in each limb. CNS abnormalities are rare. X-rays are essential to determine which bones are involved.

**Treatment**

• Prosthetic devices

Treatment consists mainly of prosthetic devices, which are most valuable for lower-limb deficiencies and for completely or almost completely absent upper limbs. If any activity in an arm or hand exists, no matter how great the malformation, functioning capacity must be thoroughly assessed before a prosthesis or surgical procedure is recommended. Therapeutic amputation of any limb or portion of a limb should be considered only after evaluating the functional and psychologic implications of the loss and when essential for fitting a prosthesis.

An upper-limb prosthesis should be designed to serve as many needs as possible so that the number of devices is kept to a minimum. Children use a prosthesis most successfully when it is fitted early and becomes an integral part of their body and body image during the developmental years. Devices used during infancy should be as simple and durable as possible; eg, a hook rather than a bioelectric arm. With effective orthopedic and ancillary support, most children with congenital amputations lead normal lives.

## Craniofacial Abnormalities

Various craniofacial abnormalities result from maldevelopment of the 1st and 2nd visceral arches, which form facial bones and ears during the 2nd mo of gestation. Causes include over 500 genetic syndromes as well as prenatal factors (eg, inadequate folate [folic acid]).

These deformities include cleft lip and cleft palate, various named syndromes (see Table 294-1), hypertelorism (widely spaced eyes), and many other rarer deformities. Most infants with craniofacial abnormalities have normal intelligence.

**Cleft palate and cleft lip:** The most common 1st arch deformities are cleft palate and cleft lip, which occur in 1/700 to 800 births. Both environmental and genetic factors are thought to contribute. Prenatal maternal use of tobacco and alcohol may increase risk. Having one affected child increases risk of having a second one. Folate, taken just before becoming pregnant and through the 1st trimester, decreases the risk.

The cleft may vary from involvement of only the soft palate to a complete fissure of the soft and hard palates, the alveolar process of the maxilla, and the lip. The mildest form is a bifid uvula. An isolated cleft lip can occur.

A cleft palate interferes with feeding and speech development and increases the risk of ear infections. Goals of treatment are to ensure normal feeding, speech, and maxillofacial growth and to avoid formation of fistulas.

Early treatment, pending surgical repair, depends on the specific abnormality but may include specially designed bottle nipples (to facilitate flow), dental appliances (to occlude the cleft so suckling can occur), a feeder that can be squeezed to deliver formula, taping, and an artificial palate molded to the child's own palate. The frequent episodes of acute otitis media must be recognized and treated.

Ultimate treatment is surgical closure; however, timing of surgery, which may interfere with growth centers around the premaxilla, is somewhat controversial. For a cleft palate, a 2-stage procedure is often done. The

[Table 294-1. Common Craniofacial Syndromes]

cleft lip, nose, and soft palate are repaired during infancy (at age 3 to 6 mo). Then, the residual hard palate cleft is repaired at age 15 to 18 mo. Surgery can result in significant improvement, but if deformities are severe or treatment is inadequate, patients may be left with a nasal voice, compromised appearance, and a tendency to regurgitate. Dental and orthodontic treatment, speech therapy, and counseling may be required.

**Deformities characterized by a small mandible:** These deformities include

• Pierre Robin sequence

• Treacher Collins syndrome

**Pierre Robin sequence** is characterized by glossoptosis (a tongue that falls to the back of the throat) and respiratory problems. A cleft palate as well as conductive hearing loss may also be present. Feeding can be difficult, and sometimes cyanosis develops because the tongue is posterior and may obstruct the pharynx. Prone positioning during feeding may help, but uncoordinated swallowing may require nasogastric gavage feedings or a gastrostomy tube. If cyanosis or respiratory problems persist,

tracheostomy or surgery to affix the tongue in a forward position (eg, sewing it to the inner lower lip) may be required. Otologic evaluation is indicated.

In **Treacher Collins syndrome**, which is associated with Pierre Robin sequence, patients have downward slant of the eyes, coloboma of the eyelid, malformed pinna (microtia), and hearing loss.

Surgical extension of the mandible can improve appearance and function. In the typical procedure, called distraction osteogenesis, an osteotomy is done, and a distraction (separator) device is attached to both pieces. Over time, the distance between the 2 pieces is widened, and new bone grows in between to enlarge the mandible.

**Agenesis of the jaw:** Congenital absence of the condyloid process (and sometimes the coronoid process, the ramus, and parts of the mandibular body) is a severe malformation. The mandible deviates to the affected side, resulting in severe malocclusion; the unaffected side is elongated and flattened. Abnormalities of the external, middle, and inner ears, temporal bone, parotid gland, masticatory muscles, and facial nerve often coexist.

X-rays of the mandible and temporomandibular joint show the degree of underdevelopment and distinguish agenesis from other conditions that result in similar facial deformities but do not involve severe structural loss.

Treatment consists of prompt reconstruction with autogenous bone grafting (costochondral graft) to limit progression of facial deformity. Often, mentoplasty, onlay grafts of bone and cartilage, and soft-tissue flaps and grafts further improve facial symmetry. Distraction osteogenesis is being increasingly used. Orthodontic treatment in early adolescence helps correct malocclusion.

**Congenital ear malformations:** Microtia and external auditory canal atresia (which causes conductive hearing loss) involve the external ear. These malformations, which frequently coexist, are often identified at or soon after birth. Occasionally, school-based screening tests identify a partially occluded external auditory canal in children with a normal pinna.

Hearing tests (see p. 431) and CT of the temporal bone are necessary to evaluate possible additional bony malformations.

Treatment can include surgery and a bone-conduction hearing aid, depending on whether the malformation is unilateral or bilateral; whether it affects hearing, learning, and social development; and whether complications (eg, facial nerve involvement, cholesteatoma, otitis media) are present. Surgery may include pinna reconstruction and the creation of an external auditory canal, tympanic membrane, and ossicles.

## Hip, Leg, and Foot Abnormalities

**Orthopedic abnormalities of the hip, leg, and foot are sometimes not apparent at birth. Causes include in utero positioning, ligamentous laxity, and skeletal deformities. Some abnormalities resolve without intervention; however, others require treatment.**

**Developmental dysplasia of the hip (DDH—formerly congenital dislocation of the hip):** DDH is abnormal development of the hip joint, leading to subluxation or dislocation; it can be unilateral or bilateral. It is more common among infants with a breech presentation, especially females, particularly those with a positive family history. It seems to result from laxity of the ligaments around the joint or from in utero positioning. Asymmetric skin creases in the thigh and groin are common, but such creases also occur in infants without DDH. If DDH remains undetected and untreated, the affected leg eventually becomes shorter, and the hip may become painful. Abduction of the hip is often impaired due to adductor spasm.

All infants are screened by physical examination. Because physical examination has limited sensitivity, high-risk infants (and those with abnormalities found during physical examination) typically should have an imaging study.

Two screening maneuvers commonly are used. The Ortolani maneuver detects the hip sliding back *into* the acetabulum, and the Barlow maneuver detects the hip sliding *out of* the acetabulum. Each hip is examined separately. Both maneuvers begin with the infant supine and the hips and knees flexed to 90° (the feet will be off the bed). To do the Ortolani maneuver, the thigh of the hip being tested is abducted (ie, the knee is moved away from the midline into a frog-leg position) and gently pulled anteriorly. Instability is indicated by the palpable, sometimes audible, clunk of the femoral head moving over the posterior rim of the acetabulum and relocating in the cavity. Next, in the Barlow maneuver, the hip is returned to the starting position and then slightly adducted (ie, the knee is drawn across the body) and the thigh is pushed posteriorly. A clunk indicates that the head of the femur is moving out of the acetabulum. Also, a difference in knee height when the child is supine with hips flexed, knees bent, and feet on the examining table (Galeazzi sign—see Fig. 294-1) suggests dysplasia, especially unilateral. Somewhat later (eg, by 3 or 4 mo of age), subluxation or dislocation is indicated by inability to completely abduct the thigh when the hip and knee are flexed; abduction is impeded by adductor spasm, which is often present even if the hip is not actually dislocated at the time of examination. Minor benign clicks are commonly detected. Although clicks usually disappear within 1 or 2 mo, they should be checked regularly. Because bilateral dysplasia may be difficult to detect at birth, periodic testing for limited hip abduction during the first year of life is advised.

Ultrasonography of the hips is recommended at 6 wk of age for infants at high risk, including those with a breech presentation, those born with other deformities (eg, torticollis, congenital foot deformity), and girls with a positive family history of DDH.

Imaging is also required when any abnormality is suspected during examination. Hip ultrasonography can accurately establish the diagnosis earlier in life. Hip x-rays are helpful after the bones have started to ossify, typically after age 4 mo.

Early treatment is critical. With any delay, the potential for correction without surgery decreases steadily. The hip usually can be reduced immediately after birth, and with growth, the acetabulum can form a nearly normal joint. Treatment is with devices, most commonly the Pavlik harness, which hold the affected hips abducted and externally rotated. The Frejka pillow and other splints may help. Padded diapers and double or triple diapering are not effective and should not be done to correct DDH.

**Femoral torsion (twisting):** The femoral head may be twisted. Torsion may be either internal (femoral anteversion—knees pointing toward each other with toes in) or external (femoral retroversion—knees pointing in opposite directions) and is common among neonates. At birth, internal torsion can be as much as 40° and still be normal. External torsion can also be prominent at birth and still be normal. Torsion is recognized by laying the child prone on the examining table. The hips are rotated externally and internally. Limitation

[**Fig. 294-1.** Galeazzi sign.]

of internal rotation indicates femoral anteversion, whereas limitation of external rotation indicates femoral retroversion.

Children with internal torsion may regularly sit in the W position (ie, knees are together and feet are spread apart) or sleep prone with legs extended or flexed and internally rotated. These children probably assume this position because it is more comfortable. The W sitting position was thought to worsen torsion, but there is little evidence that the position should be discouraged or avoided. By adolescence, internal torsion tends to gradually decrease to about 15° without intervention. Orthopedic referral and treatment, which includes derotational osteotomy (in which the bone is broken, rotated into normal alignment, and casted), is reserved for children who have a neurologic deficit such as spina bifida or those in whom torsion interferes with ambulation.

External torsion may occur if in utero forces result in an abduction or external rotation of the lower extremity. If external torsion is prominent at birth, a thorough evaluation (including x-rays or ultrasonography) for hip dislocation is indicated. External torsion typically corrects spontaneously, especially after children begin to stand and walk, but orthopedic referral is needed when excessive

torsion persists after 8 yr. Treatment includes derotational osteotomy.

**Genu varum and genu valgum:** The 2 major types of knee or femoral-tibial angular deformities are genu varum (bowlegs) and genu valgum (knock-knees). Untreated, both can cause osteoarthritis of the knee in adulthood.

**Genu varum** is common among toddlers and usually resolves spontaneously by age 18 mo. If it persists or becomes more severe, Blount disease (tibia vara) should be suspected, and rickets and other metabolic bone diseases should also be ruled out (see p. 2991). Blount disease is due to a growth disturbance of the medial aspect of the proximal tibial growth plate; genu varum and tibial torsion may occur. Blount disease may occur in early childhood or in adolescence (when it is associated with overweight). Early diagnosis of Blount disease is difficult, because x-rays may be normal; the classic x-ray finding is angulation (beaking) of the medial metaphysis. Early use of splints or braces can be effective, but surgery with or without an external fixator is often needed.

**Genu valgum** is less common and, even if severe, usually resolves spontaneously by age 9 yr. Skeletal dysplasia or hypophosphatasia should be excluded. If marked deformity persists after age 10 yr, surgical stapling of the medial distal femoral epiphysis is indicated.

**Knee dislocation:** Anterior knee dislocation with hyperextension is rare at birth but requires emergency treatment. It may occur with Larsen's syndrome, which consists of multiple congenital dislocations (eg, elbows, hips, knees), clubfoot, and characteristic facies (eg, prominent forehead, depressed nasal bridge, wide-spaced eyes), or with arthrogryposis (see p. 2969). The dislocation may be related to muscle imbalance (if myelodysplasia or arthrogryposis is present) or intrauterine positioning. Ipsilateral hip dislocation often coexists.

On examination the leg is extended and cannot be flexed more than a few degrees.

If the infant is otherwise normal, immediate treatment with daily passive flexion movements and splinting in flexion usually results in a functional knee.

**Tibial torsion:** Tibial torsion can be external (lateral) or internal (medial) twisting. External torsion occurs normally with growth: from 0° at birth to 20° by adulthood. External torsion is rarely a problem.

Internal torsion is common at birth, but it typically resolves with growth. However, an excessive degree of torsion may indicate a neuromuscular problem. Torsion also occurs with Blount disease (see p. 2973). Persistent, excessive torsion can lead to toeing-in and bowlegs.

To evaluate for tibial torsion, the angle between the axis of the foot and the axis of the thigh is measured with the child prone and the knees flexed to 90°. Typically the foot axis is 10° lateral relative to the thigh axis. This angle can also be measured by seating the child and drawing an imaginary line connecting the lateral and medial malleoli.

**Talipes equinovarus:** Sometimes called clubfoot, talipes equinovarus is characterized by plantar flexion, inward tilting of the heel (from the midline of the leg), and adduction of the forefoot (medial deviation away from the leg's vertical axis). It results from an abnormality of the talus. It occurs in about 2/1000 births, is bilateral in up to 50% of affected children, and may occur alone or as part of a syndrome. Developmental dysplasia of the hip is more common among these children. Similar deformities that result from in utero positioning can be distinguished from talipes equinovarus because they can be easily corrected passively.

Treatment requires orthopedic care, which consists initially of repeated cast applications, taping, or use of malleable splints to normalize the foot's position. If casting is not successful and the abnormality is severe, surgery may be required. Optimally, surgery is done before 12 mo, while the tarsal bones are still cartilaginous. Talipes equinovarus may recur as children grow.

**Talipes calcaneovalgus:** The foot is flat or convex and dorsiflexed with the heel turned outward. The foot can easily be approximated against the lower tibia. Developmental dysplasia of the hip is more

common among these children. Early treatment with a cast (to place the foot in the equinovarus position) or with corrective braces is usually successful.

**Metatarsus adductus:** The forefoot turns toward the midline. The foot may be supinated at rest. Usually, the foot can be passively abducted and everted beyond the neutral position when the sole is stimulated. Occasionally, an affected foot is rigid, not correcting to neutral. Developmental dysplasia of the hip is more common among these children.

The deformity usually resolves without treatment during the first year of life. If it does not, casting or surgery (abductory midfoot osteotomy) is required.

**Metatarsus varus:** The plantar surface of the foot is turned inward, so that the arch is raised. This deformity usually results from in utero positioning. It typically does not resolve after birth and may require corrective casting.

### Muscle Abnormalities

Individual muscles or groups of muscles may be absent at birth. Muscle abnormalities can occur alone or as part of a syndrome.

Partial or complete agenesis of the pectoralis major is common and occurs alone or with ipsilateral hand abnormalities and various degrees of breast and nipple aplasia, as in Poland's syndrome. Poland's syndrome may be associated with Mobius' syndrome (paralysis of the lower cranial nerves, especially the 6th, 7th, and 12th), which has been linked to autism.

In prune-belly syndrome (see p. 2988), ≥ 1 layers of the abdominal musculature are absent at birth; this often occurs with severe GU abnormalities, particularly hydronephrosis. Incidence is higher in males who often also have bilateral undescended testes. Malformations involving the feet and rectum also often coexist. Prognosis is guarded, even with early relief of urinary tract obstruction.

Treatment depends on severity of the condition and can range from minimal intervention to reconstructive surgery.

### Neck and Back Abnormalities

Neck and back abnormalities can be caused by soft-tissue or bony injuries or by vertebral anomalies. Vertebral anomalies can be singular or part of a syndrome.

**Congenital torticollis:** The head becomes tilted at or soon after birth. The most common cause is neck injury during delivery. Torticollis that develops within the first few days or weeks of life may result from hematoma, fibrosis, and contracture of the sternocleidomastoid (SCM) muscle. A nontender mass may be noted in the SCM, usually in the midsegment.

Other causes include spinal abnormalities, such as Klippel-Feil syndrome (fusion of the cervical vertebrae, short neck, and low hairline, often with urinary tract abnormalities) or atlanto-occipital fusion. CNS tumors, bulbar palsies, and ocular dysfunction are common neurologic causes but are rarely present at birth (see also Spasmodic Torticollis on p. 382). Fractures, dislocations, or subluxations of the cervical spine (especially C1 and C2) or odontoid abnormalities are rare but serious causes; permanent neurologic damage may result from spinal cord injury.

Cervical imaging should be done to exclude bony causes, which may require stabilization.

When torticollis is due to birth trauma, frequent passive SCM stretching (rotating the head and stretching the neck laterally to the opposite side) is indicated. Injections of botulinum toxin into the SCM may help in refractory cases. Untreated torticollis may lead to plagiocephaly (flattening of one side of the head) and asymmetrical facies.

**Vertebral defects:** Examples are idiopathic scoliosis (see p. 2912), which is rarely apparent at birth, and

isolated vertebral defects (eg, hemivertebrae, wedge or butterfly vertebrae), which are more likely to be diagnosed at birth. Vertebral defects should be suspected when posterior midline cutaneous, renal, or congenital lower-limb abnormalities exist. Some syndromes or associations such as VACTERL (*v*ertebral anomalies, *a*nal atresia, *c*ardiac malformations, *t*racheo*e*sophageal fistula, *r*enal anomalies and *r*adial aplasia, and *l*imb anomalies) include vertebral defects.

As children grow, the spinal curve caused by a vertebral defect or defects can progress rapidly; therefore, the spine should be monitored closely. Braces or body jackets, which may have to be worn 18 h/day, are often necessary initially. Surgery may be needed if the curvature progresses. Because renal abnormalities commonly coexist, renal ultrasonography is indicated for initial screening.

# Chapter 295. Congenital Gastrointestinal Anomalies

## Introduction

Most congenital GI anomalies result in some type of intestinal obstruction, frequently manifesting with feeding difficulties, distention, and emesis at birth or within 1 or 2 days. Infants with GI malformations have a high mortality rate, ranging from 10 to 40%; the highest rate occurs in those with congenital diaphragmatic hernia.

A common type of anomaly is atresia, in which a segment of the GI tract fails to form or develop normally. The most common type is esophageal atresia, followed by atresia in the jejunoileal region and in the duodenum.

Immediate management includes bowel decompression (by continuous nasogastric suction to prevent emesis, which can lead to aspiration pneumonia or further abdominal distention with respiratory embarrassment) and referral to a center for neonatal surgery. Also vital are maintenance of body temperature, prevention of hypoglycemia with IV 10% dextrose and electrolytes, and prevention or treatment of acidosis and infections so that the infant is in optimal condition for surgery.

Because about one third of infants with a GI malformation have another congenital anomaly (up to 50% in those with congenital diaphragmatic hernia and 70% in those with omphalocele), they should be evaluated for malformations of other organ systems, especially of the CNS, heart, and kidneys.

## High Alimentary Tract Obstruction

Esophageal, gastric, duodenal, and sometimes jejunal obstruction should be considered when excess amniotic fluid (polyhydramnios) is diagnosed, because such obstructions prevent the fetus from swallowing and absorbing amniotic fluid (jejunal obstruction—see p. 2978). An NGT should be passed into the neonate's stomach immediately after delivery. Finding large amounts of fluid in the stomach, especially if bile-stained, supports the diagnosis of upper GI obstruction, whereas inability to pass the NGT into the stomach suggests esophageal atresia (or nasal obstruction [eg, choanal atresia]). Diaphragmatic hernia sometimes causes high alimentary tract obstruction.

### Esophageal Atresia

**Esophageal atresia is incomplete formation of the esophagus, frequently associated with tracheoesophageal fistula. Diagnosis is suspected by failure to pass an NGT. Treatment is surgical repair.**

Esophageal atresia is the most common GI atresia. The estimated incidence is 1 in 3000 live births. Other congenital malformations are present in up to 50% of cases.

There are 5 major types of esophageal atresia (see Fig. 295-1). Most also involve a fistula between the trachea and esophagus.

Characteristic signs are excessive secretions, coughing and cyanosis after attempts at feeding, and aspiration pneumonia. Esophageal atresia with a distal fistula leads to abdominal distention because, as the infant cries, air from the trachea is forced through the fistula into the lower esophagus and stomach.

#### Diagnosis

• Prenatal: Ultrasonography

• Postnatal: NGT placement and x-ray

Routine prenatal ultrasonography may suggest esophageal atresia. Polyhydramnios may be present but is not diagnostic because it can occur with many other disorders. The fetal stomach bubble may be absent but only in < 50% of cases. Less commonly, there is a dilated upper esophageal pouch, but this is

typically looked for only in fetuses with polyhydramnios and no stomach bubble.

After delivery, an NGT is inserted if esophageal atresia is suspected by prenatal ultra-sonography or clinical findings; diagnosis is suggested by inability to pass the tube into the stomach. A radiopaque catheter determines the location of the atresia on x-ray. In atypical cases, a small amount of water-soluble contrast material may be needed to define the anatomy

[Fig. 295-1. Types and relative frequencies of esophageal atresia and tracheoesophageal fistula.]

under fluoroscopy. The contrast material should be quickly aspirated back because it can cause a chemical pneumonitis if it enters the lungs. This procedure should be done only by an experienced radiologist at the center where neonatal surgery will be done.

**Treatment**

• Surgical repair

Preoperative management aims to get the infant into optimal condition for surgery and prevent aspiration pneumonia, which makes surgical correction more hazardous. Oral feedings are withheld. Continuous suction with a double-lumen catheter in the upper esophageal pouch prevents aspiration of swallowed saliva. The infant should be positioned prone with the head elevated 30 to 40° and with the right side down to facilitate gastric emptying and minimize the risk of aspirating gastric acid through the fistula. If definitive repair must be deferred because of extreme prematurity, aspiration pneumonia, or other congenital malformations, gastrostomy is done to decompress the stomach. Suction through the gastrostomy tube then reduces the risk that gastric contents will reflux through the fistula into the tracheobronchial tree.

When the infant's condition is stable, extrapleural surgical repair of the esophageal atresia and closure of the tracheoesophageal fistula can be done. Occasionally, interposing a segment of colon between the esophageal segments may be required.

The most common acute complications are leakage at the anastomosis site and stricture formation. Feeding difficulties are common after successful surgical repair because of poor motility of the distal esophageal segment, which occurs in up to 85% of cases. This poor motility predisposes the infant to gastroesophageal re-flux. If medical management for reflux fails, a Nissen fundoplication may be required.

**Diaphragmatic Hernia**

**Diaphragmatic hernia is protrusion of abdominal contents into the thorax through a defect in the diaphragm. Lung compression may cause persistent pulmonary hypertension. Diagnosis is by chest x-ray. Treatment is surgical repair.**

Diaphragmatic hernia usually occurs in the posterolateral portion of the diaphragm (Bochdalek's hernia) and is on the left side in 90% of cases. The estimated incidence is 1 in 2200 live births. Anterior hernias (Morgagni's hernia) are far less common. Other congenital anomalies are present in about 50% of cases.

Loops of small and large bowel, stomach, liver, and spleen may protrude into the hemithorax on the involved side. If the hernia is large, the lung on the affected side is hypoplastic. Other pulmonary consequences include underdevelopment of the pulmonary vasculature, resulting in an elevation of pulmonary vascular resistance and hence pulmonary hypertension. Persistent pulmonary hypertension (see p. 2873) leads to right-to-left shunting at the level of the foramen ovale or through a patent ductus arteriosus, which prevents adequate oxygenation even with $O_2$ supplementation or mechanical ventilation. Persistent pulmonary hypertension is the major cause of death among infants with congenital diaphragmatic hernia.

**Symptoms and Signs**

After delivery, as the neonate cries and swallows air, the loops of intestine quickly fill with air and rapidly

enlarge, causing further acute respiratory embarrassment as the heart and mediastinal structures are pushed to the right, compressing the more normal right lung. Respiratory distress is immediate in severe cases. A scaphoid abdomen (due to displacement of abdominal viscera into the chest) is likely. Bowel sounds (and an absence of breath sounds) may be heard over the involved hemithorax. In less severe cases, mild respiratory difficulty develops a few hours or days later as abdominal contents progressively herniate through a smaller diaphragmatic defect.

**Diagnosis**

• Sometimes prenatal ultrasonography

• Chest x-ray

Sometimes diagnosis is by prenatal ultra-sonography. After delivery, diagnosis is by chest x-ray showing intestine protruding into the chest. In a large defect, there are numerous air-filled loops of intestine filling the hemithorax and contralateral displacement of the heart and mediastinal structures. If the x-ray is taken immediately after delivery before the neonate has swallowed air, the abdominal contents appear as an opaque airless mass in the hemithorax.

**Treatment**

• Surgical repair

The neonate should be immediately endotracheally intubated and ventilated in the delivery room; bag-and-mask ventilation may fill the intrathoracic viscera with air and worsen respiratory compromise. Continuous nasogastric suction with a double-lumen tube prevents swallowed air from progressing through the GI tract and causing further lung compression. Sometimes paralytic drugs are needed to prevent swallowing of air. Surgery is required to replace the intestine in the abdomen and to close the diaphragmatic defect after the neonate has had optimal management of pulmonary hypertension.

Severe persistent pulmonary hypertension requires stabilization before surgery with IV $NaHCO_3$ and inhaled nitric oxide, which may help dilate the pulmonary arteries and improve systemic oxygenation. Recent studies show improved outcome with use of extracorporeal membrane oxygenation (ECMO); however, neonates with extreme pulmonary hypoplasia still do not survive. Successful transport of a critically ill neonate with congenital diaphragmatic hernia and persistent pulmonary hypertension is very difficult. Therefore, if diaphragmatic hernia is diagnosed by prenatal ultrasonography, delivery at a pediatric center with ECMO facilities is prudent.

**Duodenal Obstruction**

**The duodenum can be obstructed by atresia, stenosis, and pressure due to an extrinsic mass.**

**Duodenal atresia:** This anomaly is the 3rd most common atresia of the GI tract. The estimated incidence is 1 in 20,000 live births. Duodenal atresia is due to the failure of canalization of the embryonic duodenum. About 30% of infants with duodenal atresia have Down syndrome. Other congenital anomalies, particularly malrotation of the intestine, occur in 50 to 70% of cases.

Diagnosis can be suspected prenatally if there is polyhydramnios, dilated bowel, as-cites, or a combination. Infants with duodenal atresia present with polyhydramnios, feeding difficulties, and emesis that may be bilious. The diagnosis is suspected by symptoms and classic double-bubble x-ray findings —one bubble is in the stomach and the other is in the proximal duodenum; little to no air is in the distal gut. An upper GI series provides definitive diagnosis but must be done carefully by a radiologist experienced with doing this procedure on children to avoid aspiration. Once the disorder is suspected, infants should receive nothing by mouth, and an NGT should be placed to decompress the stomach. Surgery is the definitive therapy.

**Duodenal stenosis:** This anomaly occurs less commonly than duodenal atresia but manifests in a similar fashion and requires surgery. It too is frequently associated with Down syndrome.

**Choledochal cyst or annular pancreas:** These anomalies may obstruct the duodenum by extrinsic pressure. Infants with choledochal cyst classically present with a triad of abdominal pain (a very difficult finding to infer in the neonate), right upper quadrant mass, and jaundice. If the cyst is large, it may also manifest with variable degrees of duodenal obstruction. Choledochal cyst is most commonly diagnosed by ultrasonography. Treatment is surgical and requires complete excision of the cyst because of the risk of developing cancer in the cyst remnants.

**Annular pancreas** is a rare congenital anomaly in which pancreatic tissue encircles the 2nd portion of the duodenum, causing duodenal obstruction; manifestation is usually during the neonatal period but may be delayed until adulthood. The diagnosis can be suggested by an upper GI series and is more definitively made with CT. Treatment is surgical.

## Jejunoileal and Large-Bowel Obstruction

(See also Meconium Ileus on p. 2801 and Meconium Plug Syndrome on p. 2802.)

Obstruction of the jejunum and ileum can occur as the result of jejunoileal atresia, mal-rotation, intestinal duplication, or meconium ileus. Large-bowel obstruction is typically caused by Hirschsprung's disease, meconium plug syndrome, and colonic or anal atresia.

In 75% of cases, no history of maternal polyhydramnios exists because much of the swallowed amniotic fluid can be absorbed from the intestine proximal to the obstruction. These disorders, other than malrotation, intestinal duplication, and Hirschsprung's disease, typically manifest in the first few days of life with feeding problems, abdominal distention, and emesis that may be bilious or fecal. The neonate may pass a small amount of meconium initially but thereafter does not pass stools. Malrotation, intestinal duplication, and Hirschsprung's disease can manifest in the first several days of life or years later.

General diagnostic approach and preoperative management include giving nothing by mouth, placing an NGT to prevent further bowel distention or possible aspiration of vomitus, correcting fluid and electrolyte disturbances, taking a plain abdominal x-ray, and then doing a contrast enema to delineate the anatomy (the enema may also relieve obstruction in meconium plug syndrome or meconium ileus). For Hirschsprung's disease, a rectal biopsy is needed.

### Jejunoileal Atresia

**Jejunoileal atresia is incomplete formation of the jejunum, usually caused by an ischemic insult.**

There are 5 major types of jejunoileal atresia:

- Type I consists of a membrane completely occluding the lumen with the intestine intact.
- Type II is a gap in the intestine with a fibrous cord between the proximal and distal segments of intestine.
- Type IIIA is a mesenteric gap without any connection between the segments.
- Type IIIB is jejunal atresia with absence of the distal superior mesenteric artery; the distal small bowel is coiled like an apple peel, and the gut is short.
- Type IV consists of multiple atretic segments.

Neonates with jejunoileal atresia usually present late during day 1 or on day 2 with increasing abdominal distention, failure to pass stools, and, finally, regurgitated feedings.

Plain abdominal x-rays are done; they may reveal dilated loops of small bowel with air-fluid levels and a paucity of air in the colon and rectum. Because about 10% of patients also have cystic fibrosis (nearly 100% if meconium ileus is also present), testing for that disease (see p. 2883) should be done.

**Treatment**

• Surgical repair

Preoperative management consists of placing an NGT, giving nothing by mouth, and providing IV fluids. Surgical repair is the definitive therapy. During surgery, the entire intestine should be inspected for multiple areas of atresia. The atretic portion is resected, usually with a primary anastomosis. If the proximal portion of the ileum is extremely dilated and difficult to anastomose to the distal, unused part of the intestine, it is sometimes safer to do a double-barreled ileostomy and defer anastomosis until the caliber of the distended proximal intestine has diminished.

Prognosis is based on the length of remaining small bowel and the presence of the ileocecal valve. Infants who subsequently develop short bowel syndrome require TPN for extended periods. They should be provided continuous enteral feedings to promote gut adaptation, maximize absorption, and minimize the use of TPN. Infants should also be provided small amounts of nutrition by mouth to maintain sucking and swallowing.

**Malrotation of the Bowel**

**Malrotation of the bowel is failure of the bowel to assume its normal place in the abdomen during intrauterine development.**

During embryonic development, the primitive bowel protrudes from the abdominal cavity. As it returns to the abdomen, the large bowel normally rotates counterclockwise, with the cecum coming to rest in the right lower quadrant. Incomplete rotation, in which the cecum ends up elsewhere (usually in the right upper quadrant or midepigastrium), may cause bowel obstruction due to retroperito-neal bands (Ladd's bands) that stretch across the duodenum or due to a volvulus of the small bowel, which, lacking its normal peritoneal attachment, twists on its narrow, stalk-like mesentery. Other malformations occur in 30 to 60% of patients, most commonly other GI malformations (eg, gastroschisis, omphalocele, diaphragmatic hernia, intestinal atresia).

Patients with malrotation can present in infancy or in adulthood with acute abdominal pain and bilious emesis, with an acute volvulus, with typical reflux symptoms, or with chronic abdominal pain. Bilious emesis in an infant is an emergency and should be evaluated immediately to make sure the infant does not have malrotation and a midgut volvulus; untreated, the risk of bowel infarction and subsequent short bowel syndrome or death is high.

Plain films of the abdomen should be done immediately. If they show dilated small bowel, a paucity of bowel gas distal to the duodenum, or both (suggesting a midgut volvulus), further diagnosis and treatment must be done emergently. Barium enema typically identifies malrotation by showing the cecum outside the right lower quadrant. If the diagnosis remains uncertain, an upper GI series can be done cautiously.

The presence of malrotation and midgut volvulus is an emergency requiring immediate surgery, which consists of Ladd's procedure with lysis of the retroperitoneal bands and relief of the midgut volvulus.

**Intestinal Duplication**

**Intestinal duplications are tubular structures attached to the intestines that share a common blood supply; their lining resembles that of the GI tract.**

Intestinal duplications are uncommon. The most common site of duplication is the jejunum and ileum followed by the esophagus, stomach, colon, and duodenum. Colonic duplication is often associated with anomalies of the urogenital system. Intestinal duplications usually manifest in the 1st or 2nd yr of life. Duplications can be asymptomatic or cause obstructive symptoms, chronic pain, or abdominal mass. If they are detected, treatment is surgical with complete resection of the duplicated portion.

**Hirschsprung's Disease**

(Congenital Megacolon)

**Hirschsprung's disease is a congenital anomaly of innervation of the lower intestine, usually limited to the colon, resulting in partial or total functional obstruction. Symptoms are obstipation and distention. Diagnosis is by barium enema and biopsy. Treatment is surgical.**

Hirschsprung's disease is caused by congenital absence of Meissner's and Auerbach's autonomic plexus in the intestinal wall. The estimated incidence is 1 in 5000 live births. Disease is usually limited to the distal colon but can involve the entire colon or even the entire large and small bowel. Males are more commonly affected unless the entire colon is involved, in which case there is no gender difference. Peristalsis in the involved segment is absent or abnormal, resulting in continuous smooth muscle spasm and partial or complete obstruction with accumulation of intestinal contents and massive dilation of the more proximal, normally innervated intestine. Skip lesions almost never occur.

### Symptoms and Signs

Patients most commonly present early in life; 15% in the first month, 60% by age 1 yr, and 85% by age 4 yr. Infants present with failure to pass meconium in the first 24 h of life, obstipation, abdominal distention, and, finally, vomiting as in other forms of distal bowel obstruction. Occasionally, infants with ultra-short segment aganglionosis have only mild or intermittent constipation, often with intervening bouts of mild diarrhea, resulting in delay in diagnosis. In older infants, symptoms and signs may include anorexia, lack of a physiologic urge to defecate, and, on digital rectal examination, an empty rectum with stool palpable higher up in the colon and an explosive passage of stool upon withdrawal of the examining finger (blast sign). The infant may also fail to thrive.

### Diagnosis

• Barium enema

• Rectal biopsy

Diagnosis should be made as soon as possible. The longer the disease goes untreated, the greater the chance of developing Hirschsprung's enterocolitis (toxic megacolon), which may be fulminant and fatal (see below). Most cases can be diagnosed in early infancy.

Initial approach is typically with barium enema or sometimes rectal suction biopsy. Barium enema may show a transition in diameter between the dilated, normally innervated colon proximal to the narrowed distal segment (which lacks normal innervation). Barium enema should be done without prior preparation, which can dilate the abnormal segment, rendering the test nondiagnostic. Because characteristic findings may not be present in the neonatal period, a 24-h post-evacuation x-ray should be taken; if the colon is still filled with barium, Hirschsprung's disease is likely. A rectal suction biopsy can disclose the absence of ganglion cells. Acetylcholinesterase staining can be done to highlight the enlarged nerve trunks. Some centers also can do rectal manometrics, which can reveal the dysmotility characteristic of the abnormal innervation. Definitive diagnosis requires a full-thickness biopsy of the rectum.

### Treatment

• Surgical repair

Treatment in the neonate typically involved a colostomy proximal to the aganglionic segment to decompress the colon and allow the neonate to grow before the 2nd stage of the procedure. Later resection of the entire aganglionic portion of the colon and a pull-through procedure was done. However, a number of centers now do a 1-stage procedure in the neonatal period. Results using laparoscopic technique are similar to those of the open method and are associated with shorter hospitalizations, earlier initiation of feeding, and less pain.

After definitive repair, the prognosis is good, although a number of infants have chronic dysmotility with

constipation, obstructive problems, or both.

### Hirschsprung's Enterocolitis

(Toxic Megacolon)

**Hirschsprung's enterocolitis is a life-threatening complication of Hirschsprung's disease resulting in a grossly enlarged colon, often followed by sepsis and shock.**

The etiology of Hirschsprung's enterocolitis seems to be marked proximal dilatation secondary to obstruction, with thinning of the colonic wall, bacterial overgrowth, and trans-location of gut bacteria. Shock can develop, and death can follow rapidly; mortality rate is 10%. Close monitoring of infants with Hirschsprung's disease is therefore essential.

Hirschsprung's enterocolitis occurs most commonly in the first several months of life before surgical correction but can occur postoperatively, typically in the first year after surgery. Infants present with fever, abdominal distention, diarrhea (which may be bloody), and, subsequently, obstipation.

Initial treatment is supportive with fluid resuscitation, decompression with an NGT and rectal tube, and broad-spectrum antibiotics to include anaerobic coverage (eg, a combination of ampicillin, gentamicin, and clindamycin). Some experts advocate saline enemas to clean out the colon, but this must be done carefully so as not to increase colonic pressure and cause perforation. Surgery is the definitive treatment for infants who have not yet undergone surgical repair, as well as for infants with perforation or necrotic gut.

### Anal Atresia

**Anal atresia is an imperforate anus.**

A fistula often extends from the anal pouch to the perineum or the urethra in males and to the vagina, the fourchette, or, rarely, the bladder in females. The blind anus and the skin of the perineum may be several centimeters apart or separated by just a thin membrane of skin covering the anal opening.

Anal atresia is obvious on routine physical examination of the neonate because the anus is not patent. If the diagnosis is missed and the neonate is fed, signs of distal bowel obstruction soon develop.

The urine should be filtered and examined for meconium, indicating the presence of a fistula to the urinary tract. Plain x-rays and fistulograms with the neonate in a lateral prone position can define the level of the lesion. A cutaneous fistula generally indicates low atresia. In such cases, definitive repair using a perineal approach is possible. If no perineal fistula exists, a high lesion is likely.

Definitive repair is usually deferred until the infant is older and the structures to be repaired are larger. Until then, a colostomy is done to relieve the obstruction.

## Defects in Abdominal Wall Closure

Several congenital defects involve the abdominal wall, allowing protrusion of the viscera.

### Omphalocele

**An omphalocele is a protrusion of abdominal viscera from a midline defect at the base of the umbilicus.**

In omphalocele, the herniated viscera are covered by a thin membrane and may be small (only a few loops of intestine) or may contain most of the abdominal viscera (intestine, stomach, liver). Immediate dangers are drying of the viscera, hypothermia and dehydration due to evaporation of water from the exposed viscera, and infection of the peritoneal surfaces. Infants with omphalocele have a very high incidence of other congenital anomalies (up to 70%), including

• Bowel atresia

• Chromosomal abnormalities (eg, Down syndrome)

• Cardiac and renal anomalies

Omphalocele can be detected by routine prenatal ultrasonography; if the disorder is present, delivery should be at a tertiary care center by personnel experienced in dealing with this disorder and the other associated congenital anomalies.

At delivery, the exposed viscera should be immediately covered with a sterile, moist, nonadherent dressing (eg, medicated petrolatum gauze) to maintain sterility and prevent evaporation.

The infant is evaluated for associated anomalies before surgical repair of the omphalocele. Primary closure is done when feasible. With a large omphalocele, the abdominal cavity may be too small to accommodate the viscera. In this case, the viscera are covered by a pouch or silo of polymeric silicone sheeting, which is progressively reduced in size over several days as the abdominal capacity slowly increases, until all of the viscera are enclosed within the abdominal cavity.

**Gastroschisis**

**Gastroschisis is protrusion of the abdominal viscera through an abdominal wall defect, usually to the right of the umbilical cord insertion.**

The estimated incidence is 1 in 2000 live births (more common than omphalocele). In gastroschisis, unlike omphalocele, there is no membranous covering over the intestine, which is markedly edematous and erythematous and is often enclosed in a fibrin mat. These findings indicate long-standing inflammation due to the intestine being directly exposed to amniotic fluid (ie, chemical peritonitis). Infants with gastroschisis have low incidence of associated congenital anomalies other than malrotation. As in omphalocele, gastroschisis can be detected by prenatal ultrasonography, and delivery should take place at a tertiary care center. Surgery is similar to that for omphalocele. It often takes several weeks before GI function recovers and oral feedings can be given; occasionally, infants have long-term problems caused by abnormal intestinal motility.

# Chapter 296. Congenital Renal and Genitourinary Anomalies

## Introduction

Congenital anatomic anomalies of the GU tract are more common than those of any other organ system. Urinary tract anomalies predispose to many complications, including infection, obstruction, stasis, calculus formation, and impaired renal function. Genital anomalies may cause sexual dysfunction or impaired fertility. Treatment of GU anomalies is often surgical.

Some congenital renal anomalies (eg, autosomal dominant polycystic kidney disease and medullary cystic disease [see Ch. 234], hereditary nephritis [see p. 2387]) typically do not manifest until adulthood.

## Renal Anomalies

**Renal agenesis:** Bilateral renal agenesis as part of a syndrome of oligohydramnios, pulmonary hypoplasia, and extremity and facial anomalies (classic Potter syndrome) is fatal within minutes to hours. Many are stillborn.

Unilateral renal agenesis is not uncommon and accounts for about 5% of renal anomalies. It usually is accompanied by ureteral agenesis with absence of the ipsilateral trigone and ureteral orifice. No treatment is necessary; compensatory hypertrophy of the solitary kidney maintains normal renal function.

**Autosomal recessive polycystic kidney disease:** Incidence of autosomal recessive polycystic kidney disease is about 1/10,000 to 1/20,000 births. Autosomal dominant polycystic kidney disease is much more common, occurring in about 1/500 to 1/1000 live births (see p. 2385).

Autosomal recessive disease affects

• Kidneys

• Liver

Kidneys are usually greatly enlarged and contain small cysts; renal failure is common in childhood.

The liver is enlarged and has periportal fibrosis, bile duct proliferation, and scattered cysts; the remainder of the hepatic parenchyma is normal. Fibrosis causes portal hypertension by age 5 to 10 yr, but hepatic function is normal or minimally impaired.

Disease severity and progression vary. Severe disease may manifest prenatally or soon after birth or in early childhood with renal-related symptoms; less severely affected patients present in late childhood or adolescence with hepatic-related symptoms.

Affected neonates have a protuberant abdomen with huge, firm, smooth, symmetric kidneys. Severely affected neonates commonly have pulmonary hypoplasia secondary to the in utero effects of renal dysfunction and oligohydramnios.

In patients aged 5 to 10 yr, signs of portal hypertension, such as esophageal and gastric varices and hypersplenism, occur. If the patient presents in adolescence, nephromegaly is less marked, renal insufficiency may be mild to moderate, and the major symptoms are those related to portal hypertension.

Diagnosis may be difficult, especially without a family history. Ultrasonography may show renal or hepatic cysts; definitive diagnosis may require biopsy. Ultrasonography in late pregnancy usually allows presumptive in utero diagnosis.

Many neonates die in the first few days or weeks of life from pulmonary insufficiency. Most who survive develop progressive renal failure often requiring renal replacement therapy. Experience with renal transplantation with or without hepatic transplantation is limited. When transplantation is done, hypersplenism must be controlled (see p. 985) to obviate difficulty with hypersplenism-induced

leukopenia, which increases the risk of systemic infection. Portal hypertension may be treated by portacaval or splenorenal shunts, which reduce morbidity but not mortality.

**Duplication anomalies:** Supernumerary collecting systems may be unilateral or bilateral and may involve the renal pelvis and ureters (accessory renal pelvis, double or triple pelvis and ureter), calyx, or ureteral orifice. Duplex kidney, a single renal mass with > 1 collecting system, differs from a fused kidney, which involves fusion of 2 renal parenchymal masses. Some duplication anomalies have ureteral ectopy with or without ureterocele. Management depends on the anatomy and function of each separately drained segment. Surgery may be needed to correct obstruction or vesicoureteral reflux.

**Fusion anomalies:** With fusion anomalies, the kidneys are joined, but the ureters enter the bladder on each side. These anomalies increase the risk of ureteropelvic junction obstruction, vesicoureteral reflux, congenital renal cystic dysplasia (see p. 2381), and injury caused by anterior abdominal trauma.

Horseshoe kidney, the most common fusion anomaly, occurs when renal parenchyma on each side of the vertebral column is joined at the corresponding (usually lower) poles; an isthmus of renal parenchyma or fibrous tissue joins at the midline. The ureters course medially and anteriorly over this isthmus and generally drain well. Obstruction, if present, is usually secondary to insertion of the ureters high in the renal pelvis. Pyeloplasty relieves the obstruction and can be done without resecting the isthmus.

Crossed fused renal ectopia is the 2nd most common fusion anomaly. The renal parenchyma (representing both kidneys) is on one side of the vertebral column. One of the ureters crosses the midline and enters the bladder on the side opposite the kidneys. When ureteropelvic junction obstruction is present, pyeloplasty is the treatment of choice.

Fused pelvic kidney (pancake kidney) is much less common. A single pelvic kidney is served by 2 collecting systems and ureters. If obstruction is present, reconstruction is needed.

**Malrotation:** Malrotation is usually of little clinical significance. Ultrasonography often shows hydronephrosis, but diagnosis is best made with IVU, which identifies an axis shift and defines the collecting system anatomy.

**Multicystic dysplastic kidney:** In this condition, a nonfunctioning renal unit consists of noncommunicating cysts with intervening solid tissue composed of fibrosis, primitive tubules, and foci of cartilage. Usually, ureteral atresia is also present. Uncommonly, the kidney develops tumors or infection, and hypertension may develop. Most experts recommend observation unless solid tissue is extensive or unusual-appearing on ultrasonography, in which case the kidney may be removed.

**Renal dysplasia:** In renal dysplasia (a histologic diagnosis), the renal vasculature, tubules, collecting ducts, or drainage apparatus develops abnormally. Diagnosis is by biopsy. If dysplasia is segmental, treatment is often unnecessary. If dysplasia is extensive, renal dysfunction may necessitate nephrologic care, including renal replacement therapy.

**Renal ectopia:** Renal ectopia (abnormal renal location) usually results when a kidney fails to ascend from its origin in the true pelvis; a rare exception occurs with a superiorly ascended (thoracic) kidney. Pelvic ectopia increases the incidence of ureteropelvic junction obstruction, vesicoureteral reflux, and multicystic renal dysplasia. Obstruction is corrected surgically. Severe reflux can be corrected surgically when indicated (if causing hypertension, recurrent infections, or renal growth retardation).

**Renal hypoplasia:** Hypoplasia usually occurs because inadequate ureteral bud branching causes an underdeveloped, small kidney with histologically normal nephrons. If hypoplasia is segmental, hypertension can occur, and ablative surgery may be needed.

## Ureteral Anomalies

Ureteral anomalies frequently occur with renal anomalies but may occur independently. Complications include

• Obstruction, infection, and calculus formation (due to urinary stasis)

• Urinary incontinence (due to abnormal termination of the ureter in the urethra, perineum, or vagina)

Diagnosis may be suggested by abnormalities on routine prenatal ultrasonography (eg, hydronephrosis) and occasionally by physical examination (eg, finding an external ectopic ureteral orifice). However, many anomalies are first suspected when children develop UTIs. Ureteral anomalies should be suspected in children with an episode of pyelonephritis or children with recurrent UTIs. Testing typically involves ultrasonography of the kidneys, ureters, and bladder before and after voiding, and then voiding cystourethrography.

Treatments are surgical.

**Duplication anomalies:** Partial or complete duplication of one or both ureters may occur with duplication of the ipsilateral renal pelvis. The ureter from the upper pole of the kidney opens at a more caudal location than the orifice of the lower pole ureter. Ectopia or stenosis of one or both orifices, vesicoureteral reflux into the lower ureter or both ureters, and ureterocele may occur. Surgery may be necessary if there is obstruction, vesicoureteral reflux, or urinary incontinence.

**Ectopic orifices:** Openings of single or duplicated ureters may be malpositioned on the lateral bladder wall, distally along the trigone, in the bladder neck, in the female urethra distal to the sphincter (leading to continuous incontinence despite a normal voiding pattern), in the genital system (prostate and seminal vesicle in the male, uterus or vagina in the female), or externally. Lateral ectopic orifices frequently lead to vesicoureteral reflux, whereas distal ectopic orifices more often cause obstruction and incontinence. Surgery is needed for obstruction and incontinence and sometimes for vesicoureteral reflux.

**Retrocaval ureter:** Anomalous development of the vena cava (pre-ureteric vena cava) allows the infrarenal vena cava to form anterior to the ureter (usually the right); a retrocaval ureter on the left occurs only with persistence of the left cardinal vein system or with complete situs inversus. Retrocaval ureter can cause ureteral obstruction. For significant ureteral obstruction, the ureter is surgically divided with uretero-ureteral anastomosis anterior to the vena cava or iliac vessel.

**Stenosis:** Narrowing may occur at any location in the ureter, most frequently at the ureteropelvic junction and less commonly at the ureterovesical junction (primary megaureter). Consequences include infection, hematuria, and obstruction. Stenoses often diminish as the child grows.

In primary megaureter, ureteral tapering and reimplantation may be needed when dilation increases or infection or obstruction occurs. In ureteropelvic junction obstruction, pyeloplasty (excision of the obstructed segment and reanastomosis) may be done by open, laparoscopic, or robotic techniques.

**Ureterocele:** Prolapse of the lower end of the ureter into the bladder with pinpoint obstruction may cause progressive ureterectasis, hydronephrosis, infection, occasional calculus formation, and impaired renal function. Treatment options include endoscopic transurethral incision and open repair.

When a ureterocele involves the upper pole of duplex ureters, treatment depends on function in that renal segment, because of the significant incidence of renal dysplasia. Removal of the affected renal segment and ureter may be preferable to obstruction repair if no segmental renal function is found or if significant renal dysplasia is suspected.

### Vesicoureteral Reflux

**Vesicoureteral reflux (VUR) is retrograde passage of urine from the bladder back into the ureter and collecting system.**

#### Etiology

VUR is most often due to congenital anomalous development of the ureterovesical junction. Incomplete development of the intramural ureteral tunnel causes failure of the normal flap valve mechanism at the

ureterovesical junction that permits reflux of bladder urine into the ureter and renal pelvis. Reflux can occur even when the tunnel is ordinarily sufficient if bladder outlet obstruction increases intravesical pressures.

**Pathophysiology**

Reflux of urine from the bladder into the ureter may damage the upper urinary tract by bacterial infection and occasionally by increased hydrostatic pressure. Bacteria in the lower urinary tract can easily be transmitted by reflux to the upper tract, leading to recurrent parenchymal infection with potential scarring and renal dysfunction. VUR is a common cause of UTI in children; about 30 to 40% of infants and toddlers with UTI have VUR.

Chronically elevated emptying pressures (> 40 cm $H_2O$) and increased bladder volume and pressure often cause progressive kidney damage, even without infection or reflux.

**Symptoms and Signs**

Symptoms and signs are typically those of UTI; these may include fever, abdominal or flank pain, dysuria or flank pain with voiding, frequency, and urgency.

**Diagnosis**

• Ultrasonography

• Voiding cystourethrography

• Sometimes radioisotope scan

Urinalysis and culture are done to detect infection; pyuria, hematuria, proteinuria, and bacteriuria may be present.

Children typically should have ultrasonography of the kidneys, ureters, and bladder before and after voiding, and then voiding cystourethrography. Renal ultrasonography evaluates kidneys for size, hydronephrosis, and scarring, and voiding cystourethrography is best to diagnose bladder outlet obstruction. A radioisotope cystogram may be used to monitor reflux. Renal cortical involvement with acute infection or scarring is precisely delineated with succimer (dimercaptosuccinic acid) nuclear scans when indicated. Urodynamic studies may show elevated filling and voiding pressures in the bladder.

Reflux findings on voiding cystourethrogram are graded on a scale from I to V (see Table 280-1 on p. 2845). Clinical severity can be classified based on reflux severity. However, the grades of reflux can be affected by bladder capacity.

• Mild: Grades I and II

• Moderate: Grade III

• Severe: Grades IV and V

**Treatment**

• Antibiotic prophylaxis

• Sometimes injection of a bulking agent or ureteral reimplantation

Mild to moderate VUR often resolves spontaneously over months to several years while daily antibacterial prophylaxis (eg, with trimethoprim/sulfamethoxazole, amoxicillin, nitrofurantoin, a cephalosporin, or sulfisoxazole) is maintained; it is very important to keep children free of infection.

Severe reflux accompanied by high-pressure storage of urine in the bladder or high intravesical pressures with voiding is treated by lowering bladder pressures with drugs (eg, oxybutynin), behavioral modification using perineal electromyography, or both.

Reflux with complications (eg, infection, impaired renal growth, renal scarring) is treated with endoscopic subtrigonal injection of a bulking agent (eg, dextranomer/hyaluronic acid) or ureteral reimplantation. Obstruction is also surgically repaired.

**Monitoring:** Reflux is monitored by voiding cystourethrography or radioisotope cystography every 1 or 2 yr depending on severity of the reflux.

Renal growth is monitored by annual ultra-sonography until age 5, then every other year until spontaneous resolution or for 3 yr after surgical correction.

## Bladder Anomalies

Congenital urinary bladder anomalies often occur without other GU abnormalities. They may cause infection, retention, incontinence, and reflux. Symptomatic anomalies may require surgery.

**Bladder diverticula:** Bladder diverticula predispose to UTIs and may coexist with vesicoureteral reflux. They are usually discovered during evaluation of recurrent UTIs in young children. Diagnosis is by voiding cystourethrography. Surgical removal of diverticula and reconstruction of the bladder wall may be needed.

**Exstrophy:** The bladder is open suprapubically, and urine drips from the opening rather than through the urethra. The bladder mucosa is continuous with the abdominal skin, and the pubic bones are separated. Despite the seriousness of the deformity, normal renal function usually is maintained. The bladder can usually be reconstructed and returned to the pelvis, although vesicoureteral reflux invariably occurs and is managed as needed. Continent urinary diversion may be used to treat a bladder reservoir that fails to expand sufficiently or has sphincter insufficiency. Reconstruction of the genitals is required.

**Megacystis syndrome:** In this syndrome, a large, thin-walled, smooth bladder without evident outlet obstruction develops, usually in girls. Megacystis syndrome is poorly understood. The syndrome may be a manifestation of a primary myoneural defect, especially when intestinal obstruction (megacystis-microcolon, intestinal hypoperistalsis syndrome) is also present. Symptoms are related to UTIs, and vesicoureteral reflux is common. Ultrasonography with the bladder empty may disclose normal-appearing upper tracts, but voiding cystourethrography may show reflux with massive upper tract dilation. Ureteral reim-plantation may be effective, although some patients benefit from antibacterial prophylaxis, timed voiding with behavioral modification, intermittent catheterization, or a combination.

## Penile and Urethral Anomalies

Congenital anomalies of the urethra in boys usually involve anatomic abnormalities of the penis and vice versa. In girls, urethral anomalies may exist without other external genital abnormalities. Surgical repair is needed when function is impaired or cosmetic correction is desired.

**Chordee:** This anomaly is ventral or rotational curvature of the penis, which is most apparent with erection and is caused by fibrous tissue along the usual course of the corpus spongiosum. It is often associated with hypospadias.

**Epispadias:** The urethra opens on the dorsum of the glans or penile shaft, or at the penopubic junction. In girls, the urethra opens between the clitoris and labia or in the abdomen. Epispadias can be partial (in 15%) or complete; the most severe form occurs with bladder exstrophy (see above). Symptoms and signs are incontinence, reflux, and UTIs. Treatment is surgical. In partial epispadias, prognosis for continence with treatment is good. In the complete form, surgical reconstruction of the penis alone may lead to persistent incontinence; bladder outlet reconstruction is required to achieve complete urinary control.

**Hypospadias:** This anomaly is caused by failure of tubularization and fusion of the urethral groove. It

almost always occurs in boys, in whom the urethra opens onto the underside of the penile shaft, at the penoscrotal junction, between the scrotal folds, or in the perineum. The foreskin fails to become circumferential and appears as a dorsal hood. Hypospadias is frequently associated with chordee.

Prognosis for functional and cosmetic correction is good. Outpatient surgery at about 6 mo of age involves construction of a neourethra using penile shaft skin or foreskin and repair of the chordee.

Hypospadias is extremely rare in girls; the urethra opens into the vaginal introitus.

**Phimosis and paraphimosis:** Phimosis, the most common penile abnormality, is constriction of the foreskin with inability to retract over the glans; it may be congenital or acquired. Paraphimosis is inability of the retracted constricting foreskin to be reduced distally over the glans. (See full discussion on p. 2457.)

Phimosis may respond to topical corticosteroids and gentle stretching; some patients require circumcision.

Paraphimosis should be reduced immediately because the constricting foreskin functions as a tourniquet, causing edema and pain. Firm circumferential compression of the edematous foreskin with the fingers may reduce edema sufficiently to allow the foreskin to be restored to its normal position by pushing the glans back through the tight foreskin using both thumbs. If this technique is ineffective, a dorsal slit done using a local anesthetic relieves the condition temporarily. Circumcision is then done when edema has resolved.

**Other penile anomalies:** Less common anomalies include penile agenesis, duplication, and lymphedema. Many anomalies also involve urethral abnormality, or other anomalies, such as exstrophy. Treatment of most anomalies is surgical and may include complete removal of the genitals with sex reassignment.

Microphallus results from androgen deficiency or insensitivity; in boys with deficiency, treatment is testosterone supplementation.

**Urethral meatal stenosis:** Most commonly acquired after newborn circumcision in boys, urethral meatal stenosis is occasionally congenital and associated with hypospadias. Meatotomy is needed for a significantly deflected stream or for a pinpoint stream.

**Urethral stricture:** Urethral stricture causes obstruction along some part of the length of the urethra. It almost always occurs in boys, is usually acquired, and typically results from a crush injury after straddle trauma. Congenital urethral stricture may manifest similarly to urethral valves and may be diagnosed by prenatal ultrasonography, or postnatally by symptoms and signs of outlet obstruction or patent urachus and is confirmed by retrograde urethrography. Initial management is often with endoscopic urethrotomy, although open urethroplasty may be necessary.

**Urethral valves:** In boys, folds in the posterior urethra may act as valves impairing urine flow. Urethral valves can cause urinary hesitancy and a weak urinary stream, UTI, overflow incontinence, myogenic bladder malfunction, vesicoureteral reflux, upper urinary tract damage, and renal insufficiency. They occasionally occur with a patent urachus. Diagnosis is often made by routine prenatal ultrasonography; cases suspected postnatally are confirmed by voiding cystourethrography. Surgery (usually via endoscopy) is done at time of diagnosis to prevent progressive renal deterioration.

A much less common anomaly, diverticulum of the anterior urethra, may act as a valve (anterior urethral valve) and is also treated endoscopically.

### Vaginal Anomalies

Most congenital anomalies of the vagina are rare. Vaginal anomalies include vaginal agenesis, obstruction, duplication, and fusion. Duplication and fusion anomalies have numerous manifestations (eg, as 2 uteri, 2 cervices, and 2 vaginas, or 2 uteri with 1 cervix and 1 vagina). Girls may also have urogenital

sinus anomalies, in which urinary and genital tracts open into a common channel, and cloacal anomalies, in which urinary, genital, and anorectal tracts open into a common channel.

Imperforate hymen manifests as a bulge at the location of the vaginal opening due to collection of uterine and vaginal secretions caused by maternal estrogens. Treatment is surgical drainage.

Diagnosis of most is by physical examination, ultrasonography, and retrograde contrast studies. Duplication and fusion anomalies may not require treatment, but others require surgical correction.

## Testicular and Scrotal Anomalies

The most common anomalies are

• Congenital hydrocele

• Undescended testes (cryptorchidism)

• Testicular torsion (see p. 2457)

Rare anomalies include scrotal agenesis, hypoplasia, ectopia, or hemangioma; penoscrotal transposition; and bifid scrotum.

**Congenital hydrocele:** A congenital hydrocele is a collection of fluid in the scrotum between layers of the tunica vaginalis. It may be isolated or may communicate with the abdominal cavity through a patent processus vaginalis (a potential hernia space). Hydrocele manifests as a painless, enlarged scrotum. The condition may resolve spontaneously but usually requires repair if it persists after 6 to 9 mo or if it enlarges.

### Cryptorchidism

(Undescended Testes)

**Cryptorchidism is failure of one or both testes to descend into the scrotum; it is typically accompanied by inguinal hernia. Diagnosis is by examination, sometimes followed by laparoscopy or a human chorionic gonadotropin stimulation test. Treatment is surgical orchiopexy.**

Cryptorchidism affects about 3% of term infants and up to 30% of preterm infants; two thirds of undescended testes spontaneously descend within the first 4 mo of life. Thus, about 0.8% of male infants require treatment.

#### Pathophysiology

Normally, the testes develop at 7 to 8 wk gestation and remain cephalad to the internal inguinal ring until about 28 wk, when they begin their descent into the scrotum guided by condensed mesenchyme (the gubernaculum). Onset of descent is mediated by hormonal (eg, androgens, mullerian-inhibiting factor), physical (eg, gubernacular regression, intra-abdominal pressure), and environmental (eg, maternal exposure to estrogenic or antiandrogenic substances) factors.

A true undescended testis remains in the inguinal canal along the path of descent or is less commonly present in the abdominal cavity or retroperitoneum. An ectopic testis is one that descends normally through the external ring but diverts to an abnormal location and lies outside the normal course of descent (eg, suprapubically, in the superficial inguinal pouch, within the perineum, or along the inner aspect of the thigh).

**Complications:** Undescended testes may cause subfertility and are associated with testicular carcinoma, mainly in the undescended testis and particularly with intra-abdominal malposition. However, in patients with one undescended testis, 10% of cancers develop on the normal side. In untreated cases

of intra-abdominal testes, testicular torsion may occur, manifesting as an acute abdomen. Almost all neonates who present with an undescended testis at birth also have an inguinal hernia (patent processus).

**Etiology**

Undescended testes are almost always idiopathic. About 10% of cases are bilateral; suspicion should be high for female virilization caused by congenital adrenal hyperplasia in phenotypic boys with bilateral, nonpalpable, undescended testes at birth (especially if associated with hypospadias).

**Symptoms and Signs**

In about 80% of cases, the scrotum is empty at birth; in the remainder of cases, a testis is palpable in the scrotum at birth but appears to ascend with linear growth because of an ectopic gubernacular attachment that restrains it from following the normal "descent" of the scrotum. Inguinal hernia rarely causes a palpable mass lesion, but the patent process is often detectable, especially in infants (but less commonly in those with ectopic undescended testes).

**Diagnosis**

• Clinical evaluation

• Sometimes laparoscopy or a human chorionic gonadotropin (hCG) stimulation test

Undescended and ectopic testes must be distinguished from hypermobile (retractile) testes, which are present in the scrotum but easily retract into the inguinal canal. Diagnosis is by physical examination; a warm environment, warm examiner's hands, and a relaxed patient are important to avoid stimulating testicular retraction.

In patients with a unilateral nonpalpable testis, a descended testis that is larger than expected suggests an atrophic undescended testis; confirmation requires abdominal laparoscopy.

For bilateral nonpalpable testes, an hCG stimulation test is done. Patients receive injections of hCG 2000 IU IM once/day for 3 to 4 days; blood levels of testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) are obtained before and testosterone levels within 24 h of the final injection. Patients with bilateral cryptorchidism should respond by producing testosterone, whereas those without testes (including genotypic females) produce none. In addition, basal levels of FSH and possibly LH are elevated.

**Treatment**

• Surgical repair

For a palpable undescended testis, treatment is surgical orchiopexy, in which the testis is brought into the scrotum and sutured into place; the associated inguinal hernia also is repaired. For nonpalpable undescended testis, abdominal laparoscopy is done; if the testis is located, it is surgically fixed in place, or if it is atrophic, the tissue is removed. Surgery should be done at about 6 mo of age because early intervention improves fertility potential and may reduce cancer risk. Also, the shorter the child, the shorter the distance necessary to place the testis into the scrotum. Atrophic undescended testes are likely the result of prenatal testicular torsion.

hCG 250 to 1000 IU IM 2 or 3 times/wk for up to 6 wk may stimulate local testosterone production and precipitate testicular descent, either complete or enough to make the testis palpable, increase its blood supply, or both, making surgery easier.

No intervention is needed for a retractile testis as long as the spermatic cord length is sufficient to allow the testis to rest in a dependent scrotal position without traction when the cremasteric reflex is not stimulated. Hypermobility usually resolves without treatment by puberty when increased testicular size

makes retraction more difficult.

## Prune-Belly Syndrome

(Triad Syndrome)

**Prune-belly syndrome consists of abdominal muscle deficiency, urinary tract abnormalities, and intra-abdominal undescended testes.**

The name "prune-belly syndrome" derives from the characteristic wrinkled appearance of the abdominal wall in neonates. The cause of this congenital syndrome, which occurs primarily but not exclusively in males, is unclear. Urinary abnormalities may include hydro-nephrosis, megaureters, vesicoureteral reflux, and urethral abnormalities. Severe cases may involve renal failure, bronchopulmonary dysplasia, and stillbirth.

Diagnosis is often made during routine prenatal ultrasonography. Further evaluation includes voiding cystourethrography, ultra-sonography, and isotope renography.

Urinary tract abnormalities may require open surgical reconstruction; orchidopexy can be done at the same time. If no urinary intervention is necessary, laparoscopic orchidopexy is done in childhood.

# Chapter 297. Congenital Renal Transport Abnormalities

## Introduction

Defects in renal tubular transport can lead to a number of metabolic disorders, some of which are serious.

For a discussion of renal transport abnormalities that are not congenital, see Ch. 237.

## Bartter Syndrome and Gitelman's Syndrome

**Bartter syndrome and Gitelman's syndrome are characterized by fluid, electrolyte, and hormonal abnormalities, including renal K, Na, Cl, and H wasting; hypokalemia; hyperaldosteronism; hyperreninemia; and normal BP. Findings include electrolyte, growth, and sometimes neuromuscular abnormalities. Diagnosis is assisted by urine electrolyte measurements and hormone assays but is typically a diagnosis of exclusion. Treatment consists of NSAIDs, K-sparing diuretics, low-dose ACE inhibitors, and electrolyte replacement.**

### Pathophysiology

Bartter syndrome and the more common Gitelman's syndrome result from deranged NaCl transport and reabsorption. In Bartter syndrome, the defect is in the ascending thick limb of the loop of Henle. In Gitelman's syndrome, the defect is in the distal tubule. Subsequent K, Na, Cl, and H wasting leads to increased renin and aldosterone release, metabolic alkalosis, hyperuricemia, and, particularly in Bartter syndrome, increased prostaglandin secretion. Hypomagnesemia is common, particularly in Gitelman's syndrome. Urinary Ca excretion is decreased in Gitelman's syndrome and is normal or increased in Bartter syndrome. In both disorders, Na wasting results in a chronically low plasma volume reflected by a normal BP despite high renin and angiotensin levels.

The features at clinical presentation vary (see Table 297-1).

[**Table 297-1.** Some Differences Between Bartter Syndrome and Gitelman's Syndrome]

### Etiology

Both syndromes are usually autosomal recessive, although sporadic cases and other types of familial patterns can occur; there are several genotypes of both syndromes.

### Symptoms and Signs

Bartter syndrome tends to manifest prenatally or during infancy or early childhood. Gitelman's syndrome tends to manifest during late childhood or adulthood. Bartter syndrome can manifest prenatally with intrauterine growth restriction and polyhydramnios. After birth, affected children with Bartter syndrome and sometimes those with Gitelman's syndrome have poor growth rates and appear undernourished. Most patients have low or low-normal BP and may have signs of volume depletion. Inability to retain K, Ca, or Mg can lead to muscle weakness, spasms, tetany, or palpitations, particularly in Gitelman's syndrome. Polydipsia, polyuria, and vomiting may also be present. Intellectual disability and nephrocalcinosis sometimes result, particularly in Bartter syndrome.

Bartter syndrome may result in premature birth and severe electrolyte disorders and symptoms, but neither Bartter syndrome nor Gitelman's syndrome typically leads to chronic renal insufficiency.

### Diagnosis

• Serum and urine electrolyte levels

• Exclusion of similar disorders

Bartter syndrome and Gitelman's syndrome should be suspected in children with characteristic symptoms or incidentally noted laboratory abnormalities, such as metabolic alkalosis and hypokalemia. Measurement of urine electrolytes shows high levels of Na, K, and Cl that are inappropriate for the euvolemic or hypovolemic state of the patient. Diagnosis is by exclusion of other disorders:

- Primary and secondary aldosteronism can often be distinguished by the presence of hypertension and normal or low plasma levels of renin (see Table 94-3 on p. 800).

- Bulimia nervosa and surreptitious vomiting or laxative abuse can often be distinguished by low levels of urinary Cl (usually < 20 mmol/L).

- Surreptitious diuretic abuse can often be distinguished by low levels of urinary Cl and by a urine assay for diuretics.

Definitive diagnosis is through genetic testing, which is not commercially available and thus is rarely done.

Gitelman's syndrome can usually be differentiated from Bartter syndrome by the presence of hypomagnesemia and hypocalciuria.

**Treatment**

- NSAIDs

- Spironolactone or amiloride

- Low-dose ACE inhibitors

- K, Mg, and Ca supplements

The combination of NSAIDs (eg, indomethacin 1 to 2 mg/kg po once/day) and a K-sparing diuretic (eg, spironolactone 150 mg po bid or amiloride 10 to 20 mg po bid) helps correct most features. Plasma electrolyte levels can be further improved by using ACE inhibitors (at low doses to minimize further hypovolemia and hypotension). However, no therapy can completely eliminate K wasting, and K supplementation (KCl 20 to 40 mEq po once/day or bid) is often necessary. Mg and Ca supplements may also be needed.

Exogenous growth hormone is sometimes considered to treat short stature in affected children, but this treatment is not widely used.

## Cystinuria

**Cystinuria is an inherited defect of the renal tubules in which resorption of the amino acid cystine is impaired, urinary excretion is increased, and cystine stones form in the urinary tract. Symptoms are colic caused by stones and perhaps urinary infection or the sequela of renal failure. Diagnosis is by measurement of cystine excretion in the urine. Treatment is with increased fluid intake and alkalinization of the urine.**

Cystinuria is inherited as an autosomal recessive trait. Heterozygotes may excrete increased quantities of cystine in the urine but seldom enough to form stones. Cystinuria should not be confused with cystinosis (see p. 2423).

**Pathophysiology**

The primary defect is in one of several genes responsible for cystine transport in the kidneys and intestine. Diminished renal tubular resorption of cystine increases cystine concentration in the urine. Cystine is poorly soluble in acidic urine, so that when its urinary concentration exceeds its solubility,

crystals precipitate and stones form.

Resorption of dibasic amino acids (lysine, ornithine, arginine) is also impaired but causes no problems because these amino acids have an alternative transport system separate from that shared with cystine. Furthermore, they are more soluble than cystine in urine, and their increased excretion does not result in crystal or stone formation. Their absorption (and that of cystine) is also decreased in the small bowel.

**Symptoms and Signs**

Symptoms, most commonly renal colic, may occur in infants but usually appear between ages 10 and 30. UTI and renal failure due to obstruction may develop.

**Diagnosis**

• Measurement of urinary cystine excretion

Radiopaque cystine stones form in the renal pelvis or bladder. Staghorn stones are common. Cystine may appear in the urine as yellow-brown hexagonal crystals. Excessive cystine in the urine may be detected with the nitroprus-side cyanide test. Diagnosis is confirmed by observing a cystine excretion of > 400 mg/day (normal is < 30 mg/day).

**Treatment**

• High fluid intake

• Alkalinization of the urine

Eventually, end-stage renal disease usually develops. Decreasing the urinary concentration of cystine decreases renal toxicity. This decrease is accomplished by increasing urine volume. Fluid intake must be sufficient to provide a urine flow rate of 3 to 4 L/day. Hydration is particularly important at night when urinary pH drops. Alkalinization of the urine to pH > 7.0 with K citrate or $KHCO_3$ 1 mEq/kg po tid to qid and perhaps acetazolamide 5 mg/kg (up to 250 mg) po at bedtime increases the solubility of cystine significantly. Mild restrictions of dietary Na (100 mEq/day) and protein (0.8 to 1.0 g/kg/day) may help reduce cystine excretion.

When high fluid intake and alkalinization do not reduce stone formation, other drugs may be tried. Penicillamine (7.5 mg/kg po qid in young children and 125 mg to 0.5 g po qid in older children) is effective, but toxicity limits its usefulness. About half of all patients develop some toxic manifestation, such as fever, rash, arthralgias, or, less commonly, nephrotic syndrome, pancytopenia, or SLE-like reaction. Pyridoxine supplements (50 mg po once/day) should be given with penicillamine. Tiopronin (100 mg to 300 mg po qid) is being used instead of penicillamine to treat some children. Captopril (0.3 mg/kg po tid) is not as effective as penicillamine but is much less toxic. Close monitoring of response to therapy is very important.

## Hartnup Disease

**Hartnup disease is a rare disease due to abnormal absorption and excretion of tryptophan and other amino acids. Symptoms are rash, CNS abnormalities, short stature, headache, and collapsing or fainting. Diagnosis is by high urinary content of tryptophan and other amino acids. Prevention is with niacinamide or niacin, and attacks are treated with nicotinamide.**

Hartnup disease is caused by a mutation in the Na-dependent neutral amino acid transporter gene that is expressed in kidney and intestinal epithelia. It is inherited as an autosomal recessive trait. Small-bowel malabsorption of tryptophan, phenylalanine, methionine, and other monoaminomonocarboxylic amino acids occurs. Accumulation of unabsorbed amino acids in the GI tract increases their metabolism by bacterial flora. Some tryptophan degradation products, including indoles, kynurenine, and serotonin, are absorbed by the intestine and appear in the urine. Renal amino acid resorption is also defective, causing a generalized aminoaciduria involving all neutral amino acids except proline and hydroxyproline.

Conversion of tryptophan to niacinamide is also defective.

**Symptoms and Signs**

Although the disorder is present from birth, symptoms may manifest in infancy, childhood, or early adulthood. Symptoms may be precipitated by sunlight, fever, drugs, or other stresses.

Poor nutritional intake nearly always precedes appearance of symptoms. Symptoms and signs are due to niacinamide deficiency and resemble those of pellagra (see p. 31), particularly the rash on parts of the body exposed to the sun; mucous membrane and neurologic symptoms also occur. Neurologic manifestations include cerebellar ataxia and mental abnormalities. Intellectual disability, short stature, headache, and collapsing or fainting are common.

**Diagnosis**

• Urine testing for amino acids

Diagnosis is made by showing the characteristic amino acid excretion pattern in the urine. Indoles and other tryptophan degradation products in the urine provide supplementary evidence of the disease.

**Treatment**

• Niacin or niacinamide supplements

• Nicotinamide for attacks

Prognosis is good, and frequency of attacks usually diminishes with aging. The number and severity of attacks can be reduced by maintaining good nutrition and supplementing the diet with niacin or niacinamide 50 to 100 mg po tid. Attacks may be treated with nicotinamide 20 mg po once/day.

## Hypophosphatemic Rickets

(Vitamin D-Resistant Rickets)

**Hypophosphatemic rickets is a disorder characterized by hypophosphatemia, defective intestinal absorption of Ca, and rickets or osteomalacia unresponsive to vitamin D. It is usually hereditary. Symptoms are bone pain, fractures, and growth abnormalities. Diagnosis is by serum phosphate, alkaline phosphatase, and 1,25-dihydroxyvitamin $D_3$ levels. Treatment is oral phosphate plus calcitriol.**

Familial hypophosphatemic rickets is usually inherited as an X-linked dominant trait; other familial patterns occur but are rarer.

Sporadic acquired cases sometimes are associated with benign small-cell mesenchymal tumors that produce a humoral factor that decreases proximal renal tubular resorption of phosphate (oncogenic rickets).

**Pathophysiology**

The observed abnormality is decreased proximal renal tubular resorption of phosphate, resulting in hypophosphatemia. This defect is due to a circulating factor or factors and is associated with a primary abnormality in osteoblast function. Decreased intestinal Ca and phosphate absorption also occurs. Deficient bone mineralization is due to low phosphate levels and osteoblast dysfunction rather than to the low Ca and elevated parathyroid hormone (PTH) levels in Ca-deficient rickets (see p. 41). Because 1,25-dihydroxyvitamin $D_3$ levels are normal to slightly low, a defect in conversion is presumed; hypophosphatemia would normally cause elevated 1,25-dihydroxyvitamin $D_3$ levels.

**Symptoms and Signs**

The disease manifests as a spectrum of abnormalities, from hypophosphatemia alone to growth retardation and short stature to severe rickets or osteomalacia. Children usually present after they begin walking, with bowing of the legs and other bone deformities, pseudofractures, bone pain, and short stature. Bony outgrowth at muscle attachments may limit motion. Rickets of the spine or pelvis, dental enamel defects, and tetany that occur in dietary vitamin D deficiency are rarely present in hypophosphatemic rickets.

**Diagnosis**

• Serum levels of Ca, phosphate, alkaline phosphatase, 1,25-dihydroxyvitamin $D_3$, and PTH

• Urinary phosphate levels

Serum phosphate levels are depressed, but urinary phosphate excretion is large. Serum Ca and PTH are normal, and alkaline phosphatase often is elevated. In Ca-deficient rickets, hypocalcemia is present, hypophosphatemia is mild or absent, and urinary phosphate is not elevated.

**Treatment**

• Oral phosphate and calcitriol

Treatment consists of neutral phosphate solution or tablets. Starting dose in children is 10 mg/kg (based on elemental phosphorus) po qid. Because this phosphate may cause hyperparathyroidism, vitamin D is given as calcitriol, initially 5 to 10 ng/kg po bid. Phosphate dose may need to be increased to achieve bone growth or relieve bone pain. Diarrhea may limit oral phosphate dosage. Increase in plasma phosphate and decrease in alkaline phosphatase concentrations, healing of rickets, and improvement of growth rate occur. Hypercalcemia, hypercalciuria, and nephrocalcinosis with reduced renal function may complicate treatment. Patients undergoing treatment need frequent follow-up evaluations.

Adults with oncogenic rickets may dramatically improve once the mesenchymal tumor that causes the disorder is removed. Otherwise, oncogenic rickets is treated with calcitriol 5 to 10 ng/kg po bid and elemental phosphorus 250 mg to 1 g po tid or qid.

# Chapter 298. Congenital Neurologic Anomalies

## Introduction

Some of the most serious neurologic anomalies (eg, anencephaly, encephalocele, spina bifida) develop in the first 2 mo of gestation and represent defects in neural tube formation (dysraphism). Others, such as lissencephaly, result from problems with neuronal migration, which occurs between 9 wk and 24 wk of gestation. Hydranencephaly and porencephaly are secondary to destructive processes that occur after the brain has formed. Some anomalies (eg, meningocele) are relatively benign.

Amniocentesis (see p. 2602) and ultra-sonography (see p. 2600) permit accurate in utero detection of many malformations. Parents need psychologic support when a malformation is detected and also genetic counseling, because the risk of having a subsequent child with such a malformation is high.

Women who *have* had a fetus or infant with a neural tube defect should take folate (folic acid) supplementation 4 mg po once/day beginning 3 mo before conception and continuing through the 1st trimester. Folate supplementation reduces the risk of neural tube defects in future pregnancies by 75%.

All women of childbearing age who *have not* had a fetus or infant with a neural tube defect should consume at least 400 µg/day of folate through diet or by taking a supplement (some experts recommend 800 µg/day to further reduce risk) and continue doing so through the 1st trimester. Although folate supplementation reduces the risk of having a child with a neural tube defect, risk reduction is less than in women who previously had a fetus or infant with a neural tube defect (ie, risk reduction is < 75%).

## Brain Anomalies

Congenital brain anomalies usually cause severe neurologic deficits; some may be fatal.

### Hydrocephalus

**Hydrocephalus is ventricular enlargement with excessive CSF. Manifestations include an enlarged head and brain atrophy. Increased cranial pressure causes irritability and a bulging fontanelle in infants. Diagnosis is by ultrasonography in neonates and young infants with an open fontanelle and by CT or MRI in older infants and children. Treatment usually is with a ventricular shunt procedure.**

Hydrocephalus is the most common cause of abnormally large heads in neonates. Hydrocephalus that develops only after the fontanelles have closed does not increase head circumference but can markedly increase intracranial pressure.

#### Etiology

Hydrocephalus can result from

• Obstruction of CSF flow (obstructive hydro-cephalus)

• Impaired resorption of CSF (communicating hydrocephalus)

**Obstruction** most often occurs in the aqueduct of Sylvius but sometimes at the outlets of the 4th ventricle (Luschka and Magendie foramina). Obstructive hydrocephalus can be caused by Dandy-Walker malformation or Chiari II type (formerly Arnold-Chiari) malformation. Dandy-Walker malformation is progressive cystic enlargement of the 4th ventricle. In Chiari II type malformation, which frequently occurs with spina bifida (see p. 2995) and syringomyelia (see p. 1812), severe elongation of the cerebellar tonsils causes them to protrude through the foramen magnum, with beaking of the colliculi and thickening of the upper cervical spinal cord.

**Impaired resorption** in the subarachnoid spaces usually results from meningeal inflammation, secondary either to infection or to blood in the subarachnoid space (eg, in the premature infant who has intraventricular hemorrhage).

### Symptoms and Signs

Neurologic findings depend on whether intracranial pressure is increased, symptoms of which in infants include irritability, high-pitched cry, vomiting, lethargy, strabismus, and bulging fontanelle. Older, verbal children may complain of headache, decreased vision, or both. Papilledema is a late sign of increased intracranial pressure; initial absence is not reassuring.

Consequences of chronic hydrocephalus may include precocious puberty in girls, learning disorders (eg, difficulties with attention, information processing, and memory), and impaired executive function (eg, problems with conceptualizing, abstracting, generalizing, reasoning, and organizing and planning information for problem-solving).

### Diagnosis

• Prenatal ultrasonography

• Neonates: Cranial ultrasonography

• Older infants and children: CT or MRI

Diagnosis is often made by routine prenatal ultrasonography. After birth, diagnosis is suspected if routine examination reveals an increased head circumference; infants may have a bulging fontanelle or widely separated cranial sutures. Similar findings can result from intracranial, space-occupying lesions (eg, subdural hematomas, porencephalic cysts, tumors). Macrocephaly may result from an underlying brain problem (eg, Alexander disease or Canavan disease) or it may be benign, such as when excessive CSF surrounds a normal brain. Children suspected of having hydro-cephalus require cranial imaging by CT, MRI, or ultrasonography (if the anterior fontanelle is open). Cranial CT or ultrasonography is used to monitor progression of hydrocephalus once an anatomic diagnosis has been made. If seizures occur, an EEG may be helpful.

### Treatment

• Usually a ventricular shunt procedure

Treatment depends on etiology, severity, and whether hydrocephalus is progressive (ie, size of the ventricles increases over time relative to the size of the brain). To temporarily reduce CSF pressure in infants, ventricular taps or serial lumbar punctures (if the hydro-cephalus is communicating) may be used. Progressive hydrocephalus usually requires a ventricular shunt. Shunts typically connect the right lateral ventricle to the peritoneal cavity or, rarely, to the right atrium via a plastic tube with a one-way, pressure-relief valve. When a shunt is first placed in an infant or older child whose fontanelle is closed, rapid withdrawal of fluid can cause subdural bleeding as the brain shrinks away from the skull. When the fontanelles are open, the skull can decrease in circumference to match the decrease in brain size; thus, some clinicians recommend an early decision regarding shunt placement so that it can be done before fontanelle closure.

In a third ventriculostomy, an opening is created endoscopically between the 3rd ventricle and the subarachnoid space, allowing CSF to drain. This procedure is often combined with ablation of the choroid plexus and is becoming more common, particularly in less developed countries where access to emergency neurosurgical care is often limited. In certain cases (eg, hydrocephalus caused by primary aqueductal stenosis), third ventriculostomy may be adequate primary treatment.

A ventricular shunt that goes to the subgaleal space may be used in infants as a temporary measure for patients who may not require a more permanent shunt.

Although some children do not need the shunt as they age, shunts are rarely removed because of the risk of bleeding and trauma. Fetal surgery to treat congenital hydrocephalus has not been successful.

**Shunt complications:** The type of ventricular shunt used depends on the neurosurgeon's experience, although ventriculoperitoneal shunts cause fewer complications than ventriculoatrial shunts. Shunt complications include

• Infection

• Malfunction

Any shunt has a risk of infection. Manifestations include chronic fever, lethargy, irritability, headache, or a combination and other symptoms and signs of increased intracranial pressure; sometimes redness becomes apparent over the shunt tubing. Antibiotics effective against the organism infecting the shunt, which may include skin flora, are given, and typically the shunt must be removed and replaced.

Shunts can malfunction due to mechanical obstruction (typically blockage at the ventricular end) or to fracture of the tubing. In either case, intracranial pressure can increase, which, if sudden, can be a medical emergency. Children present with headache, vomiting, lethargy, irritability, esotropia, or paralysis of upward gaze. Seizures may occur. If the obstruction is gradual, more subtle symptoms and signs can occur, such as irritability, poor school performance, and lethargy, which may be mistaken for depression. To assess shunt function, a shunt series (x-rays of the shunt tubing) and neuroimaging studies are done. The ability to compress the bulb that is present on many shunt systems is not a reliable sign of shunt function.

After the shunt is placed, head circumference and development are assessed, and imaging is done periodically.

**Other Brain Anomalies**

**Anencephaly:** This anomaly is absence of the cerebral hemispheres. The absent brain is sometimes replaced by malformed cystic neural tissue, which may be exposed or covered with skin. Parts of the brain stem and spinal cord may be missing or malformed. Infants are stillborn or die within days or weeks. Treatment is supportive.

**Encephalocele:** This anomaly is a protrusion of nervous tissue and meninges through a skull defect. The defect is caused by incomplete closure of the cranial vault (cranium bifidum). Encephaloceles usually occur in the midline and protrude anywhere along a line from the occiput to the nasal passages but can be present asymmetrically in the frontal or parietal regions. Small encephaloceles may resemble cephalhematomas, but x-rays show a bony skull defect at their base. Hydrocephalus (see p. 2992) often occurs with encephalocele. About 50% of affected infants have other congenital anomalies. Symptoms and signs include the visible defect, seizures, and impaired cognition, including intellectual and developmental disability.

Prognosis, which depends on the location and size of the lesion, is often good. Most encephaloceles can be repaired. Even large ones often contain mostly heterotopic nervous tissue, which can be removed without worsening functional ability. When other serious malformations coexist, the decision to repair may be more difficult.

**Malformed cerebral hemispheres:** Cerebral hemispheres may be large, small, or asymmetric; the gyri may be absent, unusually large, or multiple and small; and microscopic sections of normal-appearing brain may show disorganization of the normal laminar neuronal arrangement. Microcephaly, moderate to severe motor and intellectual disability, and epilepsy often occur with these defects. Treatment is supportive, including anticonvulsants, if needed.

**Holoprosencephaly** occurs when the embryonic prosencephalon does not undergo segmentation and cleavage. The anterior midline brain, cranium, and face are abnormal. This malformation may be caused by defects of the *sonic hedgehog* gene. Severely affected fetuses may die before birth. Treatment is

supportive.

**Lissencephaly** consists of an abnormally thick cortex, reduced or abnormal lamination, and diffuse neuronal heterotopia. It is caused by abnormal neuronal migration, the process by which immature neurons attach to radial glia and move from their points of origin near the ventricle to the cerebral surface. Several single-gene defects may cause this anomaly (eg, *LIS1*). Affected infants may have intellectual disability, muscle spasms, and seizures. Treatment is supportive, but many children die before age 2 yr.

**Polymicrogyria,** in which the gyri are small and overabundant, is believed to result from injuries occurring between 17 wk and 26 wk gestation. It can cause intellectual disability and seizures. Treatment is supportive.

**Porencephaly:** This anomaly is a cyst or cavity in a cerebral hemisphere that communicates with a ventricle. It may develop prenatally or postnatally. Porencephaly may be caused by a developmental anomaly, inflammatory disease, or a vascular accident such as intraventricular hemorrhage with parenchymal extension. Neurologic examination is usually abnormal. Diagnosis is confirmed by cranial CT, MRI, or ultrasonography. Progressive hydrocephalus occurs rarely with porencephaly. Prognosis is variable; a few children develop only minor neurologic signs and have normal intelligence. Treatment is supportive.

**Hydranencephaly** is an extreme form of porencephaly in which the cerebral hemispheres are almost totally absent. Usually, the cerebellum and brain stem are formed normally, and the basal ganglia are intact. The meninges, bones, and skin over the cranial vault are normal. Often hydranencephaly is diagnosed by prenatal ultrasonography. Neurologic examination is usually abnormal, and the infant does not develop normally. Externally, the head may appear normal, but when transilluminated, light shines completely through. CT or ultrasonography confirms the diagnosis. Children with this condition often have seizures and intellectual disability. Treatment is supportive, with shunting if head growth is excessive.

**Schizencephaly,** which many classify as a form of porencephaly, results from formation of abnormal slits, or clefts, in the cerebral hemispheres. Unlike porencephalies, however, which are thought to result from brain injury, schizencephaly is thought to represent a defect in neuronal migration and is thus a true malformation. Affected infants often have seizures and developmental delay and, depending on the location of the defect, may have focal neurologic findings such as weakness. Treatment is supportive.

**Septo-optic dysplasia:** This anomaly (also called de Morsier's syndrome) is a malformation of the front of the brain that occurs toward the end of the first month of gestation and includes optic nerve hypoplasia, absence of the septum pellucidum (the membranes that separate the front of the 2 lateral ventricles), and pituitary deficiencies. Although the cause may be multiple, abnormalities of one particular gene (*HESX1*) have been found in some children with septo-optic dysplasia.

Symptoms may include decreased visual acuity in one or both eyes, nystagmus, strabismus, and endocrine dysfunction (including growth hormone deficiency, hypothyroidism, adrenal insufficiency, diabetes insipidus, and hypogonadism). Seizures may occur. Although some children have normal intelligence, others have learning disabilities, intellectual disability, cerebral palsy, or other developmental delay. Diagnosis is by MRI. All children diagnosed with this anomaly should be screened for endocrine and developmental dysfunction. Treatment is supportive.

## Spina Bifida

**Spina bifida is defective closure of the vertebral column. Although the cause is not known, low folate levels during pregnancy increase risk. Some children are asymptomatic, and others have severe neurologic dysfunction below the lesion. Open spina bifida can be diagnosed prenatally by ultra-sonography or suggested by elevated α-fetoprotein levels in maternal serum and amniotic fluid. After birth, a lesion is typically visible on the back. Treatment is usually surgical.**

Spina bifida is one of the most serious neural tube defects compatible with prolonged life. This defect is one of the more common congenital anomalies overall, with an incidence in the US of about 1/1500. It is most common in the lower thoracic, lumbar, or sacral region and usually extends for 3 to 6 vertebral

segments. Severity ranges from occult, in which there are no apparent anomalies, to protruding sacs (spina bifida cystica), to a completely open spine (rachischisis) with severe neurologic disability and death.

In **occult spinal dysraphism** (OSD), anomalies of the skin overlying the lower back (typically in the lumbosacral area) occur; these include sinus tracts that have no visible bottom, are above the lower sacral area, or are not in the midline; hyperpigmented areas; and tufts of hair (see Fig. 298-1). These children often have anomalies in the underlying portion of the spinal cord, such as lipomas and tethering (in which the cord has an abnormal attachment).

In **spina bifida cystica**, the protruding sac can contain meninges (meningocele), spinal cord (myelocele), or both (myelomeningocele). In a myelomeningocele, the sac usually consists of meninges with a central neural plaque. If not well covered with skin, the sac can easily rupture, increasing the risk of meningitis.

**Hydrocephalus** is common because many children have a Chiari II type malformation (see p. 2992).

Other congenital anomalies, such as syringomyelia and soft-tissue masses around the spinal cord, may be present.

### Etiology

Causes seem multifactorial. Folate deficiency is a significant factor, and there seems to be a genetic component. Other risk factors include maternal use of certain drugs (eg, valproate) and maternal diabetes.

### Symptoms and Signs

Many children with minor defects are asymptomatic.

**Neurologic:** When the spinal cord or lumbosacral nerve roots are involved, as is usual, varying degrees of paralysis and sensory deficits are present below the lesion. Rectal tone is usually decreased.

Hydrocephalus (see p. 2992) may cause minimal symptoms or signs of increased intracranial pressure. Brainstem involvement may cause manifestations such as stridor, swallowing difficulties, and intermittent apnea.

**Orthopedic:** Lack of muscle innervation leads to atrophy of the legs. Because paralysis occurs in the fetus, orthopedic problems may be present at birth (eg, clubfoot, arthrogryposis of the legs, dislocated hip). Kyphosis is sometimes present and can hinder surgical closure and prevent the child from lying supine.

[**Fig. 298-1.** Forms of spina bifida.]

Scoliosis may develop later and is more common among children with higher lesions (ie, above L3).

**Urologic:** Paralysis also impairs bladder function, occasionally leading to a neurogenic bladder and, consequently, urinary reflux, which can cause hydronephrosis, frequent UTIs, and, ultimately, kidney damage.

### Diagnosis

• Ultrasonography or MRI

Spinal cord imaging, with ultrasonography or MRI, is essential in children with OSD; even children with minimal cutaneous findings may have underlying spinal abnormalities (those with overt defects do not require spinal cord imaging because the anatomy is known). Plain x-rays of the spine, hips, and, if they are malformed, lower extremities are done. Cranial imaging using ultrasonography, CT, or MRI is done to look for hydrocephalus.

Once the diagnosis of spina bifida is made, urinary tract evaluation is essential and includes urinalysis, urine culture, BUN and creatinine determination, and ultrasonography. Measurement of bladder capacity and pressure at which urine exits into the urethra can determine prognosis and intervention. Need for further testing, such as urodynamics and voiding cystourethrogram, depends on previous findings and associated anomalies.

**Screening:** Prenatal screening can be done by doing fetal ultrasonography and by measuring maternal serum levels of α-fetoprotein (see p. 2603), ideally between 16 and 18 wk gestation; levels can also be done on amniotic fluid samples if previous testing suggests an increased risk. Elevated levels suggest increased risk of spina bifida cystica (OSD rarely causes elevated levels).

### Prognosis

Prognosis varies by the level of cord involvement and the number and severity of associated anomalies. Prognosis is worse for children with higher cord level (eg, thoracic) lesions or who have kyphosis, hydrocephalus, early hydronephrosis, and associated congenital anomalies. With proper care, however, most children do well. Loss of renal function and ventricular shunt complications are the usual causes of death in older children.

### Treatment

• Surgical repair of the spinal lesion

• Sometimes a ventricular shunt

• Various measures for orthopedic and urologic complications

Without early surgical treatment, neurologic damage can progress in OSD. Treatment for all spina bifida requires a united effort by specialists from several disciplines; neurosurgical, urologic, orthopedic, pediatric, and social service evaluations are important. It is important to assess the type, vertebral segment, and extent of the lesion; the infant's health status; and associated anomalies. Discussion with the family should ascertain the family's strengths, desires, and resources, and community resources, including availability of ongoing care.

A meningomyelocele identified at birth is covered immediately with a sterile dressing. If the meningomyelocele is leaking CSF, antibiotics are started to prevent meningitis. Neurosurgical repair of a meningomyelocele or an open spine typically is done within the first 72 h after birth to reduce the risk of meningeal or ventricular infection. If the lesion is large or is in a difficult location, plastic surgeons may be consulted to ensure adequate closure.

Hydrocephalus may require a shunt procedure in the neonatal period; sometimes a ventricular shunt is inserted when the back is repaired.

Kidney function must be monitored closely, and UTI should be treated promptly. Obstructive uropathy at either the bladder outlet or ureteral level must be treated vigorously to prevent infection. When children are between 2 and 3 yr of age, or at any time if they have elevated pressure in the bladder with vesicoureteral reflux, clean intermittent catheterization is done to empty the bladder on a regular basis. Catheterization increases continence and maintains bladder and kidney health.

At around the same time, children are placed on the commode or toilet after meals to encourage fecal continence. Well-balanced diets are encouraged; stool softeners, laxatives, or a combination may be helpful to ensure regular bowel movements and to increase continence. In older children, an antegrade colonic enema procedure, in which a hole is placed through the abdominal wall into the colon to allow infusion of liquids, can improve continence. The hole is kept open by a tube (eg, a gastrostomy feeding tube).

Orthopedic care should begin early. If a club-foot is present, a cast is applied; surgery is often necessary

after casting. Hip joints are checked for dislocation. Affected children should be monitored for development of scoliosis, pathologic fractures, pressure sores, and muscle weakness and spasm.

**Prevention**

Folate supplementation (400 to 800 µg po once/day) in women beginning 3 mo before conception and continuing through the 1st trimester reduces the risk of neural tube defects (see p. 2992).

# Chapter 299. Chromosomal Anomalies

## Introduction

Chromosomal anomalies cause various disorders. Anomalies that affect autosomes (the 22 paired chromosomes that are alike in males and females) are more common than those that affect sex chromosomes (X and Y). Chromosomal abnormalities fit into several major categories:

- Trisomies (extra chromosomes)
- Translocations (anomalies in which segments of chromosomes inappropriately join with other chromosomes)
- Deletions and duplications of various chromosomes or parts of chromosomes
- Mosaicisms (anomalies in which a person starting from a single fertilized egg develops ≥ 2 cell lines differing in genotype [genetic constitution])

Some specific terms from the field of genetics are important for describing chromosomal anomalies:

- Karyotype: The full set of chromosomes in a person's cells.
- Genotype: The genetic constitution determined by the karyotype.
- Phenotype: The person's outward appearance—the biochemical, physiologic, and physical makeup as determined by the genotype and environmental factors (see p. 3374).

### Diagnosis

Lymphocytes are used for chromosomal analysis, except prenatally, when amniocytes or cells from placental chorionic villi are used (see p. 2602). A karyotype analysis involves blocking cells in mitosis during metaphase and staining the condensed chromosomes. Chromosomes from single cells are photographed, and their images are arranged, forming a karyotype.

Several techniques are used to better delineate the chromosomes:

- In classical banding (eg, G [Giemsa]-, Q [fluorescent]-, and C-banding), a dye is used to stain bands on the chromosomes.
- High-resolution chromosome analysis uses special culture methods to obtain a high percentage of prophase and prometaphase spreads. The chromosomes are less condensed than in routine metaphase analysis, and the number of identifiable bands is expanded, allowing a more sensitive karyotype analysis.
- Spectral karyotyping analysis (also called chromosome painting) uses chromosome-specific multicolor fluorescent in situ hybridization (FISH) techniques that improve the visibility of certain defects, including translocations and inversions.
- Comparative genomic hybridization is a single-step technique that allows the entire genome to be scanned for mutations, including increases (duplications) or decreases (deletions) in DNA and unbalanced translocations.

## Fragile X Syndrome

**Fragile X syndrome is a genetic abnormality in an X chromosome that leads to intellectual disability and behavioral disorders.**

Fragile X syndrome is the most common inherited cause of intellectual disability. The symptoms of fragile

X syndrome are caused by abnormalities in DNA on the X chromosome. It affects about 1/4000 males and 1/8000 females. Females with the disorder are typically less impaired than males. Fragile X is inherited in an X-linked pattern and does not always cause clinical symptoms.

Examination of the karyotype reveals a constriction at the end of the long arm of the X chromosome, followed by a thin strand of genetic material. The constriction and thin strand give the appearance of a fragile portion of the X chromosome. Sequencing of the genetic material reveals a repeating base pair triplet that is responsible for the syndrome.

### Symptoms and Signs

People with fragile X syndrome have physical, cognitive and behavioral abnormalities. They have large, protuberant ears; a prominent chin and forehead; a high arched palate; and, in postpubertal males, macroorchidism. The joints may be hyperextensible, and heart disease (mitral valve prolapse) may occur. Cognitive abnormalities may include mild to moderate intellectual disability. Features of autism may develop, including perseverative speech and behavior, poor eye contact, and social anxiety. Women may experience menopause in their mid-30s.

### Diagnosis

Fragile X syndrome is frequently not suspected until school age or adolescence, depending on the severity of the symptoms. Boys with autism and intellectual disability should be tested for fragile X syndrome. DNA testing can detect abnormal DNA on the fragile X chromosome. The greater the number of abnormal repetitions of DNA found, the more likely the child will have symptoms.

### Treatment

Early intervention, including speech and language therapy and occupational therapy, can help children with fragile X syndrome to maximize their abilities. Stimulants, antidepressants, and antianxiety drugs may be beneficial for some children.

## Down Syndrome

(Trisomy 21; Trisomy G)

**Down syndrome is an anomaly of chromosome 21 that causes intellectual disability, microcephaly, short stature, and characteristic facies. Diagnosis is suggested by physical anomalies and abnormal development and confirmed by karyotype analysis. Treatment depends on specific manifestations and anomalies.**

Overall incidence among live births is about 1/800 but increases as maternal age increases. At 20 yr of maternal age, the risk is 1/2000 births; at 35, it is 1/365; and at 40, it is 1/100. However, because most births occur among younger women, just 20% of infants with Down syndrome are born to mothers > 35 yr.

### Etiology

In about 95% of cases, there is an extra whole chromosome 21 (trisomy 21), which is almost always maternally derived. Some people with Down syndrome have the normal 46 chromosomes, but a piece of an additional chromosome 21 has been translocated to another chromosome. The most common translocation is t(14;21), in which a piece of an additional chromosome 21 is attached to chromosome 14. In about half of the cases, both parents have normal karyotypes, indicating a de novo translocation. In the other half, one parent (almost always the mother), although phenotypically normal, has only 45 chromosomes, one of which is t(14;21). Theoretically, the chance that a carrier mother will have a child with Down syndrome is 1:3, but the actual risk is lower (about 1:10). If the father is the carrier, the risk is only 1:20. The next most common translocation is t(21;22). In these cases, carrier mothers have about a 1:10 risk of having a child with Down syndrome; the risk is smaller for carrier fathers.

Down syndrome mosaicism presumably results from nondisjunction (when chromosomes fail to pass to

separate cells) during cell division in the embryo. Most affected people have two cell lines, one with 46 chromosomes and one with 47 chromosomes. The prognosis for intelligence probably depends on the proportion of trisomy 21 cells in the brain. A few people with mosaic Down syndrome have barely recognizable clinical signs and normal intelligence. If a parent has germ-line mosaicism for trisomy 21, an increased risk exists for a second affected child.

**Pathophysiology**

As with most conditions that result from chromosome imbalance, Down syndrome affects multiple systems and causes both structural and functional defects (see Table 299-1). Not all defects are present in each person.

Most people have some degree of cognitive impairment, ranging from severe (IQ 20 to 35) to mild (IQ 50 to 75). Gross motor and language delays also are evident early in life. Height is significantly reduced, and the person has an increased risk of obesity. About 40 to 50% of affected neonates have congenital heart disease; ventricular septal defect and atrioventricular canal (endocardial cushion) defect are most common. About 5% of people have GI anomalies, particularly duodenal atresia, sometimes along with annular pancreas. Hirschsprung's disease and celiac disease also are more common. Many people develop endocrinopathies, including thyroid disease (most often hypothyroidism) and diabetes. Atlanto-occipital and atlantoaxial hypermobility, as well as bony anomalies of the cervical spine, can cause atlanto-occipital and cervical instability; weakness and paralysis may result. About 60% of people have eye problems, including congenital cataracts, glaucoma, strabismus, and refractive errors. Most people have hearing loss, and ear infections are very common.

[**Table 299-1.** Some Complications of Down Syndrome*]

The aging process seems to be accelerated. The median age at death is 49; however, many reach their 50s or 60s. Life expectancy is decreased primarily by heart disease and, to a lesser degree, by increased susceptibility to infections and acute myelocytic leukemia. Many people develop clinical signs of Alzheimer's disease at an early age, and at autopsy, brains of adults with Down syndrome show typical microscopic findings. The results of recent research indicate that blacks with Down syndrome have a substantially shorter life span than whites. This finding may be the result of poor access to medical, educational, and other support services.

Affected women have a 50% chance of having a fetus that also has Down syndrome. However, many affected fetuses abort spontaneously. Men with Down syndrome are infertile, except for those with mosaicism.

**Symptoms and Signs**

Affected neonates tend to be placid, rarely cry, and have hypotonia. Most have a flat facial profile (particularly flattening of the bridge of the nose), although some appear normal at birth and then develop characteristic facial features during infancy. A flattened occiput, microcephaly, and extra skin around the back of the neck are common. The outer sides of the eyes are slanted upward, and epicanthal folds at the inner corners usually are present. Brushfield's spots (gray to white spots resembling grains of salt around the periphery of the iris) may be visible. The mouth is often held open because of a large, protruding, furrowed tongue that lacks the central fissure. The ears are often small and rounded. The hands are short and broad and often have a simian crease (a single, palmar crease). The fingers are short, with clinodactyly (incurving) of the 5th digit, which often has only 2 phalanges. The feet may have a wide gap between the 1st and 2nd toes, and a plantar furrow often extends backward on the foot. Hands and feet show characteristic dermatoglyphics.

As affected children grow, retardation of physical and mental development quickly becomes apparent. Stature is short, and the mean IQ is about 50. Behavior suggestive of attention-deficit/hyperactivity disorder is often present in childhood, and the incidence of autistic behavior is increased (particularly in those with profound intellectual disability). Depression is common among children and adults.

Symptoms of heart disease are determined by the type and extent of the cardiac anomaly. Infants with

ventricular septal defects can either be asymptomatic or show signs of heart failure (eg, labored breathing, fast respiratory rate, difficulty with feeding, sweating, poor weight gain). A high-frequency, 2/6 or louder systolic murmur may be present depending on the size of the defect. Infants with atrioventricular canal defects can show signs of heart failure or be asymptomatic. Characteristic heart sounds include a wide fixed splitting of the second sound. Murmurs may not be appreciated; however, a number of different murmurs are possible.

Infants with Hirschsprung's disease usually have delay in passage of meconium for 48 h after birth. Severely affected infants may have signs of intestinal obstruction (eg, bilious vomiting, failure to pass stool, abdominal distention). Duodenal atresia or stenosis can manifest with bilious vomiting or with no symptoms, depending on the extent of the stenosis.

**Diagnosis**

• Prenatal amniocentesis with karyotype analysis

• Sometimes neonatal karyotype analysis (if prenatal diagnosis not done)

Diagnosis may be suspected prenatally based on physical anomalies detected by fetal ultra-sonography (eg, nuchal translucency) or based on abnormal levels of plasma protein A in late 1st trimester and α-fetoprotein, β-hCG (human chorionic gonadotropin), unconjugated estriol, and inhibin in early 2nd trimester (15 to 16 wk gestation) on maternal serum screening. The diagnosis is confirmed by amniocentesis with karyotyping. Screening and diagnostic testing for Down syndrome are recommended for all women who present for prenatal care before 20 wk gestation regardless of maternal age. If diagnosis is not made prenatally, then neonatal diagnosis is based on physical anomalies and confirmed by karyotype analysis.

**Concomitant medical conditions:** Certain routine testing helps identify conditions associated with Down syndrome:

• Echocardiogram—at prenatal visit or at birth

• Thyroid screening (thyroid-stimulating hormone [TSH], or thyroxine [$T_4$] with TSH follow-up)—newborn, 6 mo, 12 mo, and annually thereafter

• Hearing evaluations—at birth, every 6 mo thereafter until 3 yr, then annually

• Ophthalmology evaluation—by 6 mo, then annually or more frequently as indicated

• X-ray screening for atlantoaxial instability—once between 3 and 5 yr, then as needed for sports (eg, Special Olympics) participation

• Celiac sprue screening—at 2 to 3 yr using anti-tissue transglutaminase antibodies and IgA anti-endomysial antibodies

• Growth—height and weight plotted at each health supervision visit using a Down syndrome growth chart

**Treatment**

The underlying disorder cannot be treated. Treatment depends on specific manifestations. Some congenital cardiac anomalies are repaired surgically. Hypothyroidism is treated with thyroid hormone replacement. Treatment should also include genetic counseling for the family, social support, and educational programming appropriate for the level of intellectual functioning (see Intellectual Disability on p. 3044).

## Trisomy 18

(Edwards' Syndrome; Trisomy E)

**Trisomy 18 is caused by an extra chromosome 18 and usually causes intellectual disability, small birth size, and many developmental anomalies, including severe microcephaly, heart defects, prominent occiput, low-set malformed ears, and a characteristic pinched facial appearance.**

Trisomy 18 occurs in 1/6000 live births, but spontaneous abortions are common. More than 95% of affected children have complete trisomy 18. The extra chromosome is almost always maternally derived, and advanced maternal age increases risk. The female:male ratio is 3:1.

### Symptoms and Signs

A history of feeble fetal activity, polyhydramnios, a small placenta, and a single umbilical artery often exist. Size at birth is markedly small for gestational age, with hypotonia and marked hypoplasia of skeletal muscle and subcutaneous fat. The cry is weak, and response to sound is decreased. The orbital ridges are hypoplastic, the palpebral fissures are short, and the mouth and jaw are small; all of these characteristics give the face a pinched appearance. Microcephaly, prominent occiput, low-set malformed ears, narrow pelvis, and a short sternum are common. A clenched fist with the index finger overlapping the 3rd and 4th fingers usually occurs. The distal crease on the 5th finger is often absent, and there is a low-arch dermal ridge pattern on the fingertips. Redundant skinfolds, especially over the back of the neck, are common. The fingernails are hypoplastic, and the big toe is shortened and frequently dorsiflexed. Club-feet and rocker-bottom feet are common. Severe congenital heart disease is common, especially patent ductus arteriosus and ventricular septal defects. Anomalies of lungs, diaphragm, GI tract, abdominal wall, kidneys, and ureters are frequent. Boys may have un-descended testes. Common muscular manifestations include hernias, separation of the rectus muscles of the abdominal wall, or both.

### Diagnosis

Diagnosis may be suspected prenatally on ultrasound (eg, with abnormalities of extremities and fetal growth restriction) or by amniocentesis or chorionic villi sampling or postnatally by appearance. Confirmation in all cases is by karyotyping.

### Treatment

No specific treatment is available. More than 50% die within the first week; < 10% are still alive at 1 yr. Those who survive have marked developmental delay and disability. Support for the family is critical.

## Trisomy 13

(Patau's Syndrome; Trisomy D)

**Trisomy 13 is caused by an extra chromosome 13 and causes abnormal forebrain, midface, and eye development; severe intellectual disability; heart defects; and small birth size.**

Trisomy 13 occurs in about 1/10,000 live births; about 80% of cases are complete trisomy 13. Advanced maternal age increases the likelihood, and the extra chromosome is usually maternally derived.

Infants tend to be small for gestational age. Midline anomalies (eg, scalp defects, dermal sinuses) are characteristic. Holoprosencephaly (failure of the forebrain to divide properly) is common. Concurrent facial anomalies can include cleft lip and cleft palate. Microphthalmia, colobomas (fissures) of the iris, and retinal dysplasia are also common. Supraorbital ridges are shallow, and palpebral fissures usually are slanted. The ears are abnormally shaped and usually low-set. Deafness is common. Loose folds of skin often are present over the back of the neck. Simian crease (a single, palmar crease), polydactyly, and hyperconvex narrow fingernails are also common. About 80% of cases have severe congenital cardiovascular anomalies; dextrocardia is common. Genitals are frequently abnormal in both sexes; cryptorchidism and an abnormal scrotum occur in boys, and a bicornuate uterus occurs in girls. Apneic spells in early infancy are frequent. Intellectual disability is severe.

### Diagnosis

Diagnosis may be suspected prenatally by abnormalities on ultrasound (eg, intrauterine growth restriction) or by amniocentesis or chorionic villi sampling and may be suspected postnatally by appearance. Confirmation in all cases is by karyotyping.

### Treatment

Most patients (80%) are so severely affected that they die before age 1 mo; < 10% survive longer than 1 yr. Support for the family is critical.

## Chromosomal Deletion Syndromes

**Chromosomal deletion syndromes result from loss of parts of chromosomes. They tend to cause severe congenital anomalies and markedly retarded mental and physical development. Chromosomal deletion syndromes are rarely suspected prenatally but may be incidentally discovered at that time if karyotyping is done for other reasons. Post-natal diagnosis is suspected by clinical appearance and is confirmed by karyotyping and other genetic analysis.**

**5p-Deletion (cri du chat syndrome):** Deletion of the end of the short arm of chromosome 5 (5p —usually paternal) is characterized by a high-pitched, mewing cry, closely resembling the cry of a kitten, which is heard in the immediate neonatal period, lasts several weeks, and then disappears. Affected neonates are hypotonic and have low birth weight, micro-cephaly, a round face with wide-set eyes, downward slanting of the palpebral fissures (with or without epicanthal folds), strabismus, and a broad-based nose. The ears are low-set, abnormally shaped, and frequently have narrow external auditory canals and preauricular tags. Syndactyly, hypertelorism, and heart anomalies occur often. Mental and physical development is markedly retarded. Many affected children survive into adulthood but have significant disability.

**4p-Deletion (Wolf-Hirschhorn syndrome):** Deletion of the short arm of chromosome 4 (4p) results in profound intellectual disability. Manifestations also may include epilepsy, a broad or beaked nose, midline scalp defects, ptosis and colobomas, cleft palate, delayed bone development, and, in boys, hypospadias and cryptorchidism. Many affected children die during infancy; those who survive into their 20s have severe disability.

**Contiguous gene syndromes:** These include microscopic and submicroscopic deletions of contiguous genes on particular parts of many chromosomes; small duplications of chromosomes also occur. The effects of duplications, however, are usually milder than those of deletions. Almost all cases are sporadic; however, mildly affected parents, as in some 22q11.21 deletions, can pass on the syndrome. Numerous syndromes have been identified, with widely varying manifestations (see Table 299-2). Deletions and duplications are often detectable with fluorescent probes and other techniques. Sometimes deletions and duplications cannot be shown cytogenetically, but their presence can be confirmed by DNA probes specific to the deleted or duplicated area.

**Telomeric deletions:** These deletions are small and often submicroscopic and may occur at either telomere (the end of a chromosome). Phenotypic changes may be minimal. Telomeric deletions may account for many cases of nonspecific intellectual disability in which the affected person has mildly dysmorphic features.

## Sex Chromosome Anomalies

**Sex chromosome anomalies may involve aneuploidy, partial deletions or duplications of sex chromosomes, or mosaicisms.**

Sex chromosome anomalies are common and cause syndromes that include a range of congenital and developmental anomalies. They are rarely suspected prenatally but may be incidentally discovered if karyotyping is done for other reasons. They are often hard to recognize at birth and may not be diagnosed until puberty.

The effects of X chromosome anomalies are not as severe as those from analogous autosomal anomalies. Females with 3 X chromosomes often appear normal physically and mentally and are fertile. In contrast, all known autosomal trisomies have devastating effects. Similarly, whereas the absence of 1 X chromosome leads to a specific syndrome (Turner's syndrome), the absence of an autosome is invariably lethal.

**Lyon hypothesis (X-inactivation):** By virtue of having 2 X chromosomes, females have 2 loci for every X-linked gene, as compared with a single locus in males. This imbalance would seem to cause a genetic "dosage" problem. However, according to the Lyon hypothesis, 1 of the 2 X chromosomes in each female somatic cell is inactivated genetically early in embryonic life (on or about day 16). In fact, no matter how many X chromosomes are present, all but 1 are inactivated. However, recent molecular genetic studies have shown that some genes on the inactivated X chromosome (or chromosomes) remain functional, and these few are essential to normal female development. *XIST* is the gene responsible for inactivating

[**Table 299-2.** Examples of Contiguous Gene Syndromes]

the genes of the X chromosome, producing RNA that triggers inactivation.

Whether the maternal or paternal X is inactivated usually is a random event within each cell at the time of inactivation; that same X then remains inactive in all descendant cells. Thus, all females are mosaics, with some cells having an active maternal X and others having an active paternal X.

Sometimes, random statistical distribution of inactivation in the relatively small number of cells present at the time of inactivation results in a particular descendant tissue having a preponderance of active maternal or paternal X (skewed inactivation). Skewed inactivation may account for the occasional manifestation of minor symptoms in females who are heterozygous for X-linked disorders such as hemophilia and muscular dystrophy (all would presumably be asymptomatic if they had a 50:50 distribution of active X chromosomes). Skewed inactivation also may occur by post-inactivation selection.

### Turner's Syndrome

**In Turner's syndrome (gonadal dysgenesis), girls are born with 1 of their 2 X chromosomes partly or completely missing. Diagnosis is based on clinical findings and is confirmed by karyotype analysis. Treatment depends on manifestations and may include surgery for cardiac anomalies and often growth hormone therapy for short stature and estrogen replacement for pubertal failure.**

Turner's syndrome occurs in about 1/4000 live female births and is the most common sex chromosome anomaly in females. However, 99% of 45,X conceptions abort spontaneously.

About 50% of affected girls have a 45,X karyotype; about 80% have lost the paternal X. Most of the other 50% are mosaics (eg, 45,X/46,XX or 45,X/47,XXX). Among mosaic girls, phenotype may vary from that of typical Turner's syndrome to normal. Occasionally, affected girls have 1 normal X and 1 X that has formed a ring chromosome. Some affected girls have 1 normal X and 1 long-arm isochromosome formed by the loss of short arms and development of a chromosome consisting of 2 long arms of the X chromosome. These girls tend to have many of the phenotypic features of Turner's syndrome; thus, deletion of the X chromosome's short arm seems to play an important role in producing the phenotype.

#### Pathophysiology

Common cardiac anomalies include coarctation of the aorta and bicuspid aortic valve. Hypertension frequently occurs with aging, even without coarctation. Renal anomalies and hemangiomas are frequent. Occasionally, telangiectasia occurs in the GI tract, with resultant GI bleeding or protein loss. Hearing loss occurs; strabismus and hyperopia (farsightedness) are common and increase the risk of amblyopia. Thyroiditis and celiac disease are more common than among the general population.

Infants are at a higher risk of developmental dysplasia of the hip. Of adolescents, 10% have scoliosis.

Osteoporosis and fractures are fairly common among women with Turner's syndrome. Gonadal dysgenesis (ovaries replaced by bilateral streaks of fibrous stroma and devoid of developing ova) occurs in 90% of females.

Intellectual disability is rare, but many have nonverbal learning disability, attention-deficit/hyperactivity disorder, or both and thus score poorly on performance tests and in mathematics, even though they score average or above in the verbal components of intelligence tests.

**Symptoms and Signs**

Many neonates are very mildly affected; however, some present with marked dorsal lymphedema of the hands and feet and with lymphedema or loose folds of skin over the back of the neck. Other frequent anomalies include a webbed neck and a broad chest with widely spaced and inverted nipples. Affected girls have short stature compared with family members. Less common findings include a low hairline on the back of the neck, ptosis, multiple pigmented nevi, short 4th metacar-pals and metatarsals, prominent finger pads with whorls in the dermatoglyphics on the ends of the fingers, and hypoplasia of the nails. Increased carrying angle at the elbow occurs.

Symptoms of cardiac anomalies depend on severity. Coarctation of the aorta can cause high BP in the upper extremities, diminished femoral pulses, and low or absent BP in the lower extremities. Gonadal dysgenesis results in the inability to undergo puberty, develop breast tissue, or begin menses. Other medical problems that are associated with Turner's syndrome develop with aging and may not be evident without screening.

**Diagnosis**

• Clinical appearance

• Karyotype analysis

• Testing for associated conditions

In neonates, diagnosis may be suspected based on the presence of lymphedema or a webbed neck. In the absence of these findings, some children are diagnosed later, based on short stature, lack of pubertal development, and amenorrhea. Diagnosis is confirmed by karyotype analysis. Echocardiography or MRI is indicated to detect cardiac anomalies.

Cytogenetic analysis and Y-specific probe studies are done for all people with gonadal dysgenesis to rule out mosaicism with a Y-bearing cell line (eg, 45,X/46,XY). These people are usually phenotypic females who have variable features of Turner's syndrome. They are at high risk of gonadal cancer, especially gonadoblastoma, and should have the gonads removed prophylactically as soon as the diagnosis is made.

**Concomitant medical conditions:** Certain routine evaluations help identify conditions associated with Turner's syndrome:

• Cardiovascular evaluation by a specialist; MRI and echocardiography at time of diagnosis to rule out coarctation and bicuspid aortic valve and every 3 to 5 yr thereafter to evaluate aortic root diameter

• Renal ultrasonography at time of diagnosis, annual urinalysis, BUN, and creatinine for patients with renal system anomalies

• Hearing evaluation by an audiologist and audiogram every 3 to 5 yr

• Evaluation for scoliosis/kyphosis at yearly examination

• Evaluation for hip dislocation

• Eye examination by pediatric ophthalmologist

• Thyroid function tests at diagnosis and every 1 to 2 yr thereafter

• Celiac screen (eg, endomysial antibody levels)

• Glucose tolerance test at diagnosis and fasting blood sugar, lipid profile annually thereafter

**Treatment**

There is no specific treatment for the underlying genetic condition. Coarctation of the aorta is usually repaired surgically. Other cardiac anomalies are monitored and repaired as needed. Lymphedema can usually be controlled with support hosiery.

Treatment with growth hormone can stimulate growth. Estrogen replacement is usually needed to initiate puberty and is typically given at age 12 to 13. Thereafter, birth control pills with a progestin are given to maintain secondary sexual characteristics. Growth hormone can be given with estrogen replacement until epiphyses are fused, at which time growth hormone is stopped. Continuation of estrogen replacement helps establish optimal bone density and skeletal development.

**Klinefelter's Syndrome (47,XXY)**

**Klinefelter's syndrome is ≥ 2 X chromosomes plus 1 Y, resulting in a phenotypic male.**

Klinefelter's syndrome is the most common sex chromosome disorder, occurring in about 1/700 live male births. The extra X chromosome is maternally derived in 60% of cases. Germ cells do not survive in the testes, leading to decreased sperm and androgens.

Affected boys tend to be tall with disproportionately long arms and legs. They often have small, firm testes, and about 30% develop gynecomastia. Puberty usually occurs at the normal age, but often facial hair growth is light. There is a predisposition for verbal learning disorders. Clinical variation is great, and many 47,XXY males have normal appearance and intellect. Many are diagnosed during an infertility evaluation (probably all 47,XXY males are sterile). Testicular development varies from hyalinized nonfunctional tubules to some production of spermatozoa; urinary excretion of follicle-stimulating hormone is frequently increased.

Mosaicism occurs in 15% of cases. These men may be fertile. Some affected men have 3, 4, and even 5 X chromosomes along with the Y. As the number of X chromosomes increases, the severity of intellectual disability and of malformations also increases. Each extra X is associated with a 15- to 16-point reduction in IQ, with language most affected, particularly expressive language skills. Males with Klinefelter's syndrome should have lifelong testosterone supplementation beginning at puberty to ensure the development of male sexual characteristics, muscle bulk, bone structure, and better psychosocial functioning.

**47,XYY Syndrome**

**47,XYY syndrome is 2 Y chromosomes and 1 X, resulting in a phenotypic male.**

The 47,XYY syndrome occurs in about 1/1000 live male births. Affected boys tend to be taller than average and have a 10- to 15-point IQ reduction compared with family members. There are few physical problems. Minor behavior disorders, hyperactivity, attention-deficit disorder, and learning disorders are more common.

**Other X Chromosome Anomalies**

About 1/1000 apparently normal females have 47,XXX (trisomy X) karyotype. Physical anomalies are rare. Menstrual irregularity and infertility sometimes occur. Affected girls may have mildly impaired intellect and may have more school problems than siblings. Advanced maternal age increases risk of the triple X

anomaly, and the extra X chromosome is usually maternally derived.

Although rare, 48,XXXX and 49,XXXXX females exist. There is no consistent pheno-type. The risk of intellectual disability and congenital anomalies increases markedly when there are > 3 X chromosomes. The genetic imbalance in early embryonic life may cause anomalous development.

# Chapter 300. Inherited Muscular Disorders

## Introduction

Inherited metabolic disorders affecting the muscles, such as disorders of mitochondrial oxidative phosphorylation and glycogen storage diseases, are discussed in Ch. 301. Only those disorders that have all or most of their effects on muscle are discussed in this chapter.

## Muscular Dystrophies

**Muscular dystrophies are inherited, progressive muscle disorders resulting from defects in one or more genes needed for normal muscle function. They are distinguished by the selective distribution of weakness and the specific nature of the genetic abnormality involved.**

Duchenne dystrophy is the most common and severe form of muscular dystrophy. Becker dystrophy, although closely related, has a later onset and causes milder symptoms. Other forms include Emery-Dreifuss dystrophy, myotonic dystrophy, limb-girdle dystrophy, facioscapulohumeral dystrophy, and congenital dystrophies.

### Duchenne Muscular Dystrophy and Becker Muscular Dystrophy

**Duchenne muscular dystrophy and Becker muscular dystrophy are X-linked recessive disorders characterized by progressive proximal muscle weakness caused by muscle fiber degeneration. Becker dystrophy has later onset and causes milder symptoms. Diagnosis is suggested clinically and is confirmed by analysis of the protein product (dystrophin) of the mutated gene. Treatment focuses on maintaining function through physical therapy and the use of braces and orthotics; prednisone is given to some patients with severe functional decline.**

Duchenne dystrophy and Becker dystrophy are caused by mutations at the Xp21 locus. In Duchenne dystrophy, this mutation results in the severe absence (< 5%) of dystrophin, a protein in the muscle cell membrane. In Becker dystrophy, the mutation results in production of abnormal dystrophin or less dystrophin. Duchenne dystrophy affects 1/3000 live male births. Becker dystrophy affects 1/30,000 live male births. Female carriers may have asymptomatic elevated CK levels and possibly calf hypertrophy.

#### Symptoms and Signs

**Duchenne dystrophy:** This disorder manifests typically between ages 2 yr and 3 yr. Weakness affects proximal muscles, typically in the lower limbs initially. Children frequently toe walk and have a waddling gait and lordosis. They fall frequently and have difficulty running, jumping, climbing stairs, and rising from the floor. Progression of weakness is steady, and limb flexion contractures and scoliosis develop. Firm pseudohypertrophy (fatty and fibrous replacement of certain enlarged muscle groups, notably the calves) develops. Most children are confined to a wheelchair by age 12 and die of respiratory complications by age 20. Cardiac involvement is usually asymptomatic, although 90% of patients have ECG abnormalities. One third have mild, nonprogressive intellectual impairment that affects verbal ability more than performance.

**Becker dystrophy:** This disorder typically becomes symptomatic much later and is milder. Ambulation is usually preserved until at least age 15, and many children remain ambulatory into adulthood. Most affected children survive into their 30s and 40s.

#### Diagnosis

• Immunostaining analysis of dystrophin

• DNA mutation analysis

Diagnosis is suspected by characteristic clinical findings, age at onset, and family history suggestive of X-linked recessive inheritance. Myopathic changes are noted on electromyography (rapidly recruited, short

duration, low-amplitude motor unit potentials) and muscle biopsy (necrosis and marked variation in muscle fiber size not segregated by motor unit). CK levels are elevated to up to 100 times normal.

Diagnosis is confirmed by analysis of dystrophin with immunostaining of biopsy samples. Dystrophin is undetectable in patients with Duchenne dystrophy. In patients with Becker dystrophy, dystrophin is typically abnormal (lower molecular weight) or present in low concentration. Mutation analysis of DNA from peripheral blood leukocytes can also confirm the diagnosis by identifying abnormalities in the dystrophin gene (deletions or duplications in about 65% and point mutations in about 25% of patients).

Carrier detection and prenatal diagnosis are possible by using conventional studies (eg, pedigree analysis, CK determinations, fetal sex determination) combined with recombinant DNA analysis and dystrophin immunostaining of muscle tissue.

**Treatment**

• Supportive measures

• Sometimes prednisone

• Sometimes corrective surgery

No specific treatment exists. Moderate exercise is encouraged for as long as possible. Passive exercises may extend the period of ambulation. Ankle-foot orthoses help prevent flexion during sleep. Leg braces may temporarily help preserve ambulation or standing. Obesity should be avoided; caloric requirements are likely to be less than normal. Genetic counseling is indicated (see p. 2598).

Daily prednisone does not cause significant long-term clinical improvement, but it possibly slows the course of the disease. No consensus on long-term effectiveness exists. Gene therapy is not yet available. Corrective surgery is sometimes needed. Respiratory insufficiency may be treated with noninvasive ventilatory support (eg, nasal mask—see p. 2290). Elective tracheotomy is gaining acceptance, allowing children with Duchenne dystrophy to live into their 20s.

**Other Forms of Muscular Dystrophy**

**Emery-Dreifuss dystrophy:** This disorder can be inherited as an autosomal dominant, autosomal recessive (the rarest), or X-linked recessive disorder. The overall incidence is unknown. Females can be carriers, but only males are affected clinically by X-linked inheritance. Genes associated with Emery-Dreifuss dystrophy encode for the nuclear membrane proteins lamin A/C (autosomal) and emerin (X-linked).

Muscle weakness and wasting can begin any time before age 20 and commonly affect the biceps and triceps and, less often, distal leg muscles. The heart is frequently involved, with atrial paralysis, conduction abnormalities (atrioventricular block), cardiomyopathy, and a high likelihood of sudden death.

Diagnosis is indicated by clinical findings, age at onset, and family history. The diagnosis is supported by mildly increased serum CK levels and myopathic features on electromyography and muscle biopsy and is confirmed by DNA testing.

Treatment involves therapy to prevent contractures. Cardiac pacemakers are sometimes lifesaving in patients with abnormal conduction.

**Myotonic dystrophy:** Myotonic dystrophy, the most common form of muscular dystrophy among whites, affects about 30/100,000 live male and female births. Inheritance is autosomal dominant with variable penetrance. Two genetic loci—DM 1 and DM 2—cause the abnormality. Symptoms and signs begin during adolescence or young adulthood and include myotonia (delayed relaxation after muscle contraction), weakness and wasting of distal limb muscles (especially in the hand) and facial muscles (ptosis is especially common), and cardiomyopathy. Intellectual disability, cataracts, and endocrine disorders can also occur.

Diagnosis is indicated by characteristic clinical findings, age at onset, and family history and is confirmed by DNA testing. Treatment includes braces for foot drop and drug therapy for myotonia (eg, mexiletine 75 to 150 mg po bid or tid).

**Limb-girdle dystrophy:** Limb-girdle dystrophy currently has 21 known subtypes, 15 autosomal recessive and 6 autosomal dominant. The overall incidence is unknown. Males and females are affected equally. Several chromosomal loci have been identified for autosomal dominant (5q [no known gene product]) and recessive (2q, 4q [beta-sarcoglycan], 13q [gamma-sarcoglycan], 15q [calpain, a Ca-activated protease], and 17q [alpha-sarcoglycan or adhalin]) forms. Structural (eg, dystrophin-associated glycoproteins) or nonstructural (eg, proteases) proteins can be affected.

Symptoms involve weakness in a limb girdle and proximal limb distribution. Onset of symptoms ranges from early childhood to adulthood; onset for autosomal recessive types tends to be during childhood, and these types primarily have a pelvic girdle distribution.

Diagnosis is indicated by characteristic clinical findings, age at onset, and family history and requires muscle histology, immunocytochemistry, Western blot analysis, and genetic testing for specific proteins.

Treatment focuses on prevention of contractures.

**Facioscapulohumeral dystrophy:** Facioscapulohumeral dystrophy is an autosomal dominant disorder characterized by weakness of the facial muscles and shoulder girdle, usually beginning at age 7 to 20. Onset is during adolescence or young adulthood and is characterized by slow progression and difficulty whistling, closing the eyes, and raising the arms (due to weakness of the scapular stabilizer muscles). Life expectancy is normal. An infantile variety, characterized by facial, shoulder, and hip girdle weakness, is rapidly progressive.

Diagnosis is indicated by characteristic clinical findings, age at onset, and family history and is confirmed by DNA testing.

Treatment consists of physical therapy.

**Congenital muscular dystrophy:** Congenital muscular dystrophy is not a single disorder but instead refers to muscular dystrophy evident at birth, occurring from any of several rare forms of muscular dystrophy. The diagnosis is suspected in any floppy neonate but must be distinguished from congenital myopathy by muscle biopsy.

Treatment consists of physical therapy, which may help preserve function.

## Congenital Myopathies

**Congenital myopathy is a term sometimes applied to hundreds of distinct neuromuscular disorders that may be present at birth, but it is usually reserved for a group of rare, inherited, primary muscle disorders that cause hypotonia and weakness at birth or during the neonatal period and, in some cases, delayed motor development later in childhood.**

The 4 most common types of congenital myopathy are

• Nemaline myopathy

• Myotubular myopathy

• Core myopathies

• Congenital fiber type disproportion

The 4 types are distinguished primarily by their histologic features, symptoms, and prognosis. Diagnosis

is indicated by characteristic clinical findings and is confirmed by muscle biopsy. Treatment consists of physical therapy, which may help preserve function.

**Nemaline myopathy:** This myopathy, the most common congenital myopathy, can be autosomal dominant or recessive; causative mutations have been identified in 6 genes, and all are related to the production of thin-filament proteins. Nemaline myopathy may be severe, moderate, or mild. Severely affected patients may experience weakness of respiratory muscles and respiratory failure. Moderate disease causes progressive weakness in muscles of the face, neck, trunk, and feet, but life expectancy may be nearly normal. Mild disease is nonprogressive, and life expectancy is normal.

**Myotubular myopathy:** This myopathy is X-linked and rare, occurring in about 1/50,000 births. It affects males primarily and results in severe skeletal muscle weakness and hypotonia, facial weakness, impaired swallowing, and respiratory muscle weakness and respiratory failure. Children with milder forms survive to adulthood.

**Core myopathies:** Inheritance is usually autosomal dominant, but recessive and sporadic forms exist. Core myopathies are characterized by regions (cores) on muscle biopsy specimens in which oxidative enzyme staining is absent; regions may be peripheral or central, focal, multiple, or extensive. Central core myopathy was the first congenital myopathy to be identified.

Most affected patients develop hypotonia and mild proximal muscle weakness as neonates, but sometimes symptoms do not manifest until adulthood. Many also have facial weakness. Weakness is nonprogressive, and life expectancy is normal, but some patients are severely affected and wheelchair bound. The gene mutation associated with central core myopathy is also associated with increased susceptibility to malignant hyperthermia.

**Congenital fiber type disproportion myopathy:** This myopathy is inherited, but the pattern is poorly understood. Hypotonia and weakness of the face, neck, trunk, and limbs are often accompanied by skeletal abnormalities and dysmorphic features. Most affected children improve with age, but a small percentage develops respiratory failure.

## Familial Periodic Paralysis

**Familial periodic paralysis is a rare autosomal condition characterized by episodes of flaccid paralysis with loss of deep tendon reflexes and failure of muscle to respond to electrical stimulation. There are 3 forms: hypokalemic, hyperkalemic, and normokalemic. Diagnosis is indicated by history and is confirmed by provoking an episode (eg, by giving dextrose and insulin to cause hypokalemia or KCl to cause hyperkalemia). Treatment depends on the form.**

The hypokalemic form of familial periodic paralysis is due to genetic mutation in the dihydropyridine receptor-associated Ca channel gene. The hyperkalemic form is due to mutations in the gene that encodes the α-subunit of the skeletal muscle Na channel (SCN4A). The cause of the normokalemic form is unclear; in some instances it may result from a mutation in a gene that encodes Na channels.

### Symptoms and Signs

**Hypokalemic:** Episodes usually begin before age 16. The day after vigorous exercise, the patient often awakens with weakness, which may be mild and limited to certain muscle groups or may affect all four limbs. Episodes are also precipitated by carbohydrate-rich meals. Ocular, bulbar, and respiratory muscles are spared. Consciousness is not altered. Serum and urine K are decreased. Weakness lasts up to 24 h.

**Hyperkalemic:** Episodes often begin at an earlier age and usually are shorter, more frequent, and less severe. Episodes are precipitated by exercise after meals or by fasting. Myotonia (delayed relaxation after muscle contraction) is common. Eyelid myotonia may be the only symptom.

**Normokalemic:** Affected patients are sensitive to K ingestion and have episodes of mild weakness that occur without any change in serum K.

**Diagnosis**

• Clinical evaluation

• Serum K level during symptoms

• Sometimes provocative testing

The best diagnostic indicator is a history of typical episodes. If measured during an episode, serum K may be abnormal. Episodes can sometimes be provoked by giving dextrose and insulin (to cause the hypokalemic form) or KCl (to cause the hyperkalemic form), but only experienced physicians should attempt provocative testing, because respiratory paralysis or cardiac conduction abnormalities may occur with provoked episodes.

**Treatment**

• Varies with type and severity

**Hypokalemic:** Episodes of paralysis are managed by giving KCl 2 to 10 g in an unsweetened oral solution or giving K IV. Following a low-carbohydrate, low-Na diet, avoiding strenuous activity or alcohol after periods of rest, and taking acetazolamide 250 to 2000 mg po once/day may help prevent hypokalemic episodes.

**Hyperkalemic:** Episodes of paralysis, if mild, can be aborted at onset by light exercise and a 2 g/kg oral carbohydrate load. Established episodes require thiazides, acetazolamide, or inhaled β-agonists. Severe attacks require Ca gluconate or insulin and dextrose IV. Regularly ingesting carbohydrate-rich, low-K meals and avoiding fasting, strenuous activity after meals, and cold exposure help prevent hyperkalemic episodes.

**Normokalemic:** Large doses of Na alleviate the weakness. Dextrose has no effect. Attacks may be prevented by avoiding excess alcohol and cold exposure. People should cool down slowly after strenuous exercise and not immediately rest. Eating some form of carbohydrate (eg, candy bar) may help as well.

# Chapter 301. Inherited Disorders of Metabolism

## Introduction

Most inherited disorders (also called inborn errors) of metabolism are caused by mutations in genes that code for enzymes; enzyme deficiency or inactivity leads to accumulation of substrate precursors or metabolites or to deficiencies of the enzyme's products. Hundreds of disorders exist, and although most inherited disorders of metabolism are extremely rare individually, collectively they are not rare. The disorders are typically grouped by the affected substrate (eg, carbohydrates, amino acids, fatty acids).

Most states routinely test all neonates for specific inherited disorders of metabolism and other conditions (see p. 2702), including phenylketonuria, tyrosinemia, biotinidase deficiency, homocystinuria, maple syrup urine disease, and galactosemia. Many states have an expanded screening program that covers many more inherited disorders of metabolism, including disorders of fatty acid oxidation and other organic acidemias.

Metabolic defects that primarily cause disease in adults (eg, gout, porphyria), are organ-specific (eg, Wilson's disease, congenital adrenal hypoplasia), or are common (eg, cystic fibrosis, hemochromatosis) are discussed elsewhere in THE MANUAL. For inherited disorders of lipoprotein metabolism, see Table 100-3 on p. 892.

## Approach to the Patient with a Suspected Inherited Disorder of Metabolism

Most inherited disorders (inborn errors) of metabolism are rare, and therefore their diagnosis requires a high index of suspicion. Timely diagnosis leads to early treatment and may help avoid acute and chronic complications, developmental compromise, and even death.

### Evaluation

Symptoms and signs tend to be nonspecific and are more often caused by something other than an inherited disorder of metabolism (eg, infection); these more likely causes should also be investigated.

**History and physical examination:** Disorders manifesting in the neonatal period tend to be more serious; manifestations of many of the disorders typically include lethargy, poor feeding, vomiting, and seizures. Disorders that manifest later tend to affect growth and development, but vomiting, seizures, and weakness may also appear.

**Growth delay** suggests decreased anabolism or increased catabolism and may be due to decreased availability of energy-generating substrates (eg, in glycogen storage disease [GSD]) or inefficient energy or protein use (eg, in organic acidemias or urea cycle defects).

**Developmental delay** may reflect chronic energy deficit in the brain (eg, oxidative phosphorylation defects), decreased supply of needed carbohydrates that are non-energy substrates for the brain (eg, lack of uridine-5′-diphosphate-galactose [UDP-galactose] in untreated galactosemia), or chronic amino acid deficit in the brain (eg, tyrosine deficiency in phenylketonuria).

**Neuromuscular symptoms**, such as seizures, muscle weakness, hypotonia, myoclonus, and muscle pain, and strokes or coma may suggest acute energy deficit in the brain (eg, hypoglycemic seizures in GSD type I, strokes in mitochondrial oxidative phosphorylation defects) or muscle (eg, muscle weakness in muscle forms of GSD). Neuromuscular symptoms may also reflect accumulation of toxic compounds in the brain (eg, hyperammonemic coma in urea cycle defects) or tissue breakdown (eg, rhabdomyolysis and myoglobinuria in patients with long-chain hydroxyacyl dehydrogenase deficiency or muscle forms of GSD).

**Congenital brain malformation** may reflect decreased availability of energy (eg, decreased ATP output in pyruvate dehydrogenase deficiency) or critical precursors (eg, decreased cholesterol in 7-dehydrocholestrol reductase deficiency or Smith-Lemli-Opitz syndrome) during fetal development.

**Autonomic symptoms** can result from hypoglycemia caused by increased glucose consumption or decreased glucose production (eg, vomiting, diaphoresis, pallor, and tachycardia in GSD or hereditary fructose intolerance) or from metabolic acidosis (eg, vomiting and Kussmaul respirations in organic acidemias). Some conditions cause both (ie, in propionic acidemia, accumulation of acyl-CoAs causes metabolic acidosis and inhibits gluconeogenesis, thus causing hypoglycemia).

**Nonphysiologic jaundice** after the neonatal period usually reflects intrinsic hepatic disease, especially when accompanied by elevation of liver enzymes, but may be due to inherited disorders of metabolism (eg, untreated galactosemia, hereditary fructose intolerance, tyrosinemia type I).

**Unusual odors in body fluids** reflect accumulation of specific compounds (eg, sweaty feet odor in isovaleric acidemia, smoky-sweet odor in maple syrup urine disease, mousy or musty odor in phenylketonuria, boiled cabbage odor in tyrosinemia).

**Change in urine color** on exposure to air occurs in some disorders (eg, darkish brown in alkaptonuria, purplish brown in porphyria).

**Organomegaly** may reflect a failure in substrate degradation resulting in substrate accumulation within the organ cells (eg, hepatomegaly in hepatic forms of GSD and many lysosomal storage diseases, cardiomegaly in GSD type II).

**Eye changes** include cataracts in galactokinase deficiency or classic galactosemia, and ophthalmoplegia and retinal degeneration in oxidative phosphorylation defects.

**Testing:** When an inherited disorder of metabolism is suspected, evaluation begins with simple metabolic screening tests, which typically include the following:

- Glucose
- Electrolytes
- CBC and peripheral smear
- Liver function tests
- Ammonia levels
- Urinalysis

Glucose measurement detects hypoglycemia or hyperglycemia; measurement may have to be timed relative to meals (eg, fasting hypoglycemia in GSD).

Electrolyte measurement detects metabolic acidosis and presence or absence of an anion gap; metabolic acidosis may need to be corroborated by ABG measurement. Non-anion gap acidosis occurs in inherited disorders of metabolism that cause renal tubular damage (eg, galactosemia, tyrosinemia type I). Anion gap acidosis occurs in inherited disorders of metabolism in which accumulation of titratable acids is typical, such as methylmalonic and propionic acidemias; it can also be caused by lactic acidosis (eg, in pyruvate decarboxylase deficiency or mitochondrial oxidative phosphorylation defects). When the anion gap is elevated, lactate and pyruvate levels should be obtained. An increase in the lactate:pyruvate ratio distinguishes oxidative phosphorylation defects from disorders of pyruvate metabolism, in which the lactate:pyruvate ratio remains normal.

CBC and peripheral smear detect hemolysis caused by RBC energy deficits or WBC defects (eg, in some pentose phosphate pathway disorders and GSD type Ib) and cytopenia caused by metabolite accumulation (eg, neutropenia in propionic acidemia due to propionyl CoA accumulation).

Liver function tests detect hepatocellular damage, dysfunction, or both (eg, in untreated galactosemia, hereditary fructose intolerance, or tyrosinemia type I).

Ammonia levels are elevated in urea cycle defects, organic acidemias, and fatty acid oxidation defects.

Urinalysis detects ketonuria (present in some GSDs and many organic acidemias); absence of ketones in the presence of acidosis suggests a fatty acid oxidation defect.

**More specific tests** may be indicated when ≥ 1 of the previously described simple screening tests support an inherited disorder of metabolism. Carbohydrate metabolites, mucopolysaccharides, and amino and organic acids can be measured directly by chromatography and mass spectrometry. Common tests include quantitative plasma amino acids, urine organic acids, plasma acylcarnitine profile, and urine acylglycine profile; these have replaced earlier nonspecific screening tests.

**Confirmatory tests** may also include biopsy (eg, liver biopsy to distinguish hepatic forms of GSDs from other disorders associated with hepatomegaly, muscle biopsy to detect ragged red fibers in mitochondrial myopathy); enzyme studies (eg, using blood and skin cells to diagnose lysosomal storage diseases); and DNA studies, which identify gene mutations that cause disease. DNA testing can be done on almost all cells (except RBCs and platelets), thus avoiding the need for tissue biopsies; however, sensitivity for any given disease is often suboptimal because not all mutations that cause disease have been characterized.

**Challenge testing** is used judiciously to detect symptoms, signs, or measurable biochemical abnormalities not detectable in the normal state. The need for challenge testing has diminished with the availability of highly sensitive metabolite detection methods, but it is still occasionally used. Examples include fasting tests (eg, to provoke hypoglycemia in hepatic forms of GSD); provocative tests (eg, fructose challenge to trigger symptoms in hereditary fructose intolerance, glucagon challenge in hepatic forms of GSD [failure to observe hyperglycemia suggests disease]); and physiologic challenge (eg, exercise stress testing to elicit lactic acid production and other deformities in muscle forms of GSD). Challenge tests are often associated with an element of risk so they must be done under well-controlled conditions with a clear plan for reversing symptoms and signs.

## Amino Acid and Organic Acid Metabolism Disorders

Defects of amino acid transport in the renal tubule are discussed in Ch. 297.

### Phenylketonuria

**Phenylketonuria (PKU) is a clinical syndrome of intellectual disability with cognitive and behavioral abnormalities caused by elevated serum phenylalanine. The primary cause is deficient phenylalanine hydroxylase activity. Diagnosis is by detecting high phenylalanine levels and normal or low tyrosine levels. Treatment is lifelong dietary phenylalanine restriction. Prognosis is excellent with treatment.**

PKU is most common among all white populations and relatively less common among Ashkenazi Jews, Chinese, and blacks. Inheritance is autosomal recessive; incidence is about 1/10,000 births among whites.

#### Pathophysiology

Excess dietary phenylalanine (ie, that not used for protein synthesis) is normally converted to tyrosine by phenylalanine hydroxylase; tetrahydrobiopterin (BH4) is an essential cofactor for this reaction. When one of several gene mutations results in deficiency or absence of phenylalanine hydroxylase, dietary phenylalanine accumulates; the brain is the main organ affected, possibly due to disturbance of myelination. Some of the excess phenylalanine is metabolized to phenylketones, which are excreted in the urine, giving rise to the term phenylketonuria. The degree of enzyme deficiency, and hence severity of hyperphenylalaninemia, varies among patients depending on the specific mutation.

**Variant forms:** Although nearly all cases (98 to 99%) of PKU result from phenylalanine hydroxylase deficiency, phenylalanine can also accumulate if BH4 is not synthesized because of deficiencies of dihydrobiopterin synthase or not regenerated because of deficiencies of dihydropteridine reductase.

Additionally, because BH4 is also a cofactor for tyrosine hydroxylase, which is involved in the synthesis of dopamine and serotonin, BH4 deficiency alters synthesis of neurotransmitters, causing neurologic symptoms independently of phenylalanine accumulation.

### Symptoms and Signs

Most children are normal at birth but develop symptoms and signs slowly over several months as phenylalanine accumulates. The hallmark of untreated PKU is severe intellectual disability. Children also manifest extreme hyperactivity, gait disturbance, and psychoses and often exhibit an unpleasant, mousy body odor caused by phenylacetic acid (a breakdown product of phenylalanine) in urine and sweat. Children also tend to have a lighter skin, hair, and eye color than unaffected family members, and some may develop a rash similar to infantile eczema.

### Diagnosis

• Routine neonatal screening

• Phenylalanine levels

In the US and many developed countries, all neonates are screened for PKU 24 to 48 h after birth with one of several blood tests; abnormal results are confirmed by directly measuring phenylalanine levels. In classic PKU, neonates often have phenylalanine levels > 20 mg/dL (1.2 mM/L). Those with partial deficiencies typically have levels < 8 to 10 mg/dL while on a normal diet (levels > 6 mg/dL require treatment); distinction from classic PKU requires a liver phenylalanine hydroxylase activity assay showing activity between 5% and 15% of normal or a mutation analysis identifying mild mutations in the gene.

BH4 deficiency is distinguished from other forms of PKU by elevated concentrations of biopterin or neopterin in urine, blood, CSF, or all 3; recognition is important, and the urine biopterin profile should be determined routinely at initial diagnosis because standard PKU treatment does not prevent neurologic damage.

Children in families with a positive family history can be diagnosed prenatally by using direct mutation studies after chorionic villus sampling or amniocentesis.

### Prognosis

Adequate treatment begun in the first days of life prevents all manifestations of disease. Treatment begun after 2 to 3 yr may be effective only in controlling the extreme hyperactivity and intractable seizures. Children born to mothers with poorly controlled PKU (ie, they have high phenylalanine levels) during pregnancy are at high risk of microcephaly and developmental deficit.

### Treatment

• Dietary phenylalanine restriction

Treatment is lifelong dietary phenylalanine restriction. All natural protein contains about 4% phenylalanine. Therefore dietary staples include low-protein natural foods (eg, fruits, vegetables, certain cereals), protein hydrolysates treated to remove phenylalanine, and phenylalanine-free elemental amino acid mixtures. Examples of commercially available phenylalanine-free products include XPhe products (XP Analog for infants, XP Maxamaid for children 1 to 8 yr, XP Maxamum for children > 8 yr); Phenex I and II; Phenyl-Free I and II; PKU-1, -2, and -3; PhenylAde (varieties); Loflex; and Plexy10. Some phenylalanine is required for growth and metabolism; this requirement is met by measured quantities of natural protein from milk or low-protein foods.

Frequent monitoring of plasma phenylalanine levels is required; recommended targets are between 2 mg/dL and 4 mg/dL (120 to 240µmol/L) for children < 12 yr and between 2 mg/dL and 10 mg/dL (120 to 600 µmol/L) for children > 12 yr. Dietary planning and management need to be initiated in women of childbearing age before pregnancy to ensure a good outcome for the child. Tyrosine supplementation is

increasingly used because it is an essential amino acid in patients with PKU. In addition, sapropterin supplementation is increasingly being used.

For those with BH4 deficiency, treatment also includes tetrahydrobiopterin 1 to 5 mg/kg po tid; levodopa, carbidopa, and 5-OH tryptophan; and folinic acid 10 to 20 mg po once/day in cases of dihydropteridine reductase deficiency. However, treatment goals and approach are the same as those for PKU.

**Disorders of Tyrosine Metabolism**

**Tyrosine is a precursor of several neurotransmitters (eg, dopamine, norepinephrine, epinephrine), hormones (eg, thyroxine), and melanin; deficiencies of enzymes involved in its metabolism lead to a variety of syndromes.**

**Transient tyrosinemia of the newborn:** Transient immaturity of metabolic enzymes, particularly 4-hydroxyphenylpyruvic acid dioxygenase, sometimes leads to elevated plasma tyrosine levels (usually in premature infants, particularly those receiving high-protein diets); metabolites may show up on routine neonatal screening for PKU.

Most infants are asymptomatic, but some have lethargy and poor feeding.

Tyrosinemia is distinguished from PKU by elevated plasma tyrosine levels.

Most cases resolve spontaneously. Symptomatic patients should have dietary tyrosine restriction (2 g/kg/day) and be given vitamin C 200 to 400 mg po once/day.

**Tyrosinemia type I:** This disorder is an autosomal recessive trait caused by deficiency of fumarylacetoacetate hydroxylase, an enzyme important for tyrosine metabolism.

Disease may manifest as fulminant liver failure in the neonatal period or as indolent sub-clinical hepatitis, painful peripheral neuropathy, and renal tubular disorders (eg, normal anion gap metabolic acidosis, hypophosphatemia, vitamin D-resistant rickets) in older infants and children. Children who do not die from associated liver failure in infancy have a significant risk of developing liver cancer.

Diagnosis is suggested by elevated plasma levels of tyrosine; it is confirmed by a high level of succinylacetone in plasma or urine and by low fumarylacetoacetate hydroxylase activity in blood cells or liver biopsy specimens. Treatment with 2(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclo-hexanedione (NTBC) is effective in acute episodes and slows progression.

A diet low in phenylalanine and tyrosine is recommended. Liver transplantation is effective.

**Tyrosinemia type II:** This rare autosomal recessive disorder is caused by tyrosine transaminase deficiency.

Accumulation of tyrosine causes cutaneous and corneal ulcers. Secondary elevation of phenylalanine, though mild, may cause neuropsychiatric abnormalities if not treated.

Diagnosis is by elevation of tyrosine in plasma, absence of succinylacetone in plasma or urine, and measurement of decreased enzyme activity in liver biopsy.

This disorder is easily treated with mild to moderate restriction of dietary phenylalanine and tyrosine.

**Alkaptonuria:** This rare autosomal recessive disorder is caused by homogentisic acid oxidase deficiency; homogentisic acid oxidation products accumulate in and darken skin, and crystals precipitate in joints.

The condition is usually diagnosed in adults and causes dark skin pigmentation (ochronosis) and arthritis. Urine turns dark when exposed to air because of oxidation products of homogentisic acid. Diagnosis is by finding elevated urinary levels of homogentisic acid (> 4 to 8 g/24 h).

There is no effective treatment, but ascorbic acid 1 g po once/day may diminish pigment deposition by increasing renal excretion of homogentisic acid.

**Oculocutaneous albinism:** Tyrosinase deficiency results in absence of skin and retinal pigmentation, causing a much increased risk of skin cancer and considerable vision loss. Nystagmus is often present, and photophobia is common (see also Albinism on p. 719).

**Disorders of Branched-Chain Amino Acid Metabolism**

**Valine, leucine, and isoleucine are branched-chain amino acids; deficiency of enzymes involved in their metabolism leads to accumulation of organic acids with severe metabolic acidosis.**

**Maple syrup urine disease:** This is a group of autosomal recessive disorders caused by deficiency of one or more subunits of a dehydrogenase active in the 2nd step of branched-chain amino acid catabolism. Although quite rare, incidence is significant (perhaps 1/200 births) in Amish and Mennonite populations.

Clinical manifestations include body fluid odor that resembles maple syrup (particularly strong in cerumen) and overwhelming illness in the first days of life, beginning with vomiting and lethargy, and progressing to seizures, coma, and death if untreated. Patients with milder forms of the disease may manifest symptoms only during stress (eg, infection, surgery).

Biochemical findings are profound ketonemia and acidemia. Diagnosis is by finding elevated plasma levels of branched-chain amino acids (particularly leucine).

Acutely, treatment with peritoneal dialysis or hemodialysis may be required, along with IV hydration and nutrition (including high-dose dextrose). Long-term management is restriction of dietary branched-chain amino acids; however, small amounts are required for normal metabolic function. Thiamin is a cofactor for the decarboxylation, and some patients respond favorably to high-dose thiamin (up to 200 mg po once/day). Liver transplantation is curative.

**Isovaleric acidemia:** The 3rd step of leucine metabolism is the conversion of isovaleryl CoA to 3-methylcrotonyl CoA, a dehydrogenation step. Deficiency of this dehydrogenase results in isovaleric acidemia, also known as "sweaty feet" syndrome, because accumulated isovaleric acid emits an odor that smells like sweat.

Clinical manifestations of the acute form occur in the first few days of life with poor feeding, vomiting, and respiratory distress as infants develop profound anion gap metabolic acidosis, hypoglycemia, and hyperammonemia. Bone marrow suppression often occurs. A chronic intermittent form may not manifest for several months or years.

Diagnosis is made by detecting elevated levels of isovaleric acid and its metabolites in blood or urine.

Acute treatment is with IV hydration and nutrition (including high-dose dextrose) and measures to increase renal isovaleric acid excretion by conjugation with glycine. If these measures are insufficient, exchange transfusion and peritoneal dialysis may be needed. Long-term treatment is with dietary leucine restriction and continuation of glycine and carnitine supplements. Prognosis is excellent with treatment.

**Propionic acidemia:** Deficiency of propionyl CoA carboxylase, the enzyme responsible for metabolizing propionic acid to methylmalonate, causes propionic acid accumulation.

Illness begins in the first days or weeks of life with poor feeding, vomiting, and respiratory distress due to profound anion gap metabolic acidosis, hypoglycemia, and hyperammonemia. Seizures may occur, and bone marrow suppression is common. Physiologic stresses may trigger recurrent attacks. Survivors may have tubular nephropathies, intellectual disability, and neurologic abnormalities. Propionic acidemia can also be seen as part of multiple carboxylase deficiency, biotin deficiency, or biotinidase deficiency.

Diagnosis is suggested by elevated levels of propionic acid metabolites, including methylcitrate and tiglate and their glycine conjugates in blood and urine, and confirmed by measuring propionyl CoA carboxylase activity in WBCs or cultured fibroblasts.

Acute treatment is with IV hydration (including high-dose dextrose) and nutrition; carnitine may be helpful. If these measures are insufficient, peritoneal dialysis or hemodialysis may be needed. Long-term treatment is dietary restriction of precursor amino acids and odd-chain fatty acids and possibly continuation of carnitine supplementation. A few patients respond to high-dose biotin because it is a cofactor for propionyl CoA and other carboxylases.

**Methylmalonic acidemia:** This disorder is caused by deficiency of methylmalonyl CoA mutase, which converts methylmalonyl CoA (a product of the propionyl CoA carboxylation) into succinyl CoA. Adenosylcobalamin, a metabolite of vitamin $B_{12}$, is a cofactor; its deficiency also may cause methylmalonic acidemia (and also homocystinuria and megaloblastic anemia). Methylmalonic acid accumulates. Age of onset, clinical manifestations, and treatment are similar to those of propionic acidemia except that cobalamin, instead of biotin, may be helpful for some patients.

**Disorders of Methionine Metabolism**

**A number of defects in methionine metabolism lead to accumulation of homocysteine (and its dimer, homocystine) with adverse effects including thrombotic tendency, lens dislocation, and CNS and skeletal abnormalities.**

Homocysteine is an intermediate in methionine metabolism; it is either remethylated to regenerate methionine or combined with serine in a series of transsulfuration reactions to form cystathionine and then cysteine. Cysteine is then metabolized to sulfite, taurine, and glutathione. Various defects in remethylation or transsulfuration can cause homocysteine to accumulate, resulting in disease.

The first step in methionine metabolism is its conversion to adenosylmethionine; this conversion requires the enzyme methionine adenosyltransferase. Deficiency of this enzyme results in methionine elevation, which is not clinically significant except that it causes false-positive neonatal screening results for homocystinuria.

**Classic homocystinuria:** This disorder is caused by an autosomal recessive deficiency of cystathionine β-synthase, which catalyzes cystathionine formation from homocysteine and serine. Homocysteine accumulates and dimerizes to form the disulfide homocystine, which is excreted in the urine. Because remethylation is intact, some of the additional homocysteine is converted to methionine, which accumulates in the blood. Excess homocysteine predisposes to thrombosis and has adverse effects on connective tissue (perhaps involving fibrillin), particularly the eyes and skeleton; adverse neurologic effects may be due to thrombosis or a direct effect.

Arterial and venous thromboembolic phenomena can occur at any age. Many patients develop ectopia lentis (lens subluxation), intellectual disability, and osteoporosis. Patients can have a marfanoid habitus even though they are not usually tall.

Diagnosis is by neonatal screening for elevated serum methionine; elevated total plasma homocysteine levels are confirmatory. Enzymatic assay in skin fibroblasts can also be done.

Treatment is a low-methionine diet, combined with high-dose pyridoxine (a cystathionine synthetase cofactor) 100 to 500 mg po once/day. Because about half of patients respond to high-dose pyridoxine alone, some clinicians do not restrict methionine intake in these patients. Betaine (trimethylglycine), which enhances remethylation, can also help lower homocysteine; dosage is 100 to 125 mg/kg po bid. Folate 500 to 1000 µg once/day is also given. With early treatment, intellectual outcome is normal or near normal.

**Other forms of homocystinuria:** Various defects in the remethylation process can result in homocystinuria. Defects include deficiencies of methionine synthase (MS) and MS reductase (MSR),

delivery of methylcobalamin and adenosylcobalamin, and deficiency of methylenetetrahydrofolate reductase (MTHFR, which is required to generate the 5-methyltetrahydrofolate needed for the MS reaction). Because there is no methionine elevation in these forms of homocystinuria, they are not detected by neonatal screening.

Clinical manifestations are similar to other forms of homocystinuria. In addition, MS and MSR deficiencies are accompanied by neurologic deficits and megaloblastic anemia. Clinical manifestation of MTHFR deficiency is variable, including intellectual disability, psychosis, weakness, ataxia, and spasticity.

Diagnosis of MS and MSR deficiencies is suggested by homocystinuria and megaloblastic anemia and confirmed by DNA testing. Patients with cobalamin defects have megaloblastic anemia and methylmalonic acidemia. MTHFR deficiency is diagnosed by DNA testing.

Treatment is by replacement of hydroxycobalamin 1 mg IM once/day (for patients with MS, MSR, and cobalamin defects) and folate in supplementation similar to characteristic homocystinuria.

**Cystathioninuria:** This disorder is caused by deficiency of cystathionase, which converts cystathionine to cysteine. Cystathionine accumulation results in increased urinary excretion but no clinical symptoms.

**Sulfite oxidase deficiency:** Sulfite oxidase converts sulfite to sulfate in the last step of cysteine and methionine degradation; it requires a molybdenum cofactor. Deficiency of either the enzyme or the cofactor causes similar disease; inheritance for both is autosomal recessive.

In its most severe form, clinical manifestations appear in neonates and include seizures, hypotonia, and myoclonus, progressing to early death. Patients with milder forms may present similarly to cerebral palsy (see p. 2896) and may have choreiform movements.

Diagnosis is suggested by elevated urinary sulfite and confirmed by measuring enzyme levels in fibroblasts and cofactor levels in liver biopsy specimens. Treatment is supportive.

### Urea Cycle Disorders

**Urea cycle disorders (UCDs) are characterized by hyperammonemia under catabolic or protein-loading conditions.**

Primary UCDs include carbamoyl phosphate synthase (CPS) deficiency, ornithine transcarbamylase (OTC) deficiency, argininosuccinate synthetase deficiency (citrullinemia), argininosuccinate lyase deficiency (argininosuccinic aciduria), and arginase deficiency (argininemia). In addition, N-acetylglutamate synthetase (NAGS) deficiency has been reported. The more "proximal" the enzyme deficiency is, the more severe the hyperammonemia; thus, disease severity in descending order is NAGS deficiency, CPS deficiency, OTC deficiency, citrullinemia, argininosuccinic aciduria, and argininemia.

Inheritance for all UCDs is autosomal recessive, except for OTC deficiency, which is X-linked.

#### Symptoms and Signs

Clinical manifestations range from mild (eg, failure to thrive, intellectual disability, episodic hyperammonemia) to severe (eg, altered mental status, coma, death). Manifestations in females with OTC deficiency range from growth failure, developmental delay, psychiatric abnormalities, and episodic (especially postpartum) hyperammonemia to a phenotype similar to that of affected males.

#### Diagnosis

• Serum amino acid profiles

Diagnosis is based on amino acid profiles. For example, elevated ornithine indicates CPS deficiency or OTC deficiency, whereas elevated citrulline indicates citrullinemia. To distinguish between CPS deficiency and OTC deficiency, orotic acid measurement is helpful because accumulation of carbamoyl phosphate in

OTC deficiency results in its alternative metabolism to orotic acid.

**Treatment**

• Dietary protein restriction

• Arginine or citrulline supplementation

• Sometimes liver transplantation

Treatment is dietary protein restriction that still provides adequate amino acids for growth, development, and normal protein turnover. Arginine has become a staple of treatment. It supplies adequate urea cycle intermediates to encourage the incorporation of more nitrogen moieties into urea cycle intermediates, each of which is readily excretable. Arginine is also a positive regulator of acetylglutamate synthesis. Recent studies suggest that oral citrulline is more effective than arginine in patients with OTC deficiency. Additional treatment is with Na benzoate, phenylbutyrate, or phenylacetate, which by conjugating glycine (Na benzoate) and glutamine (phenylbutyrate and phenylacetate) provides a "nitrogen sink."

Despite these therapeutic advances, many UCDs remain difficult to treat, and liver transplantation is eventually required for many patients. Timing of liver transplantation is critical. Optimally, the infant should grow to an age when transplantation is less risky (> 1 yr), but it is important to not wait so long as to allow an intercurrent episode of hyperammonemia (often associated with illness) to cause irreparable harm to the CNS.

## Carbohydrate Metabolism Disorders

### Glycogen Storage Diseases

**Glycogen storage diseases (GSDs) are caused by deficiencies of enzymes involved in glycogen synthesis or breakdown; the deficiencies may occur in the liver or muscles and cause hypoglycemia or deposition of abnormal amounts or types of glycogen (or its intermediate metabolites) in tissues.**

Inheritance for GSDs is autosomal recessive except for GSD type VIII/IX, which is X-linked. Incidence is estimated at about 1/25,000 births, which may be an underestimate because milder subclinical forms may be undiagnosed.

Age of onset, clinical manifestations, and severity vary by type, but symptoms and signs are most commonly those of hypoglycemia and myopathy. Diagnosis is suspected by history, examination, and detection of glycogen and intermediate metabolites in tissues by MRI or biopsy.

Diagnosis is confirmed by significant decrease of enzyme activity in liver (types I, III, VI, and VIII/IX), muscle (types IIb, III, VII, and VIII/IX), skin fibroblasts (types IIa and IV), or RBCs (type VII) or by lack of an increase in venous lactate with forearm activity/ischemia (types V and VII). Prognosis and treatment vary by type, but treatment typically includes dietary supplementation with cornstarch to provide a sustained source of glucose for the hepatic forms of GSD and exercise avoidance for the muscle forms.

**Defects in glycolysis** (rare) may cause syndromes similar to GSDs. Deficiencies of phosphoglycerate kinase, phosphoglycerate mutase, and lactate dehydrogenase mimic the myopathies of GSD types V and VII; deficiencies of glucose transport protein 2 (Fanconi-Bickel syndrome) mimic the hepatopathy of other GSD types (eg, I, III, IV, VI).

### Galactosemia

**Galactosemia is caused by inherited deficiencies in enzymes that convert galactose to glucose. Symptoms and signs include hepatic and renal dysfunction, cognitive deficits, cataracts, and premature ovarian failure. Diagnosis is by enzyme analysis of RBCs. Treatment is dietary elimination of galactose. Physical prognosis is good with treatment, but cognitive and**

**performance parameters are often subnormal.**

Galactose is found in dairy products, fruits, and vegetables. Autosomal recessive enzyme deficiencies cause 3 clinical syndromes.

**Galactose-1-phosphate uridyl transferase deficiency:** This deficiency causes classic galactosemia. Incidence is 1/62,000 births; carrier frequency is 1/125. Infants become anorectic and jaundiced within a few days or weeks of consuming breast milk or lactose-containing formula. Vomiting, hepatomegaly, poor growth, lethargy, diarrhea, and septicemia (usually *Escherichia coli*) develop, as does renal dysfunction (eg, proteinuria, aminoaciduria, Fanconi syndrome), leading to metabolic acidosis and edema. Hemolytic anemia may also occur. Without treatment, children remain short and develop cognitive, speech, gait, and balance deficits in their teenage years; many also have cataracts, osteomalacia (caused by hypercalciuria), and premature ovarian failure. Patients with the Duarte variant have a much milder phenotype.

**Galactokinase deficiency:** Patients develop cataracts from production of galactitol, which osmotically damages lens fibers; idiopathic intracranial hypertension (pseudotumor cerebri) is rare. Incidence is 1/40,000 births.

**Uridine diphosphate galactose 4-epimerase deficiency:** There are benign and severe phenotypes. Incidence of the benign form is 1/23,000 births in Japan; no incidence data are available for the more severe form. The benign form is restricted to RBCs and WBCs and causes no clinical abnormalities. The severe form causes a syndrome indistinguishable from classic galactosemia, although sometimes with hearing loss.

**Diagnosis**

• Galactose levels

• Enzyme analysis

Diagnosis is suggested clinically and supported by elevated galactose levels and the presence of reducing substances other than glucose (eg, galactose, galactose 1-phosphate) in the urine; it is confirmed by enzyme analysis of RBCs, hepatic tissue, or both. Most states require that neonates be screened for galactose-1-phosphate uridyl transferase deficiency.

**Treatment**

• Dietary galactose restriction

Treatment is elimination of all sources of galactose in the diet, most notably lactose, which is a source of galactose present in all dairy products, including milk-based infant formulas and a sweetener used in many foods. A lactose-free diet prevents acute toxicity and reverses some manifestations (eg, cataracts) but may not prevent neurocognitive deficits. Many patients require supplemental Ca and vitamins. For patients with epimerase deficiency, some galactose intake is critical to ensure a supply of uridine-5´-diphosphate-galactose (UDP-galactose) for various metabolic processes.

**Disorders of Fructose Metabolism**

**Deficiency of enzymes that metabolize fructose may be asymptomatic or cause hypoglycemia.**

Fructose is a monosaccharide that is present in high concentrations in fruit and honey and is a constituent of sucrose and sorbitol.

**Fructose 1-phosphate aldolase (aldolase B) deficiency:** This deficiency causes the clinical syndrome of hereditary fructose intolerance. Inheritance is autosomal recessive; incidence is estimated at 1/20,000 births. Infants are healthy until they ingest fructose; fructose 1-phosphate then accumulates, causing hypoglycemia, nausea and vomiting, abdominal pain, sweating, tremors, confusion, lethargy, seizures,

and coma. Prolonged ingestion may cause cirrhosis, mental deterioration, and proximal renal tubular acidosis with urinary loss of phosphate and glucose.

Diagnosis is suggested by symptoms in relation to recent fructose intake and is confirmed by enzyme analysis of liver biopsy tissue or by induction of hypoglycemia by fructose infusion 200 mg/kg IV. Diagnosis and identification of heterozygous carriers of the mutated gene can also be made by direct DNA analysis.

Short-term treatment is glucose for hypoglycemia; long-term treatment is exclusion of dietary fructose, sucrose, and sorbitol. Many patients develop a natural aversion to fructose-containing food. Prognosis is excellent with treatment.

**Fructokinase deficiency:** This deficiency causes benign elevation of blood and urine fructose levels (benign fructosuria). Inheritance is autosomal recessive; incidence is about 1/130,000 births.

The condition is asymptomatic and diagnosed accidentally when a non-glucose reducing substance is detected in urine.

**Deficiency of fructose-1,6-bisphosphatase:** This deficiency compromises gluconeogenesis and results in fasting hypoglycemia, ketosis, and acidosis. This deficiency can be fatal in neonates. Inheritance is autosomal recessive; incidence is unknown. Febrile illness can trigger episodes.

Acute treatment is oral or IV glucose. Tolerance to fasting generally increases with age.

**Disorders of Pyruvate Metabolism**

**Inability to metabolize pyruvate causes lactic acidosis and a variety of CNS abnormalities.**

Pyruvate is an important substrate in carbohydrate metabolism.

**Pyruvate dehydrogenase deficiency:** Pyruvate dehydrogenase is a multi-enzyme complex responsible for the generation of acetyl CoA from pyruvate for the Krebs cycle. Deficiency results in elevation of pyruvate and thus elevation of lactic acid levels. Inheritance is X-linked or autosomal recessive.

Clinical manifestations vary in severity but include lactic acidosis and CNS malformations and other postnatal changes, including cystic lesions of the cerebral cortex, brain stem, and basal ganglia; ataxia; and psychomotor retardation.

Diagnosis is confirmed by enzyme analysis of skin fibroblasts, DNA testing, or both.

There is no clearly effective treatment, although a low-carbohydrate or ketogenic diet and dietary thiamin supplementation have been beneficial for some patients.

**Pyruvate carboxylase deficiency:** Pyruvate carboxylase is an enzyme important for gluconeogenesis from pyruvate and alanine generated in muscle. Deficiency may be primary, or secondary to deficiency of holocarboxylase synthetase, biotin, or biotinidase; inheritance for both is autosomal recessive, and both result in lactic acidosis.

Primary deficiency incidence is < 1/250,000 births but may be higher in certain American Indian populations. Psychomotor retardation with seizures and spasticity are the major clinical manifestations. Laboratory abnormalities include hyperammonemia; lactic acidosis; ketoacidosis; elevated levels of plasma lysine, citrulline, alanine, and proline; and increased excretion of α-ketoglutarate. Diagnosis is confirmed by enzyme analysis of cultured skin fibroblasts.

Secondary deficiency is clinically similar, with failure to thrive, seizures, and other organic aciduria.

There is no effective treatment, but some patients with primary deficiency and all those with secondary deficiencies should be given biotin supplementation 5 to 20 mg po once/day.

### Other Disorders of Carbohydrate Metabolism

**Phosphoenolpyruvate carboxykinase deficiency** impairs gluconeogenesis and results in symptoms and signs similar to the hepatic forms of glycogen storage disease but without hepatic glycogen accumulation.

**Other deficiencies** include those of glycolytic enzymes or enzymes in the pentose phosphate pathway. Common examples are pyruvate kinase deficiency (see p. 941) and glucose-6-phosphate dehydrogenase (G6PD) deficiency (see p. 941), both of which may result in hemolytic anemia. Wernicke-Korsakoff syndrome (see p. 33) is caused by a partial deficiency of transketolase, which is an enzyme for the pentose phosphate pathway that requires thiamin as a cofactor.

## Fatty Acid and Glycerol Metabolism Disorders

Fatty acids are the preferred energy source for the heart and an important energy source for skeletal muscle during prolonged exertion. Also, during fasting, the bulk of the body's energy needs must be supplied by fat metabolism. Using fat as an energy source requires catabolizing adipose tissue into free fatty acid and glycerol. The free fatty acid is metabolized in the liver and peripheral tissue via β-oxidation into acetyl CoA; the glycerol is used by the liver for triglyceride synthesis or for gluconeogenesis. Primary disorders of carnitine are discussed on p. 18, but secondary carnitine deficiency is a secondary biochemical feature of many organic acidemias and fatty acid oxidation defects.

### Disorders of the β-Oxidation Cycle

**In these processes, there are numerous inherited defects, which typically manifest during fasting with hypoglycemia and acidosis; some cause cardiomyopathy and muscle weakness.**

Acetyl CoA is generated from fatty acids through repeated β-oxidation cycles. Sets of 4 enzymes (an acyl dehydrogenase, a hydratase, a hydroxyacyl dehydrogenase, and a lyase) specific for different chain lengths (very long chain, long chain, medium chain, and short chain) are required to catabolize a long-chain fatty acid completely. Inheritance for all fatty acid oxidation defects is autosomal recessive.

**Medium-chain acyl dehydrogenase deficiency (MCADD):** This deficiency is the most common defect in the β-oxidation cycle and has been incorporated into expanded neonatal screening in many states.

Clinical manifestations typically begin after 2 to 3 mo of age and usually follow fasting (as little as 12 h). Patients have vomiting and lethargy that may progress rapidly to seizures, coma, and sometimes death (which can also appear as SIDS). During attacks, patients have hypoglycemia, hyperammonemia, and unexpectedly low urinary and serum ketones. Metabolic acidosis is often present but may be a late manifestation.

Diagnosis is by detecting medium-chain fatty acid conjugates of carnitine in plasma or glycine in urine or by detecting enzyme deficiency in cultured fibroblasts; however, DNA testing can confirm most cases.

Treatment of acute attacks is with 10% dextrose IV at 1.5 times the fluid maintenance rate (see p. 2808); some clinicians also advocate carnitine supplementation during acute episodes. Prevention is a low-fat, high-carbohydrate diet and avoidance of prolonged fasting. Cornstarch therapy is often used to provide a margin of safety during overnight fasting.

**Long-chain hydroxyacyl-CoA dehydrogenase deficiency (LCHADD):** This deficiency is the 2nd most common fatty acid oxidation defect. It shares many features of MCADD, but patients may also have cardiomyopathy; rhabdomyolysis, massive creatine kinase elevations, and myoglobinuria with muscle exertion; peripheral neuropathy; and abnormal liver function. Mothers with an LCHADD fetus often have HELLP syndrome (hemolysis, elevated liver enzymes, low platelets—see p. 2670) during pregnancy.

Diagnosis is based on the presence of excess long-chain hydroxy acids on organic acid analysis and on the presence of their carnitine conjugates in an acylcarnitine profile or glycine conjugates in an

acylglycine profile. LCHADD can be confirmed by enzyme study in skin fibroblasts.

Treatment during acute exacerbations includes hydration, high-dose glucose, bed rest, urine alkalinization, and carnitine supplementation. Long-term treatment includes a high-carbohydrate diet, medium-chain triglyceride supplementation, and avoidance of fasting and strenuous exercise.

**Very long-chain acyl-coA dehydrogenase deficiency (VLCADD):** This deficiency is similar to LCHADD but is commonly associated with significant cardiomyopathy.

**Glutaric acidemia type II:** A defect in the transfer of electrons from the coenzyme of fatty acyl dehydrogenases to the electronic transport chain affects reactions involving fatty acids of all chain lengths (multiple acylcoA dehydrogenase deficiency); oxidation of several amino acids is also affected.

Clinical manifestations thus include fasting hypoglycemia, severe metabolic acidosis, and hyperammonemia.

Diagnosis is by increased ethylmalonic, glutaric, 2- and 3-hydroxyglutaric, and other dicarboxylic acids in organic acid analysis, and glutaryl and isovaleryl and other acylcarnitines in tandem mass spectrometry studies. Enzyme deficiencies in skin fibroblasts can be confirmatory.

Treatment is similar to that for MCADD, except that riboflavin may be effective in some patients.

### Disorders of Glycerol Metabolism

**Glycerol is converted to glycerol-3-phosphate by the hepatic enzyme glycerol kinase; deficiency results in episodic vomiting, lethargy, and hypotonia.**

Glycerol kinase deficiency is X-linked; many patients with this deficiency also have a chromosomal deletion that extends beyond the glycerol kinase gene into the contiguous gene region, which contains the genes for congenital adrenal hypoplasia and Duchenne muscular dystrophy. Thus, patients with glycerol kinase deficiency may have one or more of these disease entities.

Symptoms begin at any age and are usually accompanied by acidosis, hypoglycemia, and elevated blood and urine levels of glycerol.

Diagnosis is by detecting an elevated level of glycerol in serum and urine and is confirmed by DNA analysis.

Treatment is with a low-fat diet, but glucocorticoid replacement is critical for those with adrenal hypoplasia.

## Lysosomal Storage Disorders

Lysosomal enzymes break down macromolecules, either those from the cell itself (eg, when cellular structural components are being recycled) or those acquired outside the cell. Inherited defects or deficiencies of lysosomal enzymes (or other lysosomal components) can result in accumulation of undegraded metabolites. Because there are numerous specific deficiencies, storage diseases are usually grouped biochemically by the accumulated metabolite. Subgroups include

- Mucopolysaccharidoses
- Sphingolipidoses (lipidoses)
- Mucolipidoses

The most important are the mucopolysaccharidoses and sphingolipidoses. Type 2 glycogenosis is a lysosomal storage disorder, but most glycogenoses are not.

Because reticuloendothelial cells (eg, in the spleen) are rich in lysosomes, reticuloendothelial tissues are involved in a number of lysosomal storage disorders, but generally, tissues richest in the substrate are most affected. Thus the brain, which is rich in gangliosides, is particularly affected by gangliosidoses, whereas mucopolysaccharidoses affect many tissues because mucopolysaccharides are present throughout the body.

**Mucopolysaccharidoses (MPS):** MPS are inherited deficiencies of enzymes involved in glycosaminoglycan breakdown. Glycosaminoglycans (previously termed mucopolysaccharides) are polysaccharides abundant on cell surfaces and in extracellular matrix and structures. Enzyme deficiencies that prevent glycosaminoglycan breakdown cause accumulation of glycosaminoglycan fragments in lysosomes and cause extensive bone, soft tissue, and CNS changes. Inheritance is usually autosomal recessive (except for MPS type II).

Age at presentation, clinical manifestations, and severity vary by type. Common manifestations include coarse facial features, neurodevelopmental delays and regression, joint contractures, organomegaly, stiff hair, progressive respiratory insufficiency (caused by airway obstruction and sleep apnea), cardiac valvular disease, skeletal changes, and cervical vertebral subluxation.

Diagnosis is suggested by history, physical examination, bone abnormalities (eg, dysostosis multiplex) found during skeletal survey, and elevated total and fractionated urinary glycosaminoglycans. Diagnosis is confirmed by enzyme analysis of cultured fibroblasts (prenatal) or peripheral WBCs (postnatal). Additional testing is required to monitor organ-specific changes (eg, echocardiography for valvular disease, audiometry for hearing changes).

Treatment of MPS type I (Hurler's disease) is enzyme replacement with α-l-iduronidase, which effectively halts progression and reverses all non-CNS complications of the disease. Hematopoietic stem cell (HSC) transplantation has also shown promise in early studies but is ineffective for CNS disease. The combination of enzyme replacement and HSC transplantation is under study.

**Sphingolipidoses:** Sphingolipids are normal lipid components of cell membranes; they accumulate in lysosomes and cause extensive neuronal, bone, and other changes when enzyme deficiencies prevent their breakdown. Although incidence is low, carrier rate of some forms is high. Gaucher's disease is the most common sphingolipidosis. Others include Niemann-Pick, Tay-Sachs, Sandhoff's, Fabry's, Krabbe's, and cholesteryl ester storage diseases and metachromatic leukodystrophy.

### Gaucher's Disease

**Gaucher's disease is a sphingolipidosis resulting from glucocerebrosidase deficiency, causing deposition of glucocerebroside and related compounds. Symptoms and signs vary by type but are most commonly hepatosplenomegaly or CNS changes. Diagnosis is by enzyme analysis of WBCs.**

Glucocerebrosidase normally hydrolyzes glucocerebroside to glucose and ceramide. Genetic defects of the enzyme cause glucocerebroside accumulation in tissue macrophages through phagocytosis, forming Gaucher's cells. Accumulation of Gaucher's cells in the perivascular spaces in the brain causes gliosis in the neuronopathic forms. There are 3 types, which vary in epidemiology, enzyme activity, and manifestations.

**Type I** (nonneuronopathic) is most common (90% of all patients). Residual enzyme activity is highest. Ashkenazi Jews are at greatest risk; 1/12 is a carrier. Onset ranges from age 2 yr to late adulthood. Symptoms and signs include splenohepatomegaly, bone disease (eg, osteopenia, pain crises, osteolytic lesions with fractures), growth failure, delayed puberty, ecchymoses, and pingueculae. Epistaxis and ecchymoses resulting from thrombocytopenia are common. X-rays show flaring of the ends of the long bones (Erlenmeyer flask deformity) and cortical thinning.

**Type II** (acute neuronopathic) is rarest, and residual enzyme activity in this type is lowest. Onset occurs during infancy. Symptoms and signs are progressive neurologic deterioration (eg, rigidity, seizures) and death by age 2 yr.

**Type III** (subacute neuronopathic) falls between types I and II in incidence, enzyme activity, and clinical severity. Onset occurs at any time during childhood. Clinical manifestations vary by subtype and include progressive dementia and ataxia (IIIa), bone and visceral involvement (IIIb), and supranuclear palsies with corneal opacities (IIIc). Patients who survive to adolescence may live for many years.

**Diagnosis**

• Enzyme analysis

Diagnosis is by enzyme analysis of WBCs. Carriers are detected, and types are distinguished by mutation analysis. Although biopsy is unnecessary, Gaucher's cells—lipid-laden tissue macrophages in the liver, spleen, lymph nodes, or bone marrow that have a wrinkled tissue-paper appearance—are diagnostic.

**Treatment**

• Types I and III: Enzyme replacement with placental or recombinant glucocerebrosidase

• Sometimes miglustat, splenectomy, or stem cell transplantation

Enzyme replacement with placental or recombinant glucocerebrosidase is effective in types I and III; there is no treatment for type II. The enzyme is modified for efficient delivery to lysosomes. Patients receiving enzyme replacement require routine Hb and platelet monitoring, routine assessment of spleen and liver volume by CT or MRI, and routine assessment of bone disease by skeletal survey, dual-energy x-ray absorptiometry scanning, or MRI.

Miglustat (100 mg po tid), a glucosylceramide synthase inhibitor, reduces glucocerebroside concentration (the substrate for glucocerebrosidase) and is an alternative for patients unable to receive enzyme replacement.

Splenectomy may be helpful for patients with anemia, leukopenia, or thrombocytopenia or when spleen size causes discomfort. Patients with anemia may also need blood transfusions.

Bone marrow or stem cell transplantation provides a definitive cure but is considered a last resort because of substantial morbidity and mortality.

**Niemann-Pick Disease**

**Niemann-Pick disease is a sphingolipidosis caused by deficient sphingomyelinase activity, resulting in accumulation of sphingomyelin (ceramide phosphorylcholine) in reticuloendothelial cells.**

Niemann-Pick disease inheritance is autosomal recessive and appears most often in Ashkenazi Jews; 2 types, A and B, exist. Type C Niemann-Pick disease is an unrelated enzymatic defect involving abnormal cholesterol storage.

**Type A** patients have < 5% of normal sphingomyelinase activity. The disease is characterized by hepatosplenomegaly, failure to thrive, and rapidly progressive neurodegeneration. Death occurs by age 2 or 3 yr.

**Type B** patients have sphingomyelinase activity within 5 to 10% of normal. Type B is more variable clinically than type A. Hepatosplenomegaly and lymphadenopathy may occur. Pancytopenia is common. Most patients with type B have little or no neurologic involvement and survive into adulthood; they may be clinically indistinguishable from those with type I Gaucher's disease. In severe cases of type B, progressive pulmonary infiltrates cause major complications.

**Diagnosis**

• Prenatal screening

• WBC sphingomyelinase assay

Both types are usually suspected by history and examination, most notably hepatosplenomegaly. Diagnosis can be confirmed by sphingomyelinase assay on WBCs and can be made prenatally by using amniocentesis or chorionic villus sampling.

**Treatment**

Bone marrow or stem cell transplantation is under investigation as a potential treatment option.

**Tay-Sachs Disease and Sandhoff's Disease**

**Tay-Sachs disease and Sandhoff's disease are sphingolipidoses caused by hexosaminidase deficiency that causes severe neurologic symptoms and early death.**

Gangliosides are complex sphingolipids present in the brain. There are 2 major forms, $GM_1$ and $GM_2$, both of which may be involved in lysosomal storage disorders; there are 2 main types of $GM_2$ gangliosidosis, each of which can be caused by numerous different mutations.

**Tay-Sachs disease:** Deficiency of hexosaminidase A results in accumulation of $GM_2$ in the brain. Inheritance is autosomal recessive; the most common mutations are carried by 1/27 normal adults of Eastern European (Ashkenazi) Jewish origin, although other mutations cluster in some French-Canadian and Cajun populations.

Children with Tay-Sachs disease start missing developmental milestones after age 6 mo and develop progressive cognitive and motor deterioration resulting in seizures, intellectual disability, paralysis, and death by age 5 yr. A cherry-red macular spot is common.

Diagnosis is clinical and can be confirmed by enzyme assay.

In the absence of effective treatment, management is focused on screening adults of childbearing age in high-risk populations to identify carriers (by way of enzyme activity and mutation testing) combined with genetic counseling.

**Sandhoff's disease:** There is a combined hexosaminidase A and B deficiency. Clinical manifestations include progressive cerebral degeneration beginning at 6 mo, accompanied by blindness, cherry-red macular spot, and hyperacusis. It is almost indistinguishable from Tay-Sachs disease in course, diagnosis, and management, except that there is visceral involvement (hepatomegaly and bone change) and no ethnic association.

**Krabbe's Disease**

**Krabbe's disease is a sphingolipidosis that causes intellectual disability, paralysis, blindness, deafness, and pseudobulbar palsy, progressing to death.**

Krabbe's disease (galactosylceramide lipidosis, globoid cell leukodystrophy) is caused by an autosomal recessive galactocerebroside β-galactosidase deficiency.

It affects infants and is characterized by intellectual disability, paralysis, blindness, deafness, and pseudobulbar palsy, progressing to death.

Diagnosis is by detecting enzyme deficiency in WBCs or cultured skin fibroblasts.

Because bone marrow transplantation effectively delays onset of symptoms, prenatal testing or neonatal screening (routine in New York) is sometimes done.

### Metachromatic Leukodystrophy

**Metachromatic leukodystrophy is a sphingolipidosis caused by arylsulfatase A deficiency, which causes progressive paralysis and dementia resulting in death by age 10 yr.**

In metachromatic leukodystrophy (sulfatide lipidosis), arylsulfatase A deficiency causes metachromatic lipids to accumulate in the white matter of the CNS, peripheral nerves, kidney, spleen, and other visceral organs; accumulation in the nervous system causes central and peripheral demyelination. Numerous mutations exist; patients vary in age at onset and speed of progression.

The infantile form is characterized by progressive paralysis and dementia usually beginning before age 4 yr and resulting in death about 5 yr after onset of symptoms. The juvenile form manifests between 4 yr and 16 yr of age with gait disturbance, intellectual impairment, and findings of peripheral neuropathy. Contrary to the infantile form, deep tendon reflexes are usually brisk. There is also a milder adult form.

Diagnosis is suggested clinically and by findings of decreased nerve conduction velocity; it is confirmed by detecting enzyme deficiency in WBCs or cultured skin fibroblasts.

There is no effective treatment.

### Fabry's Disease

**Fabry's disease is a sphingolipidosis caused by deficiency of α-galactosidase A, which causes angiokeratomas, acroparesthesias, corneal opacities, recurrent febrile episodes, and renal or heart failure.**

Fabry's disease (angiokeratoma corporis diffusum) is an X-linked deficiency of the lysosomal enzyme α-galactosidase A, which is needed for normal trihexosylceramide catabolism. Glycolipid (globotriaosylceramide) accumulates in many tissues (eg, vascular endothelium, lymph vessels, heart, kidney).

Diagnosis in males is clinical, based on appearance of typical skin lesions (angiokeratomas) over the lower trunk and by characteristic features of peripheral neuropathy (causing recurrent burning pain in the extremities), corneal opacities, and recurrent febrile episodes. Death results from renal failure or cardiac or cerebral complications of hypertension or other vascular disease. Heterozygous females are usually asymptomatic but may have an attenuated form of disease often characterized by corneal opacities.

Diagnosis is by assay of galactosidase activity—prenatally in amniocytes or chorionic villi and postnatally in serum or WBCs.

Treatment is enzyme replacement with recombinant α-galactosidase A (agalsidase beta) combined with supportive measures for fever and pain. Kidney transplantation is effective for treating renal failure.

### Cholesteryl Ester Storage Disease and Wolman's Disease

**Cholesteryl ester storage disease and Wolman's disease are sphingolipidoses caused by lysosomal acid lipase deficiency resulting in hyperlipidemia and hepatomegaly.**

These diseases are rare, autosomal recessive disorders that result in accumulation of cholesteryl esters and triglycerides, mainly in lysosomes of histiocytes, resulting in foam cells in the liver, spleen, lymph nodes, and other tissues. Serum low-density lipoprotein (LDL) is usually elevated.

Wolman's disease is the more severe form, manifesting in the first weeks of life with poor feeding, vomiting, and abdominal distention secondary to hepatosplenomegaly; infants usually die within 6 mo.

Cholesteryl ester storage disease is less severe and may not manifest until later in life, even adulthood, at which time hepatomegaly may be detected; premature atherosclerosis, often severe, may develop.

Diagnosis is based on clinical features and detection of acid lipase deficiency in liver biopsy specimens or cultured skin fibroblasts, lymphocytes, or other tissues. Prenatal diagnosis is based on the absence of acid lipase activity in cultured chorionic villi.

There is no proven treatment, but statins reduce plasma LDL levels, and cholestyramine combined with a low-cholesterol diet has reportedly alleviated other signs.

## Mitochondrial Oxidative Phosphorylation Disorders

**Impairment of oxidative phosphorylation often, but not always, causes lactic acidosis, particularly affecting the CNS, retina, and muscle.**

Cellular respiration (oxidative phosphorylation) occurs in the mitochondria, where a series of enzymes catalyze the transfer of electrons to molecular oxygen and the generation of energy-storing ATP. Mitochondrial or nuclear genetic defects involving enzymes used in this process impair cellular respiration, decreasing the ATP:ADP ratio. Tissues with a high energy demand (eg, brain, nerves, retina, skeletal and cardiac muscle) are particularly vulnerable. The most common clinical manifestations are seizures, hypotonia, ophthalmoplegia, stroke-like episodes, muscle weakness, and cardiomyopathy.

Biochemically, there is profound lactic acidosis because the NADH:NAD ratio increases, shifting the equilibrium of the lactate dehydrogenase reaction toward lactate. The increase in the lactate:pyruvate ratio distinguishes oxidative phosphorylation defects from other genetic causes of lactic acidosis such as pyruvate carboxylase or pyruvate dehydrogenase deficiency, in which the lactate:pyruvate ratio remains normal. A large number of oxidative phosphorylation defects have been described; only the most common ones are outlined here, along with their distinguishing features.

Mitochondrial mutations and variants have also been implicated in a number of diseases of aging (eg, Parkinson's disease, Alzheimer's disease, diabetes, deafness, cancer).

**Leber's hereditary optic neuropathy (LHON):** This disease is characterized by acute or sub-acute bilateral central vision loss caused by retinal degeneration. Onset usually occurs in the patient's 20s or 30s but can occur from childhood to adulthood. Male:female ratio is 4:1. Many mutations have been defined, but 3 common ones account for 90% of those in European patients. LHON pedigrees usually show a pattern of maternal inheritance typical of mitochondrial disorders.

**Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS):** Mutations in the mitochondrial $tRNA^{leu}$ gene cause this progressive neurodegenerative disease characterized by repeated episodes of "chemical strokes," myopathy, and lactic acidosis. In many cases, cells contain both wild-type and mutant mitochondrial DNA (heteroplasmy); thus, expression is variable.

**Myoclonic epilepsy with ragged-red fibers (MERRF):** This progressive disorder is characterized by uncontrolled muscle contractions (myoclonic seizures), dementia, ataxia, and myopathy, which shows ragged-red fibers (indicating mitochondrial proliferation) with specialized stains when biopsied. Mutations are in the mitochondrial $tRNA^{lys}$ gene. Heteroplasmy is common; thus, expression is variable.

**Kearns-Sayre syndrome and chronic progressive external ophthalmoplegia (CPEO):** These disorders are characterized by ophthalmoplegia, ptosis, atypical retinitis pigmentosa, ragged-red fiber myopathy, ataxia, deafness, and cardiomyopathy typically occurring before age 20 yr. Most mutations involve contiguous deletion/duplication of part of the mitochondrial transfer RNA and other protein-coding genes.

**Neurogenic muscle atrophy and retinitis pigmentosa (NARP) and Leigh disease:** Pigmentary retinopathy in the presence of neuromuscular degeneration and Leigh disease (subacute necrotizing encephalopathy characterized by ataxias and basal ganglia degeneration) is a genetically heterogeneous syndrome. Mutations can be seen in the *ATP6* gene of the mitochondrial genomes.

## Peroxisomal Disorders

Peroxisomes are intracellular organelles that contain enzymes for β-oxidation. These enzymes overlap in function with those in mitochondria, with the exception that mitochondria lack enzymes to metabolize very long-chain fatty acids (VLCFA), those 20 to 26 carbons in length. Therefore, peroxisomal disorders generally manifest with elevated VLCFA levels (except rhizomelic chondrodysplasia). Although VLCFA levels may help screen for these disorders, other assays are also required (eg, plasma levels of phytanic, pristanic, and pipecolic acids; RBC plasmalogen levels).

There are 2 types of peroxisomal disorders: those with defective peroxisome formation and those with defects in single peroxisomal enzymes. X-linked adrenoleukodystrophy is the most common peroxisomal disorder (incidence 1/17,000 births); all others are autosomal recessive, with a combined incidence of about 1/50,000 births.

**Zellweger syndrome (ZS), neonatal adrenoleukodystrophy, and infantile Refsum's disease (IRD):** These disorders are 3 expressions of a disease continuum, from most (ZS) to least (IRD) severe. The responsible genetic defect occurs in 1 of at least 11 genes involved in peroxisomal formation or protein import (the *PEX* gene family).

Manifestations include facial dysmorphism, CNS malformations, demyelination, neonatal seizures, hypotonia, hepatomegaly, cystic kidneys, short limbs with stippled epiphyses (chondrodysplasia punctata), cataracts, retinopathy, hearing deficit, psychomotor delay, and peripheral neuropathy. Diagnosis is by detecting elevated blood levels of VLCFA, phytanic acid, bile acid intermediates, and pipecolic acid. Experimental treatment with docosahexaenoic acid (DHA—levels of which are reduced in patients with disorders of peroxisome formation) has shown some promise.

**Rhizomelic chondrodysplasia punctata:** This defect of peroxisomal biogenesis is caused by *PEX7* gene mutations and characterized by skeletal changes that include midface hypoplasia, strikingly short proximal limbs, frontal bossing, small nares, cataracts, ichthyosis, and profound psychomotor retardation. Vertebral clefts are also common. Diagnosis is by x-ray findings, serum elevation of phytanic acid, and low RBC plasmalogen levels; VLCFA levels are normal. There is no effective treatment.

**X-linked adrenoleukodystrophy:** This disorder is caused by deficiency of the peroxisomal membrane transporter ALDP, which is coded for by the gene *ABCD1*.

The cerebral form affects 40% of patients. Onset occurs between age 4 yr and 8 yr, and symptoms of attention deficit progress over time to severe behavioral problems; dementia; and vision, hearing, and motor deficits, causing total disability and death 2 to 3 yr after diagnosis. Milder adolescent and adult forms have also been described.

About 45% of patients have a milder form called adrenomyeloneuropathy (AMN); onset occurs in the 20s or 30s, with progressive paraparesis, and sphincter and sexual disturbance. About one third of these patients also develop cerebral symptoms.

Patients with any form may also develop adrenal insufficiency; about 15% have isolated Addison's disease without neurologic involvement.

Diagnosis is confirmed by isolated elevation of VLCFA. Bone marrow or stem cell transplantation may help stabilize symptoms in some cases. Adrenal steroid replacement is needed for patients with adrenal insufficiency. Dietary supplement with a 4:1 mixture of glyceryl trioleate and glyceryl trierucate (Lorenzo's oil) can normalize plasma VLCFA levels and may be beneficial in some cases but is under study.

**Classic Refsum's disease:** Genetic deficiency of a single peroxisomal enzyme, phytanoyl-CoA hydroxylase, which catalyzes metabolism of phytanic acid (a common dietary plant component), causes phytanic acid accumulation.

Clinical manifestations include progressive peripheral neuropathy, impaired vision caused by retinitis pigmentosa, hearing deficit, anosmia, cardiomyopathy and conduction defects, and ichthyosis. Onset is

usually in the 20s. Diagnosis is confirmed by elevation of serum phytanic acid and decreased levels of pristanic acid (phytanic acid elevation is accompanied by pristanic acid elevation in several other peroxisomal disorders).

Treatment is dietary restriction of phytanic acid (< 10 mg/day), which can be effective in preventing or delaying symptoms when started before symptom onset.

## Purine and Pyrimidine Metabolism Disorders

Purines are key components of cellular energy systems (eg, ATP, NAD), signaling (eg, GTP, cAMP, cGMP), and, along with pyrimidines, RNA and DNA production. Purines and pyrimidines may be synthesized de novo or recycled by a salvage pathway from normal catabolism. The end product of complete catabolism of purines is uric acid; catabolism of pyrimidines produces citric acid cycle intermediates.

### Disorders of Purine Salvage

**Lesch-Nyhan syndrome:** This is a rare, X-linked, recessive disorder caused by deficiency of hypoxanthine-guanine phosphoribosyl transferase (HPRT); degree of deficiency (and hence manifestations) vary with the specific mutation. HPRT deficiency results in failure of the salvage pathway for hypoxanthine and guanine. These purines are instead degraded to uric acid. Additionally, a decrease in inositol monophosphate and guanosyl monophosphate leads to an increase in conversion of 5-phosphoribosyl-1-pyrophosphate (PRPP) to 5-phosphoribosylamine, which further exacerbates uric acid overproduction. Hyperuricemia predisposes to gout and its complications. Patients also have a number of cognitive and behavioral dysfunctions, etiology of which is unclear; they do not seem related to uric acid.

The disease usually manifests between 3 mo and 12 mo of age with the appearance of orange sandy precipitate (xanthine) in the urine; it progresses to CNS involvement with intellectual disability, spastic cerebral palsy, involuntary movements, and self-mutilating behavior (particularly biting). Later, chronic hyperuricemia causes symptoms of gout (eg, urolithiasis, nephropathy, gouty arthritis, tophi).

Diagnosis is suggested by the combination of dystonia, intellectual disability, and self-mutilation. Serum uric acid levels are usually elevated, but confirmation by HPRT enzyme assay is usually done.

CNS dysfunction has no known treatment; management is supportive. Self-mutilation may require physical restraint, dental extraction, and sometimes drug therapy; a variety of drugs has been used. Hyperuricemia is treated with a low-purine diet (eg, avoiding organ meats, beans, sardines) and allopurinol, a xanthine oxidase inhibitor (the last enzyme in the purine catabolic pathway). Allopurinol prevents conversion of accumulated hypoxanthine to uric acid; because hypoxanthine is highly soluble, it is excreted.

**Adenine phosphoribosyltransferase deficiency:** This is a rare autosomal recessive disorder that results in the inability to salvage adenine for purine synthesis. Accumulated adenine is oxidized to 2,8-dihyroxyadenine, which precipitates in the urinary tract, causing problems similar to those of uric acid nephropathy (eg, renal colic, frequent infections, and, if diagnosed late, renal failure). Onset can occur at any age.

Diagnosis is by detecting elevated levels of 2,8-dihyroxyadenine, 8-hyroxyadenine, and adenine in urine and confirmed by enzyme assay; serum uric acid is normal.

Treatment is with dietary purine restriction, high fluid intake, and avoidance of urine alkalinization. Allopurinol can prevent oxidation of adenine; renal transplantation may be needed for end-stage renal disease.

### Disorders of Purine Nucleotide Synthesis

**Phosphoribosylpyrophosphate synthetase superactivity:** This X-linked, recessive disorder causes purine overproduction. Excess purine is degraded, resulting in hyperuricemia and gout and neurologic

and developmental abnormalities.

Diagnosis is by enzyme studies on RBCs and cultured skin fibroblasts.

Treatment is with allopurinol and a low-purine diet.

**Adenylosuccinase deficiency:** This autosomal recessive disorder causes profound intellectual disability, autistic behavior, and seizures.

Diagnosis is by identifying elevated levels of succinylaminoimidazole carboxamide ribo-side and succinyladenosine in CSF and urine.

There is no effective treatment.

**Disorders of Purine Catabolism**

**Myoadenylate deaminase deficiency (or muscle adenosine monophosphate deaminase deficiency):** The enzyme myoadenylate deaminase converts AMP to inosine and ammonia. Deficiency may be asymptomatic or it may cause exercise-induced myalgias or cramping; expression seems to be variable because, despite the high frequency of the mutant allele (10 to 14%), the frequency of the muscle phenotype is quite low in patients homozygous for the mutant allele. When symptomatic patients exercise, they do not accumulate ammonia or inosine monophosphate as do unaffected people; this is how the disorder is diagnosed.

Treatment is exercise modulation as appropriate.

**Adenosine deaminase deficiency:** Adenosine deaminase converts adenosine and deoxyadenosine to inosine and deoxyinosine, which are further broken down and excreted. Enzyme deficiency (from 1 of > 60 known mutations) results in accumulation of adenosine, which is converted to its ribonucleotide and deoxyribonucleotide (dATP) forms by cellular kinases. The dATP increase results in inhibition of ribonucleotide reductase and under-production of other deoxyribonucleotides. DNA replication is compromised as a result. Immune cells are especially sensitive to this defect; adenosine deaminase deficiency causes one form of severe combined immunodeficiency (see p. 1106).

Diagnosis is by low RBC and WBC enzyme activity.

Treatment is by bone marrow or stem cell transplantation and enzyme replacement therapy. Somatic cell gene therapy is being evaluated as well.

**Purine nucleoside phosphorylase deficiency:** This rare, autosomal recessive deficiency is characterized by immunodeficiency with severe T-cell dysfunction and often neurologic symptoms. Manifestations are lymphopenia, thymic deficiency, recurrent infections, and hypouricemia. Many patients have developmental delay, ataxia, or spasticity.

Diagnosis is by low enzyme activity in RBCs.

Treatment is with bone marrow or stem cell transplantation.

**Xanthine oxidase deficiency:** Xanthine oxidase is the enzyme that catalyzes uric acid production from xanthine and hypoxanthine. Deficiency causes buildup of xanthine, which may precipitate in the urine, causing symptomatic stones with hematuria, urinary colic, and UTIs.

Diagnosis is by low serum uric acid and high urine and plasma hypoxanthine and xanthine. Enzyme determination requires liver or intestinal mucosal biopsy and is rarely indicated.

Treatment is high fluid intake to minimize likelihood of stone formation and allopurinol in some patients.

**Disorders of Pyrimidine Metabolism**

**Uridine monophosphate synthase deficiency (hereditary orotic aciduria):** Uridine monophosphate is the enzyme that catalyzes orotate phosphoribosyltransferase and orotidine-5´-monophosphate decarboxylase reactions. With deficiency, orotic acid accumulates, causing clinical manifestations of megaloblastic anemia, orotic crystalluria and nephropathy, cardiac malformations, strabismus, and recurrent infections.

Diagnosis is by enzyme assay in a variety of tissues.

Treatment is with oral uridine supplementation.

# Chapter 302. Hereditary Periodic Fever Syndromes

## Introduction

**Hereditary periodic fever syndromes are hereditary disorders characterized by recurrent fever and other symptoms that are not explained by other causes.**

Most patients develop symptoms during childhood; < 10% develop symptoms after age 18. Disorders best characterized are

- Familial Mediterranean fever
- Hyper-IgD syndrome
- Tumor necrosis factor (TNF) receptor-associated periodic syndrome

Others include

- The hereditary cryopyrinopathies: Familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (NOMID)
- PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome
- PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis) syndrome

## Familial Mediterranean Fever

**Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent bouts of fever and peritonitis, sometimes with pleuritis, skin lesions, arthritis, and, very rarely, pericarditis. Renal amyloidosis may develop, sometimes leading to renal failure. People with genetic origins in the Mediterranean basin are most commonly affected. Diagnosis is largely clinical, although genetic testing is available. Treatment with prophylactic colchicine prevents acute attacks as well as renal amyloidosis in most patients. Prognosis is excellent with treatment.**

FMF is a disease of people with genetic origins in the Mediterranean basin, predominantly Sephardic Jews, North African Arabs, Armenians, Turks, Greeks, and Italians. However, cases have occurred among enough other groups (eg, Ashkenazi Jews, Cubans, Japanese) to caution against excluding the diagnosis solely on the basis of ancestry. Up to 50% of patients have a family history of the disorder, usually involving siblings.

### Etiology

FMF is caused by mutations in the *MEFV* gene on the short arm of chromosome 16 and is inherited in an autosomal recessive manner. The *MEFV* gene normally codes a protein (called pyrin or marenostrin) expressed in circulating neutrophils. Its presumed action is to blunt the inflammatory response, possibly by inhibiting neutrophil activation and chemotaxis. Gene mutations result in defective pyrin molecules; it is hypothesized that the altered pyrin cannot suppress minor, unknown triggers to inflammation that are normally checked by intact pyrin. The clinical consequence is spontaneous bouts of neutrophil-predominant inflammation in the abdominal cavity as well as in other sites.

### Symptoms and Signs

Onset is usually between the ages of 5 and 15 yr but may be much later or earlier, even during infancy. Attacks have no regular pattern of recurrence and vary in the same patient. They usually last 24 to 72 h, but some last ≥ 1 wk. Frequency ranges from 2 attacks/wk to 1 attack/yr (most commonly, once every 2 to 6 wk). Severity and frequency tend to decrease during pregnancy and in patients with amyloidosis.

Spontaneous remissions may last years. In some patients, the attacks have a prodromal phase.

Fever as high as 40° C, usually accompanied by peritonitis, is the major manifestation. Abdominal pain (usually starting in one quadrant and spreading to the whole abdomen) occurs in about 95% of patients and can vary in severity with each attack. Decreased bowel sounds, distention, guarding, and rebound tenderness are likely to occur at the peak of an attack and cannot be differentiated from a perforated viscus by physical examination. Consequently, many patients undergo urgent laparotomy before the correct diagnosis is made. With diaphragmatic involvement, splinting of the chest and pain in one or both shoulders may occur.

Other manifestations include acute pleurisy (in 30%); arthritis (in 25%), usually involving the knee, ankle, and hip; an erysipelas-like rash of the lower leg; and scrotal swelling and pain caused by inflammation of the tunica vaginalis of the testis. Pericarditis occurs very rarely. The pleural, synovial, and skin manifestations of FMF vary in frequency among different populations and are less frequently encountered in the US than elsewhere.

The most significant long-term complication is chronic renal failure caused by deposition of amyloid protein in the kidneys. Amyloid may also be deposited in the GI tract, liver, spleen, heart, testes, and thyroid.

FMF causes infertility or spontaneous abortion in about one third of women because peritoneal pelvic adhesions form, interfering with conception. In women with FMF, about 20 to 30% of pregnancies end in fetal loss.

Despite the severity of symptoms during acute attacks, most patients recover swiftly and remain free of illness until their next attack.

**Diagnosis**

• Clinical evaluation

• Genetic testing

Diagnosis is mainly clinical, but genetic testing is available and is particularly useful in evaluation of atypical cases. Nonspecific findings include elevations in WBCs with neutrophil predominance, ESR, C-reactive protein, and fibrinogen. Urinary excretion of > 0.5 g protein/24 h suggests renal amyloidosis. Differential diagnosis includes acute intermittent porphyria, hereditary angioedema with abdominal attacks, relapsing pancreatitis, and other hereditary relapsing fevers.

**Treatment**

• Colchicine

Prophylactic colchicine 0.6 mg po bid (some patients require qid dosing; others a single daily dose) provides complete remission or distinct improvement in about 85% of patients. For patients with infrequent attacks that involve a prodromal phase, colchicine can be reserved until initial symptoms occur and then begun at 0.6 mg po q 1 h for 4 h, then q 2 h for 4 h, then q 12 h for 48 h. Initiation of colchicine at the peak of an attack, even if delivered IV, is unlikely to be beneficial. Children often require adult dosages for effective prophylaxis. Widespread use of prophylactic colchicine has led to a dramatic reduction in the incidence of amyloidosis and subsequent renal failure.

Colchicine does not add to the increased risk of infertility and miscarriage among affected women; when taken during pregnancy, it does not increase the risk of teratogenic events. Lack of response to colchicine is often caused by poor adherence to the drug regimen, but a correlation has also been noted between poor response and diminished colchicine concentration in circulating monocytes. Weekly IV colchicine may reduce attack frequency and severity in patients who do not respond to oral colchicine. Untested alternatives in nonresponders include interferon-α 3 to 10 million units sc, prazosin 3 mg po bid, infliximab 5 mg/kg IV q 8 wk, and thalidomide initially 100 mg po once/day.

Opioids are sometimes needed for pain relief but should be used prudently to avoid addiction.

## Hyper-IgD Syndrome

**Hyper-IgD syndrome is a rare autosomal recessive disorder in which recurring attacks of chills and fever begin during the first year of life. Episodes usually last 4 to 6 days and may be triggered by physiologic stress, such as vaccination or minor trauma.**

Hyper-IgD syndrome clusters in children of Dutch, French, and other Northern European ancestry and is caused by mutations in the gene coding mevalonate kinase, an enzyme important for cholesterol synthesis. Reduction in the synthesis of anti-inflammatory isoprenylated proteins may account for the clinical syndrome.

In addition to chills and fever, patients may have abdominal pain, vomiting or diarrhea, headache, and arthralgias. Signs include cervical lymphadenopathy, splenomegaly, arthritis, skin lesions (maculopapular rash, petechiae, or purpura), and orogenital aphthous ulcers.

Diagnosis is based on history, examination, and a serum IgD level of > 14 mg/mL. Non-specific abnormalities include leukocytosis and elevated acute-phase reactants during fever; specific but insensitive findings include elevated urinary mevalonic acid.

There are no proven treatments to prevent attacks. Patients can expect to have recurrent bouts of fever throughout their life, although episodes tend to become less frequent after adolescence.

## TNF Receptor-Associated Periodic Syndrome

(Familial Hibernian Fever)

**Tumor necrosis factor (TNF) receptor-associated periodic syndrome is an autosomal dominant disorder causing recurrent fever and painful, migratory myalgias with tender overlying erythema. Levels of type 1 TNF receptors are low. Treatment is with corticosteroids and etanercept.**

TNF receptor-associated periodic syndrome was originally described in a family of Irish and Scottish pedigree but has been reported in many different ethnic groups. It results from mutations in the gene coding the TNF receptor. The mutation leads to unchecked TNF signaling, resulting in inflammation, possibly because shedding of the TNF receptor is defective.

Attacks of this rare disorder usually begin before age 20. They may last from 1 or 2 days to > 1 wk. The most distinctive features of an attack are migratory myalgia and swelling in the extremities. The overlying skin is red and tender. Other symptoms may include headache, abdominal pain, diarrhea or constipation, nausea, painful conjunctivitis, joint pain, rash, and testicular pain. Males are prone to develop inguinal hernias. Amyloidosis involving the kidneys has been reported in a minority of families.

With treatment, the prognosis is good, but it is more guarded in patients with renal amyloidosis.

### Diagnosis

Diagnosis is based on history, examination, and low levels of type 1 TNF receptor (< 1 ng/mL) when measured between attacks. Non-specific findings include neutrophilia, elevated acute-phase reactants, and polyclonal gammopathy during attacks. Patients should be screened regularly for proteinuria.

### Treatment

Attacks can be effectively treated with prednisone (at least 20 mg po once/day). Dosage may need to be increased over time.

Early therapeutic experience with etanercept, which binds and inactivates TNF, has been promising. Recommended dosage is 0.4 mg/kg sc for children and 25 mg sc for adults twice/wk. Anakinra 1.5 mg/kg sc once/day may be effective in children.

## Hereditary Cryopyrinopathies

**The hereditary cryopyrinopathies are a group of autoinflammatory conditions triggered by cold ambient temperatures; they include familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem autoinflammatory disease.**

Hereditary cryopyrinopathies represent a spectrum of progressively severe disease. They are due to mutations in the gene encoding the protein cryopyrin, which mediates inflammation and IL-1β processing. Cryopyrin activity is augmented, triggering increased release of IL-1β from inflammasomes; the result is inflammation and fever.

Typically, familial cold autoinflammatory syndrome causes a cold-induced urticarial rash accompanied by fever.

Muckle-Wells syndrome causes intermittent fevers, urticarial rash, joint pain, and progressive deafness; 25% of patients develop amyloidosis.

Neonatal-onset multisystem autoinflammatory disease tends to cause joint deformities, meningitis, delayed development, and amyloidosis, in addition to fever and rash. As many as 20% of patients die by age 20.

The cryopyrinopathies are inherited as autosomal dominant disorders. They are treated with anakinra or etanercept.

## PAPA Syndrome

**PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome is an autosomal dominant disorder that affects the skin and joints.**

PAPA syndrome is caused by mutations in a gene on chromosome 15q. The mutated gene produces a hyperphosphorylated protein that binds excessively to pyrin, thus restricting pyrin's anti-inflammatory activity.

Arthritis begins in the first decade of life and is progressively destructive. Episodes of mild trauma may trigger the arthritis. Poorly healing ulcers with undermined edges may appear, often at sites of injury (eg, at vaccination sites). Acne is usually nodulocystic and, if untreated, causes scarring.

Diagnosis is based on clinical findings and a family history. The ulcers may be biopsied. Biopsy shows superficial ulceration and neutrophilic inflammation.

Treatment with etanercept or anakinra may be useful. Acne is treated with oral tetracycline or isotretinoin.

## PFAPA Syndrome

**PFAPA (periodic fevers with aphthous stomatitis, pharyngitis, and adenitis) syndrome is a periodic fever syndrome that typically manifests between ages 2 yr and 5 yr; it is characterized by febrile episodes lasting 3 to 6 days, pharyngitis, aphthous ulcers, and adenopathy. Etiology and pathophysiology are undefined.**

PFAPA syndrome is a relatively common periodic fever among children. Although genetic causes have not been determined, this syndrome tends to be grouped with hereditary fever syndromes. It typically starts in early childhood (between ages 2 yr and 5 yr) and tends to be more common among males.

Febrile episodes last 3 to 6 days and recur about every 28 days. The syndrome causes fatigue, chills,

and occasionally abdominal pain and headache, as well as fever, pharyngitis, aphthous ulcers, and lymphadenopathy. Patients are healthy between episodes, and growth is normal.

**Diagnosis**

Diagnosis is based on clinical findings, which include the following:

• ≥ 3 febrile episodes, lasting up to 5 days and occurring at regular intervals

• Pharyngitis plus adenopathy or aphthous ulcers

• Good health between episodes and normal growth

Acute-phase reactants (eg, C-reactive protein, ESR) are elevated during a febrile episode but not between episodes. Neutropenia or other symptoms (eg, diarrhea, rash, cough) are not present; their presence suggests a different disorder.

**Treatment**

Treatment is optional; it can include glucocorticoids, cimetidine, and, rarely, tonsillectomy. Patients tend to outgrow this syndrome without sequelae.

# Chapter 303. Behavioral Concerns and Problems in Children

## Introduction

Many behaviors exhibited by children or adolescents concern parents or other adults. Behaviors or behavioral patterns become clinically significant if they are frequent or persistent and maladaptive (eg, interfere with emotional maturation or social and cognitive functioning). Severe behavioral problems may be classified as mental disorders (eg, oppositional defiant disorder—see p. 3058—or conduct disorder —see p. 3060). Prevalence rates vary according to how behavioral problems are defined and measured.

### Evaluation

Diagnosis consists of a multistep behavioral assessment. Concerns with infants and young children generally involve bodily functions (eg, eating, eliminating, sleeping), whereas in older children and adolescents interpersonal behavioral concerns (eg, activity level, disobedience, aggression) predominate.

**Problem identification:** A behavioral problem may manifest alarmingly and abruptly as a single incident (eg, setting a fire, fighting at school). More often, problems manifest gradually, and identification involves gathering information over time. Behavior is best assessed in the context of the child's

- Physical and mental development
- General health
- Temperament (eg, difficult, easygoing)
- Relationships with parents and caregivers

Direct observation of parent-child interaction during an office visit provides valuable clues, including parental response to behaviors. These observations are supplemented, whenever possible, by information from others, including relatives, teachers, and school nurses.

Interviewing parents or caregivers provides a chronology of the child's activities during a typical day. Parents are asked to provide examples of events that precede and follow the specific behavior. Parents also are asked for their interpretation of

- Typical age-related behaviors
- Expectations for the child
- Level of parenting interest
- Support (eg, social, emotional, financial) for fulfilling their parenting role
- The child's relationship with the rest of their family

**Problem interpretation:** The child's history may include factors thought to increase the likelihood of developing behavioral problems, such as exposure to toxins, complications during pregnancy, or occurrence of a serious illness in the family.

Some problems may involve the parent-child relationship and can be interpreted in a number of ways:

- **Unrealistic parental expectations:** For example, some parents may expect that a 2-yr-old will pick up toys without help. Parents may misinterpret other normal, age-related behaviors, such as oppositional behavior (eg, refusal of a 2-yr old to follow an adult's request or rule) as problematic.
- **Poor quality of parent-child interactions:** For example, children of disinterested parents may have behavioral problems.

- **Over-indulgent parenting:** Well-meaning parental reactions to a problem may worsen it (eg, overprotecting a fearful, clinging child or giving in to a manipulative child).

- **Circular behavioral pattern:** In young children, some problems represent a circular behavioral pattern in which negative parental reaction to a child's behavior causes an adverse response from the child, which in turn leads to continued negative parental reaction. In this pattern, children often respond to stress and emotional discomfort with stubbornness, back talk, aggressiveness, and temper outbursts rather than with crying. Most commonly, a parent reacts to an aggressive and resistant child by scolding, yelling, and spanking; the child then escalates the behaviors that led to the parent's initial response, and the parent reacts more forcefully.

In older children and adolescents, behavioral problems may arise as independence is sought from parental rules and supervision. Such problems must be distinguished from occasional errors in judgment.

**Treatment**

Once a behavioral problem has been identified and its etiology has been investigated, early intervention is desirable because behaviors are more difficult to change the longer they exist.

The clinician reassures parents that the child is physically well (ie, that the child's misbehavior is not a manifestation of physical illness). By identifying with parental frustrations and pointing out the prevalence of behavioral problems, the clinician often can allay parental guilt and facilitate exploration of possible sources and treatment of problems. For simple problems, parental education, reassurance, and a few specific suggestions often are sufficient. Parents should be reminded of the importance of spending at least 15 to 20 min/day in a pleasurable activity with the child, "catching the child being good." Parents also can be encouraged to regularly spend time away from the child.

For some problems, however, parents benefit from additional strategies for disciplining children and modifying behavior.

- Parents can limit the child's dependency-seeking and manipulative behavior so that mutual respect is reestablished.

- Desired and undesired behavior should be clearly defined.

- Consistent rules and limits should be established.

- Parents need to track compliance on an ongoing basis and provide appropriate rewards for success and consequences for inappropriate behavior.

- Parents should try to minimize anger when enforcing rules and increase positive contact with the child.

(NOTE: Positive reinforcement for appropriate behavior is a powerful tool with no adverse effects.)

Helping parents to understand that "discipline" implies structure and not just punishment allows them to provide the structure and clear expectations that children need. Ineffective discipline may result in inappropriate behavior. Scolding or physical punishment may briefly control a child's behavior but eventually may decrease the child's sense of security and self-esteem. Threats to leave or send the child away are damaging.

A time-out technique (see Sidebar 303-1), in which the child must sit alone in a dull place (a corner or room [other than the child's bedroom] that is not dark or scary and has no television or toys) for a brief period, is a good approach to altering unacceptable behavior. Time-outs are learning processes for the child and are best used for one inappropriate behavior or a few at one time. Physical restraint should be avoided. For children who escalate in the intensity of their reactions when put in time-out, parents may prefer to move more rapidly to redirection once they recognize the children have registered the reprimand for inappropriate behavior.

The circular behavioral pattern may be interrupted if parents ignore behavior that does not disturb others (eg, refusal to eat) and use distraction or temporary isolation to limit behavior that cannot be ignored (public tantrums).

A behavioral problem that does not change in 3 to 4 mo should be reevaluated; mental health consultation may be indicated.

## Breath-Holding Spells

**A breath-holding spell is an episode in which the child stops breathing involuntarily and loses consciousness for a short period immediately after a frightening or emotionally upsetting event or after a painful experience.**

Breath-holding spells occur in 5% of otherwise healthy children. They usually begin in the first year of life and peak at age 2. They disappear by age 4 in 50% of children and by age 8 in about 83% of children. The remainder may continue to have spells into adulthood. There are 2 forms of breath-holding spells:

- **Cyanotic form:** This form is the most common and often occurs as part of a temper tantrum or in response to a scolding or other upsetting event.

- **Pallid form:** This form typically follows a painful experience, such as falling and banging the head, but can follow frightening or startling events.

Both forms are involuntary and readily distinguished from uncommon brief periods of voluntary breath-holding by stubborn children, who invariably resume normal breathing after getting what they want or after becoming uncomfortable when they fail to get what they want.

During a cyanotic breath-holding spell, children hold their breath (without necessarily being aware they are doing so) until they lose consciousness. Typically, the child cries out, exhales, and stops breathing. Shortly afterward, the child begins to turn blue and unconsciousness ensues. A brief seizure may occur. After a few seconds, breathing resumes and normal skin color and consciousness return. It may be possible to interrupt a spell by placing a cold rag on the child's face at onset. Despite the spell's frightening nature, parents must try to avoid reinforcing the initiating behavior. As the child recovers, parents should continue to enforce household rules. Distracting the child and avoiding situations that lead to tantrums are good strategies. Cyanotic breath-holding has been found to respond to iron therapy, even in the absence of anemia, and to treatment for obstructive sleep apnea (when present).

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### Sidebar 303-1 Time-Out Technique

This disciplinary technique is best used when children are aware that their actions are incorrect or unacceptable and when they perceive withholding of attention as a punishment; typically this is not the case until age 2 yr. Care should be taken when this technique is used in group settings like daycare, because it can result in harmful humiliation.

The technique can be applied when a child misbehaves in a way that is known to result in a time-out. Usually, verbal reprimands and reminders should precede the time-out.

- The misbehavior is explained to the child, who is told to sit in the time-out chair or is led there if necessary.

- The child should sit in the chair 1 min for each year of age (maximum, 5 min).

- A child who gets up from the chair before the allotted time is returned to the chair, and the time-out is restarted. Talking and eye contact are avoided.

- When it is time for the child to get up, the caregiver asks the reason for the time-out without anger and

nagging. A child who does not recall the correct reason is briefly reminded. The child does not need to express remorse for the inappropriate behavior as long as it is clear that the child understands the reason for the time-out.

As soon as possible after the time-out, the caregiver should praise the child's good behavior, which may be easier to achieve if the child is redirected to a new activity far from the scene of the inappropriate behavior.

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During a pallid breath-holding spell, vagal stimulation severely slows the heart rate. The child stops breathing, rapidly loses consciousness, and becomes pale and limp. If the spell lasts more than a few seconds, muscle tone increases, and a seizure and incontinence may occur. After the spell, the heart speeds up again, breathing restarts, and consciousness returns without any treatment. Because this form is rare, further diagnostic evaluation and treatment may be needed if the spells occur often. Simultaneous ECG and EEG can help to differentiate cardiac and neurologic causes.

### Eating Problems

Eating problems range from age-appropriate variability in appetite to serious or even life-threatening eating disorders (see p. 1535) such as anorexia nervosa, bulimia nervosa, and binge-eating. Eating problems also can result in overeating and obesity (see p. 56). Parents of young children are often concerned that a child is not eating enough or eating too much, eating the wrong foods, refusing to eat certain foods, or engaging in inappropriate mealtime behavior (eg, sneaking food to a pet, throwing or intentionally dropping food).

Assessment includes problem frequency, duration, and intensity. Height and weight are measured and plotted on appropriate charts. Often, when parents are shown charts that show the child is growing at a normal rate, their concerns about eating diminish. Children should be assessed more thoroughly for serious eating disorders if

• They voice persistent concerns about their appearance or weight

• Their weight decreases

• Their weight begins to increase at a noticeably faster rate than their previous growth rate

However, most eating problems do not persist long enough to interfere with growth and development. If children appear well and growth is within an acceptable range, parents should be reassured and encouraged to minimize conflict and coercion related to eating. Prolonged and excessive parental concern may in fact contribute to subsequent eating disorders. Attempts to force-feed are unlikely to increase intake; children may hold food in their mouth or vomit. Parents should offer meals while sitting at a table with the family, without distractions such as television or pets, and show little emotion when putting the food in front of children. Food should be removed in 20 to 30 min without comment about what is or is not eaten. Children should participate in cleaning up any food that is thrown or intentionally dropped on the floor. These techniques, along with restricting between-meal eating to one morning and one afternoon snack, usually restore the relationship between appetite, the amount eaten, and children's nutritional needs.

### School Avoidance

Avoiding school occurs in about 5% of all school-aged children and affects girls and boys equally. It usually occurs between ages 5 and 6 and between ages 10 and 11.

The cause is often unclear, but psychologic factors (eg, anxiety, depression) and social factors (eg, having no friends, feeling rejected by peers, being bullied) may contribute. If school avoidance behaviors escalate to the point at which a child is missing a lot of school, the behaviors may be an indication of more serious problems (see p. 3049). A sensitive child may be overreacting with fear to a teacher's strictness or rebukes. Younger children tend to fake illness or make other excuses to avoid school.

Children may complain of a stomachache, nausea, or other symptoms that justify staying home. Some children directly refuse to go to school. Alternatively, children may go to school without difficulty but become anxious or develop various symptoms during the school day, often going regularly to the nurse's office. This behavior is unlike that of adolescents, who may decide not to attend school (truancy).

School avoidance tends to result in

• Poor academic performance

• Family difficulties

• Difficulties with peers

Most children recover from school avoidance, although some develop it again after a real illness or a vacation.

Home tutoring generally is not a solution. Children with school avoidance should return to school immediately, so that they do not fall behind in their schoolwork. If school avoidance is so intense that it interferes with the child's activity and if the child does not respond to simple reassurance by parents or teachers, referral to a mental health practitioner may be warranted.

Treatment should include communication between parents and school personnel, regular attendance at school, and sometimes therapy involving the family and child with a psychologist. Therapy includes treatment of underlying disorders as well as behavioral techniques to cope with the stresses at school.

## Sleep Problems

For most children, sleep problems are intermittent or temporary and often do not require treatment.

**Normal sleep:** Most children sleep for a stretch of at least 5 h by age 3 mo but then experience periods of night waking later in the first years of life, often associated with illness. With maturation, the amount of rapid eye movement (REM) sleep increases, with increasingly complex transitions between sleep stages. For most people, non-REM sleep predominates early in the night, with increasing REM as the night progresses. Thus, non-REM phenomena cluster early in the night, and REM-related phenomena occur later. Differentiating between true sleep (REM or non-REM)-related phenomena and awake behaviors can help to direct treatment.

It is important to determine whether parents view the child sleeping with them as a problem, because there is much cultural variation among sleep habits.

**Nightmares:** Nightmares are frightening dreams that occur during REM sleep. A child having a nightmare can awaken fully and vividly recall the details of the dream. Nightmares are not a cause for alarm, unless they occur very often. They can occur more often during times of stress or even when the child has seen a movie or television program containing frightening content. If nightmares occur often, parents can keep a diary to see whether they can identify the cause.

**Night terrors and sleepwalking:** Night terrors, non-REM episodes of incomplete awakening with extreme anxiety shortly after falling asleep, are most common between the ages of 3 and 8. The child screams and appears frightened, with a rapid heart rate and rapid breathing. The child seems unaware of the parents' presence, may thrash around violently, and does not respond to comforting. The child may talk but is unable to answer questions. Usually, the child returns to sleep after a few minutes. Unlike with nightmares, the child cannot recall these episodes. Night terrors are dramatic because the child screams and is inconsolable during the episode. About one third of children with night terrors also experience sleepwalking (rising from bed and walking around while apparently asleep, also called somnambulism). About 15% of children between the ages of 5 and 12 have at least one episode of sleepwalking.

Night terrors and sleepwalking almost always stop on their own, although occasional episodes may occur for years. Usually, no treatment is needed, but if a disorder persists into adolescence or adulthood and is

severe, treatment may be necessary. In children who need treatment, night terrors may sometimes respond to a sedative or certain antidepressants. There is some evidence that disrupted sleep associated with periodic leg movements often responds to iron supplementation, even in the absence of anemia. If children snore and thrash, evaluation for obstructive sleep apnea also should be considered.

**Resistance to going to bed:** Children, particularly between the ages of 1 and 2, often resist going to bed due to separation anxiety, whereas older children may be attempting to control more aspects of their environment. Young children often cry when left alone in their crib, or they climb out and seek their parents. Another common cause of bedtime resistance is delayed sleep onset time. These situations arise when children are allowed to stay up later and sleep later than usual for enough nights to reset their internal clock to a later sleep onset time. It can be difficult to move bedtime earlier, but brief treatment with an OTC antihistamine or melatonin can help children reset their clock.

Resistance to going to bed is not helped if parents stay in the room at length to provide comfort or let children get out of bed. In fact, these responses reinforce night waking, in which children attempt to reproduce the conditions under which they fell asleep. To avoid these problems, a parent may have to sit quietly in the hallway in sight of the child and make sure the child stays in bed. The child then establishes a sleep-onset routine of falling asleep alone and learns that getting out of bed is discouraged. The child also learns that the parents are available but will not provide more stories or play. Eventually, the child settles down and goes to sleep. Providing the child with an attachment object (like a teddy bear) often is helpful. A small night-light, white noise, or both also can be comforting.

**Awakening during the night:** Everyone awakens multiple times each night. Most, however, usually fall back to sleep with no intervention. Children often experience repeated night awakening after a move, an illness, or another stressful event. Sleeping problems may be worsened when children take long naps late in the afternoon or are over-stimulated by playing before bedtime.

Allowing the child to sleep with the parents because of the night awakening reinforces the behavior. Also counterproductive are playing with or feeding the child during the night, spanking, and scolding. Returning the child to bed with simple reassurance is usually more effective. A bedtime routine that includes reading a brief story, offering a favorite doll or blanket, and using a small night-light (for children > 3) is often helpful. To prevent arousal, it is important that the conditions under which the child awakens during the night are the same as those under which the child falls asleep. Parents and other caregivers should try to keep to a routine each night, so that the child learns what is expected. If children are physically healthy, allowing them to cry for a few minutes often allows them to settle down by themselves, which diminishes the night awakening.

## Temper Tantrums

**A temper tantrum is a violent emotional outburst, usually in response to frustration.**

Temper tantrums usually appear toward the end of the first year, are most common at age 2 (terrible twos) to 4, and are infrequent after age 5. If tantrums are frequent after age 5, they may persist throughout childhood.

Causes include frustration, tiredness, and hunger. Children also may have temper tantrums to seek attention, obtain something, or avoid doing something. Parents often blame themselves (because of imagined poor parenting) when the actual cause is often a combination of the child's personality, immediate circumstances, and developmentally normal behavior. An underlying mental, physical, or social problem rarely may be the cause but is likely only if tantrums last > 15 min or occur multiple times each day.

Temper tantrums may involve

• Shouting

• Screaming

• Crying

• Thrashing about

• Rolling on the floor

• Stomping

• Throwing things

The child may become red in the face and hit or kick. Some children may voluntarily hold their breath for a few seconds and then resume normal breathing (unlike breath-holding spells, which also can follow crying bouts caused by frustration—see p. 3031).

Although providing a safe setting for children to compose themselves (eg, a time-out—see Sidebar 303-1) is often effective, many children have difficulty stopping tantrums on their own. In most cases, addressing the source of the tantrum only prolongs it. It is therefore preferable to redirect the child by providing an alternative activity on which to focus. The child may benefit from being removed physically from the situation.

## Violence

Children and adolescents may engage in occasional physical confrontations, but most do not develop a sustained pattern of violent behavior or engage in violent crime. Those who become violent before puberty may be at higher risk of committing crimes.

Violent behavior is increasingly common among children and adolescents. Almost 10% of students in middle or junior high school and high school report being victims of bullying. In 2005, almost 16% of high school students in the US reported carrying a weapon at least once during the month before they were surveyed as part of a study on youth risks.

Despite growing interest in the possibility of a relationship between violent behavior and genetic defects or chromosomal anomalies, there is minimal evidence for such a relationship. However, several risk factors have been associated with violent behavior, including

• Violent discipline

• Alcohol and drug abuse

• Gang involvement

• Developmental issues

• Poverty

• Access to firearms

There seems to be a relationship between violence and access to firearms, exposure to violence through media, and exposure to child abuse and domestic violence. Children who are bullied may reach a breaking point, at which time they strike back with potentially dangerous or catastrophic results.

**Bullying:** Bullying is intentional infliction of psychologic or physical damage on less powerful children. Bullying can take several forms, including

• Persistent teasing

• Threats

- Intimidation
- Harassment
- Violent assaults

**Cyber-bullying:** This is a newly described form in which bullies use e-mail and instant messaging to convey threats. Bullies act to inflate their sense of self-worth. Bullies often report that bullying creates feelings of power and control. Both bullies and their victims are at risk of poor outcomes. Victims often tell no one about being bullied due to feelings of helplessness, shame, and fear of retaliation. Victims are at risk of physical injury, poor self-esteem, anxiety, depression, and school absence. Bullies are more likely to be incarcerated; they are less likely to remain in school, be employed, or have stable relationships as adults.

**Gang involvement:** Participation in gangs has been linked with violent behavior. Youth gangs are self-formed associations of ≥ 3 members, typically ages 13 to 24. Gangs usually adopt a name and identifying symbols, such as a particular style of clothing, the use of certain hand signs, or graffiti. Some gangs require prospective members to perform random acts of violence before membership is granted. Increasing youth gang violence has been blamed at least in part on gang involvement in drug distribution and drug use, particularly methamphetamines and heroin. Use of firearms is a frequent feature of gang violence.

### Prevention

Violence prevention should begin in early childhood. Strategies include

- Violence-free discipline in young children
- Limiting access to weapons and exposure to violence through media and video games
- Creating and maintaining a safe school environment for school-age children
- Encouraging victims to discuss problems with parents, school authorities, and their doctor
- Teaching older children and adolescents strategies for avoiding high-risk situations (eg, places or settings where others have weapons or are using alcohol or drugs) and for reacting to or defusing tense situations

# Chapter 304. Learning and Developmental Disorders

## Introduction

Developmental disorders (including attention-deficit/hyperactivity disorder, autism spectrum disorders, learning disabilities, and intellectual disability) are neurologically based conditions that can interfere with the acquisition, retention, or application of specific skills or sets of information. They may involve dysfunction in attention, memory, perception, language, problem-solving, or social interaction.

## Attention-Deficit/Hyperactivity Disorder

**Attention-deficit/hyperactivity disorder (ADHD) is a syndrome of inattention, hyperactivity, and impulsivity. The 3 types of ADHD are predominantly inattentive, predominantly hyperactive-impulsive, and combined. Diagnosis is made by clinical criteria. Treatment usually includes drug therapy with stimulant drugs, behavioral therapy, and educational interventions.**

ADHD has been classified as a developmental disorder, although increasingly it is considered a disruptive behavior disorder. ADHD affects an estimated 5 to 15% of school-aged children. However, many experts think ADHD is overdiagnosed, largely because criteria are applied inaccurately. According to the *Diagnostic and Statistical Manual of Mental Disorders* , Fourth Edition Text Revision (DSM-IV-TR), there are 3 types:

• Predominantly inattentive

• Predominantly hyperactive-impulsive

• Combined

The predominantly hyperactive-impulsive type occurs 2 to 9 times more frequently in boys; the predominantly inattentive type occurs with about equal frequency in both sexes. ADHD tends to run in families.

ADHD has no known single, specific cause. Potential causes include genetic, biochemical, sensorimotor, physiologic, and behavioral factors. Some risk factors include birth weight < 1000 g, head trauma, and lead exposure, as well as prenatal exposure to alcohol, tobacco, and cocaine. Fewer than 5% of children with ADHD have other symptoms and signs of neurologic damage. Increasing evidence implicates abnormalities in dopaminergic and noradrenergic systems with decreased activity or stimulation in upper brain stem and frontal-midbrain tracts.

### Symptoms and Signs

Onset often occurs before age 4 and invariably before age 7. The peak age for diagnosis is between ages 8 and 10; however, patients with the predominantly inattentive type may not be diagnosed until after adolescence.

Core symptoms and signs of ADHD involve

• Inattention

• Hyperactivity

• Impulsivity

These symptoms (see Table 304-1) must be more pronounced than expected for the child's developmental level; impaired academic or social function is common.

Inattention tends to appear when a child is involved in tasks that require vigilance, rapid reaction time,

visual and perceptual search, and systematic and sustained listening. Inattention and impulsivity impede development of academic skills and thinking and reasoning strategies, motivation for school, and adjustment to social demands. Children who have predominantly inattentive ADHD tend to be hands-on learners who have difficulty in passive learning situations that require continuous performance and task completion. Overall, about 20 to 60% of children with ADHD have learning disabilities, but some school dysfunction occurs in most children with ADHD.

Behavioral history can reveal low frustration tolerance, opposition, temper tantrums, aggressiveness, poor social skills and peer relationships, sleep disturbances, anxiety, dysphoria, depression, and mood swings.

Although there are no specific physical examination or laboratory findings associated with ADHD, signs can include

• Motor incoordination or clumsiness

• Nonlocalized, "soft" neurologic findings

• Perceptual-motor dysfunctions

**Diagnosis**

• Clinical criteria

Diagnosis is clinical and is based on comprehensive medical, developmental, educational, and psychologic evaluations.

DSM-IV-TR diagnostic criteria include 9 symptoms and signs of inattention, 6 of hyperactivity, and 3 of impulsivity (see Table 304-1); diagnosis using these criteria requires

[**Table 304-1.** DSM-IV-TR Symptom Criteria for ADHD*]

that symptoms and signs occur in at least 2 situations (eg, home and school) and be present before age 7. Diagnosis of the predominantly inattentive type requires at least 6 of the 9 possible symptoms and signs of inattention. Diagnosis of the hyperactive-impulsive type requires at least 6 of the 9 possible symptoms and signs of hyperactivity and impulsivity. Diagnosis of the combined type requires at least 6 symptoms and signs each of inattention and hyperactivity-impulsivity.

Differentiating between ADHD and other conditions can be challenging. Overdiagnosis must be avoided, and other conditions must be accurately identified. Many ADHD signs expressed during the preschool years could also indicate communication problems that can occur in other developmental disorders (eg, autism spectrum [pervasive developmental] disorders) or in certain learning disorders, anxiety, depression, or behavioral disorders (eg, conduct disorder). Clinicians should consider whether the child is distracted by external factors (ie, environmental input) or by internal factors (ie, thoughts, anxieties, worries). However, during later childhood, ADHD signs become more qualitatively distinct; affected children often exhibit continuous movement of the lower extremities, motor impersistence (eg, purposeless movement, fidgeting of hands), impulsive talking, and a seeming lack of awareness of their environment.

Medical assessment focuses on identifying potentially treatable conditions that may contribute to or worsen symptoms and signs. Developmental assessment focuses on determining the onset and course of symptoms and signs. Educational assessment focuses on documenting core symptoms and signs; it may involve reviewing educational records and using rating scales or checklists. However, rating scales and checklists alone often cannot distinguish ADHD from other developmental disorders or from behavioral disorders.

**Prognosis**

Traditional classrooms and academic activities often exacerbate symptoms and signs in children with untreated or inadequately treated ADHD. Social and emotional adjustment problems may be persistent. Poor acceptance by peers and loneliness tend to increase with age and with the obvious display of symptoms. Substance abuse may result if ADHD is not identified and treated.

Although hyperactivity symptoms and signs tend to diminish with age, adolescents and adults may display residual difficulties. Predictors of poor outcomes in adolescence and adulthood include

- Coexisting low intelligence
- Aggressiveness
- Social and interpersonal problems
- Parental psychopathology

Problems in adolescence and adulthood manifest predominantly as academic failure, low self-esteem, and difficulty learning appropriate social behavior. Adolescents and adults who have predominately impulsive ADHD may have an increased incidence of personality trait disorders and antisocial behavior; many continue to display impulsivity, restlessness, and poor social skills. People with ADHD seem to adjust better to work than to academic and home situations.

**Treatment**

- Behavioral therapy
- Drug therapy, typically with stimulants such as methylphenidate or dextroamphetamine

Randomized, controlled studies show behavioral therapy alone is less effective than therapy with stimulant drugs alone; combination therapy has mixed results. Although correction of the underlying neurophysiologic differences of patients with ADHD does not occur with drug therapy, drugs are effective in alleviating ADHD symptoms, and they permit participation in activities previously inaccessible because of poor attention and impulsivity. Drugs often interrupt the cycle of inappropriate behavior, enhancing behavioral and academic interventions, motivation, and self-esteem. Treatment of adults follows similar principles, but drug selection and dosing are determined on an individual basis, depending on other medical conditions.

**Drugs:** Stimulant preparations that include methylphenidate or dextroamphetamine are most widely used. Response varies greatly, and dosage depends on the severity of the behavior and the child's ability to tolerate the drug. Dosing is adjusted in frequency and amount until the optimal response is achieved.

Methylphenidate is usually started at 0.3 mg/kg po once/day (immediate-release form) and increased in frequency weekly, usually to about tid or q 4 h. If response is inadequate but drug is tolerated, dose can be increased. Most children find an optimal balance between benefits and adverse effects at individual doses between 0.3 and 0.6 mg/kg.

Dextroamphetamine is typically started (either alone or in combination with amphetamine) at 0.15 to 0.2 mg/kg po once/day, which can then be increased to bid, tid, or q 4 h. Individual doses in the range of 0.15 to 0.4 mg/kg are usually effective. Dose titration should balance effectiveness against adverse effects. In general, dextroamphetamine doses are about two thirds those of methylphenidate doses.

For methylphenidate or dextroamphetamine, once an optimal dosage is reached, an equivalent dosage of the same drug in a sustained-release form is often substituted to avoid the need for drug administration in school. Long-acting preparations include wax matrix slow-release tablets, biphasic capsules containing the equivalent of 2 doses, and osmotic release pills and transdermal patches that provide up to 12 h of coverage. Learning is often enhanced by low doses, but improvement in behavior often requires higher doses.

Dosing schedules of stimulant drugs can be adjusted to cover specific days and times (eg, during school hours, while doing homework). Drug holidays should be tried on weekends, on holidays, or during summer vacations. Placebo periods (for 5 to 10 school days to ensure reliability of observations) are recommended to determine whether the drugs are still needed.

Common adverse effects of stimulant drugs include

- Sleep disturbances (eg, insomnia)
- Depression
- Headache
- Stomachache
- Appetite suppression
- Elevated heart rate and BP

Some studies have shown slowing of growth over 2 yr of stimulant drug use, but whether slowing persists over longer periods of use remains unclear. Some patients who are sensitive to stimulant drug effects appear over-focused or dulled; decreasing the stimulant drug dosage or trying a different drug may be helpful.

Atomoxetine, a selective norepinephrine reuptake inhibitor, is also used. The drug is effective, but data are mixed regarding its efficacy compared with stimulant drugs. Many children experience nausea, sedation, irritability, and temper tantrums; rarely, liver toxicity and suicidal ideation occur. A typical starting dose is 0.5 mg/kg po once/day, titrated weekly to 1.2 to 1.4 mg/kg once/day. The long half-life allows once/day dosing but requires continuous use to be effective. The maximum recommended daily dosage is 100 mg.

Antidepressants such as bupropion, α-2 agonists such as clonidine and guanfacine, and other psychoactive drugs are sometimes used in cases of stimulant drug ineffectiveness or unacceptable adverse effects, but they are less effective and are not recommended as first-line drugs. Pemoline is no longer recommended. Sometimes these drugs are used in combination with stimulants for synergistic effects; close monitoring for adverse effects is essential.

**Behavioral management:** Counseling, including cognitive-behavioral therapy (eg, goal-setting, self-monitoring, modeling, role-playing), is often effective and helps children understand ADHD. Structure and routines are essential.

Classroom behavior is often improved by environmental control of noise and visual stimulation, appropriate task length, novelty, coaching, and teacher proximity.

When difficulties persist at home, parents should be encouraged to seek additional professional assistance and training in behavioral management techniques. Adding incentives and token rewards reinforces behavioral management and is often effective. Children with ADHD in whom hyperactivity and poor impulse control predominate are often helped at home when structure, consistent parenting techniques, and well-defined limits are established.

Elimination diets, megavitamin treatments, use of antioxidants or other compounds, and nutritional and biochemical interventions have had the least consistent effects. Biofeedback can be helpful in some cases but is not recommended for routine use because evidence of sustained benefit is lacking.

## Autism Spectrum Disorders

(Pervasive Developmental Disorders)

**Autism spectrum disorders are neurodevelopmental disorders characterized by impaired social interaction and communication, repetitive and stereotyped patterns of behavior, and uneven intellectual development often with intellectual disability. Symptoms begin in early childhood. The cause in most children is unknown, although evidence supports a genetic component; in some patients, the disorders may be caused by a medical condition. Diagnosis is based on developmental history and observation. Treatment consists of behavioral management and sometimes drug therapy.**

Autism, a neurodevelopmental disorder, is the most common of the disorders called autism spectrum disorders (ASD) or pervasive developmental disorders (PDD)—see Table 304-2. Current estimates of prevalence of ASD are in the range of 1/150. Autism is 2 to 4 times more common among boys. In recent years, there has been a rapid rise in the diagnosis of ASD, partially because of changes in diagnostic criteria.

### Etiology

The specific cause in most cases of ASD remains elusive. However, some cases have occurred with congenital rubella syndrome, cytomegalic inclusion disease, phenylketonuria, or fragile X syndrome.

Strong evidence supports a genetic component. For parents of one child with an ASD, risk of having a subsequent child with an ASD is 50 to 100 times greater. The concordance rate of autism is high in monozygotic twins. Research on families has suggested several potential target gene areas, including those related to neurotransmitter receptors (gamma-aminobutyric acid [GABA]) and CNS structural control (*HOX* genes). Environmental causes have been suspected but are unproved. There is strong evidence that vaccinations do not cause autism.

Abnormalities of brain structure and function probably underlie much of the pathogenesis

[**Table 304-2.** Autism Spectrum Disorders]

of autism. Some children with autism have enlarged ventricles, some have hypoplasia of the cerebellar vermis, and others have abnormalities of brain stem nuclei.

### Symptoms and Signs

Classic autistic disorder usually manifests in the first year of life and almost always by age 3. The disorder is characterized by

- Atypical interaction (ie, lack of attachment, inability to cuddle or to form reciprocal relationships, avoidance of eye gaze)
- Insistence on sameness (ie, resistance to change, rituals, intense attachment to familiar objects, repetitive acts)
- Speech and language problems (ranging from total muteness to delayed onset of speech to markedly idiosyncratic use of language)
- Uneven intellectual performance

Some affected children injure themselves. About 25% of affected children experience a documented loss of previously acquired skills.

All children with ASD have similar problems with interaction, behavior, and communication; however, the severity of the problems varies widely. Nevertheless, some characteristic features often point to the specific diagnosis (see Table 304-2). Children with Asperger's syndrome generally have better intellectual performance than children with classic autistic disorder. They also lack the language delays typical of children with classic autistic disorder. Children with childhood disintegrative disorder develop normally until about age 2, and then their skills deteriorate.

Current theory holds that a fundamental problem in ASD is mind blindness, the inability to imagine what another person might be thinking. This difficulty is thought to result in interaction abnormalities that, in turn, lead to abnormal language development. One of the earliest and most sensitive markers for autism is a 1-yr-old child's inability to point communicatively at objects. It is theorized that the child cannot imagine that another person would understand what was being indicated; instead, the child indicates wants only by physically touching the desired object or using the adult's hand as a tool.

Nonfocal neurologic findings include poorly coordinated gait and stereotyped motor movements. Seizures occur in 20 to 40% of these children (particularly those with an intelligence quotient [IQ] < 50).

**Diagnosis**

• Clinical evaluation

Diagnosis is made clinically and usually requires evidence of impairment of social interaction and communication and presence of restricted, repetitive, stereotyped behaviors or interests. Screening tests include the Social Communication Questionnaire and the modified checklist for autism in toddlers (M-CHAT). Formal gold standard diagnostic tests such as the Autism Diagnostic Observation Schedule (ADOS), based on criteria in the *Diagnostic and Statistical Manual of Mental Disorders* , Fourth Edition Text Revision (DSM-IV-TR), are usually given by psychologists. Children with ASD are difficult to test; they usually do better on performance items than verbal items in IQ tests and may show instances of age-appropriate performance despite cognitive limitation in most areas. Nonetheless, an IQ test given by an experienced examiner often can provide a useful predictor of outcome.

**Treatment**

• Behavioral therapy

• Speech and language therapy

• Sometimes physical and occupational therapy

• Drug therapy

Treatment is usually multidisciplinary, and recent studies show measurable benefits from intensive, behaviorally based approaches that encourage interaction and meaningful communication. Psychologists and educators typically focus on behavioral analysis and then match behavioral management strategies to specific behavioral problems at home and at school.

Speech and language therapy should begin early and use a range of media, including signing, picture exchange, and speech. Physical and occupational therapists plan and implement strategies to help affected children compensate for specific deficits in motor function and motor planning.

SSRIs may improve control of ritualistic behaviors. Antipsychotics and mood stabilizers such as valproate may help control self-injurious behavior.

Dietary interventions, including some vitamin supplements and a gluten-free and casein-free diet, have not been fully investigated. Other complementary and investigational approaches to therapy (eg, facilitated communication) have not yet shown efficacy and require additional study.

## Learning Disabilities

**Learning disabilities are conditions that cause a discrepancy between potential and actual levels of academic performance as predicted by the person's intellectual abilities. Learning disabilities involve impairments or difficulties in concentration or attention, language development, or visual and aural information processing. Diagnosis includes cognitive, educational, speech and language, medical, and psychologic evaluations. Treatment consists**

**primarily of educational management and sometimes medical, behavioral, and psychologic therapy.**

Specific learning disabilities affect the ability to understand or use spoken or written language, do mathematical calculations, coordinate movements, or focus attention on a task. These disabilities include problems in reading, mathematics, spelling, written expression or handwriting, and understanding or using verbal and nonverbal language (see Table 304-3). Most learning disabilities are complex or mixed, with deficits in more than one system.

Although the number of children with learning disabilities is unknown, about 5% of the school-age population in the US receives special educational services for learning disabilities. Among affected children, boys outnumber girls 5:1.

Learning disabilities may be congenital or acquired. No single cause has been defined, but neurologic deficits are evident or presumed. Genetic influences are often implicated. Other possible causes include

- Maternal illness or use of toxic drugs during pregnancy
- Complications during pregnancy or delivery (eg, spotting, toxemia, prolonged labor, precipitous delivery)
- Neonatal problems (eg, prematurity, low birth weight, severe jaundice, perinatal asphyxia, postmaturity, respiratory distress)

[**Table 304-3.** Common Learning Disabilities]

Potential postnatal factors include exposure to environmental toxins (eg, lead), CNS infections, cancers and their treatments, trauma, undernutrition, and severe social isolation or deprivation.

### Symptoms and Signs

Children with learning disabilities typically have at least average intelligence, although such disabilities can occur in children with lower cognitive function as well. Symptoms and signs of severe disabilities tend to manifest at an early age. Mild to moderate learning disabilities are usually not recognized until school age, when the rigors of academic learning are encountered. Affected children may have trouble learning the alphabet and may be delayed in paired associative learning (eg, color naming, labeling, counting, letter naming). Speech perception may be limited, language may be learned at a slower rate, and vocabulary may be decreased. Affected children may not understand what is read, have very messy handwriting or hold a pencil awkwardly, have trouble organizing or beginning tasks or retelling a story in sequential order, or confuse math symbols and misread numbers.

Disturbances or delays in expressive language or listening comprehension are predictors of academic problems beyond the preschool years. Memory may be defective, including short-term and long-term memory, memory use (eg, rehearsal), and verbal recall or retrieval. Problems may occur in conceptualizing, abstracting, generalizing, reasoning, and organizing and planning information for problem solving. Visual perception and auditory processing problems may occur; they include difficulties in spatial cognition and orientation (eg, object localization, spatial memory, awareness of position and place), visual attention and memory, and sound discrimination and analysis.

Some children with learning disabilities have difficulty following social conventions (eg, taking turns, standing too close to the listener, not understanding jokes); these difficulties are often components of mild autism spectrum disorders as well (see p. 3038). Short attention span, motor restlessness, fine motor problems (eg, poor printing and copying), and variability in performance and behavior over time are other early signs. Difficulties with impulse control, non-goal-directed behavior and overactivity, discipline problems, aggressiveness, withdrawal and avoidance behavior, excessive shyness, and excessive fear may occur. Learning disabilities and attention-deficit/hyperactivity disorder (ADHD) often occur together.

### Diagnosis

• Cognitive, behavioral, medical, and psychologic evaluations

Children with learning disabilities are typically identified when a discrepancy is recognized between academic potential and academic performance. Speech and language, intellectual, educational, medical, and psychologic evaluations are necessary for determining deficiencies in skills and cognitive processes. Social and emotional-behavioral evaluations are also necessary for planning treatment and monitoring progress.

**Cognitive evaluation** typically includes verbal and nonverbal intelligence testing and is usually done by school personnel. Psychoeducational testing may be helpful in describing the child's preferred manner of processing information (eg, holistically or analytically, visually or aurally). Neuropsychologic assessment is particularly useful in children with known CNS injury or illness to map the areas of the brain that correspond to specific functional strengths and weaknesses. Speech and language evaluations establish integrity of comprehension and language use, phonologic processing, and verbal memory.

**Behavioral assessment** and performance evaluation by teachers' observations of classroom behavior and determination of academic performance are essential. Reading evaluations measure abilities in word decoding and recognition, comprehension, and fluency. Writing samples should be obtained to evaluate spelling, syntax, and fluency of ideas. Mathematical ability should be assessed in terms of computation skills, knowledge of operations, and understanding of concepts.

**Medical evaluation** includes a detailed family history, the child's medical history, a physical examination, and a neurologic or neurodevelopmental examination to look for underlying disorders. Although infrequent, physical abnormalities and neurologic signs may indicate medically treatable causes of learning disabilities. Gross motor coordination problems may indicate neurologic deficits or neurodevelopmental delays. Developmental level is evaluated according to standardized criteria.

**Psychologic evaluation** helps identify ADHD, conduct disorder, anxiety disorders, depression, and poor self-esteem, which frequently accompany and must be differentiated from learning disabilities. Attitude toward school, motivation, peer relationships, and self-confidence are assessed.

### Treatment

• Educational management

• Medical, behavioral, and psychologic therapy

• Occasionally drug therapy

Treatment centers on educational management but may also involve medical, behavioral, and psychologic therapy. Effective teaching programs may take a remedial, compensatory, or strategic (ie, teaching the child how to learn) approach. A mismatch of instructional method and a child's learning disability and learning preference aggravates the disability.

Some children require specialized instruction in only one area while they continue to attend regular classes. Other children need separate and intense educational programs. Optimally and as required by US law, affected children should participate as much as possible in inclusive classes with peers who do not have learning disabilities.

Drugs minimally affect academic achievement, intelligence, and general learning ability, although certain drugs (eg, stimulants, such as methylphenidate and several amphetamine preparations—see p. 3037) may enhance attention and concentration, allowing children to respond more efficiently to instruction. Many popular remedies and therapies (eg, eliminating food additives, using antioxidants or megadoses of vitamins, patterning by sensory stimulation and passive movement, sensory integrative therapy through postural exercises, auditory nerve training, optometric training to remedy visual-perceptual and sensorimotor coordination processes) are unproved.

### Dyslexia

**Dyslexia is a general term for primary reading disorder. Diagnosis is based on intellectual, educational, speech and language, medical, and psychologic evaluations. Treatment is primarily educational management, consisting of instruction in word recognition and component skills.**

No definition of dyslexia is universally accepted; thus, incidence is undetermined. An estimated 15% of public school children receive special instruction for reading problems; about one half of these children may have persistent reading disabilities. Dyslexia is identified more often in boys than girls, but sex is not a proven risk factor for developing dyslexia.

The inability to learn derivational rules of printed language is often considered part of dyslexia. Affected children may have difficulty determining root words or word stems and determining which letters in words follow others.

Reading problems other than dyslexia are usually caused by difficulties in language comprehension or low cognitive ability. Visual-perceptual problems and abnormal eye movements are not dyslexia. However, these problems can interfere further with word learning.

### Etiology

Phonologic processing problems cause deficits in discrimination, blending, memory, and analysis of sounds. Dyslexia may affect both production and understanding of written language, which is often restricted further by problems with auditory memory, speech production, and naming or word finding. Underlying weaknesses in verbal language are often present.

### Pathophysiology

Dyslexia tends to run in families. Children with a family history of reading or learning difficulties are at higher risk. Because changes have been identified in the brains of people with dyslexia, experts believe dyslexia results predominantly from cortical dysfunction stemming from congenital neurodevelopmental abnormalities. Lesions affecting the integration or interactions of specific brain functions are suspected. Most researchers concur that dyslexia is left hemisphere-related and linked to dysfunctions in brain areas responsible for language association (Wernicke's motor speech area) and sound and speech production (Broca's area) and in the interconnection of these areas via the fasciculus arcuatus. Dysfunctions or defects in the angular gyrus, the medial occipital area, and the right hemisphere cause word recognition problems. Research suggests some malleability of brain systems in response to training.

### Symptoms and Signs

Dyslexia may manifest as

• Delayed language production

• Speech articulation difficulties

• Difficulties remembering the names of letters, numbers, and colors

Children with phonologic processing problems often have difficulty blending sounds, rhyming words, identifying the positions of sounds in words, and segmenting words into pronounceable components. They may reverse the order of sounds in words. Delay or hesitation in choosing words, substituting words, or naming letters and pictures is often an early sign. Short-term auditory memory and auditory sequencing difficulties are common.

Fewer than 20% of children with dyslexia have difficulties with the visual demands of reading. However, some children confuse letters and words with similar configurations or have difficulty visually selecting or identifying letter patterns and clusters (sound-symbol association) in words. Reversals or visual confusions can occur, most often because of retention or retrieval difficulties that cause affected children to forget or confuse the names of letters and words that have similar structures; subsequently, *d* becomes

*b*, *m* becomes *w*, *h* becomes *n*, *was* becomes *saw*, *on* becomes *no*. However, such reversals are normal in children < 8 yr.

Although dyslexia is a lifelong problem, many children develop functional reading skills. However, other children never reach adequate literacy.

**Diagnosis**

• Reading evaluation

• Speech, language, and auditory evaluations

• Psychologic evaluations

Most children with dyslexia are not identified until kindergarten or 1st grade, when they encounter symbolic learning. Children with a history of delayed language acquisition or use, who are not accelerating in word learning by the end of 1st grade, or who are not reading at the level expected for their verbal or intellectual abilities at any grade level should be evaluated. Often, the best diagnostic indicator is the child's inability to respond to traditional or typical reading approaches during 1st grade, although wide variation in reading skills can still be seen at this level. Demonstration of phonologic processing problems is essential for diagnosis.

Children suspected of having dyslexia should undergo reading, speech and language, auditory, cognitive, and psychologic evaluations to identify their functional strengths and weaknesses and their preferred learning styles. Such evaluations can be requested of school staff by the child's teacher or family based on the Individuals with Disabilities Education Act (IDEA), a US special education law. Evaluation findings then guide the most effective instructional approach.

Comprehensive reading evaluations test word recognition and analysis, fluency, reading or listening comprehension, and level of understanding of vocabulary and the reading process.

Speech, language, and auditory evaluations assess spoken language and deficits in processing phonemes (sound elements) of spoken language. Receptive and expressive language functions are also assessed. Cognitive abilities (eg, attention, memory, reasoning) are tested.

Psychologic evaluations address emotional concerns that can exacerbate a reading disability. A complete family history of mental disorders and emotional problems is obtained.

Physicians should ensure that children have normal vision and hearing, either through office-based screening or referral for formal audiologic or vision testing. Neurologic evaluations may help detect secondary features (eg, neurodevelopmental immaturity or minor neurologic abnormalities) and rule out other disorders (eg, seizures).

**Treatment**

• Educational interventions

Treatment consists of educational interventions, including direct and indirect instruction in word recognition and component skills. Direct instruction includes teaching specific phonics skills separate from other reading instruction. Indirect instruction includes integrating phonics skills into reading programs. Instruction may teach reading from a whole-word or whole-language approach or by following a hierarchy of skills from the sound unit to the word to the sentence. Multisensory approaches that include whole-word learning and the integration of visual, auditory, and tactual procedures to teach sounds, words, and sentences are then recommended.

Component skills instruction consists of teaching children to blend sounds to form words, segment words into word parts, and identify the positions of sounds in words. Component skills for reading comprehension include identifying the main idea, answering questions, isolating facts and details, and

reading inferentially. Many children benefit from using a computer to help isolate words within text samples or for word processing of written work.

Other treatments (eg, optometric training, perceptual training, auditory integration training) and drug therapies are unproved and not recommended.

## Intellectual Disability

**Intellectual disability (ID, previously called mental retardation) is characterized by significantly sub-average intellectual functioning (often expressed as an intelligence quotient < 70 to 75) combined with limitations of > 2 of the following: communication, self-direction, social skills, self-care, use of community resources, and maintenance of personal safety. Management consists of education, family counseling, and social support.**

Basing severity on intelligence quotient (IQ) alone (eg, mild, 52 to 70 or 75; moderate, 36 to 51; severe, 20 to 35; and profound, < 20) is inadequate. Classification must also account for the level of support needed, ranging from intermittent to ongoing high-level support for all activities. Such an approach focuses on a person's strengths and weaknesses, relating them to the demands of the person's environment and the expectations and attitudes of the family and community.

About 3% of the population functions at an IQ of < 70, which is at least 2 standard deviations below the mean IQ of the general population (IQ of 100); if the need for support is considered, only about 1% of the population has severe ID. Severe ID occurs in families from all socioeconomic groups and educational levels. Less severe ID (requiring intermittent or limited support) occurs most often in lower socioeconomic groups, paralleling with observations that IQ correlates best with success in school and socioeconomic status rather than specific organic factors. Nevertheless, recent studies suggest that genetic factors play roles even in milder cognitive disabilities.

### Etiology

Intelligence is both genetically and environmentally determined. Children born to parents with ID are at increased risk of a range of developmental disabilities, but clear genetic transmission of ID is unusual. Although advances in genetics, such as chromosomal microarray analysis, have increased the likelihood of identifying the cause of an ID, a specific cause cannot be identified in 60 to 80% of cases. A cause is most likely to be identified in severe cases. Deficits in language and personal-social skills may be due to emotional problems, environmental deprivation, learning disorders, or deafness rather than ID.

**Prenatal:** A number of chromosomal anomalies and genetic metabolic and neurologic disorders can cause ID (see
Table 304-4).

[**Table 304-4.** Chromosomal and Genetic Causes of Intellectual Disability*]

Congenital infections that can cause ID include rubella and those due to cytomegalovirus, *Toxoplasma gondii*, *Treponema pallidum*, or HIV.

Prenatal drug and toxin exposure (see p. 2625) can cause ID. Fetal alcohol syndrome (see p. 2799) is the most common of these conditions. Anticonvulsants such as phenytoin or valproate, chemotherapy drugs, radiation exposure, lead, and methylmercury are also causes. Severe undernutrition during pregnancy may affect fetal brain development, resulting in ID.

**Perinatal:** Complications related to prematurity, CNS bleeding, periventricular leukomalacia, breech or high forceps delivery, multiple births, placenta previa, preeclampsia, and perinatal asphyxia may increase the risk of ID. The risk is increased in small-forgestational-age infants; intellectual impairment and decreased weight share the same cause. Very low- and extremely low-birth-weight infants have variably increased chances of having ID, depending on gestational age, perinatal events, and quality of care.

**Postnatal:** Undernutrition and environmental deprivation (lack of physical, emotional, and cognitive

support required for growth, development, and social adaptation) during infancy and early childhood may be the most common causes of ID worldwide. Viral and bacterial encephalitides (including AIDS-associated neuroencephalopathy) and meningitides, poisoning (eg, lead, mercury), and accidents that cause severe head injuries or asphyxia may result in ID.

**Symptoms and Signs**

The primary manifestations are

- Delayed intellectual development
- Immature behavior
- Limited self-care skills

Some children with mild ID may not develop recognizable symptoms until preschool age. However, early identification is common among children with moderate to severe ID and among children in whom ID is accompanied by physical abnormalities or signs of a condition (eg, cerebral palsy) that may be associated with a particular cause of ID (eg, perinatal asphyxia). Delayed development is usually apparent by preschool age. Among older children, hallmark features are a low IQ combined with limitations in adaptive behavior skills. Although developmental patterns may vary, it is much more common for children with ID to experience slow progress than developmental arrest.

Some children may have cerebral palsy or other motor deficits, language delays, or hearing loss. Such motor or sensory impairments can mimic cognitive impairment but are not in themselves causes of it. As children mature, some develop anxiety or depression if they are socially rejected by other children or if they are disturbed by the realization that others see them as different and deficient. Well-managed, inclusive school programs can help maximize social integration, thereby minimizing such emotional responses.

Behavioral disorders are the reason for most psychiatric referrals and out-of-home placements for people with ID. Behavioral problems are often situational, and precipitating factors can usually be identified. Factors that predispose to unacceptable behavior include

- Lack of training in socially responsible behavior
- Inconsistent discipline
- Reinforcement of faulty behavior
- Impaired ability to communicate
- Discomfort due to coexisting physical problems and mental health disorders such as depression or anxiety

In institutional settings, overcrowding, understaffing, and lack of activities contribute.

**Diagnosis**

- Developmental and intelligence assessment
- Imaging testing
- Genetic testing

For suspected cases, development and intelligence are assessed, typically by early intervention or school staff. Standardized intelligence tests can measure subaverage intellectual ability but are subject to error, and results should be questioned when they do not match clinical findings; illness, motor or sensory

impairments, language barriers, or cultural differences may hamper a child's test performance. Such tests also have a middle-class bias but are generally reasonable in appraising intellectual ability in children, particularly in older ones. Developmental screening tests such as the Ages and Stages Questionnaire or the Parents' Evaluation of Developmental Status (PEDS) provide gross assessments of development for young children and can be given by a physician or others. Such measures should be used only for screening and not as substitutes for standardized intelligence tests, which should be given by qualified psychologists. A neurodevelopmental assessment should be initiated as soon as developmental delays are suspected. A developmental pediatrician or pediatric neurologist should investigate all cases of

- Moderate to severe developmental delays
- Progressive disability
- Neuromuscular deterioration
- Suspected seizure disorders

Establishing ID is followed by efforts to determine a cause. Accurate determination of the cause may provide a developmental prognosis, suggest plans for educational and training programs, help in genetic counseling, and relieve parental guilt. History (including perinatal, developmental, neurologic, and familial) may identify causes. An algorithm for the diagnostic evaluation of the child with ID (global developmental delay) has been proposed by the Child Neurology Society. Cranial imaging (eg, MRI) can show CNS malformations (as seen in neurodermatoses such as neurofibromatosis or tuberous sclerosis), treatable hydrocephalus, or more severe brain malformations such as schizencephaly. Genetic tests may help identify disorders such as Down syndrome (trisomy 21) via standard karyotyping, 5p-deletion (cri du chat syndrome) or DiGeorge syndrome (chromosome 22q deletion) via fluorescent in situ hybridization (FISH), or fragile X syndrome via direct DNA studies. Recently, chromosomal microarray analysis has become more widely available, affording opportunities for identifying otherwise unrecognized chromosome disruptions.

Genetic metabolic disorders may be suggested by their clinical manifestations (eg, failure to thrive, lethargy, vomiting, seizures, hypotonia, hepatosplenomegaly, coarse facial features, abnormal urinary odor, macroglossia). Isolated delays in sitting or walking (gross motor skills) and in pincer grasp, drawing, or writing (fine motor skills) may indicate a neuromuscular disorder. Specific laboratory tests are done depending on the suspected cause (see Table 304-5). Visual and auditory assessments should be done at an early age, and screening for lead poisoning is often appropriate.

[**Table 304-5.** Tests for Some Causes of Intellectual Disability]

### Prognosis

Many people with mild to moderate ID can support themselves, live independently, and be successful at jobs that require basic intellectual skills. Life expectancy may be shortened, depending on the etiology of the disability, but health care is improving long-term health outcomes for people with all types of developmental disabilities. People with severe ID are likely to require life-long support. The more severe the cognitive disability and the greater the immobility, the higher the mortality risk.

### Treatment

- Early intervention program
- Multidisciplinary team support

Treatment and support needs depend on social competence and cognitive function. Referral to an early intervention program during infancy may prevent or decrease the severity of disability resulting from a perinatal insult. Realistic methods of caring for affected children must be established.

Family support and counseling are crucial. As soon as ID is confirmed or strongly suspected, the parents should be informed and given ample time to discuss causes, effects, prognosis, education and training of the child, and the importance of balancing known prognostic risks against negative self-fulfilling prophecies in which diminished expectations result in poor functional outcomes later in life. Sensitive ongoing counseling is essential for family adaptation. If the family's physician cannot provide coordination and counseling, the child and family should be referred to a center with a multidisciplinary team that evaluates and serves children with ID; however, the family's physician should provide continuing medical care and advice.

A comprehensive, individualized program is developed with the help of appropriate specialists, including educators.

A multidisciplinary team includes

- Neurologists or developmental pediatricians
- Orthopedists
- Physical therapists and occupational therapists (who assist in managing comorbidities in children with motor deficits)
- Speech pathologists and audiologists (who help with language delays or with suspected hearing loss)
- Nutritionists (who help with treatment of undernutrition)
- Social workers (who help reduce environmental deprivation)

Affected children with concomitant mental health disorders such as depression may be given appropriate psychoactive drugs in dosages similar to those used in children without ID. Use of psychoactive drugs without behavioral therapy and environmental changes is rarely helpful.

Every effort should be made to have children live at home or in community-based residences. Although the presence of a child with ID in the home can be disruptive, it can also be extremely rewarding. The family may benefit from psychologic support and help with daily care provided by day care centers, homemakers, and respite services. The living environment must encourage independence and reinforce learning of skills needed to accomplish this goal. Whenever possible, children with ID should attend an appropriately adapted day care center or school with peers without cognitive disability. The Individuals with Disabilities Education Act (IDEA), a US special education law, stipulates that all children with disabilities should receive appropriate educational opportunities and programming in the least restrictive and most inclusive environments. As people with ID reach adulthood, an array of supportive living and work settings is available. Large residential institutions are being replaced by small group or individual residences matched to the affected person's functional abilities and needs.

**Prevention**

Genetic counseling (see also p. 2598) may help high-risk couples understand possible risks. If a child has ID, evaluation of the etiology can provide the family with appropriate risk information for future pregnancies.

High-risk couples who choose to have children often undergo prenatal testing, which enables couples to consider pregnancy termination and subsequent family planning. Testing includes

- Amniocentesis
- Ultrasonography
- Maternal serum α-fetoprotein

Amniocentesis or chorionic villus sampling may detect inherited metabolic and chromosomal disorders, carrier states, and CNS malformations (eg, neural tube defects, anencephaly). Amniocentesis is indicated for all pregnant women > 35 yr (because their risk of having an infant with Down syndrome is increased) and for women with family histories of inherited metabolic disorders. Ultrasonography may also identify CNS defects. Maternal serum α-fetoprotein is a helpful screen for neural tube defects, Down syndrome, and other abnormalities.

Rubella vaccine has all but eliminated congenital rubella as a cause. A vaccine for cytomegalovirus infection is being sought. Continuing improvements in and increased availability of obstetric and neonatal care and the use of exchange transfusion and Rho(D) immune globulin to prevent hemolytic disease of the newborn have reduced the incidence of ID; the increase in survival of very-low-birth-weight infants has kept the prevalence constant.

# Chapter 305. Mental Disorders in Children and Adolescents

## Introduction

Although it is sometimes assumed that childhood and adolescence are times of carefree bliss, as many as 20% of children and adolescents have one or more diagnosable mental disorders. Most of these disorders may be viewed as exaggerations or distortions of normal behaviors and emotions.

Like adults, children and adolescents vary in temperament. Some are shy and reticent; others are socially exuberant. Some are methodical and cautious; others are impulsive and careless. Whether a child is behaving like a typical child or has a disorder is determined by the presence of impairment and the degree of distress related to the symptoms. For example, a 12-yr-old girl may be frightened by the prospect of delivering a book report in front of her class. This fear would be viewed as social phobia only if her fears were severe enough to cause significant impairments and distress.

There is much overlap between the symptoms of many disorders and the challenging behaviors and emotions of normal children. Thus, many strategies useful for managing behavioral problems in children (see p. 3030) can also be used in children who have mental disorders. Furthermore, appropriate management of childhood behavioral problems may prevent temperamentally vulnerable children from developing a full-blown disorder.

The most common mental disorders of childhood and adolescence fall into 4 broad categories:

- Anxiety disorders
- Schizophrenia
- Mood disorders (primarily depression)
- Disruptive behavioral disorders

However, more often than not, children and adolescents have symptoms and problems that cut across diagnostic boundaries.

### Evaluation

Evaluation of mental complaints or symptoms in children and adolescents differs from that in adults in 3 important ways:

- Developmental context is critically important in children. Behaviors that are normal at a young age may indicate a serious mental disorder at an older age.
- Children exist in the context of a family system, and that system has a profound effect on children's symptoms and behaviors; normal children living in a family troubled by domestic violence and substance abuse may superficially appear to have one or more mental disorders.
- Children often do not have the cognitive and linguistic sophistication needed to accurately describe their symptoms. Thus, the clinician must rely very heavily on direct observation, corroborated by observations of other people, such as parents and teachers.

In many cases, developmental and behavioral problems (eg, poor academic progress, delays in language acquisition, deficits in social skills) are difficult to distinguish from those due to a mental disorder. In such cases, formal developmental and neuropsychologic testing should be part of the evaluation process.

Because of these factors, evaluation of children with a mental disorder is typically more complex than that of adults. However, most cases are not severe and can be competently managed by an appropriately trained primary care practitioner. However, uncertain or severe cases are best managed in consultation with a child and adolescent psychiatrist.

## Anxiety Disorders in Children and Adolescents

**Anxiety disorders are characterized by fear, worry, or dread that greatly impairs the ability to function normally and that is disproportionate to the circumstances at hand. Anxiety may result in physical symptoms. Diagnosis is clinical. Treatment is with behavioral therapy and drugs, usually SSRIs.**

Some anxiety is a normal aspect of development, as in the following:

• Most toddlers become fearful when separated from their mother, especially in unfamiliar surroundings.

• Fears of the dark, monsters, bugs, and spiders are common in 3- to 4-yr-olds.

• Shy children may initially react to new situations with fear or withdrawal.

• Fears of injury and death are more common among older children.

• Older children and adolescents often become anxious when giving a book report in front of their classmates.

Such difficulties should not be viewed as evidence of a disorder. However, if manifestations of anxiety become so exaggerated that they greatly impair functioning or cause severe distress, an anxiety disorder should be considered.

At some point during childhood, about 10 to 15% of children experience an anxiety disorder (eg, generalized anxiety disorder, social phobia, separation anxiety disorder, obsessive-compulsive disorder, specific phobia, panic disorder, acute and posttraumatic stress disorders).

### Etiology

Etiology seems to have a genetic basis but is heavily modified by psychosocial experience; heritability is polygenetic, and only a small number of the specific genes have been characterized thus far.

Anxious parents tend to have anxious children; having such parents may make children's problems worse than they otherwise might be. Even normal children have difficulty remaining calm and composed in the presence of an anxious parent, and children who are genetically predisposed to anxiety have even greater difficulty. In as many as 30% of cases, treating the parents' anxiety in conjunction with the child's anxiety is helpful (see p. 1493 for treatment of anxiety in adults).

### Symptoms and Signs

Perhaps the most common manifestation is school refusal. "School refusal" has largely supplanted the term "school phobia." Actual fear of school is exceedingly rare. Most children who refuse to go to school probably have separation anxiety, social phobia, panic, or a combination. Some have a specific phobia. The possibility that the child is being bullied at school must also be considered.

Some children complain directly about their anxiety, describing it in terms of worries—eg, "I am worried that I will never see you again" (separation anxiety) or "I am worried the kids will laugh at me" (social phobia). However, most children couch their discomfort in terms of somatic complaints: "I cannot go to school because I have a stomachache." These children are often telling the truth because an upset stomach, nausea, and headaches often develop in children with anxiety.

### Diagnosis

Diagnosis is clinical. A thorough psychosocial history can usually confirm it.

The physical symptoms that anxiety can cause in children can complicate the evaluation. In many children, considerable testing for physical disorders is done before clinicians consider an anxiety disorder.

### Prognosis

Prognosis depends on severity, availability of competent treatment, and the child's resiliency. Many children struggle with anxiety symptoms into adulthood. However, with early treatment, many children learn how to control their anxiety.

### Treatment

• Behavioral therapy

• Drugs, usually SSRIs

Anxiety disorders in children are treated with behavioral therapy (using principles of exposure and response prevention), sometimes in conjunction with drug therapy.

In behavioral therapy, children are systematically exposed to the anxiety-provoking situation in a graded fashion. By helping children remain in the anxiety-provoking situation (response prevention), therapists enable them to gradually become desensitized and feel less anxiety. Behavioral therapy is most effective when an experienced therapist knowledgeable in child development individualizes these principles.

In mild cases, behavioral therapy alone is usually sufficient, but drug therapy may be needed when cases are more severe or when access to an experienced child behavior therapist is limited. SSRIs are usually the first choice (see
Table 305-1).

Most children tolerate SSRIs without difficulty. Occasionally, upset stomach, diarrhea, or insomnia may occur. Some children have behavioral side effects (eg, activation, disinhibition—see Depressive Disorders in Children and Adolescents on p. 3055).

## Generalized Anxiety Disorder

**Generalized anxiety disorder (GAD) is a persistent state of heightened anxiety and apprehension characterized by excessive worrying, fear, and dread. Physical symptoms can include tremor, sweating, multiple somatic complaints, and exhaustion. Diagnosis is by history. Treatment is often with relaxation therapy, sometimes combined with drug therapy.**

### Symptoms and Signs

Children have multiple and diffuse worries, which are exacerbated by stress. These children often have difficulty paying attention and may be hyperactive and restless. They may sleep poorly, sweat excessively, feel exhausted, and complain of physical discomfort (eg, stomachache, muscle aches, headache).

### Diagnosis

GAD is diagnosed in children and adolescents who have prominent and impairing anxiety symptoms that are not focused enough to meet criteria for a specific disorder such as social phobia or panic disorder. GAD is also an appropriate diagnosis for children who have a specific anxiety disorder, such as separation anxiety, but also have other significant anxiety symptoms above and beyond those of the specific anxiety disorder.

Occasionally, GAD can be confused with attention-deficit/hyperactivity disorder

[**Table 305-1.** SSRIs for Treating Children ≥ 12 yr]

(ADHD—see p. 3035) because GAD can cause difficulty paying attention and can also result in

psychomotor agitation (ie, hyperactivity). A key difference is that children with ADHD tend to be no more prone to worries than children without ADHD, whereas children with GAD have many distressing worries.

**Treatment**

• Relaxation therapy

• Sometimes anxiolytic drugs, usually SSRIs

Because the focus of symptoms is diffuse, GAD is especially challenging to treat with behavioral therapy. Relaxation training is often more appropriate.

Patients who have severe GAD or who do not respond to psychotherapeutic interventions may need anxiolytic drugs. As with other anxiety disorders, SSRIs (see Table 305-1) are typically the drugs of choice. Buspirone is a useful alternative, especially for children who cannot tolerate SSRIs; starting dose is 5 mg po bid and may be gradually increased to 30 mg bid (or 20 mg tid) as tolerated. GI distress or headache may be limiting factors in dosage escalation.

**Social Phobia**

(Social Anxiety Disorder)

**Social phobia is a persistent fear of embarrassment, ridicule, or humiliation in social settings. Typically, affected children avoid situations that might provoke social scrutiny (eg, school). Diagnosis is by history. Treatment is with behavioral therapy; in severe cases, SSRIs are used.**

School refusal is often the initial presentation of social phobia, particularly in adolescents. Complaints often have a somatic focus (eg, "My stomach hurts," "I have a headache"). Some children have a history of many medical appointments and evaluations in response to these somatic complaints.

Affected children are terrified that they will humiliate themselves in front of their peers by giving the wrong answer, saying something inappropriate, becoming embarrassed, or even vomiting. In some cases, social phobia emerges after an unfortunate and embarrassing incident. In severe cases, children may refuse to talk on the telephone or even refuse to leave the house.

**Treatment**

• Behavioral therapy

• Sometimes an anxiolytic

Behavioral therapy is the cornerstone of treatment. Children should not be allowed to miss school. Absence serves only to make them even more reluctant to attend school.

If children and adolescents are not sufficiently motivated to participate in behavioral therapy or do not respond adequately to it, an anxiolytic such as an SSRI may help (see Table 305-1). Treatment with an SSRI may reduce anxiety enough to facilitate children's participation in behavioral therapy.

**Separation Anxiety Disorder**

**Separation anxiety disorder is a persistent, intense, and developmentally inappropriate fear of separation from a major attachment figure (usually the mother). Affected children desperately attempt to avoid such separations. When separation is forced, these children are distressfully preoccupied with reunification. Diagnosis is by history. Treatment is with behavioral therapy for the child and family and, for severe cases, SSRIs.**

Separation anxiety is a normal emotion in children between about age 8 mo and 24 mo (see p. 2749); it typically resolves as children develop a sense of object permanence and realize their parents will return.

In some children, separation anxiety persists beyond this time or returns later; it may be severe enough to be considered a disorder. Separation anxiety disorder commonly occurs in younger children and is rare after puberty.

**Symptoms and Signs**

Like social phobia, separation anxiety disorder often manifests as school (or preschool) refusal.

Dramatic scenes typically occur at the time of separation. Separation scenes are typically painful for both the child and attachment figure (usually the mother but can be either parent or a caregiver). Children often wail and plead with such desperation that the parent cannot leave, resulting in protracted scenes that are difficult to interrupt. When separated, children fixate on reunification with the attachment figure and are often worried that this person has been harmed (eg, in a car accident, by a serious illness). Children may refuse to sleep alone and may even insist on always being in the same room as the attachment figure.

Children often develop somatic complaints.

The child's demeanor is often normal when the attachment figure is present. This normal demeanor can sometimes give a false impression that the problem is minor.

Separation anxiety is often compounded by a parent's anxiety, which exacerbates the child's anxiety; the result is a vicious circle that can be interrupted only by sensitive and appropriate treatment of parent and child simultaneously.

**Diagnosis**

Diagnosis is by history and by observation of separation scenes.

**Treatment**

• Behavioral therapy

• Rarely anxiolytics

Treatment is with behavioral therapy that systematically enforces regular separations. The goodbye scenes should be kept as brief as possible, and the attachment figure should be coached to react to protestations matter-of-factly. Assisting children in forming an attachment to one of the adults in the preschool or school may be helpful.

In extreme cases, children may benefit from an anxiolytic such as an SSRI (see Table 305-1). However, separation anxiety disorder often affects children as young as 3 yr, and experience with these drugs in the very young is limited.

Successfully treated children are prone to relapses after holidays and breaks from school. Because of these relapses, parents are often advised to plan regular separations during these periods to help the child remain accustomed to being away from the parents.

**Obsessive-Compulsive Disorder**

**Obsessive-compulsive disorder (OCD) is characterized by obsessions, compulsions, or both. Obsessions are irresistible, persistent ideas, images, or impulses to do something. Compulsions are pathologic urges to act on an impulse, which, if resisted, result in excessive anxiety and distress. The obsessions and compulsions cause great distress and interfere with academic or social functioning. Diagnosis is by history. Treatment is with behavioral therapy and SSRIs.**

Most cases of OCD have no clear etiology. However, a few cases are thought to be associated with

group A β-hemolytic streptococcal infections. This syndrome is called pediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS). PANDAS should be considered in all children with a sudden onset of severe OCD-like symptoms because early antibiotic treatment may prevent or attenuate long-lasting impairment. Research in this area is ongoing, and if PANDAS is suspected, consultation with a specialist is strongly recommended.

**Symptoms and Signs**

Typically, OCD has a gradual, insidious onset. Most children initially hide their symptoms and report struggling with symptoms years before a definitive diagnosis is made.

Obsessions are typically experienced as worries or fears of harm (eg, contracting a deadly disease, sinning and going to hell, injuring themselves or others). Compulsions are deliberate volitional acts, usually done to neutralize or offset obsessional fears; they include checking behaviors, excessive washing, counting, or arranging, and many more. Obsessions and compulsions may have some logical connection (eg, hand washing to avoid disease) or may be illogical and idiosyncratic (eg, counting to 50 over and over to prevent grandpa from having a heart attack). If children are prevented from carrying out their compulsions, they become excessively anxious and concerned.

Most children have some awareness that their obsessions and compulsions are abnormal. Many affected children are embarrassed and secretive. Common symptoms include

- Having raw, chapped hands (the presenting symptom in children who compulsively wash)
- Spending excessively long periods of time in the bathroom
- Doing schoolwork very slowly (because of an obsession about mistakes)
- Making many corrections in schoolwork
- Engaging in repetitive or odd behaviors such as checking door locks, chewing food a certain number of times, or avoiding touching certain things
- Making frequent and tedious requests for reassurance, sometimes dozens or even hundreds of times per day—asking, eg, "Do you think I have a fever? Could we have a tornado? Do you think the car will start? What if we're late? What if the milk is sour? What if a burglar comes?"

**Diagnosis**

Diagnosis is by history. Once a comfortable relationship with a nonjudgmental therapist is established, the child with OCD usually discloses many obsessions and related compulsions. However, usually several appointments are needed to first establish trust. Children with OCD often have symptoms of other anxiety disorders, including panic attacks, separation problems, and specific phobias. This symptom overlap sometimes confuses the diagnosis.

**Prognosis**

In about 5% of children, the disorder remits after a few years, and treatment can be stopped. In the others, the disorder tends to be chronic, but normal functioning can usually be maintained with ongoing treatment. About 5% of children do not respond to treatment and remain greatly impaired.

**Treatment**

If streptococcal infection is not involved, treatment is usually a combination of behavioral therapy and an SSRI. If appropriate services are available and children are highly motivated, behavioral therapy alone may be adequate.

PANDAS is treated with antibiotics.

### Panic Disorder and Agoraphobia

**Panic disorder is characterized by recurrent, frequent (at least once/wk) panic attacks. Panic attacks are discrete spells lasting about 20 min; during attacks, children experience somatic symptoms, cognitive symptoms, or both. Panic disorder can occur with or without agoraphobia. Agoraphobia is a persistent fear of being trapped in situations or places without a way to escape easily and without help. Diagnosis is by history. Treatment is with benzodiazepines or SSRIs and behavioral therapy.**

Panic disorder is much less common among prepubertal children than among adolescents. Panic attacks can occur alone or in other anxiety disorders (eg, OCD, separation anxiety) or certain medical disorders (eg, asthma). Panic attacks can trigger an asthma attack and vice versa.

Symptoms may be cognitive, somatic, or (usually) both (see p. 1497).

Panic attacks usually develop spontaneously, but over time, children begin to attribute them to certain situations and environments. Affected children then attempt to avoid those situations, which can lead to agoraphobia. Avoidance behaviors are considered agoraphobia if they greatly impair normal functioning, such as going to school, visiting the mall, or doing other typical activities.

#### Diagnosis

• Clinical evaluation

• Evaluation for other causes

Panic disorder is diagnosed based on history, usually after a physical examination is done to rule out physical causes of somatic symptoms. Many children undergo considerable diagnostic testing before panic disorder is suspected. The presence of other disorders, especially asthma, can also complicate the diagnosis. Thorough screening for other anxiety disorders (eg, OCD, social phobia) is needed because any one of these disorders may be the primary problem causing panic attacks as a symptom.

In adults, important diagnostic criteria for panic disorder include concerns about future attacks, the implications of the attacks, and changes in behavior. However, children and younger adolescents usually lack the insight and forethought needed to develop these features, except they may change behavior to avoid situations they believe are related to the panic attack. As compared to those in adults, panic attacks in children and adolescents are often more dramatic in presentation (eg, with screaming, weeping, and hyperventilation). This display can be alarming to parents and others.

#### Prognosis

Prognosis for children and adolescents who have panic disorder with or without agoraphobia is good with treatment. Without treatment, adolescents may drop out of school, withdraw from society, and become reclusive and suicidal.

Panic disorder often waxes and wanes in severity without any discernible reason. Some patients experience long periods of spontaneous symptom remission, only to experience a relapse years later.

#### Treatment

• Usually benzodiazepines or SSRIs plus behavioral therapy

Treatment is usually a combination of drug therapy and behavioral therapy. In children, it is difficult to even begin behavioral therapy until after the panic attacks have been controlled by drugs. Benzodiazepines are the most effective drugs, but SSRIs are often preferred because benzodiazepines are sedating and may greatly impair learning and memory. However, SSRIs do not work quickly, and a short course of a benzodiazepine (eg, lorazepam 0.5 to 2.0 mg po tid) may be helpful until the SSRI is

effective.

Behavioral therapy is especially useful for agoraphobia symptoms. Drugs are rarely useful for these symptoms because children often continue to fear that they may have a panic attack, even long after attacks have been well controlled by drugs.

### Acute and Posttraumatic Stress Disorders

**Acute stress disorder (ASD) is a brief period (about 1 mo) of intrusive recollections (eg, flashbacks and nightmares), dissociation, avoidance, and anxiety occurring within 1 mo of a traumatic incident. Post-traumatic stress disorder (PTSD) causes recurring, intrusive recollections of an overwhelming traumatic incident that persist > 1 mo, as well as emotional numbing and hyperarousal. Diagnosis is by history and examination. Treatment is with behavioral therapy, SSRIs, and antiadrenergic drugs.**

Because vulnerability and temperament are different, not all children who are exposed to a severe traumatic event develop a stress disorder. Traumatic events commonly associated with these disorders include assaults, sexual assaults, car accidents, dog attacks, and injuries (especially burns). In young children, domestic violence is the most common cause of PTSD.

#### Symptoms and Signs

ASD and PTSD are closely related and are distinguished primarily by duration of symptoms. ASD is diagnosed within 1 mo of the traumatic event, and PTSD is diagnosed only after 1 mo has passed and symptoms have persisted. In a few cases, onset of PTSD symptoms may be delayed months or even years after the traumatic event.

Emotional numbing and hyperarousal are common. Emotional numbing includes the following:

- General lack of interest
- Social withdrawal
- A subjective sense of feeling numb
- A foreshortened expectation of the future (eg, thinking "I will not live to see 20")

Hyperarousal symptoms include the following:

- Jitteriness
- Exaggerated startle response
- Difficulty relaxing
- Disrupted sleep, sometimes with frequent nightmares

Typically, children with ASD are in a daze and may seem dissociated from everyday surroundings.

Children with PTSD have intrusive recollections that cause them to reexperience the traumatic event. The most dramatic kind of recollection is a flashback. Flashbacks may be spontaneous but are most commonly triggered by something associated with the original trauma. For example, the sight of a dog may trigger a flashback in children who experienced a dog attack. During a flashback, children may be in a terrified state and unaware of their current surroundings while desperately searching for a way to hide or escape; they may temporarily lose touch with reality and believe they are in grave danger. Some children have nightmares. When children reexperience the event in other ways (eg, in thoughts, mental images, or recollections), they remain aware of current surroundings, although they may still be greatly distressed.

**Diagnosis**

• Clinical evaluation

Diagnosis of ASD and PTSD is based on a history of severely frightening and horrifying trauma followed by reexperiencing, emotional numbing, and hyperarousal. These symptoms must be severe enough to cause impairment or distress.

**Prognosis**

Prognosis for children with ASD is much better than for those with PTSD, but both benefit from early treatment. Severity of the trauma, associated physical injuries, and the underlying resiliency of children and family members affect the final outcome.

**Treatment**

• SSRIs and sometimes antiadrenergic drugs

• Sometimes psychotherapy

• Behavioral therapy

SSRIs often help reduce emotional numbing and reexperiencing of symptoms but are less effective for hyperarousal. Antiadrenergic drugs (eg, clonidine, guanfacine, prazosin) may help relieve hyperarousal symptoms, but supportive data are preliminary.

Supportive psychotherapy may help children who have adjustment issues associated with trauma, as may result from disfigurement due to burns. Behavioral therapy can be used to systematically desensitize children to situations that cause them to reexperience the event. Behavioral therapy is clearly effective in reducing distress and impairment in children and adolescents with PTSD.

## Tic Disorders in Children and Adolescents

**Tics are defined as sudden, rapid, and repeating muscle movements often associated with vocalizations.**

Tics occur in a wide variety of disorders. Transient tic disorders occur in up to 25% of children—most commonly in boys. Typically, tics do not occur during sleep and can be controlled voluntarily for short periods of time. Stress and fatigue can make these tics worse.

Eventually, most tics disappear spontaneously. However, in fewer than 1% of children, tics persist. Such tics may lead to a diagnosis of Tourette's syndrome (see p. 2902), or they may be associated with obsessive-compulsive disorder, some infections, or certain drugs (eg, stimulants).

Usually, no treatment is required. If tics persist and are bothersome (eg, as in Tourette's syndrome), drugs may be used.

## Childhood Schizophrenia

(See also p. 1559.)

**Schizophrenia is the presence of hallucinations and delusions causing considerable psychosocial dysfunction and lasting ≥ 6 mo.**

Onset of schizophrenia is typically from mid-adolescence to the mid-20s. Features in adolescents and young adults are similar. Schizophrenia in prepubertal children is extremely rare; features are usually similar to those in adolescents and adults, but delusions and visual hallucinations (which may be more

common among children) may be less elaborate.

Sudden-onset psychosis in young children should always be treated as a medical emergency with a thorough medical assessment to search for a physiologic cause of the mental status change (eg, Wilson's disease, porphyrias, HIV infection, brain trauma).

Treatment is complex, and referral to a child and adolescent psychiatrist should be considered.

## Depressive Disorders in Children and Adolescents

(See also p. 1538.)

**Depressive disorders in children and adolescents are characterized by a pervasive and abnormal mood state that consists of sadness or irritability and that is severe or persistent enough to interfere with functioning or cause considerable distress. Decreased interest or pleasure in activities may be as apparent as or even more apparent than mood abnormalities. Diagnosis is by history and examination. Treatment is with antidepressants, psychotherapy, or both.**

Major depression occurs in as many as 2% of children and 5% of adolescents. Rates for other depressive disorders are unknown. The exact cause of depression in children and adolescents is unknown, but in adults, it is believed to result from interactions of genetically determined risk factors and environmental stress (particularly deprivation and loss early in life).

### Symptoms and Signs

Basic manifestations are similar to those in adults but are related to typical concerns of children, such as schoolwork and play. Children may be unable to explain inner feelings or moods. Depression should be considered when previously well-performing children do poorly in school, withdraw from society, or commit delinquent acts.

Common symptoms include

- A sad appearance
- Excessive irritability
- Apathy and withdrawal
- Reduced capacity for pleasure (often expressed as profound boredom)
- Feeling rejected and unloved
- Somatic complaints (eg, headaches, abdominal pain, insomnia)
- Persistent self-blame

In some children with major depressive disorder, the predominant mood is irritability rather than sadness (an important difference between childhood and adult forms).

Other symptoms include anorexia, weight loss (or failure to achieve expected weight gain), sleep disruption (including nightmares), despondency, and suicidal ideation. The irritability associated with childhood depression may manifest as overactivity and aggressive, antisocial behavior.

In children with intellectual disability, depressive or other mood disorders may manifest as somatic symptoms and behavioral disturbances.

Major depression in adolescents is a risk factor for academic failure, substance abuse, and suicidal

behavior (see p. 3060). While depressed, children and adolescents tend to fall far behind academically and lose important peer relationships. Untreated, major depression may remit in 6 to 12 mo, but recurrences are common.

**Diagnosis**

• Clinical evaluation

Diagnosis is based on symptoms and signs. A careful review of the history and appropriate laboratory tests are needed to exclude other disorders (eg, infectious mononucleosis, thyroid disorders, drug abuse). History should include causative factors such as domestic violence, sexual abuse and exploitation, and drug adverse effects. Questions about suicidal behavior (eg, ideation, gestures, attempts) should be asked.

Other mental disorders that can cause depressive symptoms (eg, anxiety, bipolar disorders) must be considered. Some children who eventually develop a bipolar disorder or schizophrenia may present initially with major depression.

After depression is diagnosed, the family and social setting must be evaluated to identify stresses that may have precipitated depression.

**Treatment**

• Concurrent measures directed at the family and school

• For adolescents, usually antidepressants plus psychotherapy

• For preadolescents, psychotherapy followed, if needed, by antidepressants

Appropriate measures directed at the family and school must accompany direct treatment of the child to enhance continued functioning and provide appropriate educational accommodations. Brief hospitalization may be necessary in acute crises, especially when suicidal behavior is identified.

For adolescents (as for adults), a combination of psychotherapy and antidepressants usually greatly outperforms either modality used alone. For preadolescents, the situation is much less clear. Most clinicians opt for psychotherapy in younger children; however, drugs can be used in younger children (fluoxetine can be used in children ≥ 8 yr), especially when depression is severe or has not previously responded to psychotherapy.

Usually, an SSRI (see Table 305-1) is the first choice when an antidepressant is indicated. Children should be closely monitored for the emergence of behavioral side effects (eg, disinhibition, behavioral activation—see footnote in Table 305-1). Adult-based research has suggested that antidepressants that act on both the serotonergic and adrenergic/dopaminergic systems may be modestly more effective; however, such drugs (eg, duloxetine, venlafaxine, mirtazapine; certain tricyclics, particularly clomipramine) also tend to have more adverse effects. Such drugs may be especially useful in treatment-resistant cases. Nonserotonergic antidepressants such as bupropion and desipramine may also be used with an SSRI to enhance efficacy.

There are recent concerns that antidepressants may increase risk of suicidality in a few children and adolescents. These drugs are now labeled with warnings about suicidality. Paradoxically, several studies suggest that, overall, use of antidepressants significantly reduces risk of suicide. How to interpret these contradictory findings is unclear. However, if suicide is a concern, the following should be done to reduce risk:

• Parents and mental health care practitioners should discuss the issues in depth.

• The child or adolescent should be supervised at an appropriate level.

• Psychotherapy with regularly scheduled appointments should be included in the treatment plan.

As in adults, relapse and recurrence are common. Children and adolescents should remain in treatment for at least 1 yr after symptoms have remitted. Most experts recommend that children who have experienced ≥ 2 episodes of major depression be treated indefinitely.

## Bipolar Disorder in Children and Adolescents

**Bipolar disorder is characterized by alternating periods of mania, depression, and normal mood, each lasting for weeks to months at a time. The label "bipolar" has also been applied to prepubertal children disabled by intense, unstable moods. However, in these young children, the mood states last from moments to days. In both cases, diagnosis is by history and mental status examination. Treatment is a combination of mood stabilizers (eg, lithium, certain anticonvulsants and antipsychotic drugs), psychotherapy, and antidepressants.**

Bipolar disorder typically begins during mid-adolescence through the mid-20s. In many children, the initial manifestation is one or more episodes of depression; about one third of children who have an episode of severe depression before puberty convert to bipolar disorder during their adolescent or early adult years. The term "bipolar" has been applied to prepubertal children with unstable, intense moods, but typically, the moods last only a short time. Thus, whether this condition constitutes bipolar disorder is unclear; research in this area is ongoing.

### Etiology

Etiology is unknown, but heredity is involved. Dysregulation of serotonin and norepinephrine may be involved, as may a stressful life event. Certain drugs (eg, cocaine, amphetamines, phencyclidines, certain antidepressants) and environmental toxins (eg, lead) can exacerbate or mimic the disorder. Certain disorders (eg, thyroid disorders) can cause similar symptoms.

### Symptoms and Signs

The hallmark of bipolar disorder is the manic episode. Manic episodes alternate with depressive episodes, which can be more frequent.

During a manic episode in adolescents, mood may be very positive or hyperirritable and often alternates between the 2 moods depending on social circumstances. Speech is rapid and pressured, sleep is decreased, and self-esteem is inflated. Mania may reach psychotic proportions (eg, "I have become one with God"). Judgment may be severely impaired, and adolescents may engage in risky behaviors (eg, promiscuous sex, reckless driving). Prepubertal children may experience dramatic moods, but the duration of these moods is much shorter (often lasting only a few moments) than that in adolescents. Onset is characteristically insidious, and children typically have a history of always being very temperamental and difficult to manage.

### Diagnosis

• Clinical evaluation

• Testing for toxicologic causes

Diagnosis is based on history and mental status examination. A number of medical disorders (eg, thyroid disorders, brain infections or tumors) and drug intoxication must be ruled out with appropriate medical assessment, including a toxicology screen for drugs of abuse and environmental toxins. The interviewer should also search for precipitating events, such as severe psychologic stress, including sexual abuse or incest.

### Prognosis

Prognosis for adolescents with bipolar disorder varies. Those who have mild to moderate symptoms, who

have a good response to treatment, and who remain adherent and cooperative with treatment have an excellent prognosis. However, treatment response is often incomplete, and adolescents are notoriously nonadherent to drug regimens. For such adolescents, the long-term prognosis is not as good.

Little is known about the long-term prognosis of prepubertal children diagnosed with bipolar disorder based on highly unstable and intense moods.

**Treatment**

• Mood stabilizers and antidepressants

• Psychotherapy

For adolescents and prepubertal children, mood stabilizers are used to treat manic or agitated episodes, and psychotherapy and anti-depressants treat the depressive episodes.

Mood stabilizers (see Table 305-2) roughly fall into 3 categories:

• Mood-stabilizing anticonvulsants

• Mood-stabilizing antipsychotics

• Lithium

All mood stabilizers have a potential for troubling and even dangerous adverse effects. Thus, treatment must be individualized. Furthermore, drugs that are highly successful during initial stabilization may be unacceptable for maintenance because of adverse effects, most notably weight gain.

Antidepressants may trigger a switch from depression to mania; therefore, they are usually used with a mood stabilizer.

## Disruptive Behavioral Disorders

Disruptive behavioral disorders are so-named because affected children tend to disrupt people around them, including family members, school staff, and peers. The most common disruptive behavioral disorder is attention-deficit/hyperactivity disorder (see p. 3035).

### Oppositional Defiant Disorder

**Oppositional defiant disorder (ODD) is a recurrent or persistent pattern of negative, defiant, or even hostile behavior directed at authority figures. Diagnosis is by history. Treatment is with individual psychotherapy combined with family or caretaker therapy. Occasionally, drugs may be used to reduce irritability.**

Prevalence estimates of ODD vary widely because the diagnostic criteria are highly subjective; prevalence in children and adolescents may be as high as 15%. Before puberty, affected boys greatly outnumber girls; after puberty, the difference narrows.

Although ODD is sometimes viewed as a mild version of conduct disorder, similarities between the 2 disorders are only superficial. The hallmark of ODD is an interpersonal style characterized by irritability and defiance. However, children with a conduct disorder seemingly lack a conscience and repeatedly violate the rights of others (eg, bullying, threatening or causing harm, being cruel to animals), sometimes without any evidence of irritability.

Etiology of ODD is unknown, but it is probably most common among children from families in which the adults model loud, argumentative, interpersonal conflicts. This diagnosis should not be viewed as a circumscribed disorder but rather as an indication of underlying problems that may require further

investigation and treatment.

**Symptoms and Signs**

Typically, children with ODD tend to frequently do the following:

• Lose their temper easily and repeatedly

• Argue with adults

• Defy adults

• Refuse to obey rules

• Deliberately annoy people

• Blame others for their own mistakes or misbehavior

• Be easily annoyed and angered

• Be spiteful or vindictive

Many affected children also lack social skills.

**Diagnosis**

ODD is diagnosed if children have had ≥ 4 of the above symptoms for at least 6 mo. Symptoms must also be severe and disruptive.

ODD must be distinguished from the following, which may cause similar symptoms:

• **Mild to moderate oppositional behaviors:** Such behaviors occur periodically in nearly all children and adolescents.

• **Untreated attention-deficit/hyperactivity disorder (ADHD):** The ODD-like symptoms often resolve when ADHD is adequately treated.

• **Major depressive disorder:** In some children with this disorder, the predominant mood is irritability rather than sadness. Major depressive disorder with irritability is distinguished from ODD by the presence of anhedonia and neurovegetative symptoms (eg, sleep and appetite disruption); these symptoms are easily overlooked in children.

[Table 305-2. Selected Drugs for Bipolar Disorder*]

**Treatment**

• Behavior modification therapy

• Sometimes drugs

Underlying problems (eg, family dysfunction) and coexisting disorders (eg, ADHD) should be identified and corrected. However, even without corrective measures or treatment, most children with ODD gradually improve over time.

Initially, the treatment of choice is a rewards-based behavior modification program designed to make the child's behaviors more socially appropriate. Many children can benefit from group-based therapy that builds social skills.

Sometimes drugs used to treat depressive disorders (see p. 3056) may be beneficial.

### Conduct Disorder

**Conduct disorder (CD) is a recurrent or persistent pattern of behavior that violates the rights of others or violates major age-appropriate societal norms or rules. Diagnosis is by history. Treatment of comorbid disorders and psychotherapy may help; however, many children require considerable supervision.**

Prevalence of some level of CD is about 10%. Onset is usually during late childhood or early adolescence, and the disorder is much more common among boys than girls.

Etiology is likely a complex interplay of genetic and environmental factors. Parents of adolescents with CD often have engaged in substance abuse and antisocial behaviors and frequently have been diagnosed with ADHD, mood disorders, schizophrenia, or antisocial personality disorder. However, CD can occur in children from high-functioning, healthy families.

#### Symptoms and Signs

Children or adolescents with CD lack sensitivity to the feelings and well-being of others and sometimes misperceive the behavior of others as threatening. They may act aggressively, by bullying and making threats, brandishing or using a weapon, committing acts of physical cruelty, or forcing someone into sexual activity, and have few or no feelings of remorse. Sometimes their aggression and cruelty is directed at animals. These children or adolescents may destroy property, lie, and steal. They tolerate frustration poorly and are commonly reckless, violating rules and parental prohibitions (eg, by running away from home, being frequently truant from school).

Aberrant behaviors differ between the sexes: Boys tend to fight, steal, and vandalize; girls are likely to lie, run away, and engage in prostitution. Both sexes are likely to use and abuse illicit drugs and have difficulties in school. Suicidal ideation is common, and suicide attempts must be taken seriously.

#### Diagnosis

CD is diagnosed in children or adolescents who have demonstrated ≥ 3 of the following behaviors in the previous 12 mo plus at least 1 in the previous 6 mo:

• Aggression toward people and animals

• Destruction of property

• Deceitfulness, lying, or stealing

• Serious violations of parental rules

Symptoms or behaviors must be significant enough to impair functioning in relationships, at school, or at work.

#### Prognosis

Usually, disruptive behaviors stop during early adulthood, but in about one third of cases, they persist. Many of these cases meet the criteria for antisocial personality disorder. Early onset is associated with a poorer prognosis. Some children and adolescents subsequently develop mood or anxiety disorders, somatoform and substance-related disorders, or early adult-onset psychotic disorders. Children and adolescents with CD tend to have higher rates of physical and other mental disorders.

#### Treatment

• Drugs to treat comorbid disorders

• Psychotherapy

• Sometimes placement in a residential center

Treating comorbid disorders with drugs and psychotherapy may improve self-esteem and self-control and ultimately improve control of CD. Drugs may include stimulants, mood stabilizers, and atypical antipsychotics, especially short-term use of risperidone.

Moralization and dire admonitions are ineffective and should be avoided. Individual psychotherapy, including cognitive therapy and behavior modification, may help. Often, seriously disturbed children and adolescents must be placed in residential centers where their behavior can be managed appropriately, thus separating them from the environment that may contribute to their aberrant behavior.

## Suicidal Behavior in Children and Adolescents

(See also p. 1579.)

**Suicidal behavior includes completed suicide, attempted suicide, and suicide gestures; suicidal ideation is thoughts and plans about suicide. Psychiatric referral is usually required.**

Youth suicide rates have declined in recent years after more than a decade of steady increase, only to have started climbing again. The exact reasons for these fluctuations are unclear. Many experts believe that the changing rates with which antidepressants are prescribed may be a factor. Some experts hypothesize that antidepressants have paradoxical effects, making children and adolescents more vocal about suicidal feelings but less likely to commit suicide. Nonetheless, suicide is the 2nd or 3rd leading cause of death in 15- to 19-yr-olds and remains a considerable public health concern.

### Etiology

Risk factors vary by age. Predisposing factors include

• Depression (implicated in more than one half of suicidal behaviors in adolescents)

• History of suicide in family members or close friends

• Recent death in the family

• Substance abuse

• Bipolar disorder

• Psychosis

• Conduct disorder, characterized by poor control of aggressive impulses against others, possibly redirected against self (see p. 3060)

More immediate precipitating factors can include

• Loss of self-esteem (eg, resulting from family arguments, a humiliating disciplinary episode, pregnancy, or school failure)

• Loss of a boyfriend or girlfriend

• Loss of familiar surroundings (eg, school, neighborhood, friends) due to a geographic move

Other contributing factors may include a lack of structure and boundaries, leading to an overwhelming feeling of lack of direction, and intense parental pressure to succeed accompanied by the feeling of

falling short of expectations. A frequent motive for a suicide attempt is an effort to manipulate or punish others with the fantasy "You will be sorry after I am dead."

A rise in suicides is seen after a well-publicized suicide (eg, of a rock star) and among groups (eg, a high school, a college dormitory) in which a suicide occurred, indicating the power of suggestion. Early intervention to support youths in such circumstances may be helpful.

**Treatment**

• Possibly hospitalization

• Possibly drugs to treat underlying disorders

• Psychiatric referral

Every suicide attempt is a serious matter that requires thoughtful and appropriate intervention. Once the immediate threat to life is removed, a decision regarding the need for hospitalization must be made. The decision involves balancing the degree of risk with the family's capacity to provide support. Hospitalization (even in an open medical or pediatric ward with special-duty nursing) is the surest form of short-term protection and is usually indicated if depression, psychosis, or both are suspected.

Lethality of suicidal intent can be assessed based on the following:

• Degree of forethought evidenced (eg, by writing a suicide note)

• Steps taken to prevent discovery

• Method used (eg, firearms are more lethal than pills)

• Degree of self-injury sustained

• Circumstances or immediate precipitating factors surrounding the attempt

Drugs may be indicated for any underlying disorder (eg, depression, bipolar or conduct disorder, psychosis) but cannot prevent suicide. Antidepressant use may increase risk of suicide in some adolescents. Use of drugs should be carefully monitored, and only sub-lethal amounts should be supplied.

Psychiatric referral is usually needed to provide appropriate drug treatment and psychotherapy; treatment is most successful if the primary care practitioner continues to be involved.

Rebuilding morale and restoring emotional equilibrium within the family are essential. A negative or unsupportive parental response is a serious concern and may suggest a need for a more intensive intervention such as out-of-home placement. A positive outcome is most likely if the family shows love and concern.

**Prevention**

Suicidal incidents are often preceded by behavioral changes (eg, despondent mood, low self-esteem, sleep and appetite disturbances, inability to concentrate, truancy from school, somatic complaints, and suicidal preoccupation), which often bring the child or adolescent to the physician's office. Statements such as "I wish I had never been born" or "I would like to go to sleep and never wake up" should be taken seriously as possible indications of suicidal intent. A suicidal threat or attempt represents an important communication about the intensity of experienced despair.

Early recognition of the risk factors mentioned above may help prevent a suicide attempt. In response to these early cues, to threatened or attempted suicide, or to severe risk-taking behavior, vigorous intervention is appropriate. Adolescents should be directly questioned about their unhappy or self-

destructive feelings; such direct questioning may diminish suicide risk. A physician should not provide unfounded reassurance, which can undermine the physician's credibility and further lower the adolescent's self-esteem.

The effectiveness of suicide prevention programs is being evaluated. The most effective programs are those that strive to ensure that the child has a supportive nurturing environment, ready access to mental health services, and a social setting that is characterized by respect for individual, racial, and cultural differences.

**Self-Injurious Behavior**

**Self-injurious behaviors that are sometimes confused with suicidal intentions include superficial scratching and cutting, burning the skin with cigarettes or curling irons, and crude ballpoint pen tattoos.**

In some communities, self-injurious behaviors suddenly sweep through a high school in fad-like fashion and then gradually diminish over time.

In many adolescents, these behaviors do not indicate suicidality but instead are an effort to establish autonomy, identify with a peer group, or provocatively gain parental attention. However, even when these behaviors are not an expression of suicidality, they are serious and warrant intervention. Such behaviors are often associated with illicit substance abuse and suggest that an adolescent is in great distress.

All self-injurious behaviors should be evaluated by a clinician experienced in working with troubled adolescents to assess whether suicidality is an issue and to identify the underlying distress leading to the self-injurious behaviors.

# Chapter 306. Child Maltreatment

## Introduction

**Child maltreatment is behavior toward a child that is outside the norms of conduct and entails substantial risk of causing physical or emotional harm. Four types of maltreatment are generally recognized: physical abuse, sexual abuse, emotional abuse (psychologic abuse), and neglect. The causes of child maltreatment are varied and not well understood. Abuse and neglect are often associated with physical injuries, delayed growth and development, and mental problems. Diagnosis is based on history and physical examination. Management includes documentation and treatment of any injuries and urgent physical and mental conditions, mandatory reporting to appropriate state agencies, and sometimes hospitalization or other steps such as foster care to keep the child safe.**

In 2007, 3.2 million cases of child abuse and neglect were reported in the US, and about 750,000 of these were substantiated. Both sexes are affected equally; the younger the child, the higher the rate of victimization.

More than half of all reports to Child Protective Services were made by professionals who are mandated to report maltreatment (eg, educators, law enforcement personnel, social services personnel, legal professionals, day care providers, medical or mental health personnel, foster care providers).

Of substantiated cases in the US in 2007, 59.9% involved neglect (including medical neglect); 10.8% involved physical abuse; 7.6% involved sexual abuse; and 4.2% involved psychologic maltreatment. In addition, 4.2% experienced other types of maltreatment, such as abandonment and congenital drug addictions. Many children were victims of multiple types of maltreatment.

About 1760 children died in the US from mal-treatment in 2007, about three quarters of whom were < 4 yr. One third of the deaths were attributed to neglect. In substantiated cases of abuse or neglect in 2007, > 80% of perpetrators were parents; 56.5% of perpetrators were women.

### Classification

Different forms of abuse often coexist, and overlap is considerable.

**Physical abuse:** Physical abuse is inflicting physical harm or engaging in actions that create a high risk of harm. Specific forms include shaking, dropping, striking, biting, and burning (eg, by scalding or touching with cigarettes). Abuse is the most common cause of serious head injury in infants. In toddlers, abdominal injury is common.

Infants and toddlers are the most vulnerable (perhaps because perpetrators know they cannot complain), with risk declining in the early school years and increasing again in adolescence.

Medical child abuse (previously called Munchausen syndrome by proxy) is discussed on p. 1576.

**Sexual abuse:** Any action with a child that is done for the sexual gratification of an adult or significantly older child constitutes sexual abuse (see also Pedophilia on p. 1572). Forms of sexual abuse include intercourse, which is oral, anal, or vaginal penetration; molestation, which is genital contact without intercourse; and nonspecific forms, which do not involve physical contact, including exposure, showing sexual material to a child, and forcing a child to participate in a sex act with another child or to participate in the making of sexual material.

Sexual abuse does not include sexual play, in which children close in age (typically considered < 4 yr apart) view or touch each other's genital area without force or coercion.

**Emotional abuse:** Emotional abuse is inflicting emotional harm through the use of words or actions. Specific forms include berating a child by yelling or screaming, spurning by belittling the child's abilities and achievements, intimidating and terrorizing with threats, and exploiting or corrupting by encouraging

deviant or criminal behavior. Emotional abuse can also occur when words or actions are omitted or withheld, in essence becoming emotional neglect (eg, ignoring or rejecting children or isolating them from interaction with other children or adults).

**Neglect:** Neglect is the failure to provide for or meet a child's basic physical, emotional, educational, and medical needs. Neglect differs from abuse in that it usually occurs without intent to harm. Physical neglect includes failure to provide adequate food, clothing, shelter, supervision, and protection from potential harm. Emotional neglect is failure to provide affection or love or other kinds of emotional support. Educational neglect is failure to enroll a child in school, ensure attendance at school, or provide home schooling. Medical neglect is failure to ensure that a child receives appropriate preventive care (eg, vaccinations, routine dental examinations) or needed treatment for injuries or physical or mental disorders.

**Cultural factors:** Severe corporal punishment (eg, whipping, burning, scalding) clearly constitutes physical abuse, but for lesser degrees of physical and emotional chastisement, the boundary between socially accepted behavior and abuse varies among different cultures. Likewise, certain cultural practices (eg, female genital mutilation [see p. 3067]) are so extreme as to constitute abuse. However, certain folk remedies (eg, coining, cupping, irritant poultices) often create lesions (eg, bruises, minor burns) that can mimic those caused by abuse; in such cases, the line between acceptable cultural practices and abuse may be blurred.

Similarly, failing to obtain life-saving treatment (eg, for diabetic ketoacidosis or meningitis) or failing to take children for any routine medical care is considered neglect whatever the parents' or caregivers' intent. However, in the US, certain people and cultural groups have increasingly been declining vaccination of their children, citing safety concerns. It is not clear whether this refusal of vaccination is true medical neglect; it may be considered similar to refusal of non life-saving treatments for religious reasons. In such cases, as long as the children are healthy, there is usually no need to ascertain whether the refusal constitutes medical neglect. However, in the face of illness, refusal of scientifically and medically accepted treatment often requires further investigation and sometimes legal intervention.

### Etiology

**Abuse:** Generally, abuse can be attributed to a breakdown of impulse control in the parent or caregiver. Several factors contribute.

Parental characteristics and personality features can play a role. The parent's own childhood may have lacked affection and warmth, may not have been conducive to the development of adequate self-esteem or emotional maturity, and, in most cases, also included other forms of abuse. Abusive parents may see their children as a source of unlimited and unconditional affection and look to them for the support that they never received. As a result, they may have unrealistic expectations of what their children can supply for them; they are frustrated easily and lose control; and they may be unable to give what they never experienced. Drug or alcohol use may provoke impulsive and uncontrolled behaviors toward their children. Parental mental disorders may also increase the risk of abuse.

Irritable, demanding, or hyperactive children may provoke parents' tempers, as may developmentally or physically disabled children, who often are more dependent. Sometimes strong emotional ties do not develop between parents and premature or sick infants separated from parents early in infancy or with biologically unrelated children (eg, stepchildren), increasing the risk of abuse.

Situational stress may precipitate abuse, particularly when emotional support of relatives, friends, neighbors, or peers is unavailable.

Physical abuse, emotional abuse, and neglect are associated with poverty and lower socioeconomic status. However, all types of abuse, including sexual abuse, occur across the spectrum of socioeconomic groups. The risk of sexual abuse is increased in children who have several caregivers or a caregiver with several sex partners.

**Neglect:** Neglect usually results from a combination of factors such as poor parenting, poor stress-

coping skills, unsupportive family systems, and stressful life circumstances. Neglect often occurs in impoverished families experiencing financial and environmental stresses, particularly those in which parents also have mental disorders (typically depression or schizophrenia), abuse drugs or alcohol, or have limited intellectual capacity. Children in single-parent families may be at risk of neglect due to a lower income and fewer available resources.

### Symptoms and Signs

Symptoms and signs depend on the nature and duration of the abuse or neglect.

**Physical abuse:** Skin lesions are common and may include handprints or oval fingertip marks caused by slapping or grabbing and shaking; long, bandlike ecchymoses caused by belt whipping or narrow arcuate bruises caused by extension cord whipping; multiple small round burns caused by cigarettes; symmetric scald burns of upper or lower extremities or buttocks caused by intentional immersion; bite marks; and thickened skin or scarring at the corners of the mouth caused by being gagged. Patchy alopecia, with varying hair lengths, can result from hair pulling.

Fractures frequently associated with physical abuse include rib fractures, vertebral fractures, long bone and digit fractures in nonambulatory children, and metaphyseal fractures; in children < 1 yr, about 75% of fractures are inflicted by others. Confusion and localizing neurologic abnormalities can occur with CNS injuries. Lack of visible head lesions does not exclude traumatic brain injury, particularly in infants subjected to violent shaking. These infants may be comatose or stuporous from brain injury yet lack visible signs of injury (with the common exception of retinal hemorrhage). Traumatic injury to organs within the chest or abdominal region may also occur without visible signs.

Children who are frequently abused are often fearful and irritable and sleep poorly. They may have symptoms of depression, post-traumatic stress reactions (see p. 1500), or anxiety. Violent or suicidal behavior may occur.

**Sexual abuse:** In most cases, children do not freely disclose sexual abuse and rarely exhibit behavioral or physical signs of sexual abuse. If a disclosure is made, it is generally delayed, sometimes days to years. In some cases, abrupt or extreme changes in behavior may occur. Aggressiveness or withdrawal may develop, as may phobias or sleep disturbances. Some sexually abused children act in ways that are sexually inappropriate for their age. Physical signs of sexual abuse that involves penetration may include difficulty in walking or sitting; bruises or tears around the genitals, rectum, or mouth; vaginal discharge, bleeding, or pruritus; or a sexually transmitted disease. Within a few days of the abuse, examination of the genitals, rectum, or mouth may be normal or may show healed lesions or subtle hymen changes.

**Emotional abuse:** In early infancy, emotional abuse may blunt emotional expressiveness and decrease interest in the environment. Emotional abuse commonly results in failure to thrive and is often misdiagnosed as intellectual disability or physical illness. Delayed development of social and language skills often results from inadequate parental stimulation and interaction. Emotionally abused children may be insecure, anxious, distrustful, superficial in interpersonal relationships, passive, and overly concerned with pleasing adults. Children who are spurned may have very low self-esteem. Children who are terrorized or threatened may seem fearful and withdrawn. The emotional effect on children usually becomes obvious at school age, when difficulties develop in forming relationships with teachers and peers. Often, emotional effects are appreciated only after the child has been placed in another environment or after aberrant behaviors abate and are replaced by more acceptable behaviors. Children who are exploited may commit crimes or abuse alcohol or drugs.

**Neglect:** Undernutrition, fatigue, lack of hygiene or appropriate clothing, and failure to thrive are common signs of inadequate provision of food, clothing, or shelter. Stunted growth and death resulting from starvation or exposure may occur. Neglect that involves inadequate supervision may result in preventable illness or injury.

### Diagnosis

• High index of suspicion (eg, for history that does not match physical findings or for atypical injury

patterns)

- Supportive, open-ended questioning
- Sometimes imaging and laboratory tests
- Reporting to authorities for further investigation

Evaluation of injuries and nutritional deficiencies is discussed elsewhere in THE MANUAL. Recognizing maltreatment as the cause can be difficult, and a high index of suspicion must be maintained. Because of social biases, abuse is considered less often in children living in a 2-parent household with a median-level income; child abuse can occur regardless of family composition or socioeconomic status.

Sometimes direct questions provide answers. Children who have been maltreated may describe the events and the perpetrator, but some children, particularly those who have been sexually abused, may be sworn to secrecy, threatened, or so traumatized that they are reluctant to speak (and may even deny abuse when specifically questioned). Children should be interviewed alone and in a relaxed manner, with open-ended questions (eg, "Tell me what happened"); yes-or-no questions (eg, "Did daddy do this?", "Did he touch you here?") can easily sculpt an untrue history in young children.

Examination includes observation of interactions between the child and possible perpetrators whenever possible. Documentation of the history and physical examination should be as comprehensive and accurate as possible, including recording of exact quotes from the history and photographs of injuries.

Sometimes it is unclear after the initial evaluation whether abuse occurred. In such cases, the mandatory reporting requirement of *suspected* abuse allows appropriate authorities and social agencies to investigate in depth; if their evaluation confirms abuse, appropriate legal and social interventions can be done.

**Physical abuse:** Both history and physical examination provide clues suggestive of mal-treatment.

Features suggestive of abuse in the history are

- Parental reluctance or inability to give a history of injury
- History that is inconsistent with the injury (eg, bruises on the backs of the legs attributed to a fall) or apparent stage of resolution (eg, old injuries described as recent)
- History that varies depending on the information source
- History of injury that is incompatible with the child's stage of development (eg, injuries ascribed to a fall down stairs in an infant too young to crawl)
- Inappropriate response by the parents to the severity of the injury—either overly concerned or unconcerned
- Delay in reporting the injury

Major indicators of abuse on examination are

- Atypical injuries
- Injuries incompatible with stated history

Childhood injuries resulting from falls are typically solitary and occur on the forehead, chin, or mouth or extensor surfaces of the extremities, particularly elbows, knees, forearms, and shins. Bruises on the back, buttocks, and the back of the legs are extremely rare from falls. Fractures, apart from clavicular fracture, tibial (toddler's) fractures, and distal radius (Colles') fracture, are less common in typical falls during play

or down stairs. No fractures are pathognomonic of abuse, but classic metaphyseal lesions, rib fractures (especially posterior and 1st rib), and depressed or multiple skull fractures (caused by apparently minor trauma), scapular fractures, sternal fractures, and spinous processes fractures should raise concern.

Physical abuse should be considered when an infant who is not walking has a serious injury. Young infants with minor injuries to the face should be further evaluated. The younger infant may appear to be perfectly normal or sleeping despite significant brain trauma, and inflicted acute head trauma in infants should be part of the differential diagnosis of every lethargic infant. Other hints are multiple injuries at different stages of resolution or development; cutaneous lesions specific for particular sources of injury; and repeated injury, which is suggestive of abuse or inadequate supervision.

A dilated eye examination may be useful in children < 1 yr with suspected abuse. Retinal hemorrhage occurs in 65 to 95% of cases of abusive head trauma vs < 10% of cases of accidental head trauma. It also may result from childbirth and persist for up to 4 wk. When retinal hemorrhages result from accidental trauma, the mechanism is usually obvious and life-threatening (eg, major motor vehicle crash), and the hemorrhages are typically few in number and confined to the posterior pole.

Children < 2 yr with possible physical abuse should undergo a skeletal survey for evidence of previous bony injuries (fractures in various stages of healing or subperiosteal elevations in long bones). Surveys are sometimes done on children aged 2 to 5 yr but are generally not helpful for those > 5 yr. The standard survey includes anteroposterior (AP) views of the skull and chest, lateral views of the spine and long bones, AP views of the pelvis, and AP and oblique views of the hands. Physical disorders causing multiple fractures include osteogenesis imperfecta and congenital syphilis.

**Sexual abuse:** Sexually transmitted disease of any sort in a child < 12 yr must be considered the result of sexual abuse until proved otherwise. When a child has been sexually abused, behavioral changes (eg, irritability, fearfulness, insomnia) may be the only clues initially. If sexual abuse is suspected, the perioral and rectal areas and the external genitals must be examined for evidence of injury. If the suspected abuse is thought to have occurred recently, hair samples and swabs of body fluids are obtained for legal evidence (see p. 2549). An examination involving use of a magnifying light source with a camera, such as with a specially equipped colposcope, may be helpful for documentation for legal purposes.

**Emotional abuse and neglect:** Evaluation focuses on general appearance and behavior to determine whether the child is failing to develop normally. Teachers and social workers are often the first to recognize neglect. The physician may notice a pattern of missed appointments and vaccinations that are not up-to-date. Medical neglect of life-threatening, chronic diseases, such as asthma or diabetes, can lead to a subsequent increase in office or emergency department visits and poor adherence with recommended drug regimens.

### Treatment

- Treatment of injuries
- Assurance of safety
- Family counseling and support
- Sometimes removal from the home

Treatment first addresses urgent medical needs (including possible sexually transmitted diseases) and the child's immediate safety. Referral to a pediatrician specializing in child abuse should be considered. Ultimately, treatment is directed at long-standing disturbed patterns of personal interaction. In both abuse and neglect situations, families should be approached in a helping rather than a punitive manner.

**Immediate safety:** Physicians and other professionals in contact with children (eg, nurses, teachers, day care workers, police) are required by law in all states to report incidents of suspected abuse or neglect. Every state has its own laws. Members of the general public are encouraged, but not mandated, to report suspected abuse. Any person who makes a report of abuse based on reasonable cause and in

good faith is immune from criminal and civil liability. A mandated reporter who fails to make a report can be subject to criminal and civil penalties. The reports are made to Child Protective Services or another appropriate child protection agency. In most situations, it is appropriate for professionals to tell parents that a report is being made pursuant to the law and that they will be contacted, interviewed, and possibly visited at their home. In some cases, the professional may determine that informing the parent before police or other agency assistance is available creates greater risk of injury to the child. Under those circumstances, the professional may choose to delay informing the parent or caregiver.

Representatives of child protective agencies and social workers can help the physician determine likelihood of subsequent harm and thus identify the best immediate disposition for the child. Options include

- Protective hospitalization
- Placement with relatives or in temporary housing (sometimes a whole family is moved out of an abusive partner's home)
- Temporary foster care
- Going home with prompt social service follow-up

The physician plays an important role in working with community agencies to advocate for the best and safest disposition for the child.

**Follow-up:** A source of primary medical care is fundamental. However, the families of abused and neglected children frequently relocate, making continuity of care difficult. Broken appointments are common; outreach and home visits by social workers or a public health nurse may be needed to relay the child's progress to all concerned. A local child advocacy center can help community agencies, health care practitioners, and the legal system work together as a multidisciplinary team in a more coordinated, child-friendly, and effective manner.

A close review of the family setting, prior contacts with various community service agencies, and the parents' needs is essential. A social worker can conduct such reviews and help with interviews and family counseling. Social workers also provide tangible assistance to the parents by helping them obtain public assistance and day care and homemaker services (which can relieve a parent under stress, allowing a few hours each day for relaxation) and coordinating mental health services for parents. Periodic or ongoing social work contact usually is needed.

Parent-aide programs, which employ trained nonprofessionals to relate closely to abusive and negligent parents, are available in some communities. Other parent support groups also have been successful.

Sexual abuse may have lasting effects on the child's development and sexual adaptation, particularly among older children and adolescents. Counseling or psychotherapy for the child and the adults concerned may lessen these effects.

**Removal from the home:** Although emergency temporary removal from the home until evaluation is complete and safety is ensured is not uncommon, the ultimate goal of Child Protective Services is to keep children with their family in a safe, healthy environment. If the previously described interventions do not ensure safety, consideration must be made for long-term removal and possibly termination of parental rights. This significant step requires a court petition, presented by the legal counsel of the appropriate welfare department. The specific procedure varies from state to state but usually entails family court testimony by a physician. When the court decides in favor of removing the child from the home, a disposition is arranged. The family's physician should participate in this disposition planning; if not, the physician's agreement and consent to the disposition should be sought. While the child is in temporary placement, the physician should, if possible, maintain contact with the parents and ensure that adequate efforts are being made to help them. Occasionally, children are re-abused while in foster care. The physician should be alert to this possibility. The physician's input is integral to the decision for reuniting the child and parents. As the dynamics of the family setting improve, the child may be able to return to the

parents' care. However, recurrences of abuse are common.

### Prevention

Prevention of maltreatment should be a part of every well-child office visit through education of parents or caregivers and referrals for appropriate community services of identified at-risk families. Parents who have been victims of abuse or neglect may be at risk of abusing their own children. Such parents often verbalize anxiety about their abusive background and are amenable to assistance. First-time parents and teenage parents as well as parents with several children < 5 yr are also at risk. Often, maternal risk factors for abuse are identified prenatally, eg, a mother who does not seek prenatal care, smokes, abuses drugs, or has a history of domestic violence. Medical problems during pregnancy, delivery, or early infancy that may affect the infant's health can weaken parent-infant bonding (see also p. 2754). During such times it is important to elicit the parents' feelings about their own inadequacies and the infant's well-being. How well can they tolerate an infant with many needs or health demands? Do the parents give moral and physical support to each other? Are there relatives or friends to help in times of need? The health care practitioner who is alert to clues and able to provide support in such settings goes a long way toward preventing tragic events.

## Female Genital Mutilation

Female genital mutilation is practiced routinely in parts of Africa (usually northern or central Africa), where it is deeply ingrained as part of some cultures. Women who experience sexual pleasure are considered impossible to control, are shunned, and cannot be married.

The average age of girls who undergo mutilation is 7 yr, and mutilation is done without anesthesia. Mutilation may be limited to partial clitoral excision. Infibulation, the most extreme form, is removal of the clitoris and labia, usually followed by suturing the remaining tissue closed except for a 1- to 2-cm opening for menses and urine. The legs are often bound together for weeks afterward. Traditionally, infibulated females are cut open on their wedding night.

Sequelae of genital mutilation may include operative or postoperative bleeding and infection (including tetanus). For infibulated females, recurrent urinary or gynecologic infection and scarring are possible; they have increased susceptibility to AIDS, and childbirth may result in fatal hemorrhage. Psychologic sequelae may be severe.

Female genital mutilation may be decreasing due to the influence of religious leaders who have spoken out against the practice and growing opposition in some communities.