



Pediatrics & Neonatology Journals  
[Ahmed Manfy] on TELEGRAM

*Nelson*

# TEXTBOOK OF **PEDIATRICS**

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EDITION  
**22**



**Volume 2**

## Section 1

### Clinical Manifestations of Gastrointestinal Disease

Chapter 351

#### Normal Digestive Tract Phenomena

Asim Maqbool and Chris A. Liacouras

Gastrointestinal function varies with maturity; what is a physiologic event in a newborn or infant might be a pathologic symptom at an older age. A fetus can swallow amniotic fluid as early as 12 weeks of gestation, but nutritive sucking in neonates first develops at about 34 weeks of gestation. The coordinated oral and pharyngeal movements necessary for swallowing solids develop within the first few months of life. Before this time, the tongue thrust is upward and outward to express milk from the nipple, instead of a backward motion, which propels solids toward the esophageal inlet. By 1 month of age, infants appear to show preferences for sweet and salty foods. Infants' interest in solids increases at approximately 4 months of age. The recommendation to begin solids at 6 months of age is based on nutritional and cultural concepts rather than maturation of the swallowing process (see Chapter 61). Infants swallow air during feeding, and burping is encouraged to prevent gaseous distention of the stomach.

A number of normal anatomic variations may be noted in the mouth. A **short lingual frenulum** ("tongue-tie") may be worrisome to parents but only rarely interferes with nursing, bottle feeding, eating, or speech, generally requiring no treatment. **Surface furrowing** of the tongue (a geographic or scrotal tongue) is usually a normal finding. A **bifid uvula** may be isolated or associated with a submucous cleft of the soft palate (Fig. 351.1).

**Regurgitation**, the result of gastroesophageal reflux, occurs commonly in the first year of life. Effortless regurgitation can dribble out of an infant's mouth but also may be forceful. In an otherwise healthy infant with regurgitation, volumes of emesis are commonly approximately 15–30 mL but occasionally are larger. Most often, the infant remains happy, although possibly hungry, after an episode of regurgitation. Episodes can occur from one to several times per day. Regurgitation gradually resolves in 80% of infants by 6 months of age and in 90% by 12 months. If complications develop or regurgitation persists, gastroesophageal reflux is considered pathologic rather than merely developmental and deserves further evaluation and treatment. Complications of gastroesophageal reflux include failure to thrive, pulmonary disease (apnea or aspiration pneumonitis), and esophagitis with its sequelae (see Chapters 369 and 370).

Infants and young children may be erratic eaters; this may be a worry to parents. A toddler might eat insatiably or refuse to consume food

during a meal. Toddlers and young children also tend to eat only a limited variety of foods. Parents should be encouraged to view nutritional intake over several days and not be overly concerned about individual meals. Infancy and adolescence are periods of rapid growth; high nutrient requirements for growth may be associated with voracious appetites. The reduced appetite of toddlers and preschool children is often a worry to parents who are used to the relatively greater dietary intake during infancy. Demonstration of age-appropriate growth on a growth curve is reassuring.

The number, color, and consistency of stools can vary greatly in the same infant and between infants of similar age, without apparent explanation. The earliest stools after birth consist of meconium, a dark, viscous material that is normally passed within the first 48 hours of life. With the onset of feeding, meconium is replaced by green-brown transition stools, often containing curds, and, after 4–5 days, by yellow-brown milk stools. **Stool frequency** is extremely variable in normal infants and can vary from none to seven per day. Breastfed infants can have frequent small, loose stools early (transition stools), and then after 2–3 weeks can have very infrequent soft stools. Some nursing infants might not pass any stool for 1–2 weeks and then have a normal soft bowel movement. The color of stool has little significance except for the presence of blood or absence of bilirubin products (white-gray rather than yellow-brown). The presence of vegetable matter, such as peas or corn, in the stool of an older infant or toddler ingesting solids is normal and suggests poor chewing and not malabsorption. A pattern of intermittent loose stools, known as **toddler's diarrhea**, occurs commonly between 1 and 3 years of age. These otherwise healthy growing children often drink excessive carbohydrate-containing beverages. The stools typically occur during the day and not overnight. The volume of fluid intake is often excessive; limiting sugar and unabsorbable carbohydrate-containing beverages and increasing fat in the diet often lead to resolution of the pattern of loose stools.

A protuberant abdomen is often noted in infants and toddlers, especially after large feedings. This can result from the combination of weak abdominal musculature, relatively large abdominal organs, and lordotic stance. In the first year of life, it is common to palpate the liver 1–2 cm



**Fig. 351.1** Classic submucous cleft palate with triad of bifid uvula (large arrow), furrow along the midline of the soft palate (arrowheads), and a notch in the posterior margin of the hard palate (small arrow). The midline furrow is sometimes referred to as the *zona pellucida*, reflecting the translucent nature of this area in some patients. (From Hasan A, Gardner A, Devlin M, Russell C. Submucous cleft palate with bifid uvula. *J Pediatr*. 2014;165:872.)

below the right costal margin. The normal liver is soft in consistency and percusses to normal size for age. A Riedel lobe is a thin projection of the right lobe of the liver that may be palpable low in the right lateral abdomen. A soft spleen tip might also be palpable as a normal finding. In thin young children, the vertebral column is easily palpable, and an overlying structure may be mistaken for a mass. Pulsation of the aorta can be appreciated. Normal stool can often be palpated in the left lower quadrant in the descending or sigmoid colon.

**Blood loss** from the gastrointestinal tract is never normal, but swallowed blood may be misinterpreted as gastrointestinal bleeding. Maternal blood may be ingested at the time of birth or later by a nursing infant if there is bleeding near the mother's nipple. Nasal or oropharyngeal bleeding is occasionally mistaken for gastrointestinal bleeding (see Chapter 142). Red dyes in foods or drinks can turn the stool red but do not produce a positive test result for occult blood.

**Jaundice** is common in neonates, especially among premature infants, and usually results from the inability of an immature liver to conjugate bilirubin, leading to an elevated indirect component (see Chapter 137). Persistent elevation of indirect bilirubin levels in nursing infants may be a result of breast milk jaundice, which is usually a benign entity in full-term infants. An elevated direct bilirubin is not normal and suggests liver disease, although in infants it may be a result of extrahepatic infection (urinary tract infection). The direct bilirubin fraction should account for no more than 15–20% of the total serum bilirubin. Elevations in direct bilirubin levels can follow indirect hyperbilirubinemia as the liver converts excessive indirect to direct bilirubin and the rate-limiting step in bilirubin excretion shifts from the glucuronidation of bilirubin to excretion of direct bilirubin into the bile canalculus. Indirect hyperbilirubinemia, which occurs commonly in normal newborns, tends to tint the sclerae and skin golden yellow, whereas direct hyperbilirubinemia produces a greenish yellow hue. The degree of jaundice does not always directly correlate with serum bilirubin levels. An elevated total serum bilirubin warrants closer examination, fractionation of bilirubin (direct and indirect), and ongoing surveillance. Atypical elevations of unconjugated bilirubin are associated with risk for kernicterus (see Chapter 140). Elevations in conjugated bilirubin are reviewed in the chapter on cholestasis (see Chapter 404.1).

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## Chapter 352

# Major Symptoms and Signs of Digestive Tract Disorders

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Disorders of organs outside the gastrointestinal (GI) tract can produce symptoms and signs that mimic digestive tract disorders and should be considered in the differential diagnosis (Table 352.1). In children with normal growth and development, treatment may be initiated without a formal evaluation based on a presumptive diagnosis after taking a history and performing a physical examination. Poor weight gain or weight loss is often associated with a significant pathologic process and usually necessitates a more formal evaluation.

**Table 352.1** Some Nondigestive Tract Causes of Gastrointestinal Symptoms in Children

### ANOREXIA

Systemic disease: inflammatory, neoplastic  
Cardiorespiratory compromise  
Iatrogenic: drug therapy, unpalatable therapeutic diets  
Depression  
Anorexia nervosa

### VOMITING

Inborn errors of metabolism  
Medications: erythromycin, chemotherapy, nonsteroidal antiinflammatory drugs, marijuana  
Increased intracranial pressure  
Brain tumor  
Infection of the urinary tract  
Labyrinthitis  
Adrenal insufficiency  
Pregnancy  
Psychogenic  
Abdominal migraine  
Poisoning/toxins  
Renal disease

### DIARRHEA

Infection: otitis media, urinary tract infection  
Uremia  
Medications: antibiotics, cisapride  
Tumors: neuroblastoma  
Pericarditis  
Adrenal insufficiency

### CONSTIPATION

Hypothyroidism  
Spina bifida  
Developmental delay  
Dehydration: diabetes insipidus, renal tubular lesions  
Medications: narcotics  
Lead poisoning  
Infant botulism

### ABDOMINAL PAIN

Pyelonephritis, hydronephrosis, renal colic  
Pneumonia (lower lobe)  
Pelvic inflammatory disease  
Porphyria  
Fabry disease  
Angioedema  
Endocarditis  
Abdominal migraine  
Familial Mediterranean fever  
Sexual or physical abuse  
Systemic lupus erythematosus  
School phobia  
Sickle cell crisis  
Vertebral disk inflammation  
Psoas abscess  
Pelvic osteomyelitis or myositis  
Medications  
Anterior (abdominal) cutaneous nerve entrapment syndrome (ACNES)

### ABDOMINAL DISTENTION OR MASS

Ascites: nephrotic syndrome, neoplasm, heart failure  
Discrete mass: Wilms tumor, hydronephrosis, neuroblastoma, mesenteric cyst, hepatoblastoma, lymphoma  
Pregnancy

### JAUNDICE

Hemolytic disease  
Urinary tract infection  
Sepsis  
Hypothyroidism  
Panhypopituitarism

## DYSPHAGIA

Difficulty in swallowing is termed *dysphagia*. Painful swallowing is termed *odynophagia*. **Globus** is the sensation of something stuck in the throat without a clear etiology. Swallowing is a complex process that starts in the mouth with mastication and lubrication of food that is formed into a bolus. The bolus is pushed into the pharynx by the tongue. The pharyngeal phase of swallowing is rapid and involves protective mechanisms to prevent food from entering the airway. The epiglottis is lowered over the larynx while the soft palate is elevated against the nasopharyngeal wall; respiration is temporarily arrested while the upper esophageal sphincter opens to allow the bolus to enter the esophagus. In the esophagus, peristaltic coordinated muscular contractions push the food bolus toward the stomach. The lower esophageal sphincter relaxes shortly after the upper esophageal sphincter, so liquids that rapidly clear the esophagus enter the stomach without resistance.

Dysphagia is classified as oropharyngeal dysphagia and esophageal dysphagia. **Oropharyngeal dysphagia** occurs when the transfer of the food bolus from the mouth to the esophagus is impaired (also termed *transfer dysphagia*). The striated muscles of the mouth, pharynx, and upper esophageal sphincter are affected in oropharyngeal dysphagia. Neurologic and muscular disorders can give rise to oropharyngeal dysphagia (Table 352.2). Chiari malformations, Russell-Silver syndrome, and cri du chat may present with upper esophageal sphincter

dysfunction, manifest by dysphagia with solids. The most serious complication of oropharyngeal dysphagia is life-threatening aspiration.

A complex sequence of neuromuscular events is involved in the transfer of foods to the upper esophagus. Abnormalities of the muscles involved in the ingestion process and their innervation, strength, or coordination are associated with transfer dysphagia in infants and children. In such cases, an oropharyngeal problem is usually part of a more generalized neurologic or muscular problem (botulism, diphtheria, neuromuscular disease). Painful oral lesions, such as acute viral stomatitis or trauma, occasionally interfere with ingestion. If the nasal air passage is seriously obstructed, the need for respiration causes severe distress when suckling. Although severe structural, dental, and salivary abnormalities would be expected to create difficulties, ingestion proceeds relatively well in most affected children if they are hungry.

**Esophageal dysphagia** occurs when there is difficulty in transporting the food bolus down the esophagus. Esophageal dysphagia can result from neuromuscular disorders or mechanical obstruction (Table 352.3). Primary motility disorders causing impaired peristaltic function and dysphagia are rare in children. Eosinophilic esophagitis can present with esophageal dysphagia. Achalasia is an esophageal motility disorder with associated inability of relaxation of the lower esophageal sphincter; it rarely occurs in children. Motility of the distal esophagus is disordered after surgical repair of tracheoesophageal fistula or achalasia. Abnormal motility can accompany collagen vascular disorders. Mechanical obstruction can be intrinsic or extrinsic. Intrinsic structural defects cause a fixed impediment to the passage of food bolus because of a narrowing within the esophagus, as in a stricture, web, or tumor. Extrinsic obstruction is caused by compression from vascular rings, mediastinal lesions, or vertebral abnormalities. Structural defects typically cause more problems in swallowing solids than liquids. In infants, esophageal web, tracheobronchial remnant, or vascular ring can cause dysphagia. An esophageal stricture secondary to esophagitis (chronic gastroesophageal reflux, eosinophilic esophagitis, chronic infections) occasionally has dysphagia as the first manifestation. An esophageal foreign body or a stricture secondary to a caustic ingestion also causes dysphagia. A Schatzki ring, a thin ring of mucosal tissue near the lower esophageal sphincter, is another mechanical cause of recurrent dysphagia, and again is rare in children.

When dysphagia is associated with a delay in passage through the esophagus, the patient may be able to point to the level of the chest where the delay occurs, but esophageal symptoms are usually referred

**Table 352.2** Causes of Oropharyngeal Dysphagia

### NEUROMUSCULAR DISORDERS

- Cerebral palsy
- Brain tumors
- Cerebrovascular disease/stroke
- Chiari malformation
- Polio and postpolio syndromes
- Multiple sclerosis
- Myositis
- Dermatomyositis
- Myasthenia gravis
- Muscular dystrophies
- Acquired or inherited dystonia syndrome
- Dysautonomia

### METABOLIC AND AUTOIMMUNE DISORDERS

- Hyperthyroidism
- Systemic lupus erythematosus
- Sarcoidosis
- Amyloidosis

### INFECTIOUS DISEASE

- Meningitis
- Botulism
- Diphtheria
- Lyme disease
- Neurosyphilis
- Viral infection: polio, coxsackievirus, herpes, cytomegalovirus

### STRUCTURAL LESIONS

- Inflammatory: abscess, pharyngitis
- Congenital web
- Cricopharyngeal bar
- Dental problems
- Bullous skin lesions
- Plummer-Vinson syndrome
- Zenker diverticulum
- Extrinsic compression: osteophytes, lymph nodes, thyroid swelling, aberrant right subclavian artery (dysphagia lusoria)

### OTHER

- Corrosive injury
- Side effects of medications
- After surgery
- After radiation therapy

Adapted from Gasiorowska A, Faas R. Current approach to dysphagia. *Gastroenterol Hepatol*. 2009;5(4):269–279.

**Table 352.3** Causes of Esophageal Dysphagia

### NEUROMUSCULAR

- Eosinophilic esophagitis
- Achalasia cardia
- Diffuse esophageal spasm
- Scleroderma

### GERD

#### INTRINSIC LESIONS

- Foreign bodies including pills
- Esophagitis: GERD, eosinophilic esophagitis, infections
- Stricture: corrosive injury, pill induced, peptic
- Esophageal webs
- Esophageal rings
- Esophageal diverticula
- Neoplasm
- Chagas disease

#### EXTRINSIC LESIONS

- Vascular compression
- Mediastinal lesion
- Cervical osteochondritis
- Vertebral abnormalities

GERD, Gastroesophageal reflux disease.

Adapted from Gasiorowska A, Faas R. Current approach to dysphagia. *Gastroenterol Hepatol*. 2009;5(4):269–279.

to the suprasternal notch. When a patient points to the suprasternal notch, the impaction can be found anywhere in the esophagus.

## REGURGITATION

Regurgitation is the effortless movement of stomach contents into the esophagus and mouth. It is not associated with distress, and infants with regurgitation are often hungry immediately after an episode. The lower esophageal sphincter prevents reflux of gastric contents into the esophagus. Regurgitation is a result of gastroesophageal reflux through an incompetent or, in infants, immature lower esophageal sphincter. This is often a developmental process, and regurgitation or “spitting” resolves with maturity. Regurgitation should be differentiated from vomiting, which denotes an active reflex process with an extensive differential diagnosis (Table 352.4).

## NAUSEA

Nausea has been described as an unpleasant, subjective sensation of impending/imminent vomiting, often with epigastric sensation that may be painless. Nausea is frequently associated with typical autonomic signs that accompany vomiting. Not all nausea is a prodrome to vomiting. There are multiple potential triggers to nausea, including environmental exposures (toxins, odors), unpleasant visual stimuli, visceral pain, anxiety, stress, and a variety of additional etiologies (Table 352.5).

The central nervous system (CNS) is frequently implicated for nausea. Receptors and neural pathways at the chemoreceptor trigger zone

(CTZ) are most often implicated by chemical stimuli with chemotherapy a prime example. Visceral stimuli can include ingestions, gastric hyperacidity, physical stress, psychologic stressors, mechanical distention of the stomach, and impaired GI motility; vagal and sympathetic nerves are involved in this process. Vestibular pathways are most often implicated in nausea related to motion sickness. Increased intracranial pressure can also present with nausea plus or minus vomiting.

Chronic nausea is more common in adolescents and may be coincidental with other functional GI disorders, including functional dyspepsia, delayed gastric emptying/gastroparesis, and constipation. There are gender and ethnic differences with respect to chronic nausea in adolescence, with adolescent White females with anxiety more at risk than other groups; there may be alterations in the brain-gut axis coupled with increased visceral hypersensitivity and hyperalgesia at play in the setting (see Chapter 212). Dehydration and autonomic dysfunction may also present with nausea as one facet of GI manifestations.

Nausea is often a clinical diagnosis, and while the differential diagnosis is extensive, negative findings do not equate to the patient not having nausea. Nausea is often distressing, disruptive, and may be disabling with respect to normal function. Table 352.5 reviews common medical conditions associated with nausea, as well as treatment strategies. Hydration is important in many of these conditions. Many of the medications used employ antihistamine, serotonergic, dopaminergic, and potentially even opioid pathways (although these are still controversial). These agents are active at both the CNS and GI level, with significant brain-gut axis interplay. Complementary and

**Table 352.4** Differential Diagnosis of Emesis During Childhood

INFANT	CHILD	ADOLESCENT
<b>COMMON</b> <ul style="list-style-type: none"> <li>Gastroenteritis</li> <li>Gastroesophageal reflux</li> <li>Overfeeding</li> <li>Anatomic obstruction*</li> <li>Systemic infection†</li> <li>Pertussis syndrome</li> <li>Otitis media</li> </ul>	<ul style="list-style-type: none"> <li>Gastroenteritis</li> <li>Systemic infection</li> <li>Gastritis</li> <li>Toxic ingestion/poisoning</li> <li>Pertussis syndrome</li> <li>Medication</li> <li>Reflux (GERD)</li> <li>Sinusitis</li> <li>Otitis media</li> <li>Anatomic obstruction*</li> <li>Eosinophilic esophagitis</li> </ul>	<ul style="list-style-type: none"> <li>Gastroenteritis</li> <li>GERD</li> <li>Systemic infection</li> <li>Toxic ingestion/poisoning/marijuana</li> <li>Gastritis</li> <li>Sinusitis</li> <li>Inflammatory bowel disease</li> <li>Appendicitis</li> <li>Migraine</li> <li>Pregnancy</li> <li>Medications</li> <li>Ipecac abuse, bulimia</li> <li>Concussion</li> </ul>
<b>RARE</b> <ul style="list-style-type: none"> <li>Adrenogenital syndrome</li> <li>Inborn errors of metabolism</li> <li>Brain tumor (increased intracranial pressure)</li> <li>Subdural hemorrhage</li> <li>Food poisoning</li> <li>Rumination</li> <li>Renal tubular acidosis</li> <li>Ureteropelvic junction obstruction</li> <li>Pseudoobstruction</li> </ul>	<ul style="list-style-type: none"> <li>Reye syndrome</li> <li>Hepatitis</li> <li>Peptic ulcer</li> <li>Pancreatitis</li> <li>Brain tumor</li> <li>Increased intracranial pressure</li> <li>Middle ear disease/labyrinthitis</li> <li>Chemotherapy</li> <li>Achalasia</li> <li>Cyclic vomiting (migraine)</li> <li>Esophageal stricture</li> <li>Duodenal hematoma</li> <li>Inborn error of metabolism</li> <li>Pseudoobstruction</li> <li>Gastroparesis</li> </ul>	<ul style="list-style-type: none"> <li>Reye syndrome</li> <li>Hepatitis</li> <li>Peptic ulcer</li> <li>Pancreatitis</li> <li>Cholecystitis</li> <li>Brain tumor</li> <li>Increased intracranial pressure</li> <li>Concussion</li> <li>Middle ear disease/labyrinthitis</li> <li>Chemotherapy</li> <li>Cyclic vomiting (migraine)</li> <li>Biliary colic</li> <li>Renal colic</li> <li>Porphyria</li> <li>Diabetic ketoacidosis</li> <li>Adrenal insufficiency</li> <li>Pseudoobstruction</li> <li>Intestinal tumor</li> <li>Gastroparesis</li> <li>Achalasia</li> <li>Superior mesentery artery syndrome</li> <li>Distal intestinal obstruction syndrome</li> </ul>

\*Includes malrotation, pyloric stenosis, intussusception, Hirschsprung disease, adhesions, and hernias.

†Meningitis, sepsis.

GERD, Gastroesophageal reflux disease.

<b>Table 352.5 Examples of Causes and Management of Nausea</b>	
<b>FUNCTIONAL GASTROINTESTINAL DISORDERS</b>	<b>TREATMENT APPROACHES</b>
Gastroesophageal reflux	Diet and lifestyle; acid reduction, refluxate management
Esophagitis (reflux related, eosinophilic, etc.)	Acid reduction, identifying and restricting environmental/dietary triggers
Dyspepsia	Dietary and lifestyle modification; acid reduction; cyproheptadine
Gastroparesis	Smaller, more frequent meals; dietary modification; prokinetic agents ( $D_2$ antagonists such as metoclopramide and domperidone*; low-dose erythromycin or azithromycin)
Constipation	Adequate hydration, diet and lifestyle modification, stool softeners, stimulant laxatives, additional adjunct measures if/as indicated
Visceral hyperalgesia	Tricyclic antidepressants (e.g., amitriptyline), cognitive behavioral therapy, hypnotherapy, biofeedback, physical therapy for desensitization; biofeedback; stress reduction
<b>OTHER GASTROINTESTINAL DISORDERS</b>	
Gastritis (medication/NSAID induced; <i>Helicobacter pylori</i> )	Reduce/remove medications involved; treat the underlying cause
Gastrointestinal dysmotility	Adequate hydration; diet/feeding or eating modification; promotility agents
Biliary dysfunction (cholelithiasis, cholecystitis, biliary dyskinesia)	Treat the underlying cause
Fundoplication	Smaller, more frequent meals; cyproheptadine to improve gastric accommodation
<b>CENTRAL NERVOUS SYSTEM</b>	
Increased intracranial pressure	Treat underlying cause
Migraines, headaches	Migraine prophylactic agents, including cyproheptadine. Abortive medications including triptans.
Motion sickness/vestibular dysfunction	Antihistamines (e.g., diphenhydramine, hydroxyzine) anticholinergics (e.g., scopolamine)
Autonomic dysfunction	Adequate hydration, increased salt intake, diet and lifestyle modification
Chemotherapy-induced nausea and vomiting	5-HT <sub>3</sub> receptor antagonists; $D_2$ antagonists; NK-1 antagonists; butyrophenones; benzodiazepines; dexamethasone; synthetic cannabinoids
Postoperative nausea and vomiting	5-HT <sub>3</sub> receptor antagonists
<b>NON-GI AND NON-CNS ETIOLOGIES OF NAUSEA</b>	
Uremia	Treat the underlying disorder
Endocrine disorders [e.g., hypothyroidism]	Treat the underlying disorder

\* $D_2$  receptor antagonists such as metoclopramide and domperidone have a significant side effect profile, and have a U.S. Food and Drug Administration black box warning, and should be used with caution.

NK-1, Neurokinin 1.

alternative medicine approaches including using ginger, peppermint, aromatherapy, and biofeedback may be helpful. Behavior psychology and social work may be helpful in decreasing disability and enhancing functionality.

## VOMITING

Vomiting is a highly coordinated reflex process that may be preceded by increased salivation and begins with involuntary retching. Violent descent of the diaphragm and constriction of the abdominal muscles with relaxation of the gastric cardia actively force gastric contents back up the esophagus. This process is coordinated in the medullary vomiting center, which is influenced directly by afferent innervation and indirectly by the CTZ and higher CNS centers. Many acute or chronic processes can cause vomiting (see Tables 352.1 and 352.4).

Vomiting caused by obstruction of the GI tract is probably mediated by intestinal visceral afferent nerves stimulating the vomiting center (Table 352.6). If obstruction occurs below the second part of the duodenum, vomitus is usually bile stained. Emesis can also become bile stained with repeated vomiting in the absence of obstruction when duodenal contents are refluxed into the stomach. Nonobstructive lesions of the digestive tract can also cause vomiting; this includes diseases of the upper bowel, pancreas, liver, or biliary tree. CNS or metabolic derangements and cyclic vomiting syndrome (see Chapter 390) can lead to severe, persistent emesis. Marijuana use among teens has also led to cannabis hyperemesis syndrome (see Chapter 157.3).

Potential complications of emesis are noted in Table 352.7. Broad management strategies for vomiting in general and specific causes of emesis are noted in Tables 352.8 and 352.9.

## DIARRHEA

Diarrhea is best defined as excessive loss of fluid and electrolyte in the stool. Acute diarrhea is defined as sudden onset of excessively loose stools of >10 mL/kg/day in infants and >200 g/24 hr in older children, which lasts <14 days. When the episode lasts longer than 14 days, it is called *chronic* or *persistent diarrhea*.

Normally, a young infant has approximately 5 mL/kg/day of stool output; the volume increases to 200 g/24 hr in an adult. The greatest volume of intestinal water is absorbed in the small bowel; the colon concentrates intestinal contents against a high osmotic gradient. The small intestine of an adult can absorb 10–11 L/day of a combination of ingested and secreted fluid, whereas the colon absorbs approximately 0.5 L. Disorders that interfere with absorption in the small bowel tend to produce voluminous diarrhea, whereas disorders compromising colonic absorption produce lower-volume diarrhea. **Dysentery** (small-volume, frequent bloody stools with mucus, tenesmus, and urgency) is the predominant symptom of colitis.

The basis of all diarrheas is disturbed intestinal solute transport and water absorption. Water movement across intestinal membranes is passive and is determined by both active and passive fluxes of solutes, particularly sodium, chloride, and glucose. The pathogenesis of most episodes of diarrhea can be explained by secretory, osmotic, or motility abnormalities or a combination of these (Table 352.10).

**Secretory diarrhea** occurs when the intestinal epithelial cell solute transport system is in an active state of secretion. It is often caused by a secretagogue, such as cholera toxin, binding to a receptor on the surface epithelium of the bowel and thereby stimulating intracellular accumulation of cyclic adenosine monophosphate or cyclic guanosine monophosphate. Some intraluminal fatty acids and bile salts cause the colonic mucosa to secrete through this

**Table 352.6** Causes of Gastrointestinal Obstruction

<b>ESOPHAGUS</b>	Ileal atresia Meconium ileus Meckel diverticulum with volvulus or intussusception Inguinal hernia Internal hernia Intestinal duplication Pseudoobstruction
<b>Congenital</b>	
Esophageal atresia	
Vascular rings	
Schatzki ring	
Tracheobronchial remnant	
<b>Acquired</b>	
Esophageal stricture	
Foreign body	
Achalasia	
Chagas disease	
Collagen vascular disease	
<b>STOMACH</b>	
<b>Congenital</b>	
Antral webs	
Pyloric stenosis	
<b>Acquired</b>	
Bezoar, foreign body	
Pyloric stricture (ulcer)	
Chronic granulomatous disease of childhood	
Eosinophilic gastroenteritis	
Crohn disease	
Epidermolysis bullosa	
<b>SMALL INTESTINE</b>	
<b>Congenital</b>	
Duodenal atresia	
Annular pancreas	
Malrotation/volvulus	
Malrotation/Ladd bands	
	<b>Acquired</b>
	Meconium plug
	Hirschsprung disease
	Colonic atresia, stenosis
	Imperforate anus
	Rectal stenosis
	Pseudoobstruction
	Volvulus
	Colonic duplication
	<b>COLON</b>
<b>Congenital</b>	
	Meconium plug
	Hirschsprung disease
	Colonic atresia, stenosis
	Imperforate anus
	Rectal stenosis
	Pseudoobstruction
	Volvulus
	Colonic duplication
	<b>Acquired</b>
	Ulcerative colitis (toxic megacolon)
	Chagas disease
	Crohn disease
	Fibrosing colonopathy (cystic fibrosis)

**Table 352.7** Complications of Vomiting

COMPLICATION	PATHOPHYSIOLOGY	HISTORY, PHYSICAL EXAMINATION, AND LABORATORY STUDIES
Metabolic	Fluid loss in emesis HCl loss in emesis Na, K loss in emesis Acidosis	Dehydration Alkalosis; hypochloremia Hyponatremia; hypokalemia Dehydration
Nutritional	Emesis of calories and nutrients Anorexia for calories and nutrients	Malnutrition; "failure to thrive"
Mallory-Weiss tear	Retching → tear at lesser curve of gastroesophageal junction	Forceful emesis → hematemesis
Esophagitis	Chronic vomiting → esophageal acid exposure	Heartburn; Hemoccult + stool
Aspiration	Aspiration of vomitus, especially in context of obtundation	Pneumonia; neurologic dysfunction
Shock	Severe fluid loss in emesis or in accompanying diarrhea Severe blood loss in hematemesis	Dehydration (accompanying diarrhea can explain acidosis?) Blood volume depletion
Pneumomediastinum, pneumothorax	Increased intrathoracic pressure	Chest x-ray
Petechiae, retinal hemorrhages	Increased intrathoracic pressure	Normal platelet count

From Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy*, 2nd ed. Philadelphia: Elsevier; 2004: p. 318.

**Table 352.8** Pharmacologic Therapies for Vomiting Episodes

DISORDER – THERAPEUTIC CLASS	DRUG	DOSAGE	COMMENTS
<b>REFLUX – ANTACIDS</b>			
Histamine-2 receptor antagonist	Famotidine (Pepcid)	<3 months: 0.5 mg/kg/dose PO daily ≥ 3 months: 0.5 mg/kg/dose PO twice daily Children >40 kg: 20 mg twice daily, max: 40 mg/dose	<ul style="list-style-type: none"> <li>H2RAs are associated with tachyphylaxis</li> <li>Ranitidine was withdrawn in 2020</li> <li>Cimetidine has antiandrogenic potential, can stimulate prolactin secretion, and may be subject to drug interactions due to enzyme inhibition</li> </ul>
	Nizatidine (Axicid)	<12 years: 5 mg/kg/dose PO twice daily* ≥12 years: 150 mg PO twice daily, max 300 mg/day	
	Cimetidine	<16 years: 30-40 mg/kg/day PO divided 2-3x daily,* max: 400 mg/dose ≥16 years: 400 mg PO 4 times daily or 800 mg PO twice daily	
Proton pump inhibitors	Omeprazole (Prilosec) Lansoprazole (Prevacid) Esomeprazole (Nexium) Pantoprazole (Protonix)	1-2 mg/kg/day PO in 1-2 divided doses Maximum dose: omeprazole, esomeprazole, pantoprazole: 40 mg/dose; lansoprazole: 30 mg/dose	<ul style="list-style-type: none"> <li>Administer 30 minutes before first meal of the day for optimal effect</li> <li>Long-term side effects include increased risk of infections, bone health abnormalities, hypomagnesemia, vitamin B12 deficiency</li> <li>Consider weaning in patients on prolonged course (&gt;6 months) to avoid rebound symptoms</li> </ul>
<b>GASTROPARESIS – PROKINETICS</b>			
Dopamine antagonist	Metoclopramide (Reglan)	0.1-0.2 mg/kg/dose PO/IV every 6 to 8 hours, max: 10 mg/dose	<ul style="list-style-type: none"> <li>Use minimum effective dose and limit duration due to increased risk of extrapyramidal symptoms (EPS) with cumulative exposure</li> <li>Although some clinicians use diphenhydramine to limit EPS, anticholinergic effects of diphenhydramine may negate prokinetic benefit</li> </ul>
Motilin agonist	Erythromycin	5 mg/kg/dose PO 3-4 times daily, titrate up to 10 mg/kg/dose, max: 250 mg/dose	<ul style="list-style-type: none"> <li>Prescribe suspension for optimal pharmacokinetic profile in patients with hypomotility</li> <li>Cycling or drug-holidays may mitigate tachyphylaxis</li> <li>Subject to drug interactions due to CYP3A4 inhibition</li> <li>Associated with QTc prolongation, consider baseline EKG and/or periodic monitoring in patients with risk factors (underlying cardiac disorder, concomitant QT prolonging medications, electrolyte derangements)</li> <li>Routine use of other macrolides (azithromycin, clarithromycin) is not recommended due to limited data to support use, unknown optimal dose/frequency, and concerns for antibiotic resistance</li> </ul>

*Continued*

**Table 352.8** Pharmacologic Therapies for Vomiting Episodes—cont'd

DISORDER – THERAPEUTIC CLASS	DRUG	DOSAGE	COMMENTS
Serotonin (5HT-4) agonist	Cisapride	Consult GI specialist	<ul style="list-style-type: none"> <li>Withdrawn from the market in most countries due to QTc prolongation risk</li> <li>Use restricted to regulated/limited-access programs with specialist supervision</li> </ul>
	Prucalopride* (Motegrity)	>4 years: 0.04 mg/kg/dose PO once daily, max: 2 mg/dose Dosing range 0.02-0.06 mg/kg/dose to accommodate tablets	<ul style="list-style-type: none"> <li>Approved for constipation in adults, but a single-center retrospective study showed improvement in children with refractory upper GI symptoms</li> </ul>
Cholinergic agonist	Bethanechol*	0.1-0.2 mg/kg/dose PO 3 to 4 times daily, max: 10 mg/dose	<ul style="list-style-type: none"> <li>Administer before feeds/meals</li> <li>Stimulates antral contractions but does not impact gastric emptying</li> <li>Caution when using with anticholinergic agents (e.g., glycopyrrolate) due to potential for reduced efficacy/negating effect</li> </ul>
<b>CHEMOTHERAPY-INDUCED NAUSEA/VOMITING (CINV), POSTOPERATIVE, GENERAL</b>			
Serotonin 5HT3 antagonist	Ondansetron (Zofran)	0.1-0.15 mg/kg/dose PO/IV q8h, max: 24 mg/day Single dose regimen: 0.3 mg/kg/dose PO/IV, max: 16 mg/dose	<ul style="list-style-type: none"> <li>Adverse effects: constipation, headache, QTc prolongation</li> <li>Dose varies based on chemotherapy emetogenicity</li> </ul>
	Granisetron (Kytril)	≥2 years: 0.01 mg/kg/dose PO/IV q12h, max: 2 mg/dose *Single daily dose: 0.02-0.04 mg/kg PO/IV	
Phenothiazine	Prochlorperazine (Compazine)	≥2 years: 0.1 mg/kg/dose PO/IV q6-8h PRN, max: 10 mg/dose	<ul style="list-style-type: none"> <li>Due to safety concerns (EPS, sedation, respiratory depression), routine use of phenothiazines is not recommended</li> <li>Consider concomitant diphenhydramine to decrease risk of dystonic reactions</li> <li>Promethazine is associated with extravasation; IV/IM administration is generally avoided</li> </ul>
	Promethazine (Phenergan)	≥2 years: 0.25 to 0.5 mg/kg/dose PO/rectal q4-6h PRN, max: 25 mg/dose	
	Chlorpromazine (Thorazine)	≥6 months: 0.5 to 1 mg/kg/dose PO/IM/IV q6-8h PRN	
Substance P / neurokinin 1 antagonist	Aprepitant (Emend), for CINV	≥6 months and children <30 kg: 3 mg/kg PO on day 1, then 2 mg/kg once daily on days 2 and 3 Children >30 kg: 125 mg PO daily on day 1, then 80 mg PO daily on days 2 and 3	<ul style="list-style-type: none"> <li>Subject to drug interactions due to enzyme inhibition</li> </ul>
Steroids	Dexamethasone, for CINV	0.1 mg/kg/dose or 3 mg/m <sup>2</sup> /dose PO/IV q12h-24h	<ul style="list-style-type: none"> <li>Reported regimens vary, dose depends on chemotherapy emetogenicity</li> <li>May require dose reduction with concomitant aprepitant</li> </ul>

**Table 352.8** Pharmacologic Therapies for Vomiting Episodes—cont'd

DISORDER – THERAPEUTIC CLASS	DRUG	DOSAGE	COMMENTS
MOTION SICKNESS, VESTIBULAR DISORDERS			
Antihistamine	Diphenhydramine (Benadryl)	0.5-1 mg/kg/dose PO/IV/IM q6-8h, max: 50 mg/dose	<ul style="list-style-type: none"> <li>Anticholinergic effects may contribute to decreased motility</li> <li>Dimenhydrinate is available as 50 mg tablets, prescribe in 12.5 mg increments</li> <li>Do not cut or manipulate scopolamine transdermal patches</li> <li>Withdrawal (cholinergic rebound) symptoms reported with long-term use, limit duration or consider weaning with extended use</li> </ul>
	Dimenhydrinate (Dramamine)	>2 years: 1 to 1.5 mg/kg/dose PO q6-8h, max: 25 mg/dose	
	Meclizine (Antivert)	>2 to <12 years: 6.25 mg to 12.5 mg PO three times daily PRN >12 years: 25 mg to 50 mg PO 1 to 4 times daily, max: 100 mg/day	
	Scopolamine (Transderm-Skop)	>15 kg: 1 transdermal patch applied behind the ear every 3 days	
MISCELLANEOUS			
<i>Visceral Hypersensitivity, Feeding Intolerance</i>	Cyproheptadine*	0.25 mg/kg/day PO in 1-3 divided doses, usual max: 4 mg/dose	<ul style="list-style-type: none"> <li>Consider starting with bedtime dose and titrating up to prevent daytime sedation</li> <li>Associated with tachyphylaxis</li> <li>Benefit reported in patients with visceral hypersensitivity</li> <li>Anticholinergic effects may decrease motility</li> </ul>
Pseudo-obstruction Somatostatin analog	Octreotide*	0.5 to 1 mcg/kg subQ once daily, max: 100 mcg/dose	May cause bradycardia, hypoglycemia
Adrenal Crisis	Hydrocortisone	100 mg/m <sup>2</sup> IV/IM x1, followed by 25 mg/m <sup>2</sup> /dose IV/IM q6h, max: 100 mg/day Taper as clinically indicated	Reported regimens vary, refer to individual protocols

\*Limited data available

**Table 352.9** Supportive and Nonpharmacologic Therapies for Vomiting Episodes

DISEASE	THERAPY
All	Treat cause <ul style="list-style-type: none"> <li>Obstruction: operate</li> <li>Allergy: change diet (<math>\pm</math>steroids)</li> <li>Metabolic error: Rx defect</li> <li>Acid peptic disease: H<sub>2</sub>Ras, PPIs, etc.</li> </ul>
COMPLICATIONS	
Dehydration	IV fluids, electrolytes
Hematemesis	Transfuse, correct coagulopathy
Esophagitis	H <sub>2</sub> Ras, PPIs
Malnutrition	NG or NJ drip feeding useful for many chronic conditions
Meconium ileus	Gastrografin enema
DIOS	Gastrografin enema; balanced colonic lavage solution (e.g., GoLYTELY)
Intussusception	Barium enema; air reduction enema
Hematemesis	Endoscopic: injection sclerotherapy or banding of esophageal varices; injection therapy, fibrin sealant application, or heater probe electrocautery for selected upper GI tract lesions
Sigmoid volvulus	Colonoscopic decompression
Reflux	Positioning; dietary measures (infants: rice cereal, 1 tbs/oz of formula)
Psychogenic components	Psychotherapy; tricyclic antidepressants; anxiolytics (e.g., diazepam: 0.1 mg/kg PO tid-qid)

DIOS, Distal intestinal obstruction syndrome; GI, gastrointestinal; H<sub>2</sub>RA, H<sub>2</sub>-receptor antagonist; NG, nasogastric; NJ, nasojejunal; PPIs, proton pump inhibitors; tbs, tablespoon. From Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy*. 2nd ed. Philadelphia: Elsevier; 2004: p. 319.

**Table 352.10** Mechanisms of Diarrhea

PRIMARY MECHANISM	DEFECT	STOOL EXAMINATION	EXAMPLES	COMMENT
Secretory	Decreased absorption, increased secretion, electrolyte transport	Watery, normal osmolality with ion gap <100 mOsm/kg	Cholera, toxicogenic <i>Escherichia coli</i> ; carcinoid, VIP, neuroblastoma, congenital chloride diarrhea, <i>Clostridium difficile</i> , cryptosporidiosis (AIDS)	Persists during fasting; bile salt malabsorption can also increase intestinal water secretion; no stool leukocytes
Osmotic	Maldigestion, transport defects ingestion of unabsorbable substances	Watery, acidic, and reducing substances; increased osmolality with ion gap >100 mOsm/kg	Lactase deficiency, glucose-galactose malabsorption, lactulose, laxative abuse	Stops with fasting; increased breath hydrogen with carbohydrate malabsorption; no stool leukocytes
Increased motility	Decreased transit time	Loose to normal-appearing stool, stimulated by gastrocolic reflex	Irritable bowel syndrome, thyrotoxicosis, postvagotomy dumping syndrome	Infection can also contribute to increased motility
Decreased motility	Defect in neuromuscular unit(s) stasis (bacterial overgrowth)	Loose to normal-appearing stool	Pseudoobstruction, blind loop	Possible bacterial overgrowth
Decreased surface area (osmotic, motility)	Decreased functional capacity	Watery	Short bowel syndrome, celiac disease, rotavirus enteritis	Might require elemental diet plus parenteral alimentation
Mucosal invasion	Inflammation, decreased colonic reabsorption, increased motility	Blood and increased WBCs in stool	<i>Salmonella</i> , <i>Shigella</i> infection; amebiasis; <i>Yersinia</i> , <i>Campylobacter</i> infection	Dysentery evident in blood, mucus, and WBCs

VIP, Vasoactive intestinal peptide; WBC, white blood cell.

From Kliegman RM, Greenbaum LA, Lye PS. eds. *Practical Strategies in Pediatric Diagnosis and Therapy*. 2nd ed. Philadelphia: Elsevier; 2004: p 274.

mechanism. Diarrhea not associated with an exogenous secretagogue can also have a secretory component (congenital microvillus inclusion disease). Secretory diarrhea is usually of large volume and persists even with fasting. The stool osmolality is predominantly indicated by the electrolytes, and the ion gap is 100 mOsm/kg or less. The ion gap is calculated by subtracting the concentration of electrolytes from total osmolality:

$$\text{Ion gap} = \text{Stool osmolality} - [(\text{Stool Na} + \text{stool K}) 2]$$

**Osmotic diarrhea** occurs after ingestion of a poorly absorbed solute. The solute may be one that is normally not well absorbed (magnesium, phosphate, lactulose, or sorbitol) or one that is not well absorbed because of a disorder of the small bowel (lactose with lactase deficiency or glucose with rotavirus diarrhea). Malabsorbed carbohydrate is fermented in the colon, and short-chain fatty acids are produced. Although short-chain fatty acids can be absorbed in the colon and used as an energy source, the net effect is increase in the osmotic solute load. This form of diarrhea is usually of lesser volume than a secretory diarrhea and stops with fasting. The osmolality of the stool will not be explained by the electrolyte content, because another osmotic component is present and so the anion gap is >100 mOsm.

Motility disorders can be associated with rapid or delayed transit and are not generally associated with large-volume diarrhea. Slow motility can be associated with bacterial overgrowth leading to diarrhea. The differential diagnosis of common causes of acute and chronic diarrhea is noted in Table 352.11.

## CONSTIPATION

Any definition of constipation is relative and depends on stool consistency, stool frequency, and difficulty in passing the stool. A normal child might have a soft stool only every second or third day without difficulty; this is not constipation. A hard stool passed with

difficulty every third day should be treated as constipation. Constipation can arise from defects either in filling or emptying the rectum (Table 352.12).

A nursing infant might have very infrequent stools of normal consistency, which is usually a normal pattern. True constipation in the neonatal period is most likely secondary to Hirschsprung disease, intestinal pseudoobstruction, or hypothyroidism.

Defective rectal filling occurs when colonic peristalsis is ineffective (in cases of hypothyroidism or opiate use and when bowel obstruction is caused either by a structural anomaly or by Hirschsprung disease). The resultant colonic stasis leads to excessive drying of stool and a failure to initiate reflexes from the rectum that normally trigger evacuation. Emptying the rectum by spontaneous evacuation depends on a defecation reflex initiated by pressure receptors in the rectal muscle. Therefore stool retention can also result from lesions involving these rectal muscles, the sacral spinal cord afferent and efferent fibers, or the muscles of the abdomen and pelvic floor. Disorders of anal sphincter relaxation can also contribute to fecal retention.

Constipation tends to be self-perpetuating, whatever its cause. Hard, large stools in the rectum become difficult and even painful to evacuate; thus more retention occurs and a vicious circle ensues. Distention of the rectum and colon lessens the sensitivity of the defecation reflex and the effectiveness of peristalsis. Fecal impaction is common and leads to other problems. Eventually, watery content from the proximal colon might percolate around hard retained stool and pass per rectum unperceived by the child. This involuntary **encopresis** may be mistaken for diarrhea. Constipation itself does not have deleterious systemic organic effects, but urinary tract stasis with increased risk of urinary tract infections can accompany severe long-standing cases and constipation can generate anxiety, having a marked emotional impact on the patient and family.

**Table 352.11** Differential Diagnosis of Diarrhea

INFANT	CHILD	ADOLESCENT
<b>ACUTE</b>		
<b>Common</b>		
Gastroenteritis (viral > bacterial > protozoal) Systemic infection Antibiotic associated Overfeeding	Gastroenteritis (viral > bacterial > protozoal) Food poisoning Systemic infection Antibiotic associated	Gastroenteritis (viral > bacterial > protozoal) Food poisoning Antibiotic associated
<b>Rare</b>		
Primary disaccharidase deficiency Hirschsprung toxic colitis Adrenogenital syndrome Neonatal opiate withdrawal	Toxic ingestion Hemolytic uremic syndrome Intussusception	Hyperthyroidism Appendicitis
<b>CHRONIC</b>		
<b>Common</b>		
Postinfectious secondary lactase deficiency Cow's milk or soy protein intolerance (allergy) Chronic nonspecific diarrhea of infancy Excessive fruit juice (sorbitol) ingestion Celiac disease Cystic fibrosis AIDS enteropathy	Postinfectious secondary lactase deficiency Irritable bowel syndrome Celiac disease Cystic fibrosis Lactose intolerance Excessive fruit juice (sorbitol) ingestion Giardiasis Inflammatory bowel disease AIDS enteropathy	Irritable bowel syndrome Inflammatory bowel disease Lactose intolerance Giardiasis Laxative abuse (anorexia nervosa) Constipation with encopresis
<b>Rare</b>		
Primary immune defects Autoimmune enteropathy IPEX and IPEX-like syndromes Glucose-galactose malabsorption Microvillus inclusion disease (microvillus atrophy) Congenital transport defects (chloride, sodium) Primary bile acid malabsorption Factitious syndrome by proxy Hirschsprung disease Shwachman syndrome Secretory tumors Acrodermatitis enteropathica Lymphangiectasia Abetalipoproteinemia Eosinophilic gastroenteritis Short bowel syndrome	Primary and acquired immune defects Secretory tumors Pseudoobstruction Sucrase-isomaltase deficiency Eosinophilic gastroenteritis Secretory tumors	Secretory tumor Primary bowel tumor Parasitic infections and venereal diseases Appendiceal abscess Addison disease

IPEX, Immunodysregulation polyendocrinopathy enteropathy X-linked.

From Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy*, 2nd ed. Philadelphia: Elsevier; 2004: p. 272.**Table 352.12** Causes of Constipation

<b>NONORGANIC (FUNCTIONAL): RETENTIVE</b>	
<b>Anatomic</b>	
Anal stenosis, atresia with fistula Imperforate anus Anteriorly displaced anus Intestinal stricture (postnecrotizing enterocolitis) Anal stricture	<b>Drugs</b> Anticholinergics Narcotics Methylphenidate Phenytoin Antidepressants Chemotherapeutic agents (vincristine) Pancreatic enzymes (fibrosing colonopathy) Lead, arsenic, mercury Vitamin D intoxication Calcium channel blocking agents
<b>Abnormal Musculature</b>	
Prune-belly syndrome Gastroschisis Down syndrome Muscular dystrophy	<b>Metabolic Disorders</b> Hypokalemia Hypercalcemia Hypothyroidism Diabetes mellitus, diabetes insipidus Porphyria
<b>Intestinal Nerve or Muscle Abnormalities</b>	
Hirschsprung disease Pseudoobstruction (visceral myopathy or neuropathy) Intestinal neuronal dysplasia Spinal cord lesions Tethered cord Autonomic neuropathy Spinal cord trauma Spina bifida Chagas disease	<b>Intestinal Disorders</b> Celiac disease Cow's milk protein intolerance Cystic fibrosis (meconium ileus equivalent) Inflammatory bowel disease (stricture) Tumor Connective tissue disorders Systemic lupus erythematosus Scleroderma
	<b>Psychiatric Diagnosis</b> Anorexia nervosa

## ANOREXIA

*Anorexia* means prolonged lack of appetite. Hunger and satiety centers are located in the hypothalamus; it seems likely that afferent nerves from the GI tract to these brain centers are important determinants of the anorexia that characterizes many diseases of the stomach and intestine. Satiety is stimulated by distention of the stomach or upper small bowel, the signal being transmitted by sensory afferents, which are especially dense in the upper gut. Chemoreceptors in the intestine, influenced by the assimilation of nutrients, also affect afferent flow to the appetite centers. Impulses reach the hypothalamus from higher centers, possibly influenced by pain or the emotional disturbance of an intestinal disease. Other regulatory factors include hormones, ghrelin, leptin, and plasma glucose, which, in turn, reflect intestinal function.

## ABDOMINAL PAIN

There is considerable variation among children in their perception and tolerance for abdominal pain. This is one reason the evaluation of chronic abdominal pain is difficult. A child with **functional abdominal pain** (also known as centrally mediated abdominal pain syndrome or brain-gut axis dysfunction) may be as uncomfortable as one with an organic cause. It is very important to distinguish between organic and nonorganic (functional) abdominal pain because the approach for the management is based on this (Table 352.13). Normal growth and physical examination (including a rectal examination) and the absence of anemia or hematochezia are reassuring in a child who is suspected of having functional pain.

A specific cause may be difficult to find, but the nature and location of a pain-provoking lesion can usually be determined from the clinical description. Two types of nerve fibers transmit painful stimuli in the abdomen. In skin and muscle, A fibers mediate sharp localized pain; C fibers from viscera, peritoneum, and muscle transmit poorly localized, dull pain. These afferent fibers have cell bodies in the dorsal root

ganglia, and some axons cross the midline and ascend to the medulla, midbrain, and thalamus. Pain is perceived in the cortex of the post-central gyrus, which can receive impulses arising from both sides of the body. In the gut, the usual stimulus provoking pain is tension or stretching. Inflammatory lesions can lower the pain threshold, but the mechanisms producing pain or inflammation are not clear. Tissue metabolites released near nerve endings probably account for the pain caused by ischemia. Perception of these painful stimuli can be modulated by input from both cerebral and peripheral sources. Psychologic factors are particularly important. Tables 352.14 and 352.15 list features of abdominal pain. Pain that suggests a potentially serious organic etiology is associated with age younger than 5 years; fever; weight loss; bile- or blood-stained emesis; jaundice; hepatosplenomegaly; back or flank pain or pain in a location other than the umbilicus; awakening from sleep in pain; referred pain to shoulder, groin, or back; elevated erythrocyte sedimentation rate, white blood cell count, or CRP; anemia; edema; hematochezia; or a strong family history of inflammatory bowel disease or celiac disease (see Table 352.13).

**Visceral pain** tends to be dull and aching and is experienced in the dermatome from which the affected organ receives innervations. So, most often, the pain and tenderness are not felt over the site of the disease process. Painful stimuli originating in the liver, pancreas, biliary tree, stomach, or upper bowel are felt in the epigastrium; pain from the distal small bowel, cecum, appendix, or proximal colon is felt at the umbilicus; and pain from the distal large bowel, urinary tract, or pelvic organs is usually suprapubic. The pain from the cecum, ascending colon, and descending colon sometimes is felt at the site of the lesion because of the short mesocecum and corresponding mesocolon. The pain caused by appendicitis is initially felt in the periumbilical region, and pain from the transverse colon is usually felt in the suprapubic region. The shifting (localization) of pain is a pointer toward diagnosis; for example, periumbilical pain of a few hours localizing to the right lower quadrant suggests appendicitis. Radiation of pain can be helpful in diagnosis; in biliary colic the radiation of pain is toward the inferior angle of the right scapula, pancreatic pain is radiated to the back, and the renal colic pain is radiated to the inguinal region on the same side.

Differentiating abdominal wall pain from visceral pain is important and can prevent unnecessary testing. Nerve entrapment is one of the more common causes in adults. **Costochondritis** can be differentiated from underlying pain by palpating the rib margins, which should reproduce the pain. Treatment with topical anesthetics and NSAIDs if needed usually resolve pain within a few days. **Slipped rib syndrome** can follow overuse or even minor trauma to the ribs on either side. The name originates from a popping/slipping sensation that is often reported. Slipped rib syndrome may be mistaken for hepatobiliary, splenic, pancreatic, esophageal, or gastric etiologies, among others. Rib fractures, costochondritis, perichondritis [Tietze syndrome], and pleuritic pain may also present as an etiology. **Anterior (abdominal) cutaneous nerve entrapment syndrome (ACNES)** may produce acute, recurrent, or chronic unilateral localized abdominal pain. Nerve entrapment is most common at the lateral border of the rectus muscle.

**Somatic pain** is intense and usually well localized. When the inflamed viscus comes in contact with a somatic organ such as the parietal peritoneum or the abdominal wall, pain is localized to that site. Peritonitis gives rise to generalized abdominal pain with rigidity, involuntary guarding, rebound tenderness, and cutaneous hyperesthesia on physical examination.

**Referred pain** from extraintestinal locations, from shared central projections with the sensory pathway from the abdominal wall, can give rise to abdominal pain, as in pneumonia when the parietal pleural pain is referred to the abdomen (Fig. 352.1).

## GASTROINTESTINAL HEMORRHAGE

Bleeding can occur anywhere along the GI tract, and identification of the site may be challenging (Table 352.16). Bleeding that originates in the esophagus, stomach, or duodenum can cause **hematemesis**. When exposed to gastric or intestinal juices, blood quickly darkens to

**Table 352.13** Red Flags and Clues to an Organic Cause of Abdominal Pain

Age <5 yr old
Localized pain in nonperumbilical site
Referred pain
Sudden onset of excruciating pain
Crescendo nature of pain
Sudden worsening of pain
Fever (high fever >39.4°C suggests pneumonia, pyelonephritis, dysentery, cholangitis, more than perforation or abscess)
Jaundice
Distention*
Dysphagia
Dysuria
Emesis (especially bilious)
Anorexia
Weight loss, failure to thrive
Positive family history (metabolic disorders, peptic ulcer disease) <sup>†</sup>
Change in urine or stool color (blood, acholic) or frequency
Vaginal discharge
Menstrual abnormalities (amenorrhea)
Sexual activity
Delayed sexual development (chronic pain)
Anemia
Elevated erythrocyte sedimentation rate
Elevated stool calprotectin
Specific physical findings (hepatomegaly, splenomegaly, absent bowel sounds, adnexal tenderness, palpable mass, involuntary guarding, focal or diffuse tenderness, positive rectal examination results, perianal disease, joint swelling, rashes)

\*Consider 5 Fs: fat, feces, flatus (aerophagia, obstruction), fluid (ascites, hydronephrosis, cysts), and fetus (pregnancy or fetal-like abnormal growth [e.g., tumors]).

<sup>†</sup>Family history is also positive for chronic pain syndromes (constipation, irritable bowel, dysmenorrhea, and lactase or sucrose deficiency).

Modified from Miranda A. Abdominal pain. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*. 2nd ed. Philadelphia: Elsevier; 2023: Table 13.8, p. 229.

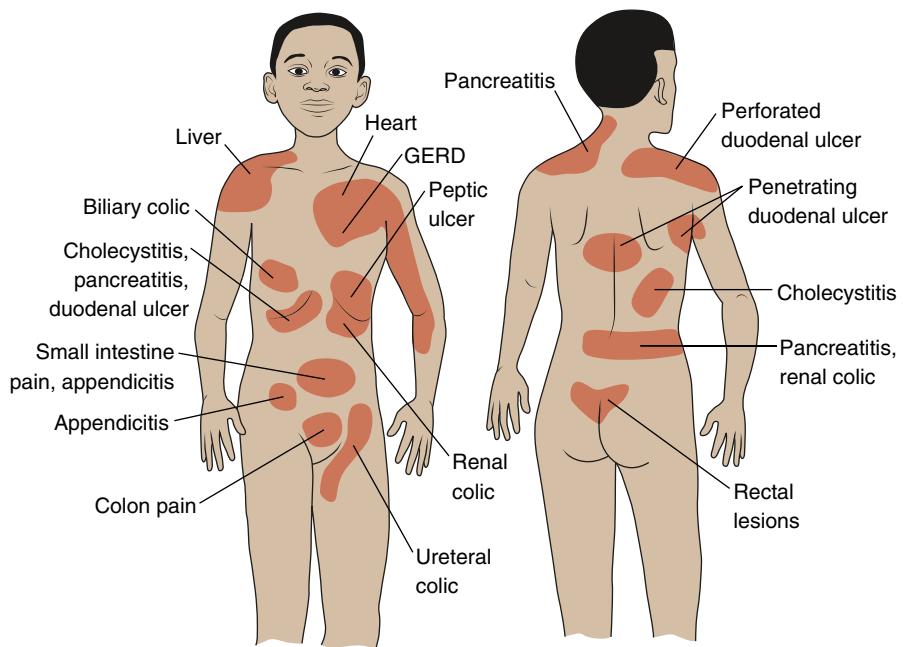
**Table 352.14** Chronic Abdominal Pain in Children

DISORDER	CHARACTERISTICS	KEY EVALUATIONS
<b>NONORGANIC</b>		
Functional abdominal pain	Nonspecific pain, often perumbilical	Hx and PE; tests as indicated
Irritable bowel syndrome	Intermittent cramps, diarrhea, and constipation	Hx and PE
Nonulcer dyspepsia	Peptic ulcer-like symptoms without abnormalities on evaluation of the upper GI tract	Hx; esophagogastroduodenoscopy
<b>GASTROINTESTINAL TRACT</b>		
Chronic constipation	Hx of stool retention, evidence of constipation on examination	Hx and PE; plain x-ray of abdomen
Lactose intolerance	Symptoms may be associated with lactose ingestion; bloating, gas, cramps, and diarrhea	Trial of lactose-free diet; lactose breath hydrogen test
Parasite infection (especially <i>Giardia</i> )	Bloating, gas, cramps, and diarrhea	Stool evaluation for O&P; specific immunoassays for <i>Giardia</i>
Excess fructose or sorbitol ingestion	Nonspecific abdominal pain, bloating, gas, and diarrhea	Large intake of apples, fruit juice, or candy or chewing gum sweetened with sorbitol
Crohn disease	See Chapter 382.2	
Peptic ulcer	Burning or gnawing epigastric pain; worse on awakening or before meals; relieved with antacids	Esophagogastroduodenoscopy, upper GI contrast x-rays, or MRI enteroscopy
Esophagitis	Epigastric pain with substernal burning	Esophagogastroduodenoscopy
Meckel diverticulum	Perumbilical or lower abdominal pain; may have blood in stool (usually painless)	Meckel scan or enteroclysis
Recurrent intussusception	Paroxysmal severe cramping abdominal pain; blood may be present in stool with episode	Identify intussusception during episode or lead point in intestine between episodes with contrast studies of GI tract
Internal, inguinal, or abdominal wall hernia	Dull abdomen or abdominal wall pain	PE, CT of abdominal wall
Chronic appendicitis or appendiceal mucocele	Recurrent RLQ pain; often incorrectly diagnosed, may be rare cause of abdominal pain	Barium enema, CT
<b>GALLBLADDER AND PANCREAS</b>		
Cholelithiasis	RUQ pain, might worsen with meals	Ultrasound of gallbladder
Choledochal cyst	RUQ pain, mass ± elevated bilirubin	Ultrasound or CT of RUQ
Recurrent pancreatitis	Persistent boring pain, might radiate to back, vomiting	Serum amylase and lipase ± serum trypsinogen; ultrasound, CT, or MRI-ERCP of pancreas
<b>GENITOURINARY TRACT</b>		
Urinary tract infection	Dull suprapubic pain, flank pain	Urinalysis and urine culture; renal scan
Hydronephrosis	Unilateral abdominal or flank pain	Ultrasound of kidneys
Urolithiasis	Progressive, severe pain; flank to inguinal region to testicle	Urinalysis, ultrasound, IVP, CT
Other genitourinary disorders	Suprapubic or lower abdominal pain; genitourinary symptoms	Ultrasound of kidneys and pelvis; gynecologic evaluation
<b>MISCELLANEOUS CAUSES</b>		
Abdominal migraine	See text; nausea, family Hx migraine	Hx
Abdominal epilepsy	Might have seizure prodrome	EEG (can require >1 study, including sleep-deprived EEG)
Gilbert syndrome	Mild abdominal pain (causal or coincidental?); slightly elevated unconjugated bilirubin	Serum bilirubin
Familial Mediterranean fever	Paroxysmal episodes of fever, severe abdominal pain, and tenderness with other evidence of polyserositis	Hx and PE during an episode, DNA diagnosis
Sickle cell crisis	Anemia	Hematologic evaluation
Lead poisoning	Vague abdominal pain ± constipation	Serum lead level
IgA vasculitis (Henoch-Schönlein purpura)	Recurrent, severe crampy abdominal pain, occult blood in stool, characteristic rash, arthritis	Hx, PE, urinalysis
Angioneurotic edema	Swelling of face or airway, crampy pain	Hx, PE, upper GI contrast x-rays, serum C1 esterase inhibitor
Acute intermittent porphyria	Severe pain precipitated by drugs, fasting, or infections	Spot urine for porphyrins
Anterior cutaneous nerve entrapment syndrome (ACNES)	Exquisite localized (~2 × 2 cm) tenderness that is replicable, most often RLQ	Pain relief within 15 min of abdominal wall injection of local anesthetic; may need surgery

ERCP, Endoscopic retrograde cholangiopancreatography; EEG, electroencephalogram; GI, gastrointestinal; Hx, history; IVP, intravenous pyelography; O&P, ova and parasites; PE, physical exam; RLQ, right lower quadrant; RUQ, right upper quadrant.

**Table 352.15** Distinguishing Features of Acute Abdominal Pain in Children

DISEASE	ONSET	LOCATION	REFERRAL	QUALITY	COMMENTS
Pancreatitis	Acute	Epigastric, left upper quadrant	Back	Constant, sharp, boring	Nausea, emesis, tenderness
Intestinal obstruction	Acute or gradual	Perumbilical-lower abdomen	Back	Alternating cramping (colic) and painless periods	Distention, obstipation, emesis, increased bowel sounds
Appendicitis	Acute (1-3 days)	Perumbilical, then localized to lower right quadrant; generalized with peritonitis	Back or pelvis if retrocecal	Sharp, steady	Anorexia, nausea, emesis, local tenderness, fever with peritonitis
Intussusception	Acute	Perumbilical-lower abdomen	None	Cramping, with painless periods	Hematochezia, knees in pulled-up position
Urolithiasis	Acute, sudden	Back (unilateral)	Groin	Sharp, intermittent, cramping	Hematuria
Urinary tract infection	Acute	Back	Bladder	Dull to sharp	Fever, costovertebral angle tenderness, dysuria, urinary frequency
Pelvic inflammatory disease	Acute	Pelvis, lower quadrant	Upper thigh	Aching, peritoneal signs	Vaginal discharge, fever
Small bowel obstruction	Acute to subacute	Perumbilical	None	Cramping diffuse	Emesis and obstipation
Ruptured ectopic pregnancy	Acute sudden	Pelvis, lower quadrant	None	Sharp, intense, localized	Vaginal bleeding, shock



**Fig. 352.1** Common sites of referred pain from the abdominal viscera. When a patient gives a history of referred pain from the viscera, the pain's location may not be directly over the impaired organ. Visceral embryologic development is the mechanism of the referred pain pattern. Pain is referred to the site where the organ was located in fetal development.

resemble coffee grounds; massive bleeding is likely to be red. Red or maroon blood in stools, **hematochezia**, signifies either a distal bleeding site or massive hemorrhage above the distal ileum. Moderate to mild bleeding from sites above the distal ileum tends to cause blackened stools of tarry consistency (**melena**); major hemorrhages in the duodenum or above can also cause melena.

Erosive damage to the mucosa of the GI tract is the most common cause of bleeding, although variceal bleeding secondary to portal hypertension occurs often enough to require consideration. Prolapse gastropathy producing subepithelial hemorrhage and Mallory-Weiss

lesions secondary to mucosal tears associated with emesis are causes of upper intestinal bleeds. Vascular malformations are a rare cause in children; they are difficult to identify (Figs. 352.2 and 352.3). Upper intestinal bleeding is evaluated with esophagogastroduodenoscopy. Evaluation of the small intestine is facilitated by capsule endoscopy. The capsule-sized imaging device is swallowed in older children or placed endoscopically in younger children. Lower GI bleeding is investigated with a colonoscopy. In brisk intestinal bleeding of unknown location, a tagged red blood cell scan is helpful in locating the site of the bleeding, although CT angiography is usually diagnostic. Occult blood

**Table 352.16** Differential Diagnosis of Gastrointestinal Bleeding in Childhood

INFANT	CHILD	ADOLESCENT
<b>COMMON</b>		
Bacterial enteritis Milk protein allergy intolerance Intussusception Swallowed maternal blood Anal fissure Lymphonodular hyperplasia	Bacterial enteritis Anal fissure Colonic polyps Intussusception Peptic ulcer/gastritis Swallowed epistaxis Prolapse (traumatic) gastropathy secondary to emesis Mallory-Weiss syndrome	Bacterial enteritis Inflammatory bowel disease Peptic ulcer/gastritis Prolapse (traumatic) gastropathy secondary to emesis Mallory-Weiss syndrome Colonic polyps Anal fissure
<b>RARE</b>		
Volvulus Necrotizing enterocolitis Meckel diverticulum Stress ulcer, gastritis Coagulation disorder (hemorrhagic disease of newborn) Esophagitis	Esophageal varices Esophagitis Meckel diverticulum Lymphonodular hyperplasia IgA vasculitis (Henoch-Schönlein purpura) Foreign body Hemangioma, arteriovenous malformation Sexual abuse Hemolytic-uremic syndrome Inflammatory bowel disease Coagulopathy Duplication cyst Angiodysplasia Angiodysplasia with von Willebrand disease Blue rubber bleb nevus syndrome	Hemorrhoids Esophageal varices Esophagitis Pill ulcer Telangiectasia-angiodysplasia Graft versus host disease Duplication cyst Angiodysplasia Angiodysplasia with von Willebrand disease Blue rubber bleb nevus syndrome



**Fig. 352.2** Intestinal angiodysplasia. A 7-year-old boy had tarry stool for days. Panendoscopy showed multiple cherry red flat spots in the gastric mucosa, compatible with the findings of angiodysplasia in CT angiography. (From Chuang F, Lin JS, Yeung C, et al. Intestinal angiodysplasia: an uncommon cause of gastrointestinal bleeding in children. Pediatr Neonatol. 2011;52:214–218, Fig. 2.)

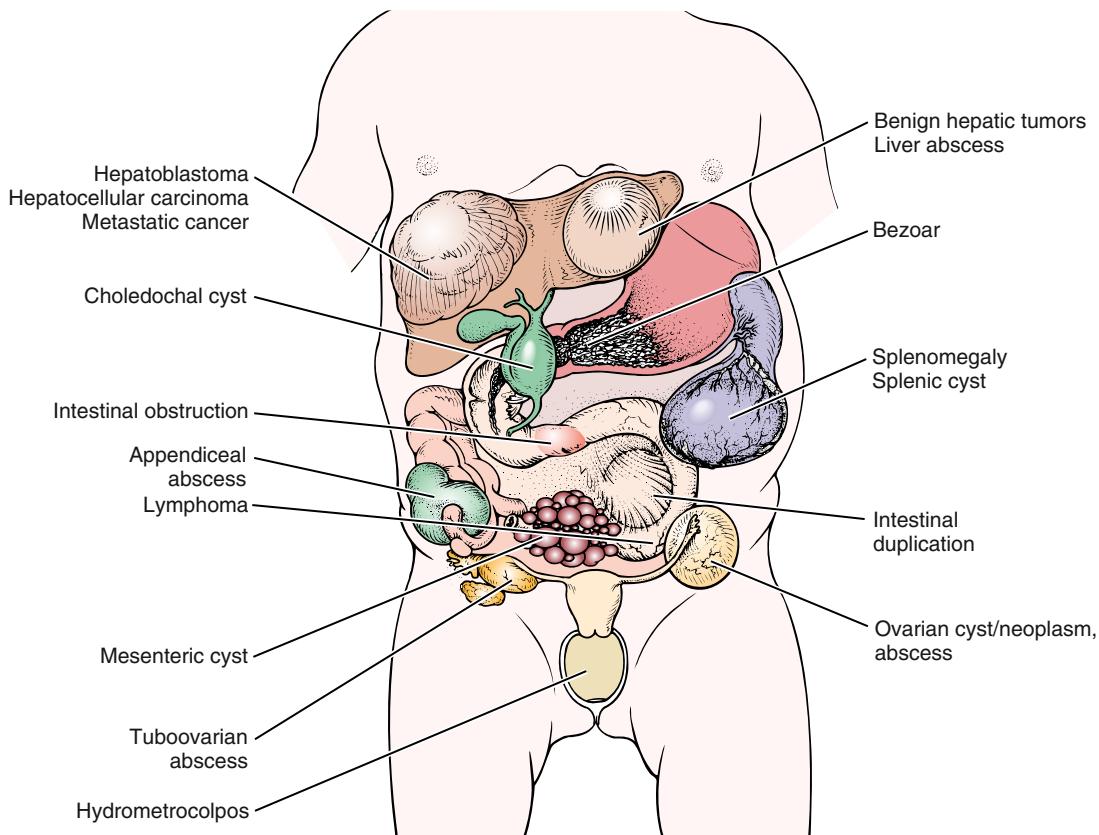
in stool is usually detected by using commercially available fecal occult blood testing cards, which are based on a chemical reaction between the chemical guaiac and oxidizing action of a substrate (hemoglobin), giving a blue color. The guaiac test is very sensitive, but random testing can miss chronic blood loss, which can lead to iron-deficiency anemia. GI hemorrhage can produce hypotension and tachycardia but rarely causes GI symptoms; brisk duodenal or gastric bleeding can lead to nausea, vomiting, or diarrhea. The breakdown products of intraluminal blood might tip patients into hepatic coma if liver function is already compromised and can lead to elevation of serum bilirubin.



**Fig. 352.3** Operative features of blue rubber bleb nevus syndrome. These lesions are similar to cutaneous lesions. (From Hasosah MY, Abdul-Wahab AA, Bin-Yahab SA, et al. Blue rubber bleb nevus syndrome: extensive small bowel vascular lesions responsible for gastrointestinal bleeding. J Pediatr Child Health. 2010;46:63–65. Fig. 3.)

### ABDOMINAL DISTENTION AND ABDOMINAL MASSES

Enlargement of the abdomen can result from diminished tone of the wall musculature or from increased content: fluid, gas, or solid. Ascites, the accumulation of fluid in the peritoneal cavity, distends the abdomen both in the flanks and anteriorly when it is large in volume. This fluid shifts with movement of the patient and conducts a percussion wave. Ascitic fluid is usually a transudate with a low protein concentration resulting from reduced plasma colloid osmotic pressure of hypoalbuminemia and/or from raised portal venous pressure. In cases of portal hypertension, the fluid leak probably occurs from lymphatics on the liver surface and from visceral peritoneal capillaries, but ascites does not usually develop until the serum albumin level falls. Sodium excretion in the urine decreases greatly as the ascitic fluid accumulates, and thus additional dietary sodium goes directly to the peritoneal



**Fig. 352.4** Location of select intrabdominal tumors and masses. (From Densmore JC, Densmore EM. Abdominal masses. In Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Fig. 20.1, p. 354.)

space, taking with it more water. When ascitic fluid contains a high protein concentration, it is usually an exudate caused by an inflammatory or neoplastic lesion.

When fluid distends the gut, either obstruction or imbalance between absorption and secretion should be suspected. The factors causing fluid accumulation in the bowel lumen often cause gas to accumulate too. The result may be audible gurgling noises. The source of gas is usually swallowed air but endogenous flora can increase considerably in malabsorptive states and produce excessive gas when substrate reaches the lower intestine. Gas in the peritoneal cavity (pneumoperitoneum) is usually caused by a perforated viscus and can cause abdominal distention depending on the amount of gas leak. A tympanitic percussion note, even over solid organs such as the liver, indicates a large collection of gas in the peritoneum.

An abdominal organ can enlarge diffusely or be affected by a discrete mass (Fig. 352.4). In the digestive tract, such discrete masses can occur in the lumen, wall, omentum, or mesentery. In a constipated child, mobile, nontender fecal masses are often found. Congenital anomalies, cysts, or inflammatory processes can affect the wall of the gut. Gut wall neoplasms are extremely rare in children. The pathologic enlargement of liver, spleen, bladder, and kidneys can give rise to abdominal distention.

#### ACKNOWLEDGMENT

Thanks to Astrela Moore, PharmD, Clinical Pharmacy Specialist at Children's Hospital of Philadelphia, for reviewing, verifying, and updating the pharmacotherapy table.

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## Section 2

# The Oral Cavity

## Chapter 353

# Development and Developmental Anomalies of the Teeth

Vineet K. Dhar

Newborn infants do not have teeth for about first 6 months after birth (predentate period). At this stage, the upper and lower alveolar ridges in the mouth, also known as gum pads, house the primary (deciduous) and some permanent tooth buds. The primary dentition period starts with eruption of the first primary tooth; all 20 primary teeth erupt by 3 years of age. The permanent teeth start erupting around 6 years of age, and the transition to full permanent dentition is completed by 13 years of age. The transition time between primary and permanent dentition, when a mix of primary and permanent teeth are present, is referred to as mixed dentition.

### DEVELOPMENT OF TEETH

#### Initiation

The primary teeth form in dental crypts that arise from a band of epithelial cells incorporated into each developing jaw. By 12 weeks of fetal life, each of these epithelial bands (**dental laminae**) has five areas of rapid growth on each side of the maxilla and the mandible, seen as rounded, budlike enlargements. Organization of adjacent mesenchyme takes place in each area of epithelial growth, and the two elements together are the beginning of a tooth.

After the formation of these crypts for the 20 primary teeth, another generation of tooth buds forms lingually (toward the tongue); these will develop into the succeeding permanent incisors, canines, and premolars that eventually replace the primary teeth. This process takes place from approximately 3-4 months of gestation for the central incisors to approximately 24-30 months of age for the second premolars. On the other hand, the permanent first, second, and third molars arise from extension of the dental laminae distal to the second primary molars; buds for these teeth develop approximately at birth, 3 years of age, and 7-10 years of age, respectively.

#### Histodifferentiation–Morphodifferentiation

As the epithelial bud proliferates, the deeper surface invaginates and a mass of mesenchyme becomes partially enclosed. The epithelial cells differentiate into the ameloblasts that lay down an organic matrix that forms enamel; the mesenchyme forms the dentin and dental pulp.

#### Calcification

After the organic matrix has been laid down, the deposition of the inorganic mineral crystals takes place from several sites of calcification that later coalesce. The characteristics of the inorganic portions of a tooth can be altered by disturbances in formation of the matrix, decreased availability of minerals, or the incorporation of foreign materials. Such disturbances can affect the color, texture, or thickness of the tooth surface. Calcification of primary teeth begins at 3-4 months in utero and concludes postnatally at approximately 12 months, with mineralization of the second primary molars (Table 353.1).

#### Eruption

At the time of tooth bud formation, each tooth begins a continuous movement toward the oral cavity. Table 353.1 lists the times of eruption

**Table 353.1** Calcification, Crown Completion, and Eruption

TOOTH	FIRST EVIDENCE OF CALCIFICATION	CROWN COMPLETED	ERUPTION
<b>PRIMARY DENTITION</b>			
<b>Maxillary</b>			
Central incisor	3-4 mo in utero	4 mo	7.5 mo
Lateral incisor	4.5 mo in utero	5 mo	8 mo
Canine	5.5 mo in utero	9 mo	16-20 mo
First molar	5 mo in utero	6 mo	12-16 mo
Second molar	6 mo in utero	10-12 mo	20-30 mo
<b>Mandibular</b>			
Central incisor	4.5 mo in utero	4 mo	6.5 mo
Lateral incisor	4.5 mo in utero	4½ mo	7 mo
Canine	5 mo in utero	9 mo	16-20 mo
First molar	5 mo in utero	6 mo	12-16 mo
Second molar	6 mo in utero	10-12 mo	20-30 mo
<b>PERMANENT DENTITION</b>			
<b>Maxillary</b>			
Central incisor	3-4 mo	4-5 yr	7-8 yr
Lateral incisor	10 mo	4-5 yr	8-9 yr
Canine	4-5 mo	6-7 yr	11-12 yr
First premolar	1½ - 1¾ yr	5-6 yr	10-11 yr
Second premolar	2-2¼ yr	6-7 yr	10-12 yr
First molar	At birth	2½ - 3 yr	6-7 yr
Second molar	2½ - 3 yr	7-8 yr	12-13 yr
Third molar	7-9 yr	12-16 yr	17-21 yr
<b>Mandibular</b>			
Central incisor	3-4 mo	4-5 yr	6-7 yr
Lateral incisor	3-4 mo	4-5 yr	7-8 yr
Canine	4-5 mo	6-7 yr	9-10 yr
First premolar	1¾ - 2 yr	5-6 yr	10-12 yr
Second premolar	2½ - 2 ½ yr	6-7 yr	11-12 yr
First molar	At birth	2½ - 3 yr	6-7 yr
Second molar	2½ - 3 yr	7-8 yr	11-13 yr
Third molar	8-10 yr	12-16 yr	17-21 yr

Modified from Logan WHG, Kronfeld R. Development of the human jaws and surrounding structures from birth to age 15 years. J Am Dent Assoc. 1993;20:379.

of the primary and permanent teeth. Occasionally the permanent teeth may erupt behind the primary teeth (“shark tooth”); this usually causes no problems.

#### Anomalies Associated with Eruption Pattern

Delayed eruption of the 20 primary teeth can be familial or indicate systemic or nutritional disturbances such as hypopituitarism, hypothyroidism, cleidocranial dysplasia, trisomy 21, and multiple other syndromes. Failure of eruption of single or small groups of teeth can arise from local causes such as malpositioned teeth, supernumerary teeth, cysts, or retained primary teeth. Premature loss of primary teeth is commonly caused by premature *eruption* of the permanent teeth. If the entire dentition is advanced for age and gender, precocious puberty or hyperthyroidism should be considered.

**Natal teeth** are observed in approximately 1 in 2,000 newborn infants, usually in the position of the mandibular central incisors. Natal teeth are present at birth, whereas **neonatal teeth** erupt in the first month of life. Attachment of natal and neonatal teeth is generally limited to the gingival margin, with little root formation or bony support. They may be a supernumerary or a prematurely erupted primary tooth. A radiograph can easily differentiate between the two conditions. Natal teeth are associated with cleft palate, Pierre Robin syndrome, mesoectodermal dysplasia syndrome (Ellis-van Creveld), oculomandibulofacial syndrome (Hallermann-Streiff), pachyonychia

**Table 353.2** Syndromes with Natal Teeth

SYNDROME	ASSOCIATED ANOMALIES	INHERITANCE/GENE ABNORMALITY/PREVALENCE
Ellis-van Creveld (chondroectodermal dysplasia)	Bilateral postaxial polydactyly of hands, chondrodysplasia of long bones resulting in dwarfism, ectodermal dysplasia affecting nails/teeth, congenital heart malformation	Autosomal-recessive EVC, EVC2 $7/1 \times 10^6$
Hallermann-Streiff	Dyscephaly, hypotrichosis, micro-ophthalmia, cataracts, beaked nose, micrognathia, proportionate short stature	Sporadic Not known $>150$ cases to date
Pachyonychia congenita (1: Jadassohn-Lewandowsky) (2: Jackson-Lawler)	Dystrophic nails, palmoplantar keratosis, hyperhidrosis, follicular keratosis, oral leukokeratosis, cutaneous cysts	Autosomal-dominant Keratin gene variants: type I: 6a/16, type 2:6b/17 $0.071/1 \times 10^6$ 9:5 male to female
Pallister-Hall (hypothalamic hamartoblastoma)	Hypothalamic hamartoblastoma, craniofacial abnormalities, postaxial polydactyly, cardiac and renal defects	Autosomal-dominant GLI3 $>13$ cases to date 8:5 male to female
Wiedemann-Rautenstrauch	Endocrine dysfunction, aged facies, frontal and biparietal bossing, small facial bones, sparse scalp hair, prominent scalp veins, small beaked nose, low-set ears	Autosomal-recessive POLR3A $>30$ cases to date
Natal teeth, patent ductus arteriosus, intestinal pseudoobstruction	Dilatation/hypermobility of small bowel, short or microcolon without obstruction, incomplete rotation of midgut, patent ductus arteriosus	X-linked recessive Not known 2 cases to date, brothers

Modified from Hebert AA. Mucous membrane disorders. In Schachner LA, Hansen RC, eds. *Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2011: Table 9.2, p. 654.

congenita, and other anomalies (Table 353.2). A family history of natal teeth or premature eruption is present in 15–20% of affected children.

Natal or neonatal teeth occasionally result in pain and refusal to feed and can produce maternal discomfort because of abrasion or biting of the nipple during nursing. If the tooth is mobile, there is a danger of detachment, with aspiration of the tooth. Because the tongue lies between the alveolar processes during birth, it can become lacerated (**Riga-Fede disease**). Decisions regarding extraction of prematurely erupted primary teeth must be made on an individual basis.

**Exfoliation failure** occurs when a primary tooth is not shed before the eruption of its permanent successor. Most often the primary tooth exfoliates eventually, but in some cases the primary tooth needs to be extracted. This occurs most commonly in the mandibular incisor region.

### Anomalies Associated with Tooth Development

Both failures and excesses of tooth initiation are observed. Developmentally missing teeth can result from environmental insult, a genetic defect involving only teeth, or the manifestation of a syndrome.

### Anomalies of Number

**Anodontia**, or absence of teeth, occurs when no tooth buds form (ectodermal dysplasia, or familial missing teeth) or when there is a disturbance of a normal site of initiation (the area of a palatal cleft). The teeth that are most commonly absent are the third molars, the maxillary lateral incisors, and the mandibular second premolars.

If the dental lamina produces more than the normal number of buds, **supernumerary teeth** occur, most often in the area between the maxillary central incisors. Because they tend to disrupt the position and eruption of the adjacent normal teeth, their identification by radiographic examination is important. Supernumerary teeth also occur with cleidocranial dysplasia (see Chapter 356) and in the area of cleft palates.

### Anomalies of Size

**Twinning**, in which two teeth are joined together, is most often observed in the mandibular incisors of the primary dentition. It can result from gemination, fusion, or concrescence. **Gemination** is the result of the division of one tooth germ to form a bifid crown on a single root with a common pulp canal; an extra tooth appears to be present in the dental arch. **Fusion** is the joining of incompletely developed teeth that, due to pressure, trauma, or crowding, continue to develop as one tooth. Fused teeth are sometimes joined along their entire length; in other cases, a single wide crown is supported on two roots. **Concrescence** is the attachment of the roots of closely approximated adjacent teeth by an excessive deposit of cementum. This type of twinning, unlike the others, is found most often in the maxillary molar region.

Disturbances during differentiation can result in alterations in dental morphology, such as **macrodontia** (large teeth) or **microdontia** (small teeth). The maxillary lateral incisors can assume a slender, tapering shape (**peg-shaped laterals**).

### Anomalies of Shape

**Dens in dente** or **dens invaginatus** presents as *tooth within tooth* appearance, which results from invagination of inner enamel epithelium caused by disruption during morphodifferentiation. Dens invaginatus presents as an extra cusp on anterior or posterior teeth, which contains enamel, dentin, and sometimes even pulp tissue. In the anterior teeth the cusp is talon shaped and presents in the cingulum area.

**Taurodontism** is more common in permanent molars and is characterized by elongated pulp chamber with short-stunted roots due to failure or late invagination of Hertwig epithelial root sheath. It may be associated with several syndromic conditions such as Down syndrome, tricho-dento-osseous syndrome, ectodermal dysplasia (hypohidrotic), and amelogenesis imperfecta (hypomaturation-hypoplastic type).

**Dilaceration** is an abnormal bend or curve in root possibly due to trauma. It may be subsequent to injury to the primary predecessor tooth.



**Fig. 353.1** Amelogenesis imperfecta, hypoplastic type. The enamel defect results in areas of missing or thin enamel, as well as grooves and pits.



**Fig. 353.2** Dentinogenesis imperfecta. The bluish, opalescent sheen on several of these teeth results from genetically defective dentin. This condition may be associated with osteogenesis imperfecta. (From Nazif MM, Martin BS, McKibben DH, et al. Oral disorders. In Zitelli BJ, Davis HW, eds. *Atlas of Pediatric Physical Diagnosis*. 4th ed. Philadelphia: Mosby; 2002: p. 703.)

### Anomalies of Structure

**Amelogenesis imperfecta** represents a group of hereditary conditions that manifest in enamel defects of the primary and permanent teeth without evidence of systemic disorders (Fig. 353.1). There are four subtypes: hypoplastic (type I), hypomaturational (type II), hypocalcified (type III), and hypomaturational-hypoplastic-taurodontism (type IV). Of the multiple subtypes, there are 19 genes inherited predominantly as autosomal dominant or recessive traits. The teeth are covered by only a thin layer of abnormally formed enamel through which the yellow underlying dentin is seen. The primary teeth are generally affected more than the permanent teeth. Susceptibility to caries is low, but the enamel is subject to destruction from abrasion. Complete coverage of the crown may be indicated for dentin protection, to reduce tooth sensitivity, and for improved appearance.

**Dentinogenesis imperfecta**, or hereditary opalescent dentin, is a condition analogous to amelogenesis imperfecta in which the odontoblasts fail to differentiate normally, resulting in poorly calcified dentin (Fig. 353.2). This autosomal dominant disorder can also occur in patients with **osteogenesis imperfecta**. The enamel-dentin junction is altered, causing enamel to break away. The exposed dentin is then susceptible to abrasion, in some cases worn to the gingiva. The teeth are opaque and pearly, and the pulp chambers are generally obliterated by calcification. Both primary and permanent teeth are usually involved. If there is excessive wear of the teeth, selected complete coverage of the teeth may be indicated to prevent further tooth loss and improve appearance.

Localized disturbances of calcification that correlate with periods of illness, malnutrition, premature birth, or birth trauma are common. **Hypocalcification** appears as opaque white patches or horizontal lines on the tooth; **hypoplasia** is more severe and manifests as pitting or areas devoid of enamel. Systemic conditions, such as renal failure and cystic fibrosis, are associated with enamel defects. Local trauma to the primary incisors can also affect calcification of permanent incisors.

**Fluorosis** (mottled enamel) can result from systemic fluoride consumption  $>0.05$  mg/kg/day during enamel formation. This high fluoride consumption can be caused by residing in an area of high fluoride content of the drinking water ( $>2.0$  ppm), swallowing excessive fluoridated toothpaste, or inappropriate fluoride prescriptions. Excessive fluoride during enamel formation affects ameloblastic function, resulting in inconspicuous white, lacy patches on the enamel to severe brownish discoloration and hypoplasia. The latter changes are usually seen with fluoride concentrations in the drinking water  $>5.0$  ppm.

### Anomalies of Color

Discolored teeth can result from incorporation of foreign substances into developing enamel. Neonatal hyperbilirubinemia can produce blue to black discoloration of the primary teeth. Porphyria produces a red-brown discoloration. Tetracyclines are extensively incorporated into bones and teeth and, if administered during the period of formation of enamel, can result in brown-yellow discoloration and hypoplasia of the enamel. Such teeth fluoresce under ultraviolet light. The period at risk extends from approximately 4 months of gestation to 7 years of age. Repeated or prolonged therapy with tetracycline carries the highest risk.

**Teething** is associated with primary tooth eruption and may manifest with benign symptoms such as gingival hyperemia, irritability, sucking fingers, and drooling; some infants have no symptoms or symptoms not identified by their parents. Low-grade fever is an inconsistent finding. The treatment of symptoms of teething is often unnecessary but could include oral analgesics and iced teething rings. Teething remedies containing benzocaine may cause methemoglobinemia and are not recommended. “Natural” (homeopathic) teething remedies may contain toxic additives and should be avoided. In addition, teething necklaces and bracelets are a risk for foreign body aspiration and choking.

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## Chapter 354

# Disorders of the Oral Cavity Associated with Other Conditions

Vineet K. Dhar

Disorders of the teeth and surrounding structures can occur in isolation or in combination with other systemic conditions (Table 354.1). Most commonly, medical conditions that occur during tooth development can affect tooth formation or appearance. Damage to teeth during their development is permanent.

**Table 354.1** Dental Problems Associated with Selected Medical Conditions

MEDICAL CONDITION	COMMON ASSOCIATED DENTAL OR ORAL FINDINGS
Cleft lip and palate	Missing teeth, extra (supernumerary) teeth, shifting of arch segments, feeding difficulties, speech problems
Kidney failure	Mottled enamel (permanent teeth), facial dysmorphology
Cystic fibrosis	Stained teeth with extensive medication, mottled enamel
Immunosuppression	Oral candidiasis with potential for systemic candidiasis, cyclosporine-induced gingival hyperplasia
Low birthweight	Palatal groove, narrow arch with prolonged oral intubation; enamel defects of primary teeth
Heart defects with susceptibility to bacterial endocarditis	Bacteremia from dental procedures or trauma
Neutrophil chemotactic deficiency	Aggressive periodontitis (loss of supporting bone around teeth)
Diabetes mellitus type 1 (uncontrolled)	Aggressive periodontitis
Neuromotor dysfunction	Oral trauma from falling; malocclusion (open bite); gingivitis from lack of hygiene
Prolonged illness (generalized) during tooth formation	Enamel hypoplasia of crown portions forming during illness
Seizures	Gingival enlargement if phenytoin is used
Maternal infections	Syphilis: abnormally shaped teeth
Vitamin D-dependent rickets	Enamel hypoplasia

## Chapter 355

# Malocclusion

Vineet K. Dhar

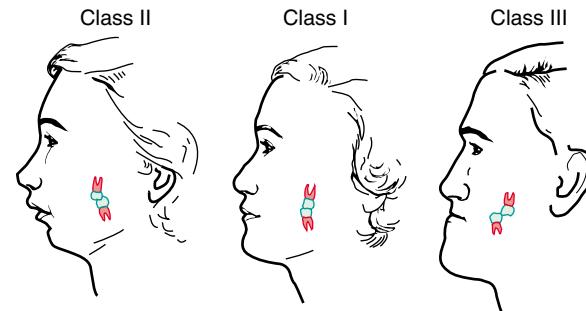
The oral cavity is essentially a masticatory instrument. The purpose of the anterior teeth is to bite off large portions of food. The posterior teeth reduce foodstuff to a soft, moist bolus. The cheeks and tongue force the food onto the areas of tooth contact. Establishing a proper relationship between the mandibular and maxillary teeth is important for both physiologic and cosmetic reasons.

### VARIATIONS IN GROWTH PATTERNS

Growth patterns are classified into three main types of occlusion, determined when the jaws are closed and the teeth are held together (Fig. 355.1). According to the Angle classification of malocclusion, in **class I occlusion** (normal), the cusps of the posterior mandibular teeth interdigitate ahead of and inside of the corresponding cusps of the opposing maxillary teeth. This relationship provides a normal facial profile.

In **class II malocclusion**, *buck teeth*, the cusps of the posterior mandibular teeth are behind and inside the corresponding cusps of the maxillary teeth. This common occlusal disharmony is found in approximately 45% of the population. The facial profile can give the appearance of a *receding chin* (*retrognathia*) (mandibular deficiency) or protruding front teeth. The resultant increased space between upper and lower anterior teeth encourage finger sucking and tongue-thrust habits. In addition, children with pronounced class II malocclusions are at greater risks of damage to the incisors as a consequence of trauma. Treatment includes orthodontic retraction of the maxilla or stimulation of the mandible.

In **class III malocclusion**, *underbite*, the cusps of the posterior mandibular teeth interdigitate a tooth or more ahead of their opposing maxillary counterparts. The anterior teeth appear in crossbite with the mandibular incisors protruding beyond the maxillary incisors. The facial profile gives the appearance of a *protruding chin* (*prognathia*) with or without an appearance of maxillary deficiency. If necessary,



**Fig. 355.1** Angle classification of occlusion. The typical correspondence between the facial-jaw profile and molar relationship is shown. (Data from Borrie FR, Bearn DR, Innes NP, et al. Interventions for the cessation of non-nutritive sucking habits in children. Cochrane Database Syst Rev. 2015;31:CD008694.)

treatment includes mandibular excess reduction osteotomy or orthodontic maxillary facial protraction.

The molar relationship in primary dentition/baby teeth also has three main types. The **flush terminal plane** relationship, where the distal surface of mandibular second primary molar is flush with the distal surface of maxillary second primary molar, is most common and can translate into class I occlusion or class II malocclusion in permanent dentition. The **mesial step** relationship, where the distal surface of mandibular second primary molar lies mesial to the distal surface of maxillary second primary molar, is the second most common and often translates into class I occlusion or sometimes into class III malocclusion in permanent dentition. Lastly, the **distal step** relationship, where the distal surface of the mandibular second primary molar lies distal to the distal surface of maxillary second primary molar, almost always translates into class II occlusion in permanent dentition.

### CROSSBITE

Normally, the mandibular teeth are in a position just inside the maxillary teeth so that the outside mandibular cusps or incisal edges meet the central portion of the opposing maxillary teeth. A reversal of this relation is referred to as a crossbite. Crossbites can be anterior, involving the incisors; can be posterior, involving the molars; or can involve single or multiple teeth; or can be unilateral or bilateral. Functional posterior crossbites that involve lateral shift of the mandible during closure may result in dental, skeletal adjustments, and even asymmetric condylar positioning; therefore an early diagnosis and correction is recommended.

### OPEN AND CLOSED BITES

If the posterior mandibular and maxillary teeth make contact with each other, but the anterior teeth are still apart, the condition is called an *open bite*. Open bites can result from skeletal growth pattern or digit sucking. If digit sucking is terminated before skeletal and dental growth is complete, the open bite might resolve naturally. If mandibular anterior teeth occlude inside the maxillary anterior teeth in an overclosed position, the condition is referred to as a *closed* or *deep bite*.

Treatment of open and closed bites consists of orthodontic correction, generally performed in the preteen or teenage years. Some severe cases require orthognathic surgery to position the jaws optimally in a vertical direction.

### DENTAL CROWDING

Overlap of incisors can result when the jaws are too small, or the teeth are too large for adequate alignment of the teeth. Growth of the jaws is mostly in the posterior aspects of the mandible and maxilla; therefore inadequate space for the teeth at 7 or 8 years of age will not resolve with growth of the jaws. Spacing in the primary dentition is normal and favorable for adequate alignment of successor teeth.

### DIGIT SUCKING

Various and conflicting etiologic theories and recommendations for correction have been proposed for digit sucking in children. Prolonged digit sucking can cause flaring of the maxillary incisor teeth, an open bite, and a posterior crossbite. The prevalence of digit sucking decreases steadily from the age of 2 years to approximately 10% by the age of 5 years. The earlier the habit is discontinued after the eruption of the permanent maxillary incisors (age 7-8 years), the greater the likelihood that there will be lessening effects on the dentition.

A variety of treatments have been suggested, from behavioral modification to insertion of an appliance with extensions that serves as a reminder when the child attempts to insert the digit. Unfortunately, a systematic review has found only low-quality evidence of the effectiveness of interventions such as orthodontic appliances and psychologic interventions. The greatest likelihood of success occurs in cases in which the child desires to stop. Stopping of the habit will not rectify a malocclusion caused by a prior deviant growth pattern.

## Chapter 356

# Cleft Lip and Palate

Vineet K. Dhar

Clefts of the lip and palate are distinct entities that are closely related embryologically, functionally, and genetically. It is thought that cleft of the lip appears because of hypoplasia of the mesenchymal layer, resulting in a failure of the medial nasal and maxillary processes to join. Cleft of the palate results from failure of palatal shelves to approximate or fuse.

### INCIDENCE AND EPIDEMIOLOGY

The incidence of cleft lip with or without cleft palate is approximately 1 in 1,000 births. The reported incidence of cleft palate alone in the United States is 1 in 1,687 births. Clefts of the lip are more common in males. Possible causes include maternal drug exposure, a syndrome-malformation complex, or genetic factors. Although clefts of lips and palates appear to occur sporadically, the presence of susceptible genes appears important. There are approximately 400 syndromes associated with cleft lip and palates. There are families in which a cleft lip or palate, or both, is inherited in a dominant fashion (**van der Woude syndrome**), and careful examination of parents is important to distinguish this type from others, because the recurrence risk is 50%. Ethnic factors also affect the incidence of cleft lip and palate; the incidence varies by race, with Asian children most likely to be affected. Cleft lip may be associated with other cranial facial anomalies, whereas cleft palate may be associated with central nervous system anomalies.

### CLINICAL MANIFESTATIONS

Cleft lip can vary from a small notch in the vermillion border to a complete separation involving skin, muscle, mucosa, tooth, and bone. Clefts of the lip may be unilateral (more often on the left side) or bilateral and can involve the alveolar ridge (Fig. 356.1).

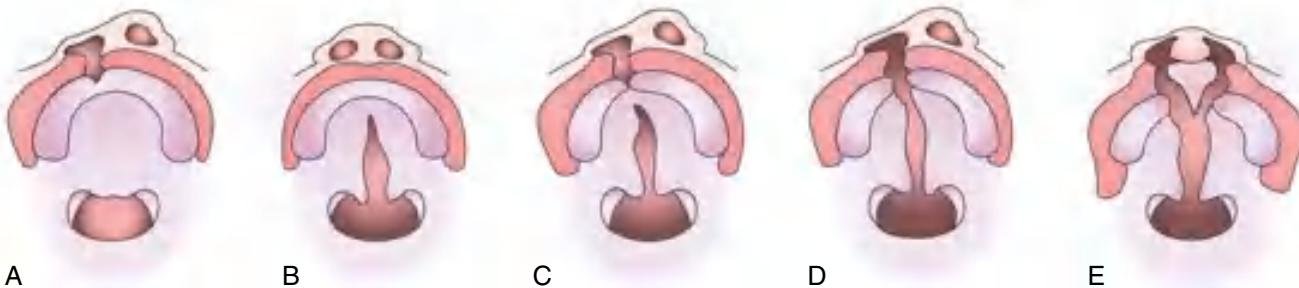
Isolated cleft palate occurs in the midline and might involve only the uvula or can extend into or through the soft and hard palates to the incisive foramen. When associated with cleft lip, the defect can involve the midline of the soft palate and extend into the hard palate on one or both sides, exposing one or both of the nasal cavities as a unilateral or bilateral cleft palate. The palate can also have a **submucosal cleft** indicated by a bifid uvula, partial separation of muscle with intact mucosa, or a palpable notch at the posterior of the palate (see Fig. 356.1).

### TREATMENT

A complete program of habilitation for the child with a cleft lip or palate can require years of special treatment by a team consisting of a pediatrician, plastic surgeon, otolaryngologist, oral and maxillofacial surgeon, pediatric dentist, prosthodontist, orthodontist, speech therapist, geneticist, medical social worker, psychologist, and public health nurse.

The immediate problem in an infant born with a cleft lip or palate is feeding. Although some advocate the construction of a plastic obturator to assist in feedings, most believe that, with the use of soft artificial nipples with large openings, a squeezable bottle, and proper instruction, feeding of infants with clefts can be achieved.

Surgical closure of a cleft lip is usually performed by 3 months of age, when the infant has shown satisfactory weight gain and is free of any oral, respiratory, or systemic infection. Modification of the Millard rotation-advancement technique is the most commonly used technique; a staggered suture line minimizes notching of the lip from retraction of scar tissue. The initial repair may be revised at 4 or 5 years of age. Corrective surgery on the nose may be delayed until adolescence. Nasal surgery can also be performed at the time of the lip repair. Cosmetic results depend on the extent of the original deformity,



**Fig. 356.1** Nonsyndromic orofacial clefts. A, Cleft lip and alveolus. B, Cleft palate. C, Incomplete unilateral cleft lip and palate. D, Complete unilateral cleft lip and palate. E, Complete bilateral cleft lip and palate. (From Shaw WC. *Orthodontics and Occlusal Management*. Oxford, UK: Butterworth-Heinemann; 1993.)

healing potential of the individual patient, absence of infection, and the skill of the surgeon.

Because clefts of the palate vary considerably in size, shape, and degree of deformity, the timing of surgical correction should be individualized. Criteria such as width of the cleft, adequacy of the existing palatal segments, morphology of the surrounding areas (width of the oropharynx), and neuromuscular function of the soft palate and pharyngeal walls affect the decision. The goals of surgery are the union of the cleft segments, intelligible and pleasant speech, reduction of nasal regurgitation, and avoidance of injury to the growing maxilla.

In an otherwise healthy child, closure of the palate is usually done before 1 year of age to enhance normal speech development. When surgical correction is delayed beyond the third year, a contoured speech bulb can be attached to the posterior of a maxillary denture so that contraction of the pharyngeal and velopharyngeal muscles can bring tissues into contact with the bulb to accomplish occlusion of the nasopharynx and help the child to develop intelligible speech.

A cleft palate usually crosses the alveolar ridge and interferes with the formation of teeth in the maxillary anterior region. Teeth in the cleft area may be displaced, malformed, or missing. Missing teeth or teeth that are nonfunctional are replaced by prosthetic devices.

### POSTOPERATIVE MANAGEMENT

During the immediate postoperative period, special nursing care is essential. Gentle aspiration of the nasopharynx minimizes the chances of the common complications of atelectasis or pneumonia. The primary considerations in postoperative care are maintenance of a clean suture line and avoidance of tension on the sutures. The infant is fed with a specially designed bottle, and the arms are restrained with elbow cuffs. A fluid or semifluid diet is maintained for 3 weeks. The patient's hands, toys, and other foreign bodies must be kept away from the surgical site.

### SEQUELAE

Recurrent otitis media and subsequent hearing loss are frequent with cleft palate. Displacement of the maxillary arches and malposition of the teeth usually require orthodontic correction. Misarticulations and velopharyngeal dysfunction are often associated with cleft lip and palate and may be present or persist because of physiologic dysfunction, anatomic insufficiency, malocclusion, or inadequate surgical closure of the palate. Such speech is characterized by the emission of air from the nose and by a hypernasal quality with certain sounds, or by compensatory misarticulations (glottal stops). Before and sometimes after palatal surgery, the speech defect is caused by inadequacies in function of the palatal and pharyngeal muscles. The muscles of the soft palate and the lateral and posterior walls of the nasopharynx constitute a valve that separates the nasopharynx from the oropharynx during swallowing

and in the production of certain sounds. If the valve does not function adequately, it is difficult to build up enough pressure in the mouth to make such explosive sounds as p, b, d, t, h, y, or the sibilants s, sh, and ch, and such words as "cats," "boats," and "sisters" are not intelligible. After operation or the insertion of a speech appliance, speech therapy is necessary.

### VELOPHARYNGEAL DYSFUNCTION

The speech disturbance characteristic of the child with a cleft palate can also be produced by other osseous or neuromuscular abnormalities where there is an inability to form an effective seal between oropharynx and nasopharynx during swallowing or phonation. In a child who has the potential for abnormal speech, adenoidectomy can precipitate overt hypernasality. If the neuromuscular function is adequate, compensation in palatopharyngeal movement might take place and the speech defect might improve, although speech therapy is necessary. In other cases, slow involution of the adenoids can allow gradual compensation in palatal and pharyngeal muscular function. This might explain why a speech defect does not become apparent in some children who have a submucous cleft palate or similar anomaly predisposing to palatopharyngeal incompetence.

### Clinical Manifestations

Although clinical signs vary, the symptoms of velopharyngeal dysfunction are similar to those of a cleft palate. There may be hypernasal speech (especially noted in the articulation of pressure consonants such as p, b, d, t, h, v, f, and s); conspicuous constricting movement of the nares during speech; inability to whistle, gargle, blow out a candle, or inflate a balloon; loss of liquid through the nose when drinking with the head down; otitis media; and hearing loss. Oral inspection might reveal a cleft palate or a relatively short palate with a large oropharynx; absent, grossly asymmetric, or minimal muscular activity of the soft palate and pharynx during phonation or gagging; or a submucous cleft.

Velopharyngeal dysfunction may also be demonstrated radiographically. The head should be carefully positioned to obtain a true lateral view; one film is obtained with the patient at rest and another during continuous phonation of the vowel u as in "boom." The soft palate contacts the posterior pharyngeal wall in normal function, whereas in velopharyngeal dysfunction such contact is absent.

In selected cases of velopharyngeal dysfunction, the palate may be retropositioned or pharyngoplasty may be performed using a flap of tissue from the posterior pharyngeal wall. Dental speech appliances have also been used successfully. The type of surgery used is best tailored to the findings on nasoendoscopy.

## Chapter 357

# Syndromes with Oral Manifestations

Vineet K. Dhar

Many syndromes have distinct or accompanying facial, oral, and dental manifestations (see Apert syndrome, Chapter 631.9; Crouzon disease, Chapter 631.9; Down syndrome, [Chapter 99.2](#)).

Osteogenesis imperfecta is often accompanied by effects on the teeth, termed **dentinogenesis imperfecta** (see [Chapter 353](#), [Fig. 353.2](#)). Depending on the severity of presentation, treatment of the dentition varies from routine preventive and restorative monitoring to covering affected posterior teeth with stainless steel crowns to prevent further tooth loss and improve appearance. Dentinogenesis imperfecta can also occur in isolation without the bony effects.

Another syndrome, **cleidocranial dysplasia**, has orofacial features such as frontal bossing, hypoplastic maxilla, and supernumerary teeth. The primary teeth can be overretained, and the permanent teeth remain unerupted. Supernumerary teeth are common, especially in the premolar area. Extensive dental rehabilitation may be needed to correct severe tooth crowding and unerupted and supernumerary teeth.

**Ectodermal dysplasias** are a heterogeneous group of conditions in which oral manifestations range from little or no involvement (the dentition is completely normal) to cases in which the teeth can be totally or partially absent or malformed (see [Chapter 690](#)). Because alveolar bone does not develop in the absence of teeth, the alveolar processes can be either totally or partially absent, and the resultant overclosure of the mandible causes the lips to protrude. Facial development is otherwise not disturbed. Teeth, when present, can range from normal to small and conical. If aplasia of the buccal and labial salivary glands is present, dryness and irritation of the oral mucosa can occur. People with ectodermal dysplasia might need partial or full dentures, even at a very young age. The vertical height between the jaws is thus restored, improving the position of the lips and facial contours, as well as restoring masticatory function.

**Pierre Robin syndrome** consists of micrognathia and is usually accompanied by a high arched or cleft palate ([Fig. 357.1](#)). The tongue is usually of normal size, but the floor of the mouth is foreshortened. The air passages can become obstructed, particularly on inspiration, usually requiring treatment to prevent suffocation. The infant should be maintained in a prone or partially prone position so that the tongue falls forward to relieve respiratory obstruction. Some patients require tracheostomy. Mandibular distraction procedures in the neonate can improve mandibular size, enhance respiration, and facilitate oral feedings.

Sufficient spontaneous mandibular growth can take place within a few months to relieve the potential airway obstruction. Often the growth of the mandible achieves a normal profile in 4–6 years. Of children with Pierre Robin syndrome, 30–50% have **Stickler syndrome** (types I–VI), an autosomal dominant condition that includes other findings such as prominent joints, arthritis, hypotonia, hypermobile joints, mitral valve prolapse, hearing loss, spine problems (scoliosis, kyphosis, platyspondyly), and ocular problems (high myopia, glaucoma, cataracts, retinal detachment). Symptoms may vary greatly even within a family. Pathogenic variants are noted in the genes that produce collagen (*COL2A1* in most; *COL11A1* in others) in many, but not all, patients with Stickler syndrome. Other syndromes are associated with Pierre Robin syndrome, including 22Q11.2 deletion syndrome (velocardiofacial syndrome).

**Mandibulofacial dysostosis** (Treacher Collins syndrome or Franceschetti syndrome) is an autosomal dominant syndrome that

primarily affects the face. The facial appearance varies but is characterized by downward-sloping palpebral fissures, colobomas of the lower eyelids, sunken cheekbones, blind fistulas opening between the angles of the mouth and the ears, malformed pinnae, atypical hair growth extending toward the cheeks, receding chin, and large mouth. Facial clefts, abnormalities of the ears, and deafness are common. The mandible is usually hypoplastic; the ramus may be deficient, and the coronoid and condylar processes are flat or even aplastic. The palatal vault may be either high or cleft. Dental malocclusions are common. The teeth may be missing, hypoplastic, or displaced or be in an open bite position. Initially, the primary concern is breathing and feeding problems. Surgery to restore normal structure of the face can be performed, which may include repair of cleft palate, zygomatic and orbit reconstruction, reconstruction of the lower eyelid, external ear reconstruction, and orthognathic surgery.

**Hemifacial microsomia** presentation can be quite variable but is usually characterized by unilateral hypoplasia of the mandible and can be associated with partial paralysis of the facial nerve, underdeveloped ear, and blind fistulas between the angles of the mouth and the ears. Severe facial asymmetry and malocclusion can develop because of the absence or hypoplasia of the mandibular condyle on the affected side. Congenital condylar deformity tends to increase with age. Early craniofacial surgery may be indicated to minimize the deformity. This disorder can be associated with ocular and vertebral anomalies (oculoauriculovertebral spectrum, including Goldenhar syndrome); therefore radiographs of the vertebrae and ribs should be considered to determine the extent of skeletal involvement.

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**Fig. 357.1** Pierre Robin syndrome. (From Clark DA. *Atlas of Neonatology*. 7th ed. Philadelphia: Saunders; 2000. p. 144.)

## Chapter 358

# Dental Caries

Vineet K. Dhar

### Etiology

The development of dental caries depends on interrelationships among the tooth surface, dietary carbohydrates, and specific oral bacteria. Organic acids produced by bacterial fermentation of dietary carbohydrates reduce the pH of dental plaque adjacent to the tooth to a point where demineralization occurs. The initial demineralization appears as an opaque **white spot lesion** on the enamel, and with progressive loss of tooth mineral, cavitation of the tooth occurs (Fig. 358.1).

The group of microorganisms, *Streptococcus mutans*, is the main bacteria associated with the development of dental caries. These bacteria have the ability to adhere to enamel, produce abundant acid, and survive at low pH. Once the enamel surface cavitates, other oral bacteria (lactobacilli) can colonize the tooth, produce acid, and foster further tooth demineralization. Demineralization from bacterial acid production is determined by the frequency of carbohydrate consumption and by the type of carbohydrate. Sucrose is the most cariogenic sugar because one of its by-products during bacterial metabolism is glucan, a polymer that enables bacteria to adhere more readily to tooth structures. Dietary behaviors, such as consuming sweetened beverages in a nursing bottle or frequently consuming sticky candies, increase the cariogenic potential of foods because of the long retention of sugar in the mouth.

### Epidemiology

As per the 2011–2012 National Health and Nutrition Examination Survey (NHANES), approximately 15% of children ranging from 2 to 8 years of age had one or more primary teeth affected by dental caries (Fig. 358.2). In the permanent dentition, over 10% of children age 12–15 years had dental caries and one fourth of children were affected by age 16–19 years (Fig. 358.3).

### Clinical Manifestations

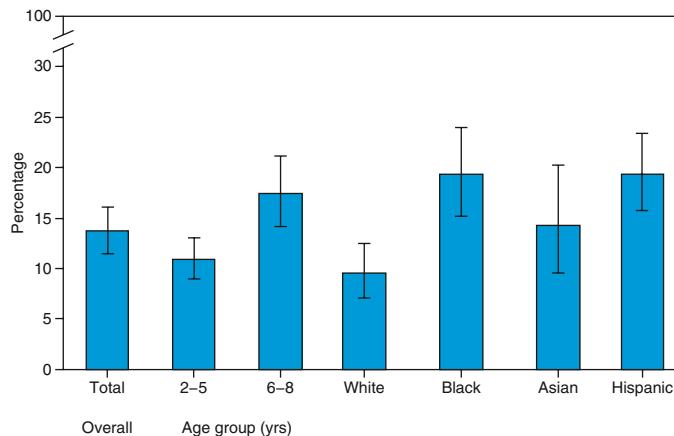
Dental caries of the primary dentition usually begins in the pits and fissures. Small lesions may be difficult to diagnose by visual inspection, but larger lesions are evident as darkened or cavitated lesions on the tooth surfaces (Fig. 358.4). Rampant dental caries in infants and toddlers, referred to as **early childhood caries**, is the result of early colonization of the child with cariogenic bacteria and the frequent ingestion of sugar, either in the bottle or in solid foods. The carious process in



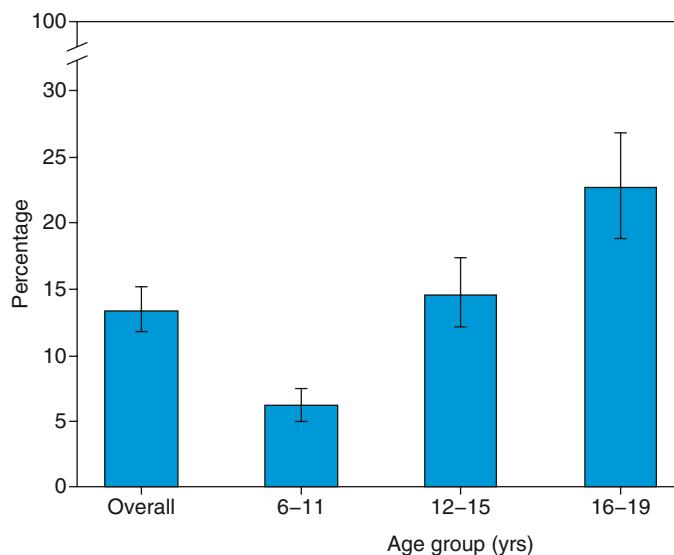
**Fig. 358.1** Initial carious lesions (white spot lesions) around the necks of the maxillary central incisors.

this situation is initiated earlier and consequently can affect the maxillary incisors first and then progress to the molars as they erupt.

The prevalence of untreated caries was significantly higher in children between 3 and 9 years of age living at or below 100% of federal poverty level compared with those above the poverty level. Along with



**Fig. 358.2** Prevalence\* of untreated dental caries† in primary teeth‡ among children age 2–8 yr, by age group, and race/Hispanic origin—National Health and Nutrition Examination Survey, 2011–2014. \*With 95% confidence intervals indicated with error bars. †Untreated dental caries is defined as tooth decay (dental cavities) that has not received appropriate treatment. Data were collected by dentists in the mobile examination center as part of the oral health component of the National Health and Nutrition Examination Survey. ‡Primary teeth are the first teeth (baby teeth), that are shed and replaced by permanent teeth. (From Centers for Disease Control and Prevention: Prevalence of untreated dental caries in primary teeth among children aged 2–8 years, by age group and race/Hispanic origin—National Health and Nutrition Examination Survey, 2011–2014. MMWR. 2017;66[9]:261.)



**Fig. 358.3** Prevalence\* of untreated dental caries† in permanent teeth among children and adolescents age 6–19 yr, by age group—National Health and Nutrition Examination Survey, United States, 2011–2014. \*With 95% confidence intervals indicated with error bars. †Untreated dental caries (i.e., dental cavities) are defined as tooth decay that has not received appropriate treatment. Data were collected by dentists in the mobile examination center as part of the oral health component of the National Health and Nutrition Examination Survey. (From Centers for Disease Control and Prevention: Prevalence of untreated dental caries in permanent teeth among children and adolescents aged 6–19 years, by age group—National Health and Nutrition Examination Survey, United States, 2011–2014. MMWR. 2017;66[1]:36.)



**Fig. 358.4** Rampant caries in a 3-yr-old child. Note darkened and cavitated lesions on the fissure surfaces of mandibular molars.

high frequency of sugar consumption and colonization with cariogenic bacteria, other enabling factors include low socioeconomic status of the family, other family members with carious teeth, recent immigrant status of the child, and the visual presence of dental plaque on the child's teeth. Children who develop caries at a young age are known to be at high risk for developing further caries as they get older. Therefore the appropriate prevention of early childhood caries can result in the elimination of major dental problems in toddlers and less decay in later childhood.

Among adolescents, the prevalence of dental caries was higher in age group 16–19 years (67%) compared with age group 12–15 years (50%). Overall, the caries experience did not significantly differ by race, Hispanic origin, and poverty levels.

### COMPLICATIONS

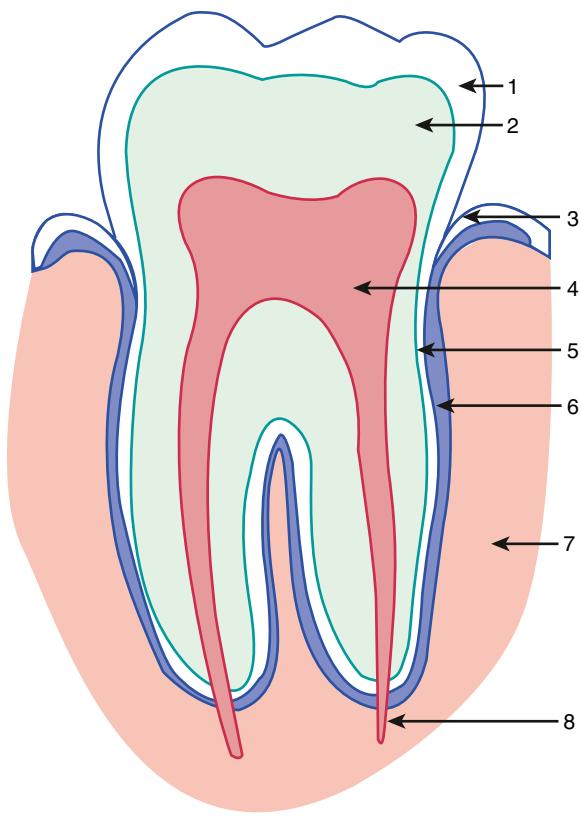
Left untreated, dental caries usually destroy most of the tooth and invade the dental pulp (Fig. 358.5), leading to an inflammation of the pulp (**pulpitis**) and significant pain. Pulpitis can progress to pulp necrosis, with bacterial invasion of the alveolar bone causing a **dental abscess** (Fig. 358.6). Red flags for serious spreading of dental infection are noted in Table 358.1. Infection of a primary tooth can disrupt normal development of the successor permanent tooth. In some cases, this process leads to spread of infection to other facial spaces (Fig. 358.7; Table 358.2).

### TREATMENT

The age at which dental caries occurs is important in dental management. Children younger than 3 years of age lack the developmental ability to cooperate with dental treatment and often require sedation or general anesthesia to repair carious teeth. After 4 years of age, children can generally cope with dental restorative care with the use of local anesthesia. Children with neurologic impairment or developmental delay may require general anesthesia for dental procedures at older ages.

Current evidence supports the use of a chronic disease management model to modify risk factors and manage dental caries. The disease management includes at-home strategies and in-office preventive, minimally invasive, and invasive interventions for treating dental caries. Minimally invasive strategies such as interim therapeutic restorations and silver diamine fluoride application can be used to arrest active carious lesions. Conventional dental treatment, using silver amalgam, plastic composite, or stainless steel crowns, can restore most teeth affected with dental caries. If caries involves the dental pulp, a partial removal of the pulp (pulpotomy) or complete removal of the pulp (pulpectomy) may be required. If a tooth requires extraction, a space maintainer may be indicated to prevent migration of teeth, which subsequently leads to malposition of permanent successor teeth.

Clinical management of the pain and infection associated with untreated dental caries varies with the extent of involvement and the medical status of the patient. Dental infection localized to the dentoalveolar unit can be managed by local measures (extraction, pulpectomy).



**Fig. 358.5** Basic dental anatomy: 1, enamel; 2, dentin; 3, gingival margin; 4, pulp; 5, cementum; 6, periodontal ligament; 7, alveolar bone; 8, neurovascular bundle.

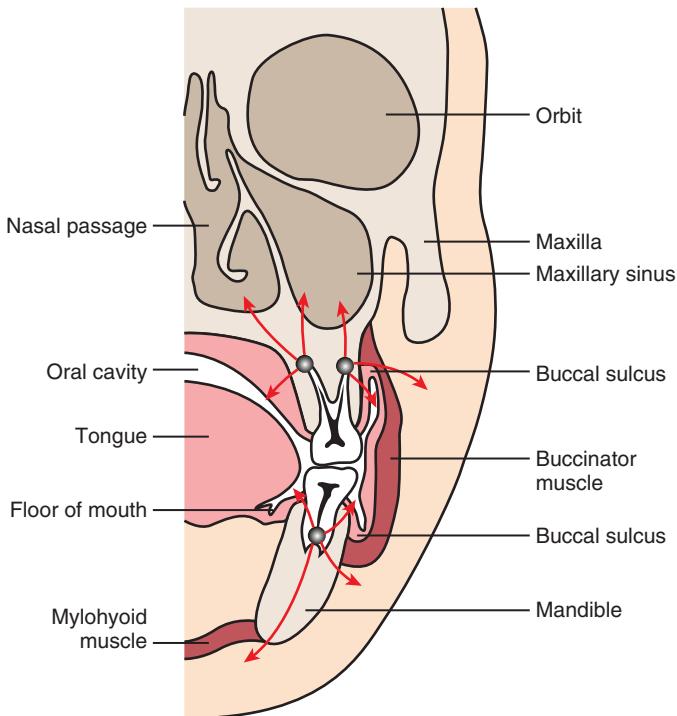


**Fig. 358.6** Facial swelling from an abscessed primary molar. Resolution of the inflammation can be achieved by a course of antibiotics, followed by either extraction or root canal of the offending tooth.

**Table 358.1** Red Flags Suggestive of a Spreading Dental Infection

- Pyrexia
- Tachycardia or tachypnea
- Trismus; may be relative due to pain or absolute due to a collection within the muscle causing muscle spasm in cases of masticator space involvement
- Raised tongue and floor of mouth, drooling
- Periorbital cellulitis
- Difficulty with speaking, swallowing, and breathing
- Hypotension
- Increased white blood cell count
- Lymphadenopathy
- Dehydration

From Robertson DP, Keys W, Rautemaa-Richardson R, et al. Management of severe acute dental infections. *BMJ*. 2015;350:h1300. Box 3, p. 151.



**Fig. 358.7** Spread of infection in the maxillofacial region is complicated by the variety of vital structures. Routes of spread are determined by fascial planes and this affects the presentation and management of each subdivision of cervicofacial infection. (From Robertson DP, Keys W, Rautemaa-Richardson R, et al. Management of severe acute dental infections. *BMJ*. 2015;350:h1300. Fig. 3, p. 151.)

Oral antibiotics are indicated for dental infections associated with fever, cellulitis, and facial swelling or if it is difficult to anesthetize the tooth in the presence of inflammation. Penicillin is the antibiotic of choice, except in patients with a history of allergy to this agent. Clindamycin and erythromycin are suitable alternatives. Oral analgesics, such as ibuprofen, are usually adequate for pain control.

**Table 358.2** Clinical Presentation of Odontogenic Infections by Location

TYPE OF INFECTION	CLINICAL PRESENTATION
Dentoalveolar	Swelling of the alveolar ridge with periodontal, periapical, and subperiosteal abscess
Submental space	Firm midline swelling beneath the chin; caused by infection from the mandibular incisors
Submandibular space	Swelling of the submandibular triangle of the neck around the angle of the mandible; caused by mandibular molar infections; trismus typical
Sublingual space	Swelling of the floor of the mouth with possible elevation of the tongue and dysphagia
Retropharyngeal space	Stiff neck, sore throat, dysphagia, raspy voice; caused by infections of the molars; infection of retropharyngeal space has a high potential to spread to the mediastinum
Buccal space	Swelling of the cheek; caused by infection of premolar or molar tooth
Masticator space	Swelling on either side of the mandibular ramus; caused by infection of the mandibular third molar; trismus present
Canine space	Swelling of the anterior cheek with loss of the nasolabial fold and possible extension to the infraorbital region

From Ogle OE. Odontogenic infections. *Dent Clin North Am*. 2017;61:235–252. Table 1.

## PREVENTION

Dental caries screening, risk assessment, and preventive management in young children need to be part of the scope of medical providers because children younger than 3 years of age often are not under the care of a dentist. Prevention of early childhood caries is critical because, if primary dental care is not initiated or does not succeed, teeth may develop dental caries requiring restorative care. Dental restorative care to treat caries in young children may require the use of sedation or general anesthesia with its associated high costs and possible health risks, and there is high recurrence of carious lesions once they develop.

Because they are seeing infants and toddlers on a periodicity schedule, physicians have an important role in screening children younger than 3 years of age for dental caries; providing preventive instructions; applying preventive measures, such as fluoride varnish; and referring the child to a dentist if problems exist.

## Fluoride

The most effective preventive measure against dental caries is communal water supplies with optimal fluoride content. Water fluoridation at the level of 0.7–1.2 mg fluoride per liter (ppm F) was introduced in the United States in the 1940s. Because fluoride from water supplies is now one of several sources of fluoride, the Department of Health and Human Services proposes to not have a fluoride range, but instead to limit the recommendation to the lower limit of 0.7 ppm F. The rationale is to balance the benefits of preventing dental caries with reducing the chance of fluorosis. Children who reside in areas with fluoride-deficient water supplies or who consume primarily bottled water, and are at risk for caries, benefit from dietary fluoride supplements (Table 358.3). If the patient

**Table 358.3** Supplemental Fluoride Dosage Schedule

AGE	FLUORIDE IN HOME WATER		
	<0.3 (PPM)	0.3-0.6 (PPM)	>0.6 (PPM)
6 mo-3 yr	0.25*	0	0
3-6 yr	0.50	0.25	0
6-16 yr	1.00	0.50	0

\*Milligrams of fluoride per day.

uses a private water supply, it is necessary to get the water tested for fluoride levels before prescribing fluoride supplements. To avoid potential overdoses, no fluoride prescription should be written for more than a total of 1 mg/day of fluoride. However, because of confusion regarding fluoride supplements among practitioners and parents, association of supplements with fluorosis, and lack of parent compliance with the daily administration, supplements may no longer be the first-line approach for preventing caries in preschool-age children.

Topical fluoride on a daily basis can be achieved by using fluoridated toothpaste. Supervised use of less than a *pea-sized* amount of toothpaste (approximately 0.25 g) on the toothbrush in children between 3 and 6 years of age reduces the risk of fluorosis. Children younger than 3 years of age should brush with less than a *smear* or *grain-sized* amount of fluoridated toothpaste. Professional topical fluoride applications performed semiannually reportedly reduce caries by approximately 30%. Fluoride varnish is ideal for professional applications in preschool children because of ease of use, even with non-dental health providers, and its safety because of single-dose dispensers. Products that are available come in containers of 0.25, 0.4, or 0.6 mL of varnish, corresponding to 5.6, 9.0, and 13.6 mg fluoride, respectively. Fluoride varnish should be administered twice a year for preschool children at moderate caries risk and 4 times a year for children at high caries risk.

### Oral Hygiene

Daily brushing, especially with fluoridated toothpaste, helps prevent dental caries. Most children younger than 8 years of age do not have the coordination required for adequate tooth brushing. Accordingly, parents should assume responsibility for the child's oral hygiene, with the degree of parental involvement appropriate to the child's changing abilities.

### Diet

Frequent consumption of sweetened fruit drinks is not generally recognized by parents for its high cariogenic potential. Consuming sweetened beverages in a nursing bottle or sippy cup should be discouraged and special efforts made to instruct parents that their child should consume sweetened beverages only at meal times and not exceed 6 oz/day.

### Dental Sealant

Plastic dental sealants have been shown to be effective in preventing caries on the pit and fissure of the primary and permanent molars. Sealants are most effective when placed soon after teeth erupt and used in children with deep grooves and fissures in the molar teeth. Sealants have been shown to reduce the incidence of caries by 85% over 7 years.

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## Chapter 359

# Periodontal Diseases

Vineet K. Dhar

The periodontium includes the gingiva, alveolar bone, cementum, and periodontal ligament (see Fig. 358.5).

### GINGIVITIS

Poor oral hygiene results in the accumulation of dental plaque at the tooth-gingival interface that activates an inflammatory response, expressed as localized or generalized reddening and swelling of the gingiva. More than half of American school children experience gingivitis. In severe cases, the gingiva spontaneously bleeds and there is oral malodor. With proper oral hygiene (careful tooth brushing and flossing) complete resolution can be expected. Fluctuations in hormonal levels during the onset of puberty can increase inflammatory responses to plaque. Gingivitis in healthy children is unlikely to progress to periodontitis (inflammation of the periodontal ligament resulting in loss of alveolar bone).

### AGGRESSIVE PERIODONTITIS IN CHILDREN (PREPUBERTAL PERIODONTITIS)

Periodontitis in children before puberty is a rare disease that often begins between the time of eruption of the primary teeth and the age of 4 or 5 years. The disease occurs in localized and generalized forms. There is rapid bone loss, often leading to premature loss of primary teeth. It is often associated with systemic problems, including neutropenia, leukocyte adhesion or migration defects, hypophosphatasia, Papillon-Lefèvre syndrome, leukemia, and Langerhans cell histiocytosis. However, in many cases, there is no apparent underlying medical problem. Nonetheless, diagnostic workups are necessary to rule out underlying systemic disease.

Treatment includes aggressive professional teeth cleaning, strategic extraction of affected teeth, and antibiotic therapy. There are few reports of long-term successful treatment to reverse bone loss surrounding primary teeth.

### AGGRESSIVE PERIODONTITIS IN ADOLESCENTS

Localized aggressive periodontitis (LAGP) in adolescents is characterized by rapid attachment and alveolar bone loss, on at least two first molars and incisors. Overall prevalence in the United States is <1%, but the prevalence among Black people is reportedly 2.5%. This form of periodontitis is associated with a strain of *Aggregatibacter* (*Actinobacillus*) bacteria. In addition, the neutrophils of patients with aggressive periodontitis can have chemotactic or phagocytic defects. If left untreated, affected teeth lose their attachment and can exfoliate. Treatment varies with the degree of involvement. Patients whose disease is diagnosed at onset are usually managed by surgical or nonsurgical debridement in conjunction with antibiotic therapy. Prognosis depends on the degree of initial involvement and compliance with therapy.

Generalized aggressive periodontitis (GAgP) occurs more in adolescents and young adults and is characterized by generalized interproximal attachment loss and bone loss, including three teeth that are not first molars and incisors.

### CYCLOSPORINE- OR PHENYTOIN-INDUCED GINGIVAL OVERGROWTH

The use of cyclosporine to suppress organ rejection or phenytoin for anticonvulsant therapy, and in some cases calcium channel blockers, is associated with generalized enlargement of the gingiva.

Phenytoin and its metabolites have a direct stimulatory action on gingival fibroblasts, resulting in accelerated synthesis of collagen. Phenytoin induces less gingival hyperplasia in patients who maintain meticulous oral hygiene.

Gingival hyperplasia occurs in 10–30% of patients treated with phenytoin. Severe manifestations can include gross enlargement of the gingiva, sometimes covering the teeth; edema and erythema of the gingiva; secondary infection, resulting in abscess formation; migration of teeth; and inhibition of exfoliation of primary teeth and subsequent impaction of permanent teeth. Treatment should be directed toward prevention and, if possible, discontinuation of cyclosporine or phenytoin. Patients undergoing long-term treatment with these drugs should receive frequent dental examinations and oral hygiene care. Severe forms of gingival overgrowth are treated by gingivectomy, but the lesion recurs if drug use is continued.

### ACUTE PERICORONITIS

Acute inflammation of the flap of gingiva that partially covers the crown of an incompletely erupted tooth is common in mandibular permanent molars. Accumulation of debris and bacteria between the gingival flap and tooth precipitates the inflammatory response. A variant of this condition is a gingival abscess caused by entrapment of bacteria because of orthodontic bands or crowns. Trismus and severe pain may be associated with the inflammation. Untreated cases can result in facial space infections and facial cellulitis.

Treatment includes local debridement and irrigation, warm saline rinses, and antibiotic therapy. When the acute phase has subsided, resection of the gingival flap prevents recurrence. Early recognition of the partial impaction of mandibular third molars and their subsequent extraction prevents these areas from developing pericoronitis.

### NECROTIZING PERIODONTAL DISEASE (ACUTE NECROTIZING ULCERATIVE GINGIVITIS)

Necrotizing periodontal disease, in the past sometimes referred to as “trench mouth,” is a distinct periodontal disease associated with oral spirochetes and fusobacteria. However, it is not clear whether bacteria initiate the disease or are secondary. It rarely develops in healthy children in developed countries, with a prevalence in the United States of <1%, but is seen more often in children and adolescents from developing areas of Africa, Asia, and South America. In certain African countries, where affected children usually have protein malnutrition, the lesion can extend into adjacent tissues, causing necrosis of facial structures (cancrum oris, or noma).

Clinical manifestations of necrotizing periodontal disease include necrosis and ulceration of gingiva between the teeth, an adherent grayish pseudomembrane over the affected gingiva, oral malodor, cervical lymphadenopathy, malaise, and fever. The condition may be mistaken for acute herpetic gingivostomatitis. Dark-field microscopy of debris obtained from necrotizing lesions demonstrates dense spirochete populations.

Treatment of necrotizing periodontal disease is divided into an acute management with local debridement, oxygenating agents (direct application of 10% carbamide peroxide in anhydrous glycerol qid), and analgesics. Dramatic resolution usually occurs within 48 hours. If a patient is febrile, antibiotics (penicillin or metronidazole) may be an important adjunctive therapy. A second phase of treatment may be necessary if the acute phase of the disease has caused irreversible morphologic damage to the periodontium. The disease is not contagious.

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## Chapter 360

# Dental Trauma

Vineet K. Dhar

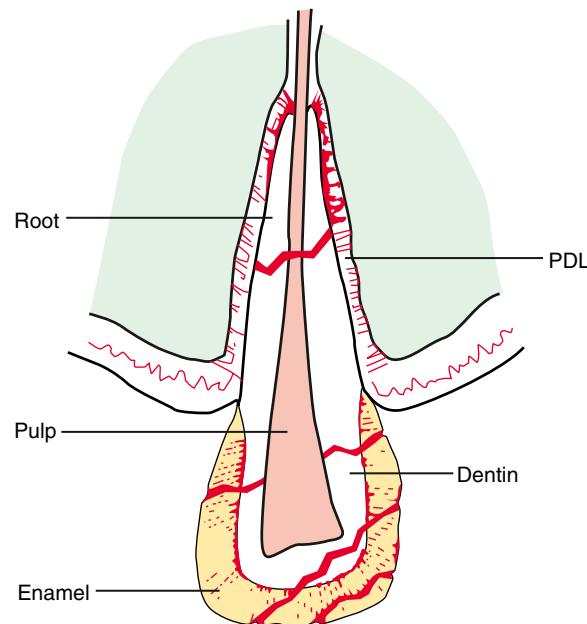
Traumatic oral injuries may be categorized into three groups: injuries to teeth, injuries to soft tissue (contusions, abrasions, lacerations, punctures, avulsions, and burns), and injuries to jaw (mandibular and/or maxillary fractures).

### INJURIES TO TEETH

Approximately 10% of children between 18 months and 18 years of age sustain significant tooth trauma. Oral injuries are second most common, covering 18% of all somatic injuries in the age-group 0–6 years. Among oral injuries, injuries to teeth are most common, followed by soft tissue injuries. There appear to be three age periods of greatest predilection: toddlers (1–3 years), usually from falls or child abuse; school-age children (7–10 years), usually from bicycle and playground accidents; and adolescents (16–18 years), often the result of fights, athletic injuries, and automobile accidents. Injuries to teeth are more common among children with protruding front teeth. Children with craniofacial abnormalities or neuromuscular deficits are also at increased risk for dental injury. Injuries to teeth can involve the hard dental tissues, the dental pulp (nerve), and injuries to the periodontal structure (surrounding bone and attachment apparatus) (Fig. 360.1; Table 360.1).

Fractures of teeth may be uncomplicated (confined to the hard dental tissues) or complicated (involving the pulp). Exposure of the pulp results in its bacterial contamination, which can lead to infection and pulp necrosis. Such pulp exposure complicates therapy and can lower the likelihood of a favorable outcome.

The teeth most often affected are the maxillary incisors. Uncomplicated crown fractures are treated by covering exposed dentin and by



**Fig. 360.1** Tooth fractures can involve enamel, dentin, or pulp and can occur in the crown or root of a tooth. PDL, Periodontal ligament. (From Pinkham JR. Pediatric Dentistry: Infancy Through Adolescence. Philadelphia: Saunders; 1988. p. 172.)

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## Chapter 360

# Dental Trauma

Vineet K. Dhar

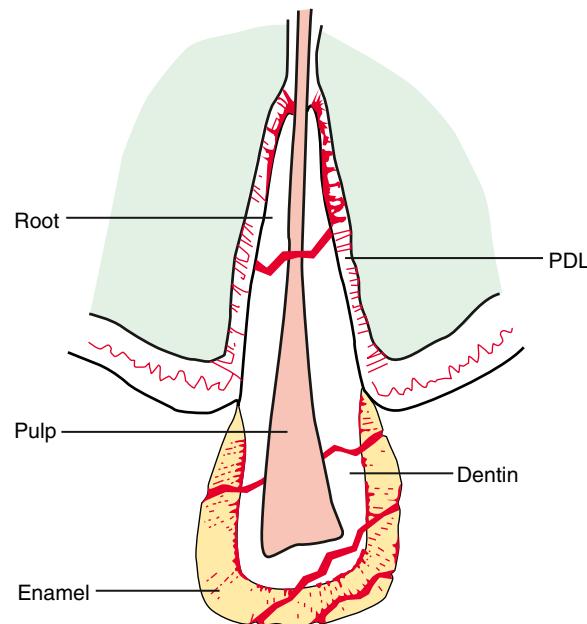
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**Table 360.1** Injuries to Crowns of Teeth

TYPE OF TRAUMA	DESCRIPTION	TREATMENT AND REFERRAL
Enamel infraction (crazing)	Incomplete fracture of enamel without loss of tooth structure	Initially might not require therapy but should be assessed periodically by dentist
Enamel fractures	Fracture of only the tooth enamel	Tooth may be smoothed or treated to replace fragment
Enamel and dentin fracture	Fracture of enamel and dentinal layer of the tooth. Tooth may be sensitive to cold or air. Pulp may become necrotic, leading to periapical abscess	Refer as soon as possible. Area should be treated to preserve the integrity of the underlying pulp
Enamel, dentin fracture involving the pulp	Bacterial contamination can lead to pulpal necrosis and periapical abscess. The tooth might have the appearance of bleeding or might display a small red spot	Refer immediately. The dental therapy of choice depends on the extent of injury, the condition of the pulp, the development of the tooth, time elapsed from injury, and any other injuries to the supporting structures. Therapy is directed toward minimizing contamination in an effort to improve the prognosis

From Josell SD, Abrams RG. Managing common dental problems and emergencies. *Pediatr Clin North Am.* 1991;38:1325–1342.

placing an aesthetic restoration. Complicated crown fractures involving the tooth pulp usually require **endodontic therapy** (root canal). Crown-root fractures and root fractures usually require extensive dental therapy. Such injuries in the primary dentition can interfere with normal development of the permanent dentition; therefore significant injuries of the primary incisor teeth are usually managed by extraction.

Traumatic oral injuries should be referred to a dentist as soon as possible. Even when the teeth appear intact, a dentist should promptly evaluate the patient. Baseline data (radiographs, mobility patterns, responses to specific stimuli) enable the dentist to assess the likelihood of future complications.

### INJURIES TO PERIODONTAL STRUCTURES

Trauma to teeth with associated injury to periodontal structures that hold the teeth usually manifests as mobile or displaced teeth. Categories of trauma to the periodontium include concussion, subluxation, intrusive luxation, extrusive luxation, and avulsion.

#### Concussion

Injuries that produce minor damage to the periodontal ligament are termed *concussions*. Teeth sustaining such injuries are not mobile or displaced but react markedly to percussion (gentle hitting of the tooth with an instrument). This type of injury usually requires no therapy and resolves without complication. Primary incisors that sustain concussion can change color, which may indicate pulpal degeneration and should be evaluated by a dentist.

#### Subluxation

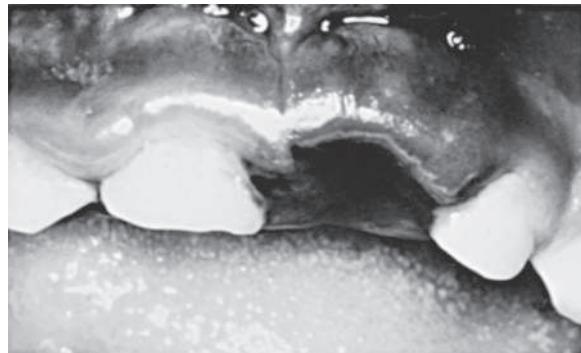
Subluxated teeth exhibit mild to moderate horizontal mobility and/or vertical mobility. Hemorrhage is usually evident around the neck of the tooth at the gingival margin. There is no displacement of the tooth. Many subluxated teeth need to be immobilized by splints to ensure adequate repair of the periodontal ligament. Some of these teeth develop pulp necrosis.

#### Intrusion

Intruded teeth are pushed up into their socket, sometimes to the point where they are not clinically visible. Intruded primary incisors can give the false appearance of being avulsed (knocked out). To rule out avulsion, a dental radiograph is indicated (Figs. 360.2 and 360.3). Intruded primary teeth are usually monitored for spontaneous repositioning or re-eruption. Depending on the severity, the intruded permanent teeth may be monitored for re-eruption or repositioned surgically or orthodontically. Some of these teeth develop pulp necrosis and infection requiring further management.

#### Extrusion

Extrusion injury is characterized by displacement of the tooth from its socket. The tooth is usually displaced to the lingual (tongue) side, with fracture of the wall of the alveolar socket. These teeth need immediate treatment; the longer the delay, the more likely the



**Fig. 360.2** Intruded primary incisor that appears avulsed (knocked out).



**Fig. 360.3** Occlusal radiograph documents intrusion of “missing tooth” presented in Figure 360.2.

tooth will be fixed in its displaced position. Therapy is directed at reduction (repositioning the tooth) and fixation (splinting). The pulp of such teeth often becomes necrotic and requires endodontic therapy. Extrusive luxation in the primary dentition is usually managed by extraction because complications of reduction and fixation can result in problems with development of permanent teeth.

#### Avulsion

If avulsed permanent teeth are replanted as soon as possible after injury, there is a good chance that normal reattachment will follow and the tooth will have a good prognosis. However, if the tooth is in a dry environment for longer than 1 hour, the ligament that holds the tooth in place has little chance for survival and failure (root resorption, ankylosis) is common. Parents confronted with this emergency situation can be instructed to do the following:

- Find the tooth.
- Briefly rinse the tooth. (Do not scrub the tooth. Do not touch the root. After plugging the sink drain, hold the tooth by the crown and rinse it under running tap water.)
- Insert the tooth into the socket. (Gently place it back into its normal position. Do not be concerned if the tooth extrudes slightly. If the parent or child is too apprehensive for replantation of the tooth, the tooth should be placed in cold cow's milk or other cold isotonic solution.)
- Go directly to the dentist. (In transit, the child should hold the tooth in its socket with a finger. The parent should place the child in an age-appropriate child seat, buckle a seatbelt around the child, and drive safely.)

After the tooth is replanted, it must be immobilized to facilitate reattachment; endodontic therapy is always required. The initial signs of complications associated with replantation can appear as early as 1 week after trauma or as late as several years later. Close dental follow-up is indicated for at least 1 year.

## PREVENTION

To minimize the likelihood of dental injuries:

- Every child or adolescent who engages in contact sports should wear a **mouth guard**, which may be constructed by a dentist or purchased at any athletic goods store.
- Helmets with face guards should be worn by children or adolescents with neuromuscular problems or seizure disorders to protect the head and face during falls.
- Helmets should also be used during biking, skiing, skating, and skateboarding.
- All children or adolescents with protruding incisors should be evaluated by a pediatric dentist or orthodontist.

## ADDITIONAL CONSIDERATIONS

Children who experience dental trauma might also have sustained head or neck trauma, and therefore, neurologic assessment is warranted. Tetanus prophylaxis should be considered with any injury that disrupts the integrity of the oral tissues. The possibility of child abuse should always be considered.

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## Chapter 361

# Common Lesions of the Oral Soft Tissues

Vineet K. Dhar

## OROPHARYNGEAL CANDIDIASIS

Oropharyngeal infection with *Candida albicans* (thrush, moniliasis) (see Chapter 280.1) is common in neonates from contact with the organism in the birth canal or contact with the breast during breastfeeding. The lesions of oropharyngeal candidiasis (OPC) appear as white plaques covering all or part of the oropharyngeal mucosa. These plaques are removable from the underlying surface, which is characteristically inflamed and has pinpoint hemorrhages. The diagnosis is confirmed by direct microscopic examination on potassium hydroxide smears and culture of scrapings from lesions. OPC is usually

self-limited in the healthy newborn infant, but topical application of nystatin to the oral cavity of the baby and to the nipples of breastfeeding mothers will hasten recovery.

OPC is also a major problem during myelosuppressive therapy. **Systemic candidiasis**, a major cause of morbidity and mortality during myelosuppressive therapy, develops almost exclusively in patients who have had prior oropharyngeal, esophageal, or intestinal candidiasis. This observation implies that prevention of OPC should reduce the incidence of systemic candidiasis. The use of oral rinses of 0.2% chlorhexidine gluconate solution along with systemic antifungals may be effective in preventing OPC, systemic candidiasis, or candidal esophagitis.

## APHTHOUS ULCERS

The aphthous ulcer (canker sore) is a distinct oral lesion (Fig. 361.1), prone to recurrence; Table 361.1 notes the differential diagnosis. Aphthous ulcers are reported to develop in 20% of the population. Their etiology is unclear, but allergic or immunologic reactions, emotional stress, genetics, and injury to the soft tissues in the mouth have been implicated. Aphthous-like lesions may be associated with inflammatory bowel disease, Behcet disease, gluten-sensitive enteropathy, periodic fever-aphthae-pharyngitis-adenitis syndrome, Sweet syndrome, HIV infection (especially if ulcers are large and slow to heal), and cyclic neutropenia (see Table 361.1). Clinically, these ulcers are characterized by well-circumscribed, ulcerative lesions with a white necrotic base surrounded by a red halo. The lesions generally last 10–14 days and heal without scarring. Nonprescription palliative therapies, such as benzocaine and topical lidocaine, are effective, as are topical steroids. Use of soft tissue dental lasers may help manage aphthous ulcers by accelerating wound healing and reducing pain. Tetracycline is beneficial with severe outbreaks, but caution is necessary in pregnant women, because it is classified as U.S. Food and Drug Administration (FDA) pregnancy category D. In younger children ( $\leq 8$  years), tetracycline can affect developing teeth and cause permanent staining of the teeth.

## HERPETIC GINGIVOSTOMATITIS

After an initial incubation period of approximately 1 week, the primary infection with herpes simplex virus manifests as fever and malaise, usually in a child younger than 5 years (see Chapter 299). The oral cavity can show various expressions, including the gingiva becoming erythematous, mucosal hemorrhages, and clusters of small vesicles erupting throughout the mouth. There is often involvement of the mucocutaneous margin and perioral skin (Fig. 361.2). The oral symptoms generally are accompanied by fever, lymphadenopathy, and difficulty eating and drinking. The symptoms usually regress within 2 weeks without scarring. Fluids should be encouraged because the child may become dehydrated. Analgesics and anesthetic rinses can make



**Fig. 361.1** Major aphthous in a child. (From Gürkan A, Özlü SG, Altıaylık-Özer P, et al. Recurrent aphthous stomatitis in childhood and adolescence: a single-center experience. *Pediatr Dermatol*. 2015;32[4]:476–480. Fig. 1.)

**Table 361.1** Differential Diagnosis of Oral Ulceration

CONDITION	COMMENT
<b>COMMON</b>	
Aphthous ulcers (canker sores)	Painful circumscribed lesions; recurrences
Traumatic ulcers	Accidents, chronic cheek biter, after dental local anesthesia
Hand, foot, and mouth disease	Painful; lesions on tongue, anterior oral cavity, hands, and feet
Herpangina	Painful; lesions confined to soft palate and oropharynx
Herpetic gingivostomatitis	Vesicles on mucocutaneous borders; painful, febrile
Recurrent herpes labialis	Vesicles on lips; painful
Chemical burns	Alkali, acid, aspirin; painful
Heat burns	Hot food, electrical
Medicine effect	NSAIDs, methotrexate, azathioprine, enalapril, losartan, fluoxetine, antiretroviral agents
RIME	Mycoplasma and other agents; predominant oral ulcerations with scattered cutaneous lesions
<b>UNCOMMON</b>	
Neutrophil defects	Agranulocytosis, leukemia, cyclic neutropenia; painful
Systemic lupus erythematosus	Recurrent; may be painless
Behçet syndrome	Resembles aphthous lesions; associated with genital ulcers, uveitis
Necrotizing ulcerative gingivostomatitis	Vincent stomatitis; painful
Syphilis	Chancre or gumma; painless
Oral Crohn disease	Aphthous-like; painful
Histoplasmosis	Lingual
Pemphigus	May be isolated to the oral cavity
Stevens-Johnson syndrome	May be isolated to or appear initially in the oral cavity

NSAIDs, Nonsteroidal antiinflammatory drugs; RIME, reactive infectious mucocutaneous eruption.



**Fig. 361.2** Herpetic gingivostomatitis. Lip erosions with multiple periorificial herpetic lesions involving the mucocutaneous borders. (From Paller AS, Mancini AJ, eds. Hurwitz Clinical Pediatric Dermatology. 3rd ed. Philadelphia: Saunders; 2006. p. 398.)

the child more comfortable. Oral valacyclovir, if taken within the first 3 days of symptoms in immunocompetent patients, is beneficial in shortening the duration of symptoms. Caution should be exercised to prevent autoinoculation, especially of the eyes.

### RECURRENT HERPES LABIALIS

Approximately 90% of the worldwide population develops antibodies to herpes simplex virus. In periods of quiescence, the virus is thought to remain latent in sensory neurons. Unlike primary herpetic gingivostomatitis, which manifests as multiple painful vesicles on the lips, tongue, palate, gingiva, and mucosa, recurrent herpes is generally limited to the lips. Other than the annoyance of causing pain and being a cosmetic issue, recurrent episodes generally do not involve systemic symptoms. Reactivation of the virus is thought to be the result of exposure to ultraviolet light, tissue trauma, stress, or fevers. There is little advantage of antiviral therapy over palliative therapies in an otherwise healthy patient affected by recurrent herpes.

### PARULIS

The parulis (gum boil) is a soft reddish papule located adjacent to the root of a chronically abscessed tooth. It occurs at the end-point of a draining dental sinus tract. Treatment consists of diagnosing which tooth is abscessed and extracting it or performing root canal treatment on the offending tooth.

### CHEILITIS

Cheilitis, dryness of the lips followed by scaling and cracking and accompanied by a characteristic burning sensation, is common in children. Cheilitis may be caused by sensitivity to contact substances, lip licking, vitamin deficiency, weakened immune system, or fungal or bacterial infections, and often occurs in association with fever. Treatment may include antifungal or antibacterial agents and frequent application of petroleum jelly.

### ANKYLOGLOSSIA

Ankyloglossia, or tongue-tie, is characterized by an abnormally short lingual frenum that can hinder the tongue movement, but rarely interferes with feeding or speech. It is possible that the frenum could spontaneously lengthen as the child gets older. If, in the rare event that the extent of the ankyloglossia is severe, speech may be affected and surgical correction may be indicated.

### GEOGRAPHIC TONGUE

Geographic tongue (migratory glossitis) is a benign and asymptomatic lesion that is characterized by one or more smooth bright red patches, often showing a yellow, gray, or white membranous margin on the dorsum of an otherwise normally roughened tongue. The condition has no known cause, and no treatment is indicated (see Chapter 705).

### FISSURED TONGUE

The fissured tongue (scrotal tongue) is a malformation manifested clinically by numerous small furrows or grooves on the dorsal surface (see Chapter 705). If the tongue is painful, brushing the tongue or irrigating with water can reduce the bacteria in the fissures.

### DEVELOPMENTAL (NORMAL) VARIATIONS

#### Bohn Nodules

Bohn nodules are small developmental anomalies located along the buccal and lingual aspects of the mandibular and maxillary ridges and in the hard palate of the neonate. These lesions arise from remnants of mucous gland tissue. Treatment is not necessary as the nodules usually disappear within a few weeks.

#### Dental Lamina Cysts

Dental lamina cysts are small cystic lesions located along the crest of the mandibular and maxillary ridges of the neonate. These lesions arise from epithelial remnants of the dental lamina. Treatment is not necessary; they disappear within a few weeks.

### Epstein Pearls

Epstein pearls are small developmental lesions located in the median palatal raphe region due to entrapment of epithelial remnants along the line of fusion of the palatal halves. Treatment is not necessary, as these slough off on their own within a few weeks.

### Fordyce Granules

Fordyce granules are common and almost 80% of adults have these yellow-white granules in clusters or plaquelike areas on the oral mucosa, most commonly on the buccal mucosa or lips. They are aberrant sebaceous glands. The glands are present at birth, but they can undergo hypertrophy and first appear as discrete yellowish papules during the preadolescent period in approximately 50% of children. No treatment is necessary.

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## Chapter 362

# Diseases of the Salivary Glands and Jaws

Vineet K. Dhar

With the exception of mumps (see Chapter 295), diseases of the salivary glands are rare in children. Bilateral enlargement of the submaxillary glands can occur in HIV/AIDS, cystic fibrosis, Epstein-Barr virus infection, malnutrition, COVID-19, and transiently during acute asthmatic attacks. Chronic vomiting can be accompanied by enlargement of the parotid glands. Benign salivary gland hypertrophy has been associated with endocrinopathies: thyroid disease, diabetes, and Cushing syndrome. Infiltrative disease or tumors are uncommon; red flags include facial nerve palsy, rapid growth, fixed skin, paresthesias, ulceration, or a history of radiation to the head or neck region.

### PAROTITIS

**Acute parotitis** is often caused by blockage, with further inflammation due to bacterial infection. The blockage may be due to a salivary stone or mucus plug. Stones can be removed by physical manipulation, surgery, or lithotripsy. **Recurrent parotitis** is an idiopathic swelling of the parotid gland that can occur in otherwise healthy children. The swelling is usually unilateral, but both glands can be involved simultaneously or alternately. There is little pain; the swelling is limited to the gland and usually lasts 2-3 weeks. Treatment may include local heat, massaging the gland, and antibiotics. **Suppurative parotitis** is usually caused by *Staphylococcus aureus*. It is usually unilateral and may be accompanied by fever. The gland becomes swollen, tender, and painful. Suppurative parotitis responds to antibacterial therapy based on

culture obtained from the Stensen duct or by surgical drainage. Viral causes of parotitis include mumps (often in epidemics), Epstein-Barr virus, human herpesvirus 6, enteroviruses, COVID-19, and HIV.

### RANULA

A ranula is a cyst associated with a major salivary gland in the sublingual area. It is a large, soft, mucus-containing swelling in the floor of the mouth. It occurs at any age, including infancy. The cyst should be excised, and the severed duct should be exteriorized.

### MUCOCELE

Mucocele is a salivary gland lesion caused by a blockage of a salivary gland duct. It is most common on the lower lip and has the appearance of a fluid-filled vesicle, or a fluctuant nodule with the overlying mucosa being normal in color. Treatment is surgical excision, with removal of the involved accessory salivary gland.

### CONGENITAL LIP PITS

Congenital lip pits are caused by fistulous tracts that lead to embedded mucous glands in the lower lip. They leak saliva, especially with salivary stimulation. Lip pits can be isolated anomalies, or they can be found in patients with cleft lip or palate. Treatment is surgical excision of the glandular tissue.

### ERUPTION CYST

Eruption cyst is a smooth painless swelling over the erupting tooth. If bleeding occurs in the cyst space, it may appear blue or blue-black. In most cases, no treatment is indicated, and the cyst resolves with the full eruption of the tooth.

### XEROSTOMIA

Also known as *dry mouth*, xerostomia may be associated with fever, dehydration, anticholinergic drugs, chronic graft-versus-host disease, Mikulicz disease (leukemic infiltrates), Sjögren syndrome, or tumoricidal doses of radiation when the salivary glands are within the field. Long-term xerostomia is a high-risk factor for dental caries.

### SALIVARY GLAND TUMORS

See Chapter 549.

### HISTIOCYTIC DISORDERS

See Chapter 556.

### TUMORS OF THE JAW

**Ossifying fibroma** is a common benign tumor of the jaw. It is often asymptomatic and is usually discovered on routine radiographic examinations. Treatment is resection due to the possibility of recurrence. **Central giant cell granuloma** is another common lesion thought to be reactive, rather than neoplastic. Although usually asymptomatic, it can be expansile, with or without resorption of the roots of teeth and perforation of the cortical plate. Treatment is complete curettage or surgical excision. **Dentigerous cysts** are common lesions associated with the crown of an impacted or unerupted tooth. Although usually asymptomatic, they can become large and destructive. Treatment is surgical removal.

The malignant primary tumors of the jaw in children include Burkitt lymphoma, osteogenic sarcoma, lymphosarcoma, ameloblastoma, and, more rarely, fibrosarcoma.

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## Chapter 363

# Diagnostic Radiology in Dental Assessment

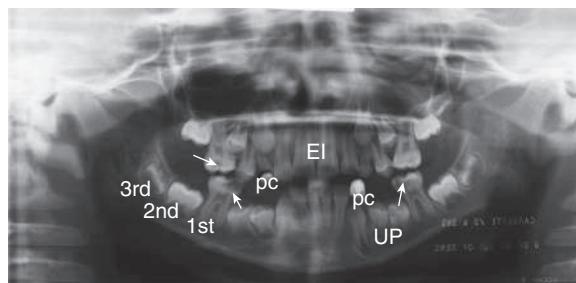
Vineet K. Dhar

Diagnostic dental radiology in children follows the as low as reasonably achievable (ALARA) principle. In children, intraoral radiographs such as bitewings and select periapical radiographs are taken during routine dental visits and repeated every 6 months to 2 years based on the caries risk assessment. Additional radiographs such as panoramic views, cephalometric radiographs, and dental cone beam computed tomography (CBCT) are taken when indicated. In general, the cumulative radiation exposure due to routine dental radiographs is minimal. In addition, precautions such as use of high-speed film, collimated beam, protective aprons and thyroid collars, proper technique, and minimizing number of exposures are all taken to keep radiation exposure minimal.

**Intraoral dental radiographs** are highly detailed, direct-exposure films that demonstrate sections of the child's teeth and supporting bone structures. The film or image receptor is placed lingual to the teeth, and the x-ray beam is directed through the teeth and supporting structures. The resulting images are used to detect dental caries, loss of alveolar bone (periodontal disease), abscesses at the roots of the teeth, and trauma to the teeth and alveolar bone. These radiographs are also used to demonstrate the developmental status of permanent teeth within the bone.

The **panoramic radiograph** provides a single tomographic image of the upper and lower jaw, including all teeth and supporting structures. The x-ray tube rotates about the patient's head with reciprocal movement of the film or image receptor during the exposure. The panoramic image shows the teeth, mandibular bodies, rami, and condyles; maxillary sinuses; and a majority of the facial buttresses. Such images are used to show abnormalities of tooth number, development and eruption pattern, cystic and neoplastic lesions, bone infections, and fracture, as well as dental caries and periodontal disease (Fig. 363.1).

**Cephalometric radiographs** are posteroanterior and lateral skull films that are taken using a **cephalostat** (head positioner) and employ techniques that clearly demonstrate the facial skeleton and soft facial tissues. Similar protocols for positioning children are used throughout the world. From these images, cranial and facial points and planes can be determined and compared with standards derived from thousands of images. A child's facial growth can be assessed serially when cephalometric radiographs are taken sequentially. Relationships among the maxilla, mandible, cranial base, and facial skeleton can be determined in a quantitative manner. Additionally, the alignment of the teeth and the relation of the teeth to the supporting bone can be serially measured.



**Fig. 363.1** A panoramic radiograph of a 10-yr-old child showing extensive dental caries of the first permanent molars (arrows), as well as normal structures: erupted first permanent molar, unerupted second molar, and unerupted third molar. EI, Erupted incisors; UP, unerupted premolars; pc, erupted primary canines.

**Dental CBCT** is a variation of traditional CT, used mainly to evaluate oral and maxillofacial regions and teeth. Dental CBCT generally delivers lower radiation exposure than traditional CT, but higher than conventional dental radiography. There are several indications for CBCT, such as evaluation of oral-maxillofacial pathologies, diagnosis of dental trauma, endodontic treatment, visualization of abnormal teeth, orthodontic assessment, or cleft palate assessment, among others.

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## Section 3

# The Esophagus

## Chapter 364

# Embryology, Anatomy, and Function of the Esophagus

Seema Khan and Sravan Kumar Reddy Matta

The esophagus is a hollow muscular tube, separated from the pharynx above and the stomach below by two tonically closed sphincters. Its primary function is to convey ingested material from the mouth to the stomach. Largely lacking digestive glands and enzymes, and exposed only briefly to nutrients, it has no active role in digestion.

## EMBRYOLOGY

The esophagus develops from the postpharyngeal foregut and can be distinguished from the stomach in the 4-week-old embryo. At the same time, the trachea begins to bud just anterior to the developing esophagus; the resulting laryngotracheal groove extends and becomes the lung. Disturbance of this stage can result in congenital anomalies such as **tracheoesophageal fistula** (see Chapter 365). The length of the esophagus is 8–10 cm at birth and doubles in the first 2–3 years of life, reaching approximately 25 cm in the adult. The abdominal portion of the esophagus is as large as the stomach in an 8-week-old fetus but gradually shortens to a few millimeters at birth, attaining a final length of approximately 3 cm by a few years of age. This intraabdominal location of both the distal esophagus and the **lower esophageal sphincter** (LES) is an important antireflux mechanism because an increase in intraabdominal pressure is also transmitted to the sphincter, augmenting its defense. Swallowing can be seen in utero as early as 16–20 weeks of gestation, helping to circulate the amniotic fluid; **polyhydramnios** is a hallmark of lack of normal swallowing or of esophageal or upper gastrointestinal tract obstruction. Sucking and swallowing are not fully coordinated before 34 weeks of gestation, a contributing factor for feeding difficulties in premature infants.

## ANATOMY

The luminal aspect of the esophagus is covered by thick, protective, non-keratinized stratified squamous epithelium, which abruptly changes to simple columnar epithelium at the stomach's upper margin at the **gastroesophageal junction (GEJ)**. This squamous epithelium is relatively

## Chapter 363

# Diagnostic Radiology in Dental Assessment

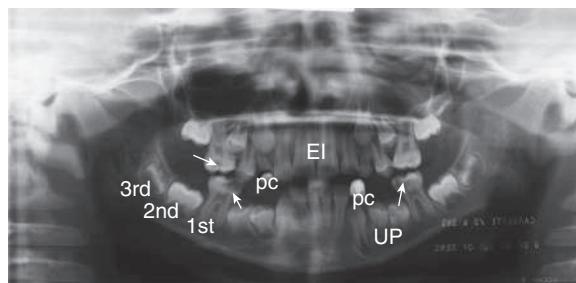
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## ANATOMY

The luminal aspect of the esophagus is covered by thick, protective, non-keratinized stratified squamous epithelium, which abruptly changes to simple columnar epithelium at the stomach's upper margin at the **gastroesophageal junction (GEJ)**. This squamous epithelium is relatively

resistant to damage by gastric secretions, in contrast to the ciliated columnar epithelium of the respiratory tract. However, chronic irritation by gastric contents can result in morphometric changes such as thickening of the basal cell layer and lengthening of papillary ingrowth into the epithelium, and subsequent metaplasia of the cells lining the lower esophagus from squamous to columnar. Deeper layers of the esophageal wall are composed successively of lamina propria, muscularis mucosae, submucosa, and the two layers of muscularis propria (circular surrounded by longitudinal). The two delimiting sphincters of the esophagus, the **upper esophageal sphincter (UES)** at the crico-pharyngeus muscle and the **LES** at the **GEJ**, constrict the esophageal lumen at its proximal and distal boundaries. The muscularis propria of the upper third of the esophagus is predominantly striated, and that of the lower two-thirds is smooth muscle. Clinical conditions involving striated muscle (cricopharyngeal dysfunction, cerebral palsy) affect the upper esophagus, whereas those involving smooth muscle (achalasia, reflux esophagitis) affect the lower esophagus. The muscular LES and the mucosal "Z-line" of the GEJ may be discrepant up to several centimeters.

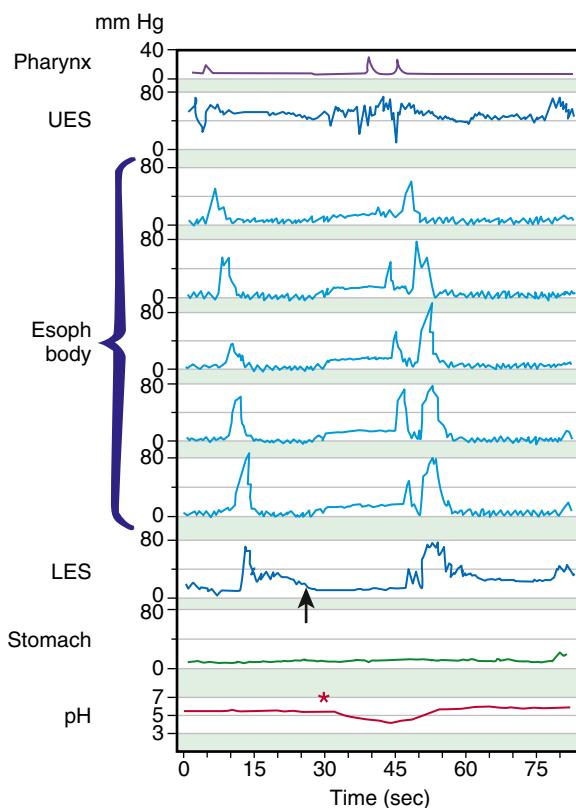
## FUNCTION

The esophagus can be divided into three areas: the UES, the esophageal body, and the LES. At rest, the tonic LES pressure is normally approximately 20 mm Hg; values <10 mm Hg are usually considered abnormal, although it seems that competence against retrograde flow of gastric material is maintained if the LES pressure is >5 mm Hg. The LES pressure rises during intragastric pressure amplifications, whether caused by gastric contractions, abdominal wall muscle contractions ("straining"), or external pressure applied to the abdominal wall. It also rises in response to cholinergic stimuli, gastrin, gastric alkalization, and certain drugs (bethanechol, metoclopramide, cisapride). The UES pressure is more variable and often higher than that of the LES; it decreases almost to zero during deep sleep and it increases markedly during stress and straining. The UES and LES relax briefly to allow material to pass through during swallowing, belching, reflux, and vomiting. They can contract in response to subthreshold levels of reflux (esophagoglottal closure reflex).

**Swallowing** is initiated by elevation of the tongue, propelling the bolus into the pharynx. The larynx elevates and moves anteriorly, pulling open the relaxing UES, while the opposed aryepiglottic folds close. The epiglottis drops back to cover the larynx and direct the bolus over the larynx and into the UES. The soft palate occludes the nasopharynx. The primary peristalsis thus initiated is a contraction originating in the oropharynx that clears the esophagus aborally (Fig. 364.1). Oropharyngeal swallowing related dysfunction may occur at multiple levels (Table 364.1). The LES, tonically contracted as a barrier against gastroesophageal reflux (GER), relaxes as swallowing is initiated, at nearly the same time as the UES relaxation. The LES relaxation persists considerably longer, until the peristaltic wave traverses it and closes it. The normal esophageal peristaltic speed is approximately 3 cm/sec; the wave takes 4 sec or longer to traverse the 12-cm esophagus of a young infant and considerably longer in a larger child. Facial stimulation by a puff of air can induce swallowing and esophageal peristalsis in healthy young infants, a reflex termed the **Santmyer swallow**.

In addition to relaxing to move swallowed material past the GEJ into the stomach, the LES normally relaxes to vent swallowed air or to allow retrograde expulsion of material from the stomach. Perhaps as an extension of these functions, the normal LES also permits physiologic reflux episodes, brief events that occur approximately five times in the first postprandial hour, particularly in the awake state, but are otherwise uncommon. **Transient LES relaxation**, not associated with swallowing, is the major mechanism underlying **pathologic reflux** (see Fig. 364.1).

The close linkage of the anatomy of the upper digestive and respiratory tracts has mandated intricate functional protections of the respiratory tract during retrograde movement of gastric contents as well as during swallowing. The protective functions include the LES tone, the bolstering of the LES by the surrounding diaphragmatic crura, and the *backup protection* of the UES tone. Secondary peristalsis, akin



**Fig. 364.1** Continuous tracing of esophageal motility showing two swallows, as indicated by the pharyngeal contraction associated with relaxation of the upper esophageal sphincter (UES) and followed by peristalsis in the body of the esophagus. The lower esophageal sphincter (LES) also displays a transient relaxation (arrow) unassociated with a swallow. There is an episode of gastroesophageal reflux (asterisk) recorded by a pH probe at the time of the transient LES relaxation. (Courtesy John Dent, FRACP, PhD and Geoffrey Davidson, MD.)

**Table 364.1** Mechanical Events of the Oropharyngeal Swallow and Evidence of Dysfunction

MECHANICAL EVENT	EVIDENCE OF DYSFUNCTION
Nasopharyngeal closure	Nasopharyngeal regurgitation Nasal voice
Laryngeal closure	Aspiration during bolus transit
Upper esophageal sphincter opening	Dysphagia Post-swallow residue/aspiration Diverticulum formation
Tongue loading and bolus propulsion	Sluggish misdirected bolus
Pharyngeal clearance	Post-swallow residue in hypopharynx/aspiration

Modified from Pandolfino JE, Kahrilas PJ. Esophageal neuromuscular function and motility disorders. In Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 10th ed. Philadelphia: Elsevier; 2016: Table 43.1.

to primary peristalsis but without an oral component, originates in the upper esophagus, triggered mainly by GER, thereby also clearing refluxed gastric contents from the esophagus. Another protective reflex is the *pharyngeal swallow* (initiated above the esophagus, but without lingual participation). There are multiple levels of protection against aspiration, including the rhythmic coordination of swallowing and breathing and a series of protective reflexes with

esophagopharyngeal afferents and efferents that close the UES or larynx. These reflexes include the esophago-UES contractile reflex, the pharyngo-UES contractile reflex, the esophagoglottal closure reflex, and two pharyngoglottal adduction reflexes. The last two reflexes have chemoreceptors on the laryngeal surface of the epiglottis and mechanoreceptors on the aryepiglottic folds as their sites of stimulus. It is likely that interactions between the esophagus and the respiratory tract, which cause extraesophageal manifestations of gastroesophageal reflux disease (GERD), will be explained by subtle abnormalities in these protective reflexes.

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## 364.1 Common Clinical Manifestations and Diagnostic Aids

Seema Khan and Sravan Kumar Reddy Matta

Manifestations of esophageal disorders include pain, obstruction or difficulty swallowing, abnormal retrograde movement of gastric contents (reflux, regurgitation, or vomiting), or bleeding; esophageal disease can also cause respiratory symptoms. Pain in the chest unrelated to swallowing (**heartburn**) can be a sign of esophagitis, but similar pain might also represent cardiac, pulmonary, or musculoskeletal disease or visceral hyperalgesia. Pain during swallowing (**odynophagia**) localizes the disease more discretely to the pharynx and esophagus and often represents inflammatory mucosal disease. Complete esophageal obstruction can be produced acutely by esophageal foreign bodies, including food impactions; can be congenital, as in esophageal atresia; or can evolve over time as a peptic stricture occludes the esophagus. Difficulty swallowing (**dysphagia**) can be produced by incompletely occlusive esophageal obstruction (by extrinsic compression, intrinsic narrowing, or foreign bodies) but can also result from dysmotility of the esophagus (whether primary/idiopathic or secondary to systemic disease). Inflammatory lesions of the esophagus without obstruction or dysmotility are a third cause of dysphagia; eosinophilic esophagitis (EoE) is also relatively common.

The most common esophageal disorder in children is **GERD** (see Chapter 369), which is from retrograde return of gastric contents into the esophagus. **Esophagitis** can be caused by GERD, by eosinophilic disease, by infection, or by caustic substances. Esophageal **bleeding** can result from severe esophagitis that produces erosions or ulcerations and can manifest as anemia or hemoccult-positive stools. More acute or severe bleeding can be from ruptured **esophageal varices**. The resulting hematemesis must be differentiated from more distal bleeding (gastric ulcer) and from more proximal bleeding (a nosebleed or hemoptysis). Respiratory symptoms of esophageal disease can result from luminal contents incorrectly being directed into the respiratory tract or to reflexive respiratory responses to esophageal stimuli.

### DIAGNOSTIC AIDS

The esophagus can be evaluated by radiography, endoscopy, histology, scintigraphy, manometry, pH-metry (linked as indicated with other polysomnography), and multichannel intraluminal impedance. Contrast (usually barium) radiographic study of the esophagus usually incorporates fluoroscopic imaging over time so that motility and anatomy can be assessed. Although most often requested to evaluate for GERD, it is neither sensitive nor specific for this purpose; it can detect complications of GERD (stricture) or conditions mimicking GERD (pyloric stenosis or malrotation with intermittent volvulus), or concurrent hiatal hernia complicating GERD.

Barium fluoroscopy is optimal for evaluating for structural anomalies, such as duplications; strictures; hiatal hernia; congenital esophageal stenosis or external esophageal compression by an aberrant blood vessel; or for causes of dysmotility, such as achalasia. Modifications of the routine barium fluoroscopic study are used in special situations. When an *H*-type tracheoesophageal fistula is suspected, the test is most sensitive if the radiologist, with the patient prone, distends the esophagus with barium via a nasogastric tube. The videofluoroscopic evaluation of swallowing performed with varying consistencies of barium (modified barium swallow, oropharyngeal videosophagram, or cookie swallow) optimally evaluates children with dysphagia by demonstrating incoordination of the pharyngeal and esophageal phases of swallowing and any associated aspiration.

In some centers, fiberoptic endoscopic evaluation of swallowing uses nasopharyngeal endoscopy to visualize the pharynx and larynx during swallowing of dye-enhanced foods when dysphagia, laryngeal penetration, or aspiration is suspected. This is often combined with sensory testing of the laryngeal adductor reflex in response to a calibrated puff of air through the endoscope to the arytenoids, generating the composite fiberoptic endoscopic evaluation of swallowing sensory testing that examines the mechanisms of any aspiration that is present. Endoscopy allows direct visualization of esophageal mucosa and helps therapeutically in the removal of foreign bodies and treatment of esophageal varices. Endoscopy also allows biopsy samples to be taken, thus improving the diagnosis of **endoscopy-negative GERD**, differentiating GERD from EoE, and identifying viral or fungal causes of esophagitis.

Radionuclide scintigraphy scans are helpful in evaluating the efficiency of peristalsis and demonstrating reflux episodes. They can be specific, although not very sensitive, for aspiration and can quantify gastric emptying, thus hinting at a cause for GERD. The related radionuclide salivagram can demonstrate aspiration of even minute amounts of saliva.

Esophageal manometry evaluates for dysmotility from the pharynx to the stomach; by synchronized quantitative pressure measurements along the esophagus, it detects and characterizes dysfunctions sometimes missed radiographically. Manometry is often challenging in young infants, and sphincters are optimally evaluated with special Dent sleeves, rather than the simple ports available for the esophageal body. High-resolution esophageal manometry (HRM) along with video fluoroscopic swallowing study (VFSS) to evaluate UES relaxation and pharyngeal and peristaltic pressures is now available at a few centers of expertise.

Extended pH monitoring of the distal esophagus is a sensitive test for acidic GER episodes that can quantify duration and degree of acidity, but not volume, of the reflux episodes. It is linked with polysomnography (a pneumogram) when GER is suspected to cause apnea or similar symptoms. Multichannel intraluminal impedance is a method for pH-independent detection of bolus movements in the esophagus; with a pH probe incorporated, it can distinguish between acid and nonacid liquid and gaseous reflux, the proximal extent of reflux, and several aspects of esophageal function, such as direction of bolus flow, duration of bolus presence, and bolus clearance.

The functional luminal imaging probe (FLIP) is another testing modality available in few pediatric motility centers; it is used as a diagnostic tool to guide and measure therapeutic success. FLIP is indicated in patients with EoE to assess esophageal compliance and esophagogastric junction (EGJ) distensibility in patients with achalasia.

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## Chapter 365

# Congenital Anomalies

### 365.1 Esophageal Atresia and Tracheoesophageal Fistula

Seema Khan and Sravan Kumar Reddy Matta

Esophageal atresia (EA) is the most common congenital anomaly of the esophagus, with a prevalence of 1.7 per 10,000 live births. Of these, >90% have an associated tracheoesophageal fistula (TEF). In the most common form of EA, the upper esophagus ends in a blind pouch and the TEF is connected to the distal esophagus (type C). Figure 365.1 shows the types of EA and TEF and their relative frequencies. The exact cause is still unknown; associated features include advanced maternal age, European ethnicity, maternal obesity, low socioeconomic status, and tobacco smoking. This defect has survival rates of >90%, due largely to improved neonatal intensive care, earlier recognition, and appropriate intervention. Infants weighing <1,500 g at birth and those with severe associated cardiac anomalies have the highest risk for mortality. Fifty percent of infants are *nonsyndromic* without other anomalies; the rest have syndromes with associated anomalies, most often associated with the vertebral, anorectal, (cardiac), tracheal, esophageal, renal, radial (limb) (VACTERL) syndrome. Cardiac and vertebral anomalies are seen in 32% and 24%, respectively. VACTERL is a sporadic disorder and is generally associated with normal intelligence. Genetic factors have a role in the pathogenesis of TEF in patients with other non-VACTERL syndromes as suggested by discrete pathogenic variants in syndromic cases: **Feingold syndrome** (*N-MYC*), CHARGE syndrome (coloboma of the eye; central nervous system anomalies; heart defects; atresia of the choanae; retardation of growth and/or development; genital and/or urinary defects [hypogonadism]; ear anomalies and/or deafness) (*CHD7*), and anophthalmia-esophageal-genital syndrome (*SOX2*).

#### PRESENTATION

The neonate with EA typically has frothing and bubbling at the mouth and nose after birth as well as episodes of coughing, cyanosis, and respiratory distress. Polyhydramnios is common. Feeding exacerbates these symptoms, causes regurgitation, and can precipitate aspiration. Aspiration of gastric contents via a distal fistula causes more damaging pneumonitis than aspiration of pharyngeal secretions from the blind upper pouch. The infant with an isolated TEF in the absence of EA



**Fig. 365.1** Gross type classification and esophageal atresia (EA) and trachea-esophageal fistulas (TEF). Left to right: normal anatomy, gross type B (EA with proximal TEF; 2%), gross type C (EA with distal TEF; 86%), gross type D (EA with proximal and distal TEF; 1%), gross type A (pure EA, 7%), and gross type E (TEF without EA; 4%). (From Harrington AW, Riebold J, Hernandez K, et al. Feeding and growth outcomes in infants with type C esophageal atresia who undergo early primary repair. *J Pediatr.* 2022;241:77–82, Fig. 1.)

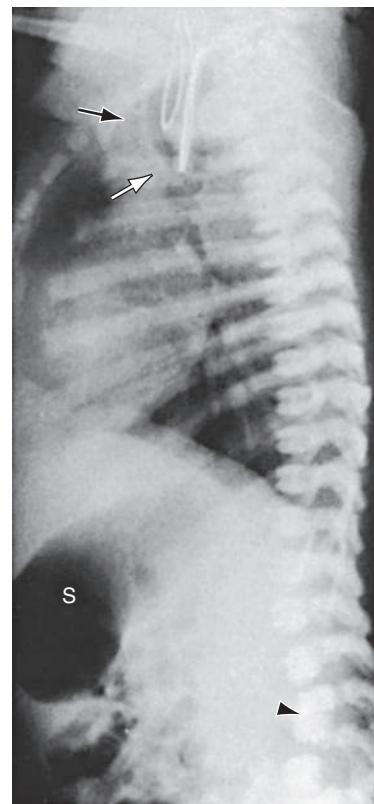
(“H-type” fistula) might come to medical attention later in life with chronic respiratory problems, including refractory bronchospasm and recurrent aspiration pneumonias.

#### DIAGNOSIS

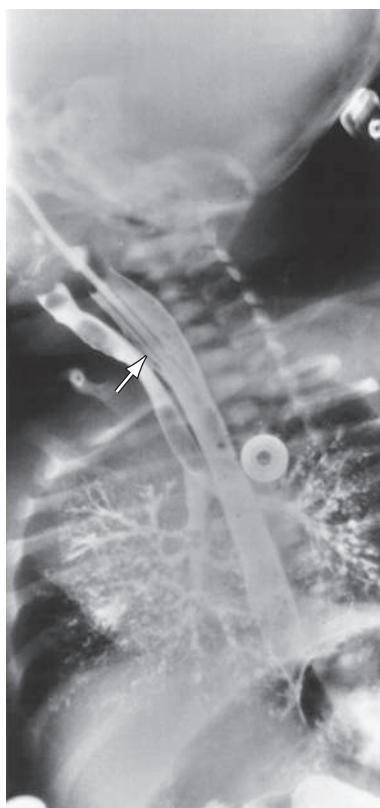
In the setting of polyhydramnios, early-onset respiratory distress and the inability to pass a nasogastric or orogastric tube in the newborn suggests EA. Imaging findings of absence of the fetal stomach bubble and maternal polyhydramnios might alert the physician to EA before birth. Plain radiography in the evaluation of respiratory distress might reveal a coiled feeding tube in the esophageal pouch and/or an air-distended stomach, indicating the presence of a coexisting TEF (Fig. 365.2). Conversely, pure EA can manifest as an airless scaphoid abdomen. In isolated TEF (H type), an esophagogram with contrast medium injected under pressure can demonstrate the defect (Fig. 365.3). Alternatively, the orifice may be detected at bronchoscopy or when methylene blue dye injected into the endotracheal tube during endoscopy is observed in the esophagus during forced inspiration. The differential diagnosis of congenital esophageal lesions is noted in Table 365.1.

#### MANAGEMENT

Initially, maintaining a patent airway, preoperative proximal pouch decompression to prevent aspiration of oral secretions, and use of antibiotics to prevent consequent pneumonia are paramount. Prone positioning minimizes movement of gastric secretions into a distal fistula, and esophageal suctioning minimizes aspiration from a



**Fig. 365.2** Tracheoesophageal fistula. Lateral radiograph demonstrating a nasogastric tube coiled (arrows) in the proximal segment of an atretic esophagus. The distal fistula is suggested by gaseous dilation of the stomach (S) and small intestine. The arrowhead depicts vertebral fusion, whereas a heart murmur and cardiomegaly suggest the presence of a ventricular septal defect. This patient demonstrated elements of the vertebral, anorectal, tracheal, esophageal, renal, and radial anomalad. (From Bafle D, Ling D, Siegel M. The esophagus. In Putman CE, Ravin CE, eds. *Textbook of Diagnostic Imaging*. Philadelphia: WB Saunders; 1988.)



**Fig. 365.3** H-type fistula (arrow) demonstrated in an infant after barium swallow on frontal-oblique chest x-ray. The tracheal aspect of the fistula is characteristically superior to the esophageal aspect. Barium is seen to outline the tracheobronchial tree. (From Wyllie R, Hyams JS, eds. *Pediatric Gastrointestinal and Liver Disease*. 3rd ed. Philadelphia: Saunders; 2006: p. 299.)

blind pouch. Endotracheal intubation with mechanical ventilation is to be avoided if possible because it can worsen distention of the stomach. Surgical ligation of the TEF and primary end-to-end anastomosis of the esophagus via right-sided thoracotomy constitute the standard surgical approach. In the premature or otherwise complicated infant, a primary closure may be delayed by temporizing with fistula ligation and gastrostomy tube placement. If the gap between the atretic ends of the esophagus is >3-4 cm (>3 vertebral bodies), primary repair cannot be done; options include using gastric, jejunal, or colonic segments interposed as a neoesophagus. Careful search must be undertaken for the common associated cardiac, renal, and other anomalies. *Thoracoscopic surgical repair is feasible and associated with favorable long-term outcomes.*

### OUTCOME

Most children with nonsyndromic EA and TEF grow up to lead normal lives, but complications are often challenging, particularly during the first 5 years of life. Complications of surgery include anastomotic leak, refistulization, and anastomotic stricture formation, necessitating endoscopic dilations. Some recurrent and refractory strictures may need esophageal stent placement or surgical stricture resection. Gastroesophageal reflux disease, resulting from intrinsic abnormalities of esophageal function, often combined with delayed gastric emptying, contributes to management challenges in many cases. Gastroesophageal reflux disease contributes significantly to the respiratory disease (**reactive airway disease**) that often complicates EA and TEF and also worsens the frequent anastomotic strictures after repair of EA.

Many patients have an associated tracheomalacia that improves as the child grows. Hence, it is important to target on prevention of long-term complications using appropriate surveillance techniques such as endoscopy or pH-Impedance.

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**Table 365.1** Clinical Aspects of Esophageal Developmental Anomalies

ANOMALY	AGE AT PRESENTATION	PREDOMINANT SYMPTOMS	DIAGNOSIS	TREATMENT
Isolated atresia	Newborns	Regurgitation of feedings Aspiration	Esophagogram* Plain film: gasless abdomen	Surgery
Atresia + distal TEF	Newborns	Regurgitation of feedings Aspiration	Esophagogram* Plain film: gas-filled abdomen	Surgery
H-type TEF	Infants to adults	Recurrent pneumonia Bronchiectasis	Esophagogram* Bronchoscopy†	Surgery
Esophageal stenosis	Infants to adults	Dysphagia Food impaction	Esophagogram* Endoscopy†	Dilation‡ Surgery§
Duplication cyst	Infants to adults	Dyspnea, stridor, cough (infants) Dysphagia, chest pain (adults)	EUS* MRI/CT†	Surgery
Vascular anomaly	Infants to adults	Dyspnea, stridor, cough (infants) Dysphagia (adults)	Esophagogram* Angiography† MRI/CT/EUS	Dietary modification‡ Surgery§
Esophageal ring	Children to adults	Dysphagia	Esophagogram* Endoscopy†	Dilation‡ Endoscopic incision§
Esophageal web	Children to adults	Dysphagia	Esophagogram* Endoscopy†	Bougienage

\*Diagnostic test of choice.

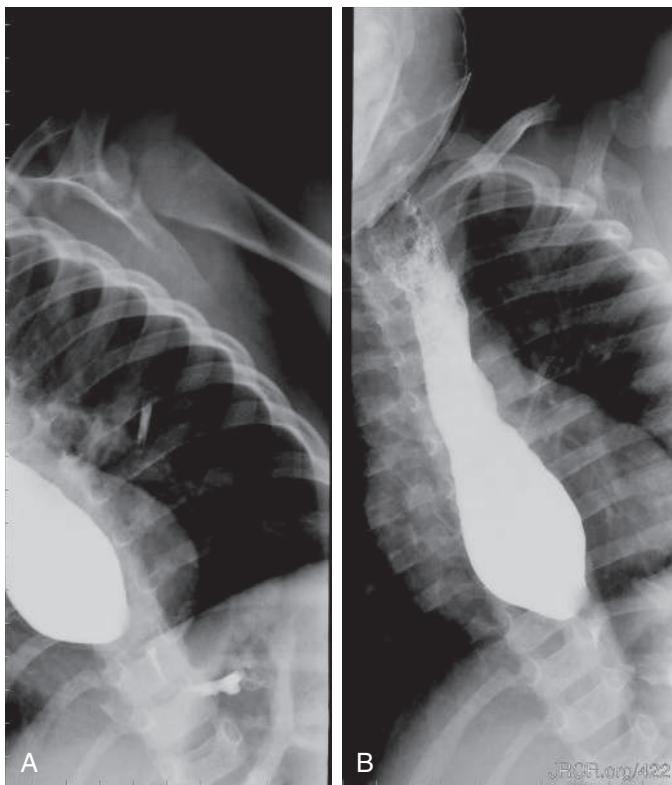
†Confirmatory test.

‡Primary therapeutic approach.

§Secondary therapeutic approach.

TEF, Tracheoesophageal fistula; EUS, endoscopic ultrasound.

From Madanick R, Orlando RC. Anatomy, histology, embryology, and developmental anomalies of the esophagus. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 10th ed. Philadelphia: Elsevier; 2016: Table 42.2.

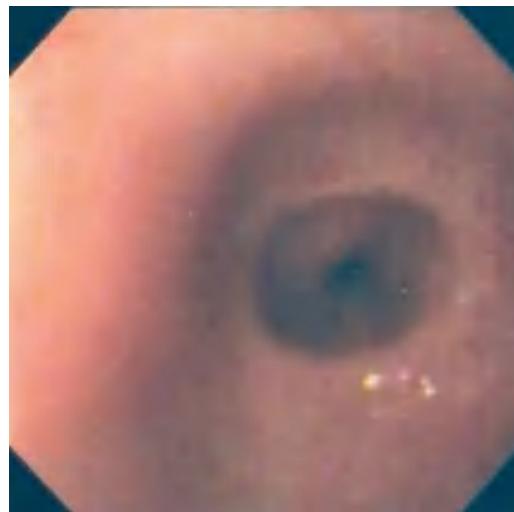


**Fig. 365.4** An 18-month-old male with congenital esophageal stenosis. Esophagogram using barium as contrast media shows an anteroposterior (AP) projection (A) and an unsuccessful attempt to obtain a lateral projection (B) due to poor collaboration of the patient. An asymmetric short narrowing of the distal esophagus is observed as well as proximal dilatation of the esophagus. Gastroesophageal reflux was not identified. (From Serrao E, Santos, A, Gaivao A. Congenital esophageal stenosis: a rare case of dysphagia. *J Radiol Case Rep.* 2010;4:8-14. Fig. 2.)

## 365.2 Laryngotracheoesophageal Clefts

Seema Khan and Sravan Kumar Reddy Matta

Laryngotracheoesophageal clefts are uncommon anomalies that result when the septum between the esophagus and trachea fails to develop fully, leading to a common channel defect between the pharyngoesophagus and laryngotracheal lumen, thus making the laryngeal closure incompetent during swallowing or reflux. Other developmental anomalies, such as EA and TEF, are seen in 20% of patients with clefts. The severity of presenting symptoms depends on the type of cleft; they are commonly classified as one of four types (I-IV) according to the inferior extent of the cleft. Early in life, the infant presents with stridor, choking, cyanosis, aspiration of feedings, and recurrent chest infections. The diagnosis is difficult and usually requires direct endoscopic visualization of the larynx and esophagus. When contrast radiography



**Fig. 365.5** An 18-month-old male with congenital esophageal stenosis. Esophagoscopy showed a circumferential, slightly noncentral narrowing at the distal esophagus, 2 cm proximal to the esophagogastric junction. (From Serrao E, Santos, A, Gaivao A. Congenital esophageal stenosis: a rare case of dysphagia. *J Radiol Case Rep.* 2010;4:8-14. Fig. 3.)

is used, material is often seen in the esophagus and trachea. Treatment is surgical repair, which can be complex if the defects are long.

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## 365.3 Congenital Esophageal Stenosis

Seema Khan and Sravan Kumar Reddy Matta

Congenital esophageal stenosis (CES) is a rare anomaly of the esophagus with clinical significance. Though the original incidence is not known, it is estimated to affect 1:25,000 to 50,000 live births. The defect results from incomplete separation of respiratory tract from the primitive foregut at the 25th day of fetal life. CES is differentiated by histology into three types: esophageal membrane/web, total bronchial remnants (TBR), and fibromuscular remnants (FMR). Symptoms vary depending on the location and severity of the defect. Higher lesions present with respiratory symptoms and lower lesions present with dysphagia and vomiting. Esophagogram (Fig. 365.4), MRI, CT, and endoscopic ultrasound are used for diagnosis. Endoscopy (Fig. 365.5) is done to evaluate mucosal abnormalities like strictures, foreign bodies, and esophagitis. Treatment option (surgical correction, bougie dilation) is chosen based on the location, severity, and type of stenosis.

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## Chapter 366

# Obstructing Disorders of the Esophagus

Seema Khan and Sravan Kumar Reddy Matta

Obstructing lesions classically produce **dysphagia to solids** earlier and more noticeably than to liquids and can manifest when the infant liquid diet begins to incorporate solids; this is in contrast to **dysphagia from dysmotility**, in which swallowing of *liquids* is affected as early as, or earlier than, solids. In most instances of dysphagia, evaluation begins with fluoroscopy, which may include videofluoroscopic evaluation of swallowing, particularly if aspiration is a primary symptom. Secondary studies are often endoscopic if intrinsic obstruction is suspected or manometric if dysmotility is suspected; other imaging studies may be used in particular cases. Congenital lesions can require surgery, whereas webs and peptic strictures might respond adequately to endoscopic (or bougie) dilation. Peptic strictures, once dilated, should prompt consideration of fundoplication for ongoing prophylaxis.

### EXTRINSIC

**Esophageal duplication cysts** are the most commonly encountered foregut duplications (see Table 365.1). These cysts are lined by intestinal epithelium, have a well-developed smooth muscle wall, and are attached to the normal gastrointestinal tract. Duplication cysts are described as either communicating or noncommunicating with the lumen of the alimentary tract. Most of these affect the distal half of the esophagus on the right side. The most common presentation is respiratory distress caused by compression of the adjacent airways. Dysphagia is a common symptom in older children. Upper gastrointestinal bleeding can occur as a result of acid-secreting gastric mucosa in the duplication wall. **Neuroenteric cysts** might contain glial elements and are associated with **vertebral anomalies**. Diagnosis is made using modalities, such as barium swallow, chest CT, and MRI, or endosonography. Treatment is surgical; laparoscopic approach to excision is also possible.

Enlarged mediastinal or subcarinal **lymph nodes**, caused by infection (tuberculosis, histoplasmosis) or neoplasm (lymphoma), are the most common external masses that compress the esophagus and produce obstructive symptoms. **Vascular anomalies** can also compress the esophagus; *dysphagia lusoria* is a term denoting the dysphagia produced by a developmental vascular anomaly, which is often an aberrant right subclavian artery or right-sided or double aortic arch (see Chapter 481.1).

### INTRINSIC

Intrinsic narrowing of the esophageal lumen can be congenital or acquired. The etiology is suggested by the location, the character of the lesion, and the clinical situation. The lower esophagus is the most common location for peptic strictures, which are generally somewhat ragged and several centimeters long. Thin membranous rings, including the **Schatzki ring** at the squamocolumnar junction, can also occlude this area. In the midesophagus, congenital narrowing may be associated with the esophageal atresia–tracheoesophageal fistula complex, in which some of the lesions might incorporate cartilage and might be impossible to dilate safely; alternatively, reflux esophagitis can induce a ragged and extensive narrowing that appears more proximal than the usual peptic stricture, often because of an associated hiatal hernia. Congenital webs or rings can narrow the upper esophagus. The upper esophagus can also be narrowed by an inflammatory stricture occurring after a caustic ingestion or due to epidermolysis bullosa.

Cricopharyngeal achalasia can appear radiographically as a cricopharyngeal bar posteriorly in the upper esophagus. **Eosinophilic esophagitis** is one of the most common causes for esophageal obstructive symptoms (see Chapter 370). Although the pathogenesis of obstructive eosinophilic esophagitis is not yet completely explained and seems to vary among individual patients, endoscopy or radiology demonstrates stricture formation in some children with eosinophilic esophagitis, and in others a noncompliant esophagus is evident, with thickened wall layers demonstrable by ultrasonography.

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## Chapter 367

# Dysmotility

Seema Khan and Sravan Kumar Reddy Matta

### UPPER ESOPHAGEAL AND UPPER ESOPHAGEAL SPHINCTER DYSMOTILITY (STRIATED MUSCLE)

Cricopharyngeal **achalasia** signifies a failure of complete relaxation of the upper esophageal sphincter (UES), whereas cricopharyngeal **incoordination** implies full relaxation of the UES but incoordination of the relaxation with the pharyngeal contraction. These entities are usually detected on videofluoroscopic evaluation of swallowing (sometimes accompanied by visible cricopharyngeal prominence, termed a *bar*), but often the most precise definition of the dysfunction is obtained with manometry. A self-limited form of cricopharyngeal incoordination occurs in infancy and remits spontaneously in the first year of life if nutrition is maintained despite the dysphagia. In children, treatment options for non-self-limited cricopharyngeal achalasia consist of dilation, Botox injection, and transcervical myotomy. It is important to evaluate such children thoroughly, including cranial MRI to detect **Arnold-Chiari malformations**, which can manifest in this way but are best treated by cranial decompression rather than esophageal surgery. Cricopharyngeal spasm may be severe enough to produce posterior pharyngeal (**Zenker**) **diverticulum** above the obstructive sphincter; this entity occurs rarely in children.

**Systemic causes** of swallowing dysfunction that can affect the oropharynx, UES, and upper esophagus include cerebral palsy, Arnold-Chiari malformations, syringomyelia, bulbar palsy or cranial nerve defects (Möbius syndrome, transient infantile paralysis of the superior laryngeal nerve), transient pharyngeal muscle dysfunction, spinal muscular atrophy, muscular dystrophy, multiple sclerosis, infections (botulism, tetanus, poliomyelitis, diphtheria), inflammatory and autoimmune diseases (dermatomyositis, myasthenia gravis, polyneuritis, scleroderma), and familial dysautonomia. All of these can produce dysphagia. Medications (nitrazepam, benzodiazepines) and tracheostomy can adversely affect the function of the UES and thereby produce dysphagia.

### LOWER ESOPHAGEAL AND LOWER ESOPHAGEAL SPHINCTER DYSFUNCTION (SMOOTH MUSCLE)

Causes of dysphagia resulting from more distal primary esophageal dysmotility include achalasia, diffuse esophageal spasm, nutcracker esophagus, and hypertensive lower esophageal sphincter (LES); all but achalasia are rare in children. Secondary causes include Hirschsprung disease, pseudoobstruction syndromes, inflammatory myopathies, scleroderma, and diabetes.

**Achalasia** is a primary esophageal motor disorder of unknown etiology characterized by loss of LES relaxation and loss of esophageal peristalsis, both contributing to a functional obstruction of the distal esophagus. Degenerative, autoimmune (antibodies to Auerbach

plexus), and infectious (Chagas disease caused by *Trypanosoma cruzi*) factors are possible causes in select cases. In rare cases, achalasia is familial or part of the achalasia, alacrima, and adrenal insufficiency, known as triple A syndrome or **Allgrove syndrome**. **Pseudoachalasia** refers to achalasia caused by various forms of cancer via obstruction of the gastroesophageal junction, infiltration of the submucosa and muscularis of the LES, or as part of the paraneoplastic syndrome with formation of anti-Hu antibodies. Pathologically, in achalasia, inflammation surrounds ganglion cells, which are decreased in number. There is selective loss of postganglionic inhibitory neurons that normally lead to sphincter relaxation, leaving postganglionic cholinergic neurons unopposed. This imbalance produces high basal LES pressures and insufficient LES relaxation. The loss of esophageal peristalsis can be a secondary phenomenon.

Achalasia manifests with regurgitation and dysphagia for solids and liquids and may be accompanied by undernutrition or chronic cough; retained esophageal food can produce esophagitis. *The presentations of chronic regurgitation/vomiting with weight loss, and chronic cough have led to misdiagnoses of anorexia nervosa and asthma, respectively.* The mean age in children is 8.8 years, with a mean duration of symptoms before diagnosis of 23 months; it is uncommon before school age. Chest radiograph shows an air-fluid level in a dilated esophagus. **Barium fluoroscopy** reveals a smooth tapering of the lower esophagus leading to the closed LES, resembling a bird's beak (Fig. 367.1). Loss of primary peristalsis in the distal esophagus with retained food and poor emptying are often present. **Manometry** is the most sensitive diagnostic test and helps differentiate the three types of achalasia; it reveals the defining features of aperistalsis in the distal esophageal body and incomplete or absent LES relaxation, often accompanied by high-pressure LES and low-amplitude esophageal body contractions (Fig. 367.2).

The goals of achalasia therapy are relief of symptoms, improvement of esophageal emptying, and prevention of megaesophagus. The two most effective treatment options are sequential repeated pneumatic dilation and laparoscopic or surgical (Heller) myotomy. Pneumatic dilation is the initial treatment of choice and does not preclude a future myotomy. Surgeons often supplement a myotomy with an antireflux procedure (fundoplication) to prevent the gastroesophageal reflux disease that otherwise often ensues when the sphincter is rendered less competent. Laparoscopic myotomy is a particularly effective procedure in adolescent and young adult males. Peroral endoscopic myotomy (POEM) is a feasible, safe, and effective alternative to the laparoscopic method. Calcium channel blockers (nifedipine) and phosphodiesterase inhibitors offer temporary relief of dysphagia. Endoscopic injection of the LES with **botulinum toxin** counterbalances the selective loss of inhibitory neurotransmitters by inhibiting the release of acetylcholine from nerve terminals and may be an effective initial therapy before a definitive procedure. Botulinum toxin is effective in 50–65% of patients and is expensive; half the patients might require a repeat injection within 1 year. Most eventually require dilation or surgery.

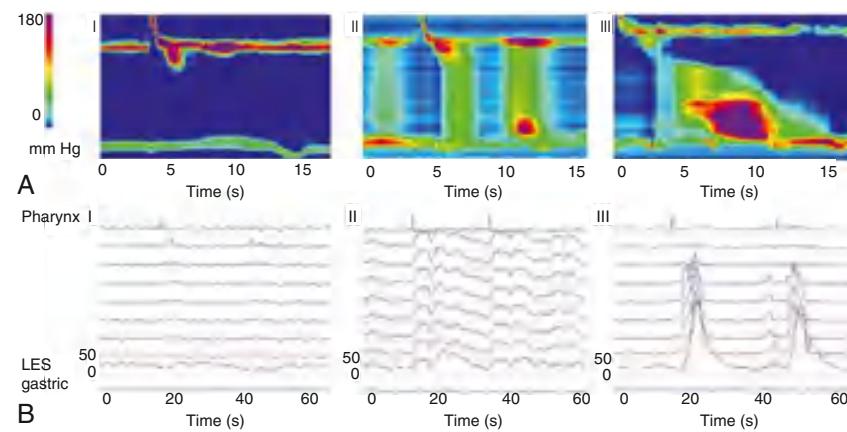
**Diffuse esophageal spasm** causes chest pain and dysphagia and affects adolescents and adults. It is diagnosed **manometrically** and can be treated with nitrates or calcium-channel-blocking agents.

**Gastroesophageal reflux disease** (see Chapter 369) constitutes the most common cause of nonspecific abnormalities of esophageal motor function, probably through the effect of the esophageal inflammation on the musculature.

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**Fig. 367.1** Barium esophagogram of a patient with achalasia demonstrating dilated esophagus and narrowing at the lower esophageal sphincter. Note retained secretions layered on top of barium in the esophagus.



**Fig. 367.2** Based on the residual wave type on high-resolution esophageal manometry (HRM), three subtypes of achalasia can be determined. A, No distal pressurization is observed in type I (AI), whereas panesophageal pressurizations and spastic contractions are observed in type II (AII) and type III (AIII), respectively. B, A similar classification can be made when conventional manometry is used. Note that pressure recordings in type II achalasia are similar in every line tracing, compatible with panesophageal pressurization. LES, Lower esophageal sphincter. (From Rohof WO, Salvador R, Annese V. Outcomes of treatment for achalasia depend on manometric subtype. *Gastroenterology*. 2013;144:718–725. Fig. 1.)

## Chapter 368

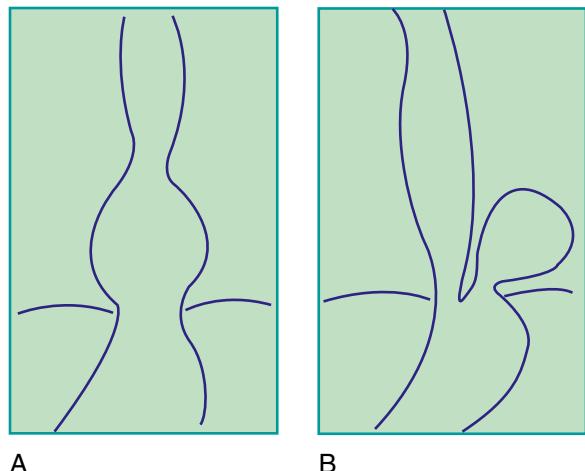
# Hiatal Hernia

Seema Khan and Sravan Kumar Reddy Matta

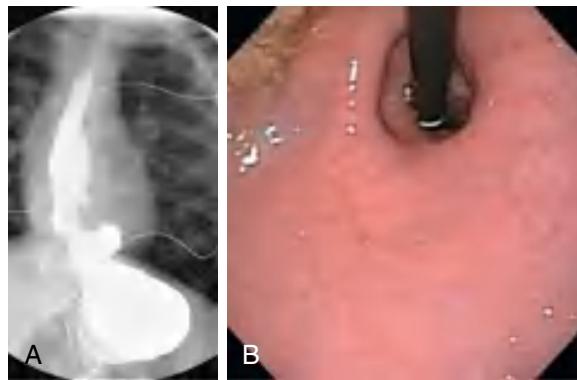
Herniation of the stomach through the esophageal hiatus can occur as a common sliding hernia (type 1), in which the gastroesophageal junction slides into the thorax, or it can be paraesophageal (type 2), in which a portion of the stomach (usually the fundus) is insinuated next to the esophagus inside the gastroesophageal junction in the hiatus (Figs. 368.1 and 368.2). A combination of sliding and

paraesophageal types (type 3) is present in some patients. Sliding hernias are often associated with gastroesophageal reflux disease (see Chapter 369), especially in developmentally delayed children. The relationship to hiatal hernias in adults is unclear. Diagnosis is usually made by an upper gastrointestinal series and upper endoscopy. Medical treatment is not directed at the hernia but at the gastroesophageal reflux, unless failure of medical therapy prompts correction of the hernia at the time of fundoplication.

A paraesophageal hernia can be an isolated congenital anomaly or associated with gastric volvulus, or it may be encountered after fundoplication for gastroesophageal reflux, especially if the edges of a dilated esophageal diaphragmatic hiatus have not been approximated. Fullness after eating and upper abdominal pain are the usual symptoms. Infarction of the herniated stomach is rare.



**Fig. 368.1** Types of esophageal hiatal hernia. A, Sliding hiatal hernia, the most common type. B, Paraesophageal hiatal hernia.



**Fig. 368.2** A, An upper gastrointestinal series shows a large hiatal hernia that extends above the diaphragm and impedes the exit of contrast from the esophagus into the stomach. Contrast is also noted to reflux to the upper esophagus. B, A retroflexed view of the hernia from the stomach during an upper endoscopy.

## Chapter 369

# Gastroesophageal Reflux Disease

Seema Khan and Sravan Kumar Reddy Matta

Gastroesophageal reflux disease (GERD) is the most common esophageal disorder in children of all ages. Gastroesophageal reflux (GER) signifies the retrograde movement of gastric contents across the lower esophageal sphincter (LES) into the esophagus, which occurs physiologically every day in all infants, older children, and adults. Physiologic GER is exemplified by the effortless regurgitation of normal infants and runs an uncomplicated course. Natural history studies observe that it is uncommon for physiologic GER to have onset before 1 week and to persist beyond 6 months of age, and usually peaks between 3 and 4 months. The phenomenon becomes **pathologic GERD** in infants and children who manifest or report bothersome symptoms because of frequent or persistent GER, producing esophagitis-related symptoms, or extraesophageal presentations, such as respiratory (cough, wheezing, hoarse voice) symptoms, nutritional effects, or growth failure. However, the clinical differentiation between GER and GERD is not straightforward in nonverbal infants who may present with excess crying, fussiness, and intermittent feeding and sleep problems while thriving well, due to non-GERD causes or even to variations of normal infant behavior. Pediatricians may try multiple therapeutic options as they try to diagnose and treat these behaviors. Concerned parents and caregivers may also influence the management through requests for interventions they may have heard about through the internet, or from other parents. As a consequence, we are seeing widespread prescriptions of histamine 2 receptor antagonists (H<sub>2</sub>RAs) and proton pump inhibitors (PPIs) to treat neonates and infants with physiologic GER. It is profoundly important for pediatricians and pediatric gastroenterologists to instead address this challenge and curb the trend for over investigation and over treatment through more effective educational campaigns, reassurance of parents, and emphasizing the benign nature of the diagnosis that is best handled with a conservative approach.

## PATOPHYSIOLOGY

Factors determining the esophageal manifestations of reflux include the duration of esophageal exposure (a product of the frequency and duration of reflux episodes), the causticity of the refluxate, and the susceptibility of the esophagus to damage. The LES, defined as a high-pressure zone by manometry, is supported by the crura of the diaphragm at the gastroesophageal junction and, together with valvelike functions of the esophagogastric junction anatomy, form the antireflux barrier. In the context of even the normal intraabdominal pressure augmentations that occur during daily life, the frequency of reflux episodes is increased by insufficient LES tone, by abnormal frequency of LES relaxations, and by hiatal herniation that prevents the LES pressure from being proportionately augmented by the crura during abdominal straining. Normal intraabdominal pressure augmentations may be further exacerbated by straining or respiratory efforts. The duration of reflux episodes is increased by lack of swallowing (e.g., during sleep) and by defective esophageal peristalsis. Vicious cycles ensue because chronic esophagitis produces esophageal peristaltic dysfunction (low-amplitude waves, propagation disturbances), decreased LES tone, and inflammatory esophageal shortening that induces hiatal herniation, all worsening reflux.

**Transient LES relaxation (TLESR)** is the primary mechanism allowing reflux to occur and is defined as simultaneous relaxation of both LES and the surrounding crura. TLESRs occur independent of swallowing, reduce LES pressure to 0–2 mm Hg (above gastric), and last 10–60 seconds; they appear by 26 weeks of gestation. A vagovagal reflex, composed of afferent mechanoreceptors in the proximal stomach, a brainstem pattern generator,

and efferents in the LES, regulates TLESRs. Gastric distention (postprandially, or from abnormal gastric emptying or air swallowing) is the main stimulus for TLESRs. Whether GERD is caused by a higher frequency of TLESRs or by a greater incidence of reflux during TLESRs is debated; each is likely in different persons. Straining during a TLESR makes reflux more likely, as do positions that place the gastroesophageal junction below the air-fluid interface in the stomach. Other factors influencing gastric pressure-volume dynamics, such as increased movement, straining, obesity, large-volume or hyperosmolar meals, gastroparesis, a large sliding hiatal hernia, and increased respiratory effort (coughing, wheezing), can have the same effect.

## EPIDEMIOLOGY AND NATURAL HISTORY

**Infant reflux** becomes evident in the first few months of life, peaks at 4 months, and resolves in up to 88% by 12 months and in nearly all by 24 months. *Happy spitters* are infants who have recurrent regurgitation without exhibiting discomfort or refusal to eat and failure to gain weight. Symptoms of GERD in **older children** tend to be chronic, waxing and waning, but completely resolving in no more than half, which resembles adult patterns (Table 369.1). The histologic findings of esophagitis persist in infants who have naturally resolving symptoms of reflux. GERD likely has genetic predispositions: family clustering of GERD symptoms, endoscopic esophagitis, hiatal hernia, Barrett esophagus, and adenocarcinoma have been identified. As a continuously variable and common disorder, complex inheritance involving multiple genes and environmental factors is likely. Genetic linkage is indicated by the strong evidence of GERD in studies with monozygotic twins. A pediatric autosomal dominant form with otolaryngologic and respiratory manifestations has been located to chromosome 13q14, and the locus is termed GERD1.

## CLINICAL MANIFESTATIONS

Most of the common clinical manifestations of esophageal disease can signify the presence of GERD and are generally thought to be mediated by the pathogenesis involving acid GER (Table 369.2). Although less noxious for the esophageal mucosa, non-acid-reflux events are recognized to play an important role in extraesophageal disease manifestations. **Infantile reflux** manifests more often with regurgitation (especially postprandially), signs of esophagitis (irritability, arching, choking, gagging, feeding aversion), and resulting failure to thrive; symptoms resolve spontaneously in the majority of infants by 12–24 months. **Older children** can have regurgitation during the preschool years; this complaint diminishes somewhat as children age, and complaints of abdominal and chest pain supervene in later childhood and adolescence. Occasional children present with food refusal or neck contortions (arching, turning of head) that is termed **Sandifer syndrome**. The respiratory presentations are also age dependent: GERD in infants may manifest as obstructive apnea or as stridor or lower airway disease in which reflux complicates primary airway disease such as laryngomalacia or bronchopulmonary dysplasia. Otitis media, sinusitis, lymphoid hyperplasia, hoarseness, vocal cord nodules, and laryngeal edema have all been associated with GERD. Airway manifestations in older children are more commonly related to asthma or to otolaryngologic disease such as laryngitis or sinusitis. Despite the high prevalence of GERD symptoms in asthmatic children, data showing direction of causality are conflicting.

Neurologically challenged children are at an increased risk for GERD. It is not well established if the greater risk is conferred due to inadequate defensive mechanisms and/or inability to express symptoms. A low clinical threshold is important in the early identification and prompt treatment of GERD symptoms in these individuals.

## DIAGNOSIS

For most of the typical GERD presentations, particularly in older children, a thorough history and physical examination suffice initially to reach the diagnosis. This initial evaluation aims to identify the pertinent positives in support of GERD and its complications and the negatives that make other diagnoses unlikely. The history may be facilitated and standardized by questionnaires (e.g., the Infant Gastroesophageal Reflux Questionnaire [I-GERQ], and its derivative, the I-GERQ-R), which also permit quantitative scores to be evaluated for their diagnostic discrimination and for evaluative assessment of improvement or worsening of symptoms. The clinician should be alerted to the

**Table 369.1** Symptoms According to Age

MANIFESTATIONS	INFANTS	CHILDREN	ADOLESCENTS AND ADULTS
Impaired quality of life	+++	+++	+++
Regurgitation	++++	+	+
Excessive crying/irritability	+++	+	-
Vomiting	++	++	+
Food refusal/feeding disturbances/anorexia	++	+	+
Persisting hiccups	++	+	+
Failure to thrive	++	+	-
Abnormal posturing/Sandifer syndrome	++	+	-
Esophagitis	+	++	+++
Persistent cough/aspiration pneumonia	+	++	+
Wheezing/laryngitis/ear problems	+	++	+
Laryngomalacia/stridor/croup	+	++	-
Sleeping disturbances	+	+	+
Anemia/melena/hematemesis	+	+	+
Apnea/BRUE/desaturation	+	-	-
Bradycardia	+	?	?
Heartburn/pyrosis	?	++	+++
Epigastric pain	?	+	++
Chest pain	?	+	++
Dysphagia	?	+	++
Dental erosions/water brush	?	+	+
Hoarseness/globus pharyngeus	?	+	+
Chronic asthma/sinusitis	-	++	+
Laryngostenosis/vocal nodule problems	-	+	+
Stenosis	-	(+)	+
Barrett/esophageal adenocarcinoma	-	(+)	+

++, Very common; ++ common; + possible; (+) rare; - absent; ? unknown; BRUE, brief resolved unexplained event; previously called ALTE, or apparent life-threatening event. From Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*. 4th ed. Philadelphia: WB Saunders; 2011: Table 22.3, p. 235.

possibility of other important diagnoses in the presence of any *alarm or warning signs*: bilious emesis, frequent projectile emesis, gastrointestinal bleeding, lethargy, organomegaly, abdominal distention, dysphagia, odynophagia, micro- or macrocephaly, hepatosplenomegaly, anorexia, failure to thrive, diarrhea, fever, bulging fontanelle, and seizures. The important differential diagnoses to consider in the evaluation of an infant or a child with chronic vomiting are milk and other food allergies, eosinophilic esophagitis, pyloric stenosis, intestinal obstruction (especially malrotation with intermittent volvulus), nonesophageal inflammatory diseases, infections, inborn errors of metabolism, hydro-nephrosis, increased intracranial pressure, rumination, and bulimia. Focused diagnostic testing, depending on the presentation and the differential diagnosis, can then supplement the initial examination.

Most of the esophageal tests are of some use in particular patients with suspected GERD. **Contrast (usually barium) radiographic** study of the esophagus and upper gastrointestinal tract is performed in children with vomiting and dysphagia to evaluate for achalasia, esophageal strictures and stenosis, hiatal hernia, and gastric outlet or intestinal obstruction (Fig. 369.1). It has poor sensitivity and specificity in the diagnosis of GERD as a result of its limited duration and the inability to differentiate physiologic GER from GERD. Furthermore, contrast radiography neither accurately assesses mucosal inflammation nor correlates with severity of GERD.

Extended esophageal pH monitoring of the distal esophagus, no longer considered the sine qua non of a GERD diagnosis, provides a quantitative

and sensitive documentation of acidic reflux episodes, the most important type of reflux episodes for pathologic reflux. The distal esophageal pH probe is placed at a level corresponding to 87% of the nares-LES distance, based on regression equations using the patient's height, on fluoroscopic visualization, or on manometric identification of the LES. Normal values of distal esophageal acid exposure ( $\text{pH} < 4$ ) are generally established as  $< 5\text{--}8\%$  of the total monitored time, but these quantitative normals are insufficient to establish or disprove a diagnosis of pathologic GERD. The most important indications for esophageal pH monitoring are for assessing efficacy of acid suppression during treatment, evaluating apneic episodes in conjunction with a pneumogram and perhaps impedance, and evaluating atypical GERD presentations such as chronic cough, stridor, and asthma. Dual pH probes, adding a proximal esophageal probe to the standard distal one, are used in the diagnosis of extraesophageal GERD, identifying upper esophageal acid exposure times of 1% of the total time as threshold values for abnormality.

**Endoscopy** allows diagnosis of erosive esophagitis (Fig. 369.2) and complications such as strictures or Barrett esophagus; esophageal biopsies can diagnose histologic reflux esophagitis in the absence of erosions while eliminating allergic and infectious causes. Endoscopy is also used therapeutically to dilate reflux-induced strictures. Radionuclide scintigraphy using technetium can demonstrate aspiration and delayed gastric emptying when these are suspected.

**Table 369.2** Symptoms and Signs That May Be Associated with Gastroesophageal Reflux

SYMPTOMS	SIGNS
Recurrent regurgitation with or without vomiting	Esophagitis
Weight loss or poor weight gain	Esophageal stricture
Irritability in infants	Barrett esophagus
Ruminative behavior	Laryngeal/pharyngeal inflammation
Heartburn or chest pain	Recurrent pneumonia
Hematemesis	Anemia
Dysphagia, odynophagia	Dental erosion
Wheezing	Feeding refusal
Stridor	Dystonic neck posturing (Sandifer syndrome)
Cough	Apnea spells
Hoarseness	Apparent life-threatening events

From Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*. 4th ed. Philadelphia: Saunders; 2011: Table 22.1, p. 235.

The multichannel **intraluminal impedance** is a cumbersome test, but with potential applications both for diagnosing GERD and for understanding esophageal function in terms of bolus flow, volume clearance, and (in conjunction with manometry) motor patterns associated with GERD. Because of the multiple sensors and a distal pH sensor, it is possible to document acidic reflux ( $\text{pH} < 4$ ), weakly acidic reflux ( $\text{pH } 4\text{-}7$ ), and weakly alkaline reflux ( $\text{pH } > 7$ ) with multichannel intraluminal impedance. It is an important tool in those with respiratory symptoms, particularly for the determination of nonacid reflux, but must be cautiously applied in routine clinical evaluation because of limited evidence-based parameters for GERD diagnosis and symptom association.

Esophageal manometry is not useful in demonstrating gastroesophageal reflux but might be of use to evaluate TLESR.

**Laryngotracheobronchoscopy** evaluates for visible airway signs that are associated with extraesophageal GERD, such as posterior laryngeal inflammation and vocal cord nodules; it can permit diagnosis of silent aspiration (during swallowing or during reflux) by bronchoalveolar lavage with subsequent quantification of lipid-laden macrophages in airway secretions. Detection of pepsin in tracheal fluid is a marker of reflux-associated aspiration of gastric contents. Esophageal manometry permits evaluation for dysmotility, particularly in preparation for antireflux surgery.

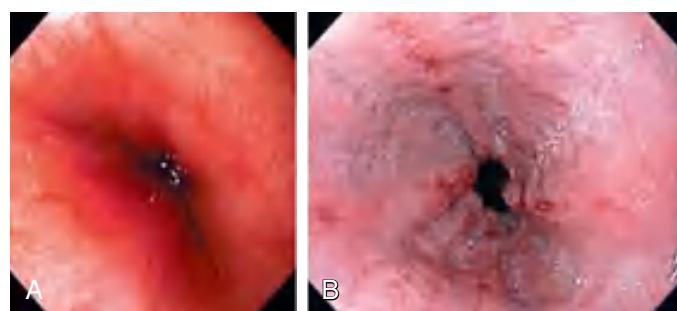
**Empirical antireflux therapy**, using a time-limited trial of high-dose PPI, is a cost-effective strategy for diagnosis in adults; although not formally evaluated in older children, it has also been applied to this age group (Fig. 369.3). Failure to respond to such empirical treatment, or a requirement for the treatment for prolonged periods, mandates formal diagnostic evaluation.

## MANAGEMENT

The conservative therapy and lifestyle modifications that form the foundation of GERD therapy can be effectively implemented through education and reassurance for parents. Dietary measures for infants include normalization of any abnormal feeding techniques, volumes, and frequencies. Thickening of feeds or use of commercially prethickened formulas increases the percentage of infants with no regurgitation, decreases the frequency of daily regurgitation and emesis, and increases the infant's weight gain. However, caution should be exercised when managing preterm infants because of the possible association between xanthan gum-based thickened feeds and necrotizing enterocolitis. The evidence does not clearly favor one type of thickener over another; the addition of a tablespoon of rice or oat cereal per ounce of formula results in a greater caloric density (30 kcal/oz) and reduced crying time, although it might not modify the number of nonregurgitant reflux episodes. Caution must be exercised while using rice cereal, as studies show increased risk of arsenic exposure in children with excessive rice and rice product consumption. A short trial (2 weeks) of a hypoallergenic diet in infants may be used to exclude milk or soy protein allergy before



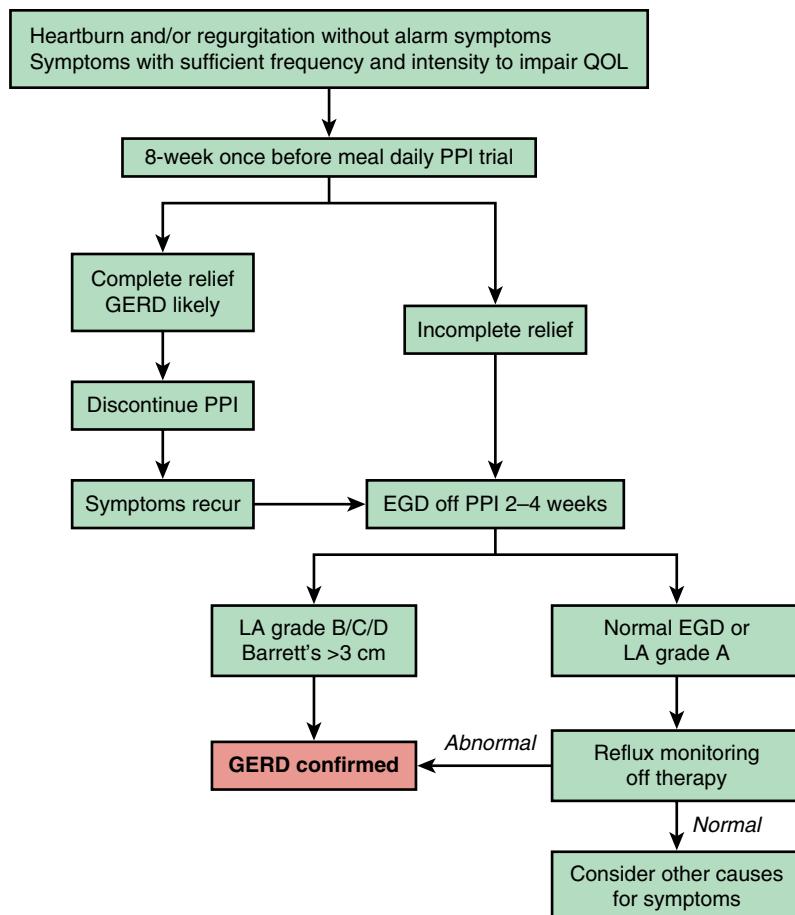
**Fig. 369.1** Barium esophagogram demonstrating free gastroesophageal reflux. Note stricture caused by peptic esophagitis. Longitudinal gastric folds above the diaphragm indicate the unusual presence of an associated hiatal hernia.



**Fig. 369.2** Endoscopic image of a normal esophagus (A) and erosive peptic esophagitis (B).

pharmacotherapy. A combination of modified feeding volumes, hydrolyzed infant formulas, proper positioning, and avoidance of tobacco smoke exposure satisfactorily improve GERD symptoms in 24–59% of infants with GERD. Older children should be counseled to avoid acidic or reflux-inducing foods, particularly if these trigger symptoms (tomatoes, chocolate, mint), and beverages (juices, carbonated and caffeinated drinks, alcohol). Weight reduction for obese patients and elimination of smoke exposure are other crucial measures at all ages.

**Positioning measures** are particularly important for infants who cannot control their positions independently. Seated position worsens infant reflux and should be avoided in infants with GERD. Esophageal pH monitoring demonstrates more reflux episodes in infants in supine and side positions compared with the prone position, but evidence that the supine position reduces the risk of sudden infant death syndrome (SIDS) has led the American Academy of Pediatrics and the North American Society of Pediatric Gastroenterology and Nutrition to recommend supine positioning during sleep. When the infant is awake and observed, prone position and upright carried position can be used to minimize



**Fig. 369.3** Diagnostic algorithm for GERD. EGD, Esophagogastroduodenoscopy; LA, Los Angeles; PPI, proton pump inhibitor; QOL, quality of life. (From Katz PO, Dunbar KB, Schnoll-Sussman FH, et al. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2022;117:27–56. Fig. 1, p. 33.)

reflux. Lying in the flat supine position and semi-seated positions (e.g., car seats, infant carriers) in the postprandial period are considered provocative positions for GER and therefore should be avoided. The efficacy of positioning for older children is unclear, but some evidence suggests a benefit to left side position and head elevation during sleep. The head should be elevated by elevating the head of the bed, rather than using excess pillows, to avoid abdominal flexion and compression that might worsen reflux, and increases the risk of SIDS (see Chapter 423).

**Pharmacotherapy** is directed at ameliorating the acidity of the gastric contents or at promoting their aboral movement and should be considered for those symptomatic infants and children who are either highly suspected or proven to have GERD. Antacids are the most commonly used antireflux therapy and are readily available over the counter. They provide rapid but transient relief of symptoms by acid neutralization. The long-term regular use of antacids cannot be recommended because of side effects of diarrhea (magnesium antacids) and constipation (aluminum antacids) and rare reports of more serious side effects of chronic use.

H<sub>2</sub>RAs (cimetidine, famotidine, and nizatidine) have been used as antisecretory agents that act by selective inhibition of histamine receptors on gastric parietal cells. It is important to note that ranitidine, one of the most popular H<sub>2</sub>RAs was recalled by the FDA in 2020 due to the discovery that it contained concerning amounts of a potential carcinogen called N-nitrosodimethylamine (NDMA). H<sub>2</sub>RAs were beneficial in the treatment of mild to moderate reflux esophagitis. They have been recommended because of their excellent overall safety profile, *but they are superseded by PPIs in this role*.

PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole) provide the most potent acid blockade effect by blocking the hydrogen–potassium adenosine triphosphatase channels of the final common pathway in gastric acid secretion. PPIs are superior to H<sub>2</sub>RAs in the treatment of severe and erosive esophagitis. Pharmacodynamic studies indicate that children require higher doses of PPIs than adults on a per-weight basis. The use of PPIs to treat infants and children deemed

to have GERD on the basis of symptoms is common; however, an important systematic review of the efficacy and safety of PPI therapy in pediatric GERD reveals no clear benefit for PPI over placebo use in *suspected infantile GERD* (crying, arching behavior). Limited pediatric data are available to draw definitive conclusions about potential complications implicated with PPI use, such as respiratory infections, *Clostridium difficile* infection, osteopenic bone fractures (noted in adults), hypomagnesemia, and kidney damage; most randomized controlled studies have not confirmed these side effects.

**Prokinetic agents** available in the United States include metoclopramide (dopamine-2 and 5-HT<sub>3</sub> antagonist), bethanechol (cholinergic agonist), and erythromycin (motilin receptor agonist). Most of these increase LES pressure, some improve gastric emptying or esophageal clearance, but none affects the frequency of TLESRs. The available controlled trials *have not* demonstrated much efficacy for GERD. The FDA announced a black box warning for metoclopramide, linking its chronic use (longer than 3 months) with tardive dyskinesia, the rarely reversible movement disorder. Baclofen is a centrally acting γ-aminobutyric acid agonist that decreases reflux by decreasing TLESRs in healthy adults and in a small number of neurologically impaired children with GERD. Other agents of interest include peripherally acting γ-aminobutyric acid agonists devoid of central side effects, and metabotropic glutamate receptor 5 antagonists that are reported to reduce TLESRs but are as yet inadequately studied for this indication in children.

Cisapride is a serotonergic-receptor agonist with a prokinetic effect that is only available in the United States through a limited access program because of its cardiac side effects (QT prolongation, dysrhythmias).

Surgery, usually **fundoplication**, is effective therapy for intractable GERD in children, particularly those with refractory esophagitis or strictures and those at risk for significant morbidity from chronic pulmonary disease. It may be combined with a gastrostomy for feeding or venting. The availability of potent acid-suppressing medication mandates more-rigorous analysis of the relative risks (or costs) and benefits of this

relatively irreversible therapy compared with long-term pharmacotherapy. Some of the risks of fundoplication include a wrap that is *too tight* (producing dysphagia or gas-bloat) or *too loose* (and thus incompetent). Surgeons may choose to perform a *tight* (360 degrees, Nissen) or variations of a *loose* (<360 degrees, Thal, Toupet, Boix-Ochoa) wrap, or to add a gastric drainage procedure (pyloroplasty) to improve gastric emptying, based on their experience and the patient's disease. Preoperative accuracy of the diagnosis of GERD and the skill of the surgeon are two of the most important predictors of successful outcome. Long-term studies suggest that fundoplications often become incompetent in children, as in adults, with reflux recurrence rates of up to 14% for Nissen and up to 20% for loose wraps (the rates may be highest with laparoscopic procedures); this fact currently combines with the potency of PPI therapy that is available to shift practice toward long-term pharmacotherapy in many cases. Fundoplication procedures may be performed as open operations, by laparoscopy, or by endoluminal (gastroplication) techniques. Pediatric experience is limited with endoscopic application of radiofrequency therapy (Stretta procedure) to a 2-3 cm area of the LES and cardia to create a high-pressure zone to reduce reflux.

Total esophagogastric dissociation is performed in selective neurologically impaired children with repeated failed fundoplications and with severe life-threatening GERD.

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### 369.1 Complications of Gastroesophageal Reflux Disease

Seema Khan and Sravan Kumar Reddy Matta

#### ESOPHAGEAL: ESOPHAGITIS AND SEQUELAE—STRICTURE, BARRETT ESOPHAGUS, ADENOCARCINOMA

**Esophagitis** can manifest as irritability, arching, and feeding aversion in infants; chest or epigastric pain in older children; and, rarely, as hematemesis, anemia, or Sandifer syndrome at any age. Erosive esophagitis is found in approximately 12% of children with GERD symptoms and is more common in boys, older children, neurologically challenged children, children with severe chronic respiratory disease, and in those with hiatal hernia. Prolonged and severe esophagitis leads to formation of strictures, generally located in the distal esophagus, producing dysphagia, and requiring repeated esophageal dilations and often fundoplication. Long-standing esophagitis predisposes to metaplastic transformation of the normal esophageal squamous epithelium into intestinal columnar epithelium, termed **Barrett esophagus**, a precursor of esophageal adenocarcinoma. A large multicenter prospective study of 840 consecutive children who underwent elective endoscopies reported a 25.7% prevalence for reflux esophagitis, and a mere 0.12% for Barrett esophagus in children without neurologic disorders or tracheoesophageal anomalies. Both Barrett esophagus and adenocarcinoma occur more in White males and in those with increased duration, frequency, and severity of reflux symptoms. This transformation increases with age to plateau in the fifth decade; adenocarcinoma is rare in childhood. Barrett esophagus, uncommon in children, warrants periodic surveillance biopsies, aggressive pharmacotherapy, and fundoplication for progressive lesions.

#### NUTRITIONAL

Esophagitis and regurgitation may be severe enough to induce failure to thrive because of caloric deficits. Enteral (nasogastric or nasojejunal, or percutaneous gastric or jejunal) or parenteral feedings are sometimes required to treat such deficits.

#### EXTRAESOPHAGEAL: RESPIRATORY ("ATYPICAL") PRESENTATIONS

GERD should be included in the differential diagnosis of children with unexplained or refractory otolaryngologic and respiratory complaints. GERD can produce respiratory symptoms by direct contact of the refluxed gastric contents with the respiratory tract (aspiration, laryngeal penetration, or microaspiration) or by reflexive interactions between the

esophagus and respiratory tract (inducing laryngeal closure or bronchospasm). Often, GERD and a primary respiratory disorder, such as asthma, interact and a vicious cycle between them worsens both diseases. Many children with these extraesophageal presentations do not have typical GERD symptoms, making the diagnosis difficult. These atypical GERD presentations require a thoughtful approach to the differential diagnosis that considers a multitude of primary otolaryngologic (infections, allergies, postnasal drip, voice overuse) and pulmonary (asthma, cystic fibrosis) disorders. Therapy for the GERD must be more intense (usually incorporating a PPI) and prolonged (usually at least 3-6 months). In these cases a multidisciplinary approach involving otolaryngology, pulmonary for airway disease, and gastroenterology for reflux disease is often warranted for specialized diagnostic testing and for optimizing intensive management.

#### APNEA AND STRIDOR

These upper airway presentations have been linked with GERD in case reports and epidemiologic studies; temporal relationships between them and reflux episodes have been demonstrated in some but not all patients by esophageal pH-multichannel intraluminal impedance studies, and a beneficial response to therapy for GERD provides further support in a number of case series. An evaluation of 1,400 infants with apnea attributed the apnea to GERD in 50%, but other studies have failed to find an association. Apnea and brief resolved unexplained event (BRUE)-like presentation (previously called an "apparent life-threatening event"; see Chapter 424) caused by reflux is generally obstructive due to laryngospasm that may be conceived as an abnormally intense protective reflex. At the time of such apnea, infants have often been provocatively positioned (supine or flexed seated), have been recently fed, and have shown signs of obstructive apnea, with unproductive respiratory efforts. *The evidence suggests that for the large majority of infants presenting with apnea and BRUE, GERD is not causal.* Stridor triggered by reflux generally occurs in infants anatomically predisposed toward stridor (laryngomalacia, micrognathia). Spasmodic croup, an episodic frightening upper airway obstruction, can be an analogous condition in older children. Esophageal pH probe studies might fail to demonstrate linkage of these manifestations with reflux because of the buffering of gastric contents by infant formula and the episodic nature of the conditions. Pneumograms can fail to identify apnea if they are not designed to identify obstructive apnea by measuring nasal airflow.

**Reflux laryngitis** and other otolaryngologic manifestations (also known as laryngopharyngeal reflux) can be attributed to GERD. **Hoarseness**, voice fatigue, throat clearing, chronic cough, pharyngitis, sinusitis, otitis media, and a sensation of globus have been cited. Laryngopharyngeal signs of GERD include edema and hyperemia (of the posterior surface), contact ulcers, granulomas, polyps, subglottic stenosis, and interarytenoid edema. The paucity of well-controlled evaluations of the association contributes to the skepticism with which these associations may be considered. Other risk factors irritating the upper respiratory passages can predispose some patients with GERD to present predominantly with these complaints.

Many studies have reported a strong association between asthma and reflux as determined by history, pH-multichannel intraluminal impedance, endoscopy, and esophageal histology. GERD symptoms are present in ~23% (19–80%) of children with asthma; abnormal pH results are noted in ~63%, and esophagitis in ~35% of asthmatic children. However, this association does not clarify the direction of causality in individual cases and thus does not indicate which patients with asthma are likely to benefit from anti-GERD therapy. Children with asthma who are particularly likely to have GERD as a provocative factor are those with symptoms of reflux disease, those with refractory or steroid-dependent asthma, and those with nocturnal worsening of asthma. Endoscopic evaluation that discloses esophageal sequelae of GERD provides an impetus to embark on the aggressive (high dose and many months' duration) therapy of GERD.

Dental erosions constitute the most common oral lesion of GERD, the lesions being distinguished by their location on the lingual surface of the teeth. The severity seems to correlate with the presence of reflux symptoms and the presence of an acidic milieu as the result of reflux in the proximal esophagus and oral cavity. The other common factors that can produce similar dental erosions are juice consumption and bulimia.

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## Chapter 370

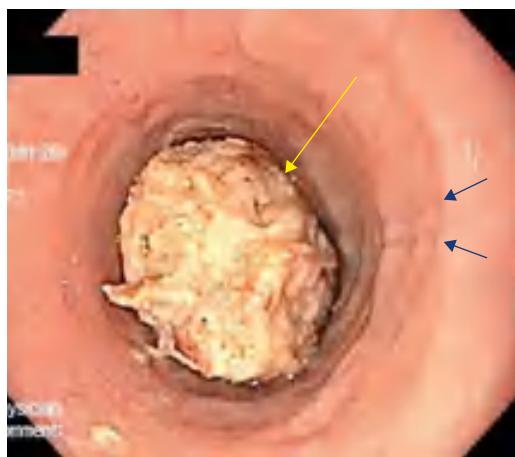
# Eosinophilic Esophagitis, Pill Esophagitis, and Infective Esophagitis

Seema Khan

### **EOSINOPHILIC ESOPHAGITIS**

Eosinophilic esophagitis (EoE) is a chronic esophageal disorder characterized by esophageal dysfunction and infiltration of the esophageal epithelium by  $\geq 15$  eosinophils per high-power field (hpf). The proposed diagnostic criteria are the clinical presentation of esophageal dysfunction in association with esophageal epithelial infiltration of at least 15 eosinophils per hpf or  $\sim 60$  eosinophils per mm $^2$ ; a careful evaluation of non-EoE disorders was warranted. Proton pump inhibitors (PPIs) should be considered as another treatment option rather than a diagnostic criterion to differentiate from gastroesophageal reflux disease (GERD). EoE is a global disease, with incidence and prevalence rates in children of 5 and 29.5 per 100,000. Although infants and toddlers present commonly with vomiting, feeding problems, and poor weight gain, older children and adolescents usually experience solid food dysphagia with occasional food impactions (Figs. 370.1 and 370.2) or strictures and may complain of heartburn and chest or epigastric pain. Many patients are male. The mean age at diagnosis is 7 years (range: 1-17 years), and the duration of symptoms is 3 years. Many patients have other atopic diseases (or a positive family history) and associated food allergies; laboratory abnormalities can include peripheral eosinophilia and elevated immunoglobulin E (IgE) levels. The pathogenesis involves mainly T-helper type 2 (Th2) cytokine-mediated (interleukin [IL]-5 and -13) pathways leading to production of a potent eosinophil chemoattractant, eotaxin-3, by esophageal epithelium.

The eosinophilic esophagitis endoscopic reference score (ERES), based on commonly observed features of edema (E), rings (R; Fig. 370.3), exudates (E; see Fig. 370.3), furrows (F; Fig. 370.4), and strictures (S), has utility in diagnosis and monitoring response to treatment. Esophageal histology reveals profound eosinophilia, with a currently acceptable cutoff for diagnosis chosen at  $\geq 15-20$  eosinophils per hpf. Up to 30% children with EoE have grossly visible normal esophageal mucosa or endoscopy.



**Fig. 370.1** Endoscopic visualization of esophageal food impaction (yellow arrow) and mucosal rings (blue arrows).

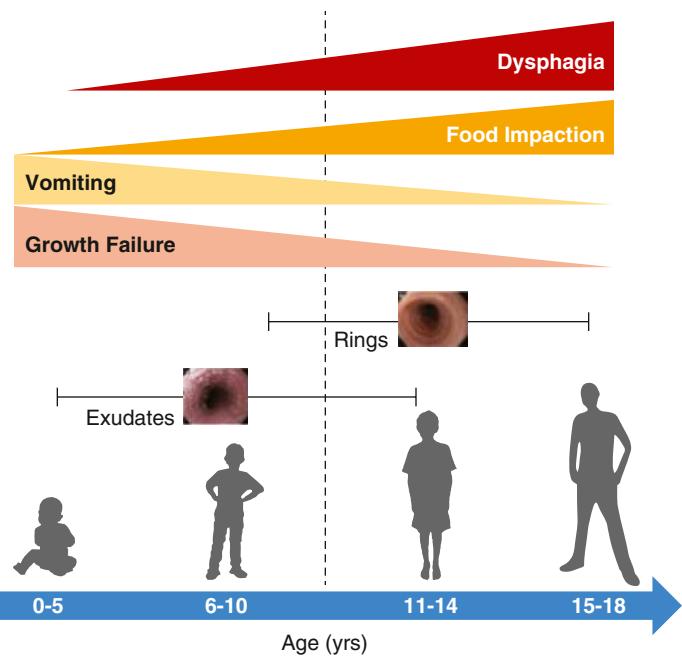
The role of acid in the pathogenesis and treatment of EoE has been the subject of intense research with studies arguing for and against acid suppression. It is important to highlight that gastric acid, among other functions, activates important digestive enzymes and thereby facilitates digestion of food. Acid suppression is postulated to promote absorption of relatively larger intact proteins with allergenic potential as a consequence of reduced food digestion. Dilated esophageal epithelial intercellular spaces that have been described secondary to proton pump inhibition may increase mucosal permeability of food antigens and further provoke allergic pathways. Retrospective studies have shown that infants treated with histamine receptor antagonists and PPIs are at risk for developing EoE at an earlier age compared to matched control infants. EoE is differentiated from GERD by concurrent atopic diseases, its general lack of erosive esophagitis, its greater eosinophil density, and its normal esophageal pH-multichannel intraluminal impedance results. A favorable response to PPI therapy should not be considered diagnostic of GERD, as approximately 50% of children with EoE also demonstrate histologic response. Observations in children and adults with EoE are notable for striking similarities between PPI responders and PPI nonresponders with regard to symptoms, histology, molecular signature, and mechanistic features. This response may be because of an acid suppressive action or downregulation of Th2 allergic cell pathway, an antieosinophil effect of the PPI class that is mediated by inhibition of eotaxin-3 secretion. Evaluation of EoE should include a search for food (aerodigestive) and environmental allergies via skin prick (IgE mediated) and patch (non-IgE mediated) tests to guide decisions regarding dietary elimination and future food challenges.

**Initial treatment** involves dietary restrictions that take one of three forms: elimination diets guided by circumstantial evidence and food allergy test results, “6-food elimination diet” removing the major food allergens (milk, soy, wheat, egg, peanuts and tree nuts, seafood), and trial of an elemental diet composed exclusively of an amino acid-based formula. Elimination diets are generally successful, with highest histologic response observed in nearly 91% on the elemental diet, in 73% who undergo empiric dietary elimination, and 48% with a targeted elimination diet. The major drawbacks of these dietary therapies lie in their cost, difficult access, and lower quality of life, any or all of which influence adherence and outcome.

Topically acting swallowed corticosteroids (fluticasone without spacer, viscous budesonide suspension) are the only therapy strongly recommended based on moderate quality evidence as first-line therapy, as well as for those who refuse, fail to adhere, or have a poor response to restricted diets. Histologic remission is observed in 68–77% children and adults treated with fluticasone for 3 months. Histologic recurrence after discontinuation of fluticasone is common, and emphasizes the need for maintenance therapy. Ideal approaches carefully balance the risks of adrenocortical insufficiency as well as bone demineralization and fungal infections against the risk of EoE evolving from an inflammatory to fibrostenotic disease, which can produce esophageal stenosis and strictures. Therapies under investigation include esophageal-specific delivery formulation of topical corticosteroids and monoclonal antibodies against IL-13 (RPC4046) and IL-5 (mepolizumab, reslizumab). Dupilumab, a monoclonal antibody that inhibits IL-4 and IL-13 signaling, administered by subcutaneous injection, is approved for patients  $\geq 12$  years of age with EoE. Histologic remission and improvement of dysphagia symptoms has occurred during dupilumab therapy with minor side effects (injection site reactions, upper respiratory tract infections, arthralgias, herpes viral infections). Patients require periodic endoscopy and histologic reassessment to accurately monitor response to treatment, particularly given that there can be a significant disconnect between symptoms and histology in the evolution of the disease. Expert clinical guidelines stress the need for long-term studies to develop systematic treatment and best follow-up protocols.

### **INFECTIVE ESOPHAGITIS**

Uncommon, and most often affecting immunocompromised children, infective esophagitis is caused by fungal agents, such as

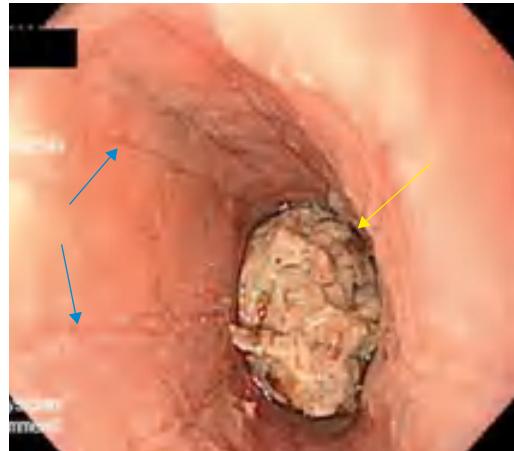


**Fig. 370.2** Eosinophilic esophagitis. Graphical representation of symptoms and endoscopic findings by age. (Modified from Oliva S, Dias JA, Rea F, et al. Characterization of eosinophilic esophagitis from the European pediatric eosinophilic esophagitis registry [pEER] or ESGHAN. *J Pediatr Gastroenterol Nutr.* 2022;75[3]:325–333. Fig. 2.)



**Fig. 370.3** Endoscopic image of eosinophilic esophagitis with characteristic mucosal appearance of furrowing and white specks.

*Candida albicans* and *Torulopsis glabrata*; viral agents, such as herpes simplex (HSV), cytomegalovirus (CMV), HIV, and varicella zoster; and, rarely, bacterial infections, including diphtheria and tuberculosis, or parasites. The typical presenting signs and symptoms are odynophagia, dysphagia, and retrosternal or chest pain; there may also be fever, nausea, and vomiting. *Candida* is the leading cause of infective esophagitis in immunocompetent and immunocompromised children and presents with concurrent oropharyngeal infection in the majority of immunocompromised patients. It may also be an incidental finding in asymptomatic patients, notably in



**Fig. 370.4** Endoscopy photograph showing mucosal furrowing (blue arrows) characteristic of eosinophilic esophagitis in a patient with food impaction (yellow arrow).

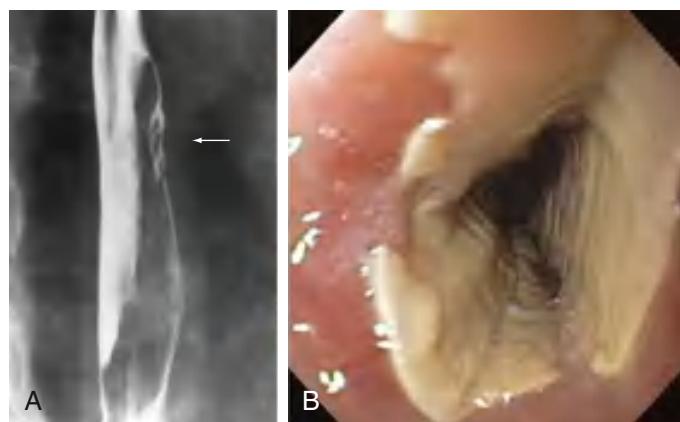
those with EoE receiving topical swallowed corticosteroids. Esophageal viral infections can also manifest in immunocompetent hosts as an acute febrile illness. Infectious esophagitis, like other forms of esophageal inflammation, occasionally progresses to esophageal stricture. Diagnosis of infectious esophagitis is made by endoscopy, usually notable for white plaques in *Candida*, multiple superficial ulcers or *volcano ulcers* in HSV, and single deep ulcer in CMV. Histopathologic examination solidifies the diagnosis with the detection of yeast and pseudohyphae in *Candida*; tissue invasion distinguishes esophagitis from mere colonization. Multinucleated giant cells with intranuclear Cowdry type A (eosinophilic) and type B (ground glass appearance) inclusions in HSV, and both intranuclear and intracytoplasmic inclusions producing an *owl's eye* appearance in CMV are typically described. Adding polymerase chain reaction, tissue-viral culture, and immunocytochemistry enhances the

diagnostic sensitivity and precision. Treatment is with appropriate antimicrobial agents: azole therapy, particularly oral fluconazole for *Candida*; oral acyclovir for HSV; and oral valganciclovir for CMV, or alternatively intravenous ganciclovir in severe CMV disease.

### PILL ESOPHAGITIS

This acute injury is produced by contact with a damaging agent. Medications implicated in pill esophagitis include tetracycline, doxycycline, potassium chloride, ferrous sulfate, nonsteroidal antiinflammatory medications, cloxacillin, and alendronate (Table 370.1). Most often the offending tablet is ingested at bedtime with inadequate water. This practice often produces acute discomfort followed by progressive retrosternal pain, odynophagia, and dysphagia. Endoscopy shows a focal lesion often localized to one of the anatomic narrowed regions of the esophagus or to an unsuspected pathologic narrowing (Fig. 370.5). Treatment is supportive; lacking much evidence, sucralfate, antacids, topical anesthetics, and bland or liquid diets are often used. The offending pill may be restarted after complete resolution of symptoms, if deemed necessary, though with clear emphasis on ingestion with an adequate volume of water, usually at least 4 oz.

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**Fig. 370.5** A, Barium esophagogram showing esophageal ulceration secondary to tetracycline, with the arrow pointing to an area of ulcerations. B, Endoscopic image of a tetracycline-induced esophageal burn. (From Katzka DA. Esophageal disorders caused by medications, trauma, and infection. In Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 10th ed. Philadelphia: Elsevier; 2016: Fig. 46.1).

**Table 370.1** Medications Commonly Associated with Esophagitis or Esophageal Injury

#### ANTIBIOTICS

Clindamycin  
Doxycycline  
Penicillin  
Rifampin  
Tetracycline

#### ANTIVIRAL AGENTS

Nelfinavir  
Zalcitabine  
Zidovudine

#### BISPHOSPHONATES

Alendronate  
Etidronate  
Pamidronate

#### CHEMOTHERAPEUTIC AGENTS

Bleomycin  
Cytarabine  
Dactinomycin  
Daunorubicin  
5-Fluorouracil  
Methotrexate  
Vincristine  
NSAIDs  
Aspirin  
Ibuprofen  
Naproxen

#### OTHER MEDICATIONS

Ascorbic acid  
Ferrous sulfate  
Lansoprazole  
Multivitamins  
Potassium chloride  
Quinidine  
Theophylline

NSAIDs, Nonsteroidal antiinflammatory drugs.

From Katzka DA. Esophageal disorders caused by medications, trauma, and infection. In Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 10th ed. Philadelphia: Elsevier; 2016: Box 46.1.

## Chapter 371

# Esophageal Perforation

Seema Khan

The majority of esophageal perforations in children are from blunt trauma (automobile injury, gunshot wounds, child abuse) or are iatrogenic. Cardiac massage, the Heimlich maneuver, nasogastric tube placement, traumatic laryngoscopy or endotracheal intubation, excessively vigorous postpartum suctioning of the airway during neonatal resuscitation, difficult upper endoscopy, sclerotherapy of esophageal varices, esophageal compression by a cuffed endotracheal tube, and dilation for therapy of achalasia and strictures have all been implicated. Esophageal rupture has followed forceful vomiting in patients with anorexia and has followed esophageal injury due to caustic ingestion, foreign body ingestion, food impactions, pill esophagitis, or eosinophilic esophagitis. Drinking cold, carbonated beverages rapidly is also known to cause esophageal perforation.

Spontaneous esophageal rupture (**Boerhaave syndrome**) is less common and is associated with sudden increases in intraesophageal pressure brought on by situations such as vomiting, coughing, or straining to stool. Children and adults with eosinophilic esophagitis have also been described with Boerhaave syndrome in the setting of forceful emesis in the aftermath of esophageal food impaction. The prevalence of esophageal perforation in a large retrospective analysis was reported to be 0.05%, the majority of whom were low birthweight (<1,000 g) and ≤28 weeks' gestational age. Importantly, esophageal perforation was not associated with an increased mortality in this pediatric cohort. In older children, as in adults, the tear occurs on the distal left lateral esophageal wall, because the smooth muscle layer here is weakest; in neonates (neonatal Boerhaave syndrome), spontaneous rupture is on the right.

Symptoms of esophageal perforation include pain, neck tenderness, dysphagia, subcutaneous crepitus, fever, and tachycardia; several patients with cervical-level esophageal perforations have displayed cold water polydipsia in an attempt to soothe pain in the throat.

Imaging studies are important for a rapid and accurate diagnosis. Perforations in the proximal thoracic esophagus tend to create signs (pneumothorax, effusions) in the left chest, whereas the signs of distal tears are more often on the right. Plain radiography (posteroanterior and lateral views) and CT of the neck and chest are often used, with the latter as more sensitive and accurate in diagnosis. Signs of perforation include pneumomediastinum, mediastinal widening, subcutaneous emphysema, pneumothorax, hydrothorax, pleural effusion, and lung collapse. If these x-rays are normal, an esophagogram using water-soluble contrast media should be performed, but esophagograms miss >30% of cervical perforations. Therefore, a negative water-soluble contrast esophagogram should be followed by a barium study; the greater density of barium can better demonstrate a small defect, although it has a higher risk of inflammatory mediastinitis. Endoscopy may also be useful but carries a 30% false-negative rate.

Treatment must be individualized. Small tears in contained perforations with minimal mediastinal contamination in hemodynamically stable patients can be treated conservatively with broad-spectrum antibiotics, nothing given orally, gastric drainage, and parenteral nutrition. Endoscopic techniques, considered less invasive and morbid, are now being used more frequently and include clips for defects <2 cm, and placement of stents and suturing for larger defects. Chest exploration and direct surgical repair is infrequently indicated these days. Mortality rates range between 20% and 28%, with poor prognosis correlated with delayed diagnosis and interventions.

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## Chapter 372

# Esophageal Varices

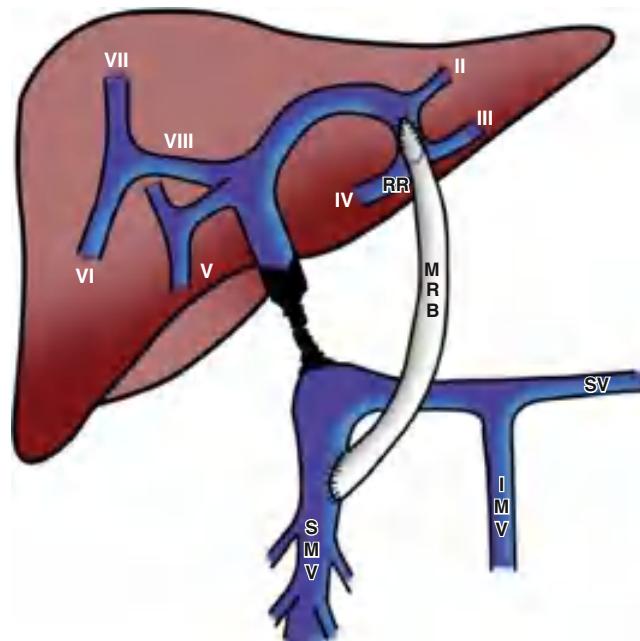
Seema Khan

Esophageal varices form in adults and children with portal hypertension with hepatic venous pressure gradient >10 mm Hg and pose a risk for bleeding at >12 mm Hg (see Chapter 415). Spontaneous decompression of this hypertension through portosystemic collateral circulation via the coronary vein, in conjunction with the left gastric veins, gives rise to esophageal varices. Most esophageal varices are *uphill varices*; less commonly, those that arise in the absence of portal hypertension and with superior vena cava obstruction are *downhill varices*. Their treatment is directed at the underlying cause of the superior vena cava abnormality. Hemorrhage from esophageal varices is the major cause of morbidity and mortality from portal hypertension. Presentation is with significant hematemesis and melena; whereas most patients have liver disease, some children with extrahepatic portal venous obstruction (EHPVO) might have been previously asymptomatic. Any child with hematemesis and splenomegaly should be presumed to have esophageal variceal bleeding until proved otherwise. The leading causes of pediatric portal hypertension, biliary atresia, and EHPVO are uniquely distinct from diseases encountered in adults. Hence, children tend to tolerate variceal bleeding better because they have generally well compensated liver disease, with studies reporting mortality risk <1% after initial variceal bleed. The likelihood of esophageal varices in children with EHPVO increases from 1% to 22%, and small (13%) to large (54%) at 1 year and 5 years of age, respectively. Upper endoscopy is the preferred diagnostic test for esophageal varices, as it provides definitive diagnosis and delineation of details that aid in predicting the risk for bleeding, as well as enabling therapy for acute bleeding episodes via either sclerotherapy or band ligation. A report

comprising a large series of children with biliary atresia and portal hypertension described endoscopic findings of large varices, red marks, and the presence of gastric varices as predictive of bleeding. Noninvasive methods of evaluating varices include barium contrast studies, ultrasound, computerized tomography, magnetic resonance, and elastography, but they are not recommended for routine diagnostic evaluation because of suboptimal accuracy compared to endoscopy.

Primary prophylaxis with the goal of preventing an initial hemorrhage can decrease the incidence of esophageal bleeding; the various modalities used are nonselective  $\beta$ -blockade (e.g., propranolol or nadolol), sclerotherapy, ligation, and portosystemic shunt surgery. Variceal band ligation is regarded as the preferred endotherapy and can be feasibly performed in children weighing more than 10 kg. Meso-Rex bypass surgery should be offered to children with EHPVO as both primary and secondary prophylaxis in the appropriate context (Fig. 372.1). Due to insufficient evidence, the same cannot be recommended regarding endoscopic therapies and non-selective  $\beta$  blockers for primary prophylaxis in children. In contrast, adults do have a reduced risk of first-time variceal bleeding with endoscopic variceal ligation when compared with untreated controls as well as patients treated with  $\beta$ -blockade; a decrease in mortality is only noted compared with the control group (see Chapter 415). The management of acute variceal bleeding must include attention to hemodynamic stability through blood transfusion, vasoactive drugs (e.g., octreotide), short-term antibiotic use, and endoscopy to perform ligation or sclerotherapy, as needed. Transjugular intrahepatic portosystemic shunt should be considered for variceal bleeding refractory to medical and endoscopic therapy. Secondary prophylaxis to reduce recurrence of bleeding uses non-selective  $\beta$ -blockade and obliteration of varices through serial treatment via ligation or sclerotherapy. The only randomized controlled pediatric study has shown superiority of ligation over sclerotherapy in reducing the risk for rebleeding and complications.

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**Fig. 372.1** Meso-Rex bypass between the superior mesenteric vein (SMV) and the Rex recess (RR) of the left portal vein. IMV, Inferior mesenteric vein; MRB, Meso-Rex bypass; SV, splenic vein. (From Brichard M, Iesari S, Lerut J, et al. Meso-Rex bypass for the management of extrahepatic portal vein obstruction in adults. *Hepatobiliary Pancreat Dis Int*. 2022;21:25-32. Fig. 3.)

Imaging studies are important for a rapid and accurate diagnosis. Perforations in the proximal thoracic esophagus tend to create signs (pneumothorax, effusions) in the left chest, whereas the signs of distal tears are more often on the right. Plain radiography (posteroanterior and lateral views) and CT of the neck and chest are often used, with the latter as more sensitive and accurate in diagnosis. Signs of perforation include pneumomediastinum, mediastinal widening, subcutaneous emphysema, pneumothorax, hydrothorax, pleural effusion, and lung collapse. If these x-rays are normal, an esophagogram using water-soluble contrast media should be performed, but esophagograms miss >30% of cervical perforations. Therefore, a negative water-soluble contrast esophagogram should be followed by a barium study; the greater density of barium can better demonstrate a small defect, although it has a higher risk of inflammatory mediastinitis. Endoscopy may also be useful but carries a 30% false-negative rate.

Treatment must be individualized. Small tears in contained perforations with minimal mediastinal contamination in hemodynamically stable patients can be treated conservatively with broad-spectrum antibiotics, nothing given orally, gastric drainage, and parenteral nutrition. Endoscopic techniques, considered less invasive and morbid, are now being used more frequently and include clips for defects <2 cm, and placement of stents and suturing for larger defects. Chest exploration and direct surgical repair is infrequently indicated these days. Mortality rates range between 20% and 28%, with poor prognosis correlated with delayed diagnosis and interventions.

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## Chapter 372

# Esophageal Varices

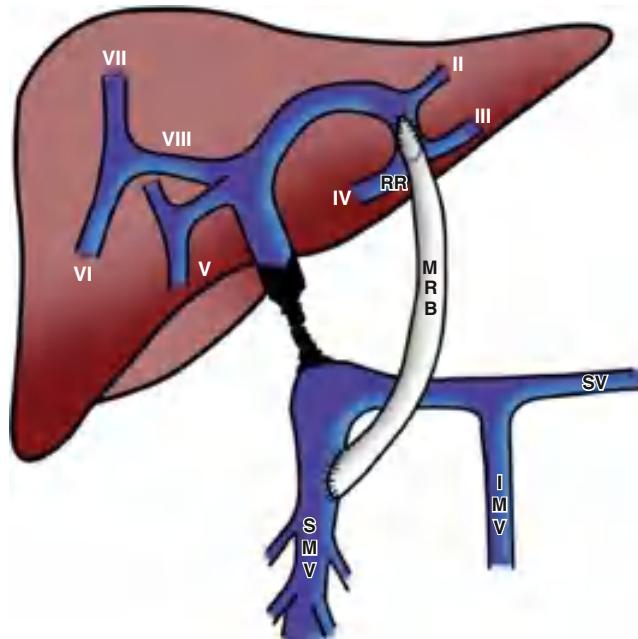
Seema Khan

Esophageal varices form in adults and children with portal hypertension with hepatic venous pressure gradient >10 mm Hg and pose a risk for bleeding at >12 mm Hg (see Chapter 415). Spontaneous decompression of this hypertension through portosystemic collateral circulation via the coronary vein, in conjunction with the left gastric veins, gives rise to esophageal varices. Most esophageal varices are *uphill varices*; less commonly, those that arise in the absence of portal hypertension and with superior vena cava obstruction are *downhill varices*. Their treatment is directed at the underlying cause of the superior vena cava abnormality. Hemorrhage from esophageal varices is the major cause of morbidity and mortality from portal hypertension. Presentation is with significant hematemesis and melena; whereas most patients have liver disease, some children with extrahepatic portal venous obstruction (EHPVO) might have been previously asymptomatic. Any child with hematemesis and splenomegaly should be presumed to have esophageal variceal bleeding until proved otherwise. The leading causes of pediatric portal hypertension, biliary atresia, and EHPVO are uniquely distinct from diseases encountered in adults. Hence, children tend to tolerate variceal bleeding better because they have generally well compensated liver disease, with studies reporting mortality risk <1% after initial variceal bleed. The likelihood of esophageal varices in children with EHPVO increases from 1% to 22%, and small (13%) to large (54%) at 1 year and 5 years of age, respectively. Upper endoscopy is the preferred diagnostic test for esophageal varices, as it provides definitive diagnosis and delineation of details that aid in predicting the risk for bleeding, as well as enabling therapy for acute bleeding episodes via either sclerotherapy or band ligation. A report

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Primary prophylaxis with the goal of preventing an initial hemorrhage can decrease the incidence of esophageal bleeding; the various modalities used are nonselective  $\beta$ -blockade (e.g., propranolol or nadolol), sclerotherapy, ligation, and portosystemic shunt surgery. Variceal band ligation is regarded as the preferred endotherapy and can be feasibly performed in children weighing more than 10 kg. Meso-Rex bypass surgery should be offered to children with EHPVO as both primary and secondary prophylaxis in the appropriate context (Fig. 372.1). Due to insufficient evidence, the same cannot be recommended regarding endoscopic therapies and non-selective  $\beta$  blockers for primary prophylaxis in children. In contrast, adults do have a reduced risk of first-time variceal bleeding with endoscopic variceal ligation when compared with untreated controls as well as patients treated with  $\beta$ -blockade; a decrease in mortality is only noted compared with the control group (see Chapter 415). The management of acute variceal bleeding must include attention to hemodynamic stability through blood transfusion, vasoactive drugs (e.g., octreotide), short-term antibiotic use, and endoscopy to perform ligation or sclerotherapy, as needed. Transjugular intrahepatic portosystemic shunt should be considered for variceal bleeding refractory to medical and endoscopic therapy. Secondary prophylaxis to reduce recurrence of bleeding uses non-selective  $\beta$ -blockade and obliteration of varices through serial treatment via ligation or sclerotherapy. The only randomized controlled pediatric study has shown superiority of ligation over sclerotherapy in reducing the risk for rebleeding and complications.

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## Chapter 373

# Ingestions

### 373.1 Foreign Bodies in the Esophagus

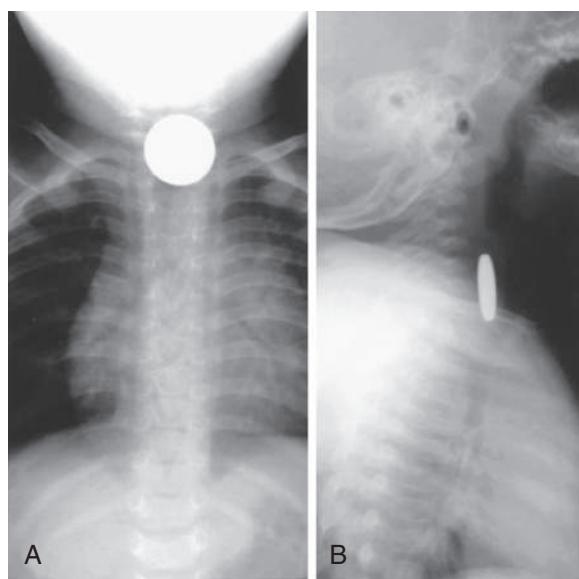
Seema Khan

The majority (80%) of accidental foreign-body ingestions occur in children, most of whom are 5 years of age or younger. Older children and adolescents with developmental delays and those with psychiatric disorders are also at increased risk. Most ingested foreign bodies are associated with a good outcome as they pass spontaneously through an anatomically normal digestive tract. The presentation of a foreign body lodged in the esophagus constitutes an emergency and is associated with significant morbidity and mortality because of the potential for perforation and sepsis. Although coins are by far the most commonly ingested foreign body, followed by small toy items, it is the ingestion of batteries and multiple magnets that could lead to life-threatening complications. Food impactions are less common in children than in adults and usually occur in children in association with eosinophilic esophagitis (diagnosed in 92% of those presenting with food impactions and dysphagia), repair of esophageal atresia, and Nissen fundoplication. Most esophageal foreign bodies lodge at the level of the cricopharyngeus (upper esophageal sphincter), the aortic arch, or just superior to the diaphragm at the gastroesophageal junction (lower esophageal sphincter).

At least 30% of children with esophageal foreign bodies may be totally asymptomatic, so any history of foreign-body ingestion should be taken seriously and investigated. An initial bout of choking, gagging, and coughing may be followed by excessive salivation, dysphagia, food refusal, emesis, or pain in the neck, throat, or sternal notch regions. Respiratory symptoms such as stridor, wheezing, cyanosis, or dyspnea may be encountered if the esophageal foreign body impinges on the larynx or membranous posterior tracheal wall. Cervical swelling, erythema, or subcutaneous crepitations suggest perforation of the oropharynx or proximal esophagus.

Evaluation of the child with a history of foreign-body ingestion starts with plain anteroposterior radiographs of the neck, chest, and abdomen, along with lateral views of the neck and chest. The flat surface of a coin in the esophagus is seen on the anteroposterior view and the edge on the lateral view (Fig. 373.1). The reverse is true for coins lodged in the trachea; here, the edge is seen anteroposteriorly and the flat side is seen laterally. Disk-shaped button batteries can look like coins and can be differentiated on close examination by the double halo (not obvious in the new slimmer batteries) and step-off (indicating the negative pole) on anteroposterior and lateral views, respectively (Fig. 373.2). The use of button batteries has been increasingly popular, leading to a sharp rise in accidental ingestions, and an increase in morbidity and mortality. The latter is thought to be due to both an increase in diameter and a change to lithium cells. Children younger than 5 years of age with ingestion of batteries  $\geq 20$  mm are considered to have the highest risk for catastrophic events such as necrosis, tracheoesophageal fistula, perforation, stricture, vocal cord paralysis, mediastinitis, and aortoenteric fistula (Fig. 373.3). Materials such as plastic, wood, glass, aluminum, and bones may be radiolucent; failure to visualize the object with plain films in a symptomatic patient warrants urgent endoscopy. CT scan with three-dimensional reconstruction may increase the sensitivity of imaging a foreign body. Although barium contrast studies may be helpful in the occasional asymptomatic patient with negative plain films, their use is to be discouraged because of the potential of aspiration, as well as making subsequent visualization and object removal more difficult.

In managing the child with an esophageal foreign body, it is important to assess risk for airway compromise and to obtain a chest CT scan and surgical consultation in cases of suspected airway perforation. Treatment of esophageal foreign bodies usually merits endoscopic visualization of the



**Fig. 373.1** Radiographs of a coin in the esophagus. When foreign bodies lodge in the esophagus, the flat surface of the object is seen in the anteroposterior view (A) and the edge is seen in the lateral view (B). The reverse is true for objects in the trachea. (Courtesy Beverley Newman, MD.)

object and underlying mucosa and removal of the object using an appropriately designed foreign body–retrieving accessory instrument through the endoscope and with an endotracheal tube protecting the airway. Sharp objects in the esophagus, multiple magnets or a single magnet with a metallic object, or foreign bodies associated with respiratory symptoms mandate urgent removal within 12 hours of presentation. Button batteries, in particular, must be emergently removed within 2 hours of presentation regardless of the timing of the patient's last oral intake, because they can induce mucosal injury in as little as 1 hour of contact time and involve all esophageal layers within 4 hours (see Fig. 373.3; Fig. 373.4). In cases of delayed endoscopic intervention, frequent ingestion of honey and sucralose are recommended as mitigation measures to reduce injury. Asymptomatic blunt objects and coins lodged in the esophagus can be observed for up to 24 hours in anticipation of passage into the stomach. If there are no problems in handling secretions, meat impactions can be observed for up to 24 hours. In patients without prior esophageal surgeries, glucagon (0.05 mg/kg intravenously; maximum pediatric dose, 0.5 mg; adult dose, 1–2 mg) can sometimes be useful in facilitating passage of distal esophageal food boluses by decreasing the lower esophageal sphincter pressure. The use of meat tenderizers or gas-forming agents can lead to perforation and are not recommended. An alternative technique for removing esophageal coins impacted for <24 hours, performed most safely by experienced radiology personnel, consists of passage of a Foley catheter beyond the coin at fluoroscopy, inflating the balloon, and then pulling the catheter and coin back simultaneously with the patient in a prone oblique position. Concerns about the lack of direct mucosal visualization and, when tracheal intubation is not used, the lack of airway protection prompt caution in the use of this technique. Bougienage of esophageal coins toward the stomach in selected uncomplicated pediatric cases has been suggested to be an effective, safe, and economical modality where endoscopy might not be routinely available.

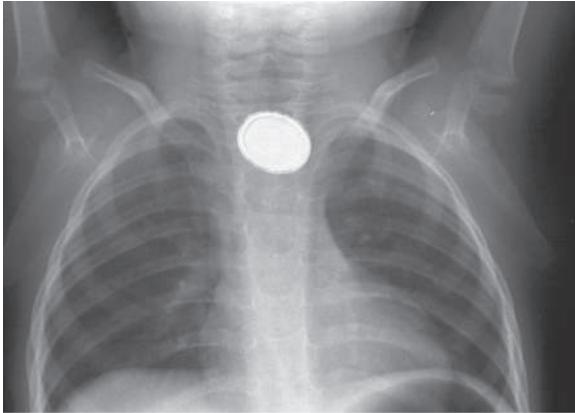
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### 373.2 Caustic Ingestions

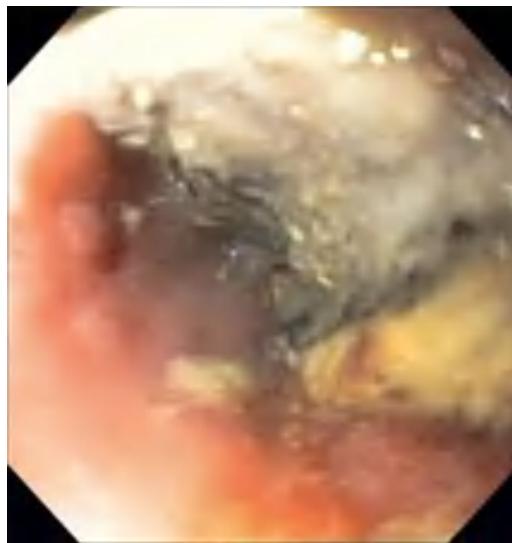
Seema Khan

Ingestion of caustic substances is a worldwide public health problem accounting for a significant burden on healthcare resources. According

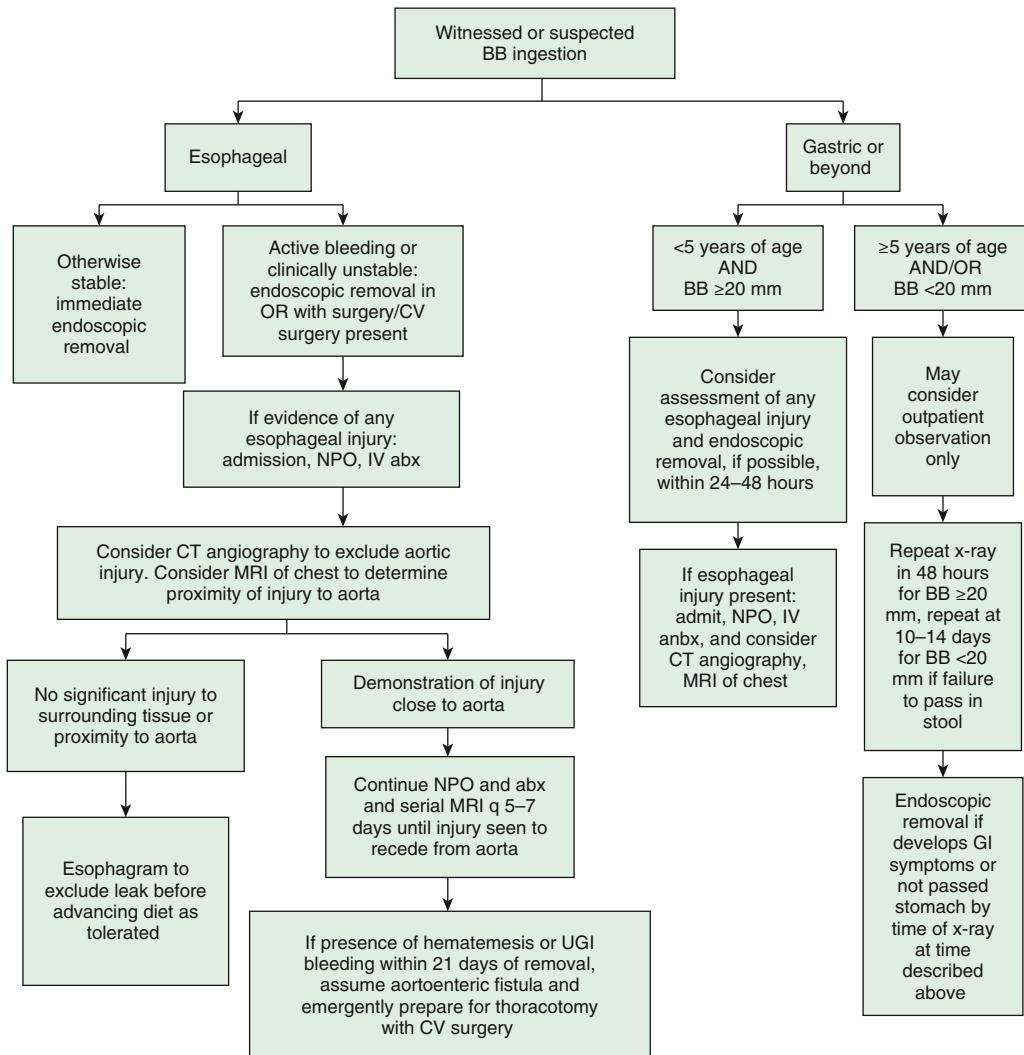
to an inpatient database of U.S. pediatric hospital discharges in 2009, the estimated number of caustic ingestions was 807 (95% confidence interval [CI], 731–882) cases, amounting to \$22.9 million in total hospital charges. The medical sequelae of caustic ingestions are esophagitis, necrosis, perforation, and stricture formation (see Chapter 94). Most cases (70%) are accidental ingestions of liquid alkali substances that produce severe, deep liquefaction necrosis; drain decloggers are



**Fig. 373.2** Disk battery impacted in esophagus. Note the double rim. (From Wyllie R, Hyams JS, eds. *Pediatric Gastrointestinal and Liver Disease*, 3rd ed. Philadelphia: Saunders; 2006.)



**Fig. 373.3** Severe esophageal injury at site of button battery (BB) removal, with necrosis and eschar. (From Leinwand K, Brumbaugh DE, Kramer RE. Button battery ingestion in children—a paradigm for management of severe pediatric foreign-body ingestions. *Gastrointest Endosc Clin North Am*. 2016;26:99–118. Fig. 1.)



**Fig. 373.4** Proposed management algorithm for ingestion of button battery (BB) in children. Abx, Antibiotics; CV, cardiovascular; GI, gastrointestinal; IV, intravenous; NPO, nil per os; OR, operating room; q, every; UGI, upper gastrointestinal series. (From Kramer RE, Lerner DG, Lin T, et al. Management of ingested foreign bodies in children: a clinical report of the NASPGHAN endoscopy committee. *J Pediatr Gastroenterol Nutr*. 2015;60[4]:562–574. Fig. 1.)

**Table 373.1** Ingestible Caustic Materials Around the House

CATEGORY	MOST DAMAGING AGENTS	OTHER AGENTS
Alkaline drain cleaners, milking machine pipe cleaners	Sodium or potassium hydroxide	Ammonia, sodium hypochlorite, aluminum particles
Acidic drain openers	Hydrochloric acid, sulfuric acid	
Toilet cleaners	Hydrochloric acid, sulfuric acid, phosphoric acid, other acids	Ammonium chloride, sodium hypochlorite
Oven and grill cleaners	Sodium hydroxide, perborate (borax)	
Denture cleaners	Persulfate (sulfur), hypochlorite (bleach)	
Dishwasher detergent		
Liquid	Sodium hydroxide	
Powdered	Sodium hypochlorite	
Packaged	Sodium carbonate	
Bleach	Sodium hypochlorite	Ammonia salt
Swimming pool chemicals	Acids, alkalis, chlorine	
Battery acid (liquid)	Sulfuric acid	
Disk batteries	Electric current	Zinc or other metal salts
Rust remover	Hydrofluoric, phosphoric, oxalic, and other acids	
Household delimers	Phosphoric acid, hydroxyacetic acid, hydrochloric acid	
Barbeque cleaners	Sodium and potassium hydroxide	
Glyphosate surfactant (RoundUp) acid	Glyphosate herbicide	Surfactants
Hair relaxer	Sodium hydroxide	
Weed killer	Dichlorophenoxyacetate, ammonium phosphate, propionic acid	

Source: National Library of Medicine: *Health and Safety Information on Household Products* (website). <http://householdproducts.nlm.nih.gov/>. From Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*, 4th ed. Philadelphia: Saunders; 2011: Table 19.1, p. 198.

most common, and because they are tasteless, more is ingested (Table 373.1). **Acidic agents** (20% of cases) are bitter, so less may be consumed; they produce coagulation necrosis and a somewhat protective thick eschar. They can produce severe gastritis, and volatile acids can result in respiratory symptoms. Children younger than 5 years of age account for half of the cases of caustic ingestions, and boys are far more often involved than girls.

Caustic ingestions produce signs and symptoms such as vomiting, drooling, refusal to drink, oral burns, dysphagia, dyspnea, abdominal pain, hematemesis, and stridor. Twenty percent of patients develop esophageal strictures. Absence of oropharyngeal lesions does not exclude the possibility of significant esophagogastric injury, which can lead to perforation or stricture. The absence of symptoms is usually associated with no or minimal lesions; hematemesis, respiratory distress, or presence of at least three symptoms predicts severe lesions. An upper endoscopy is recommended as the most efficient means of rapid identification of tissue damage and must be undertaken in all symptomatic children within the first 24–48 hours of ingestion. In select situations when endoscopy may not be possible, CT of the chest and abdomen should be considered in the evaluation of transmural and extraesophageal injury, as well as in anticipation of emergent surgical planning.

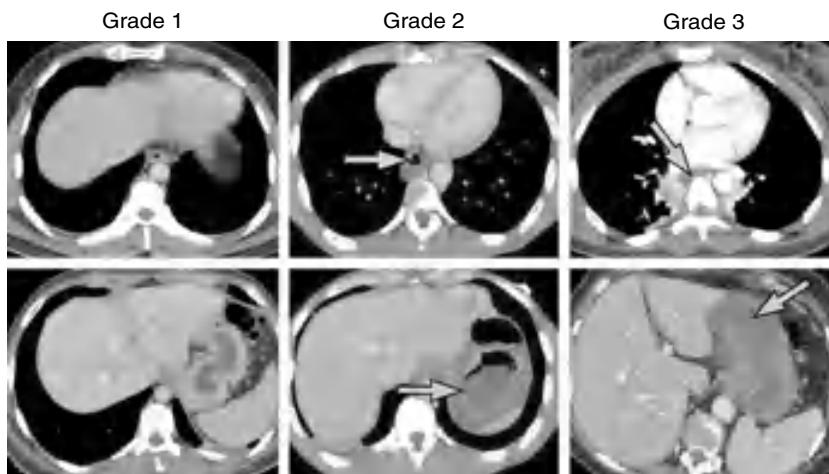
Dilution by water or milk is recommended as acute treatment, but neutralization, induced emesis, and gastric lavage are contraindicated. Treatment depends on the severity and extent of damage (Table 373.2, Fig. 373.5). Stricture risk is increased by circumferential ulcerations, white plaques, and sloughing of the mucosa and is reported to occur in 70–100% of grade 2b and grade 3 caustic esophagitis. Strictures can require treatment with dilation, and in some severe cases, surgical resection and colon or small bowel interposition are needed. Silicone stents (self-expanding) placed endoscopically after a dilation procedure can be an alternative and conservative approach to the management of strictures. Rare late cases of superimposed esophageal carcinoma are reported. The role of corticosteroids is controversial; they are not recommended in grade 1 burns, but they can reduce the risk of strictures in more-advanced caustic esophagitis. Many centers also use proton pump inhibitors as well as antibiotics in the initial treatment of caustic esophagitis on the premise that reducing superinfection in the necrotic tissue bed will, in turn, lower the risk of stricture formation. Studies examining the role of antibiotics in caustic esophagitis have not reported a clinically significant benefit even in those with grade 2 or greater severity of esophagitis.

There may be an increase of esophageal (not gastric) carcinoma following a caustic ingestion.

**Table 373.2** Classification of Caustic Injury

GRADE	VISIBLE APPEARANCE	CLINICAL SIGNIFICANCE
Grade 0	History of ingestion but no visible damage or symptoms	Able to take fluids immediately
Grade 1	Edema, loss of normal vascular pattern, hyperemia, no transmucosal injury	Temporary dysphagia, able to swallow within 0-2 days, no long-term sequelae
Grade 2a	Transmucosal injury with friability, hemorrhage, blistering, exudate, scattered superficial ulceration	Scarring, no circumferential damage (no stenosis), no long-term sequelae
Grade 2b	Grade 2a plus discrete ulceration and/or circumferential ulceration	Small risk of perforation, scarring that may result in later stenosis
Grade 3a	Scattered deep ulceration with necrosis of the tissue	Risk of perforation, high risk of later stenosis
Grade 3b	Extensive necrotic tissue	High risk of perforation and death, high risk of stenosis

From Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*, 4th ed. Philadelphia: Saunders; 2011: Table 19.2, p. 199.



**Fig. 373.5** CT grading of corrosive injuries of the esophagus and the stomach. Grade 1, normal appearance; grade 2, wall and soft tissue edema, increased wall enhancement (arrow); grade 3, transmural necrosis with absent wall enhancement (arrow). (From Chirica M, Bonavina L, Kelly MD, et al. Caustic ingestion. *Lancet*. 2017;389:2041–2050. Fig. 1.)

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## Section 4

# Stomach and Intestines

### Chapter 374

## Normal Development, Structure, and Function of the Stomach and Intestines

Asim Maqbool and Chris A. Liacouras

### DEVELOPMENT

The primitive gut is recognizable by the fourth week of gestation and is composed of the foregut, midgut, and hindgut. The **foregut** gives rise to the upper gastrointestinal tract, which includes the esophagus, stomach, and duodenum to the level of the insertion of the common bile duct.

The **midgut** gives rise to the rest of the small bowel and the large bowel to the level of the midtransverse colon. The **hindgut** forms the remainder of the colon and upper anal canal. The rapid growth of the midgut causes it to protrude out of the abdominal cavity through the umbilical ring during fetal development. The midgut subsequently returns to the peritoneal cavity and rotates counterclockwise until the cecum lies in the right lower quadrant. The process is normally complete by the eighth week of gestation.

The liver derives from the hepatic diverticulum that evolves into parenchymal cells, bile ducts, vascular structures, and hematopoietic and Kupffer cells. The extrahepatic bile ducts and gallbladder develop first as solid cords that canalize by the third month of gestation. The dorsal and ventral pancreatic buds grow from the foregut by the fourth week of gestation. The two buds fuse by the sixth week. Exocrine secretory capacity is present by the fifth month.

*Cis*-regulatory genomic sequences govern gene expression during development. Modules of *cis* sequences are linked and allow a cascade of gene regulation that controls functional development. Extrinsic factors have the capacity to influence gene expression. In the gut, several growth factors, including growth factor-β, insulin-like growth factor, and growth factors found in human colostrum (human growth factor and epidermal growth factor), influence gene expression.

Propulsion of food down the gastrointestinal tract relies on the coordinated action of muscles in the bowel wall. The contractions are regulated by the enteric nervous system under the influence of a variety of peptides and hormones. The enteric nervous system is derived from neural crest cells that migrate in a cranial to caudal fashion. Migration of the neural crest tissue is complete by the 24th week of gestation.

Interruption of the migration results in **Hirschsprung disease**. Newborn bowel motor patterns are different from adults. Normal fasting upper gastrointestinal motility is characterized by a triphasic pattern known as the migrating motor complex. Migrating motor complexes occur less often in neonates, and they have more nonmigrating phasic activity. This leads to ineffective propulsion, particularly in premature infants. Motility in the fed state consists of a series of ring contractions that spread caudad over variable distances.

### DIGESTION AND ABSORPTION

The wall of the stomach, small bowel, and colon consists of four layers: mucosa, submucosa, muscularis, and serosa. Eighty-five percent of the gastric mucosa is lined by oxytic glands containing cells that secrete hydrochloric acid, pepsinogen, and intrinsic factor, and mucous and endocrine cells that secrete peptides having paracrine and endocrine effects. Pepsinogen is a precursor of the proteolytic enzyme pepsin, and intrinsic factor is required for the absorption of vitamin B<sub>12</sub>. Pyloric glands are located in the antrum and contain gastrin-secreting cells. Acid production and gastrin levels are inversely related to each other except in pathologic secretory states. Acid secretion is low at birth but increases dramatically by 24 hours. Acid and pepsin secretions peak in the first 10 days and decrease from 10 to 30 days after birth. Intrinsic factor secretion rises slowly in the first 2 weeks of life.

The small bowel is approximately 270 cm long at birth in a term neonate and grows to an adult length of 450–550 cm by 4 years of age. The mucosa of the small intestine is composed of villi, which are finger-like projections of the mucosa into the bowel lumen that significantly expand the absorptive surface area. The mucosal surface is further expanded by a brush border containing digestive enzymes and transport mechanisms for monosaccharides, amino acids, dipeptides and tripeptides, and fats. The cells of the villi originate in adjacent crypts and become functional as they migrate from the crypt up the villus. The small bowel mucosa is completely renewed in 4–5 days, providing a mechanism for rapid repair after injury, but in young infants or malnourished children, the process may be delayed. Crypt cells also secrete fluid and electrolytes. The villi are present by 8 weeks of gestation in the duodenum and by 11 weeks in the ileum.

Disaccharidase activities are measurable at 12 weeks, but lactase activity does not reach maximal levels until 36 weeks. Even premature infants usually tolerate lactose-containing formulas because of carbohydrate salvage by colonic bacteria. In children of African and Asian ethnicity, lactase levels may begin to fall at 4 years of age, leading to intolerance to mammalian milk. Mechanisms to digest and absorb protein, including pancreatic enzymes and mucosal mechanisms to transport amino acids, dipeptides, and tripeptides, are in place by the 20th week of gestation.

Carbohydrates, protein, and fat are normally absorbed by the upper half of the small intestine; the distal segments represent a vast reserve of absorptive capacity. Most of the sodium, potassium, chloride, and water are absorbed in the small bowel. Bile salts and vitamin B<sub>12</sub> are selectively absorbed in the distal ileum, and iron is absorbed in the duodenum and proximal jejunum. Intraluminal digestion depends on the exocrine pancreas. Secretin and cholecystokinin stimulate synthesis and secretion of bicarbonate and digestive enzymes, which are released by the upper intestinal mucosa in response to various intraluminal stimuli, among them components of the diet.

**Carbohydrate digestion** is normally an efficient process that is completed in the distal duodenum. Starches are broken down to glucose, oligosaccharides, and disaccharides by pancreatic amylase. Residual glucose polymers are broken down at the mucosal level by glucoamylase. Lactose is broken down at the brush border by lactase, forming glucose and galactose; sucrose is broken down by sucrase-isomaltase to fructose and glucose. Galactose and glucose are primarily transported into the cell by a sodium- and energy-dependent process, whereas fructose is transported by facilitated diffusion.

**Proteins** are hydrolyzed by pancreatic enzymes, including trypsin, chymotrypsin, elastase, and carboxypeptidases, into individual amino acids and oligopeptides. The pancreatic enzymes are secreted as proenzymes, which are activated by release of the mucosal enzyme enterokinase. Oligopeptides are further broken down at the brush border by peptidases into dipeptides, tripeptides, and amino acids. Protein can enter the cell by separate noncompetitive carriers that can transport individual amino acids or dipeptides and tripeptides similar to those in the renal tubule. The human

gut is capable of absorbing antigenic intact proteins in the first few weeks of life because of *leaky* junctions between enterocytes. Entry of potential protein antigens through the mucosal barrier might have a role in later food- and microbe-induced symptoms.

**Fat absorption** occurs in two phases. Dietary triglycerides are broken down into monoglycerides and free fatty acids by pancreatic lipase and colipase. The free fatty acids are subsequently emulsified by bile acids, forming micelles with phospholipids and other fat-soluble substances, and are transported to the cell membrane, where they are absorbed. The fats are reesterified in the enterocyte, forming chylomicrons that are transported through the intestinal lymphatics to the thoracic duct. Medium-chain fats are absorbed more efficiently and can directly enter the cell. They are subsequently transported to the liver via the portal system. Fat absorption can be affected at any stage of the digestion and absorption process. Decreased pancreatic enzymes occur in cystic fibrosis, cholestatic liver disease leads to poor bile salt production and micelle formation, celiac disease affects mucosal surface area, abnormal chylomicron formation occurs in abetalipoproteinemia, and intestinal lymphangiectasia affects transport of the chylomicrons.

Fat absorption is less efficient in the neonate compared with adults. Premature infants can lose up to 20% of their fat calories compared with up to 6% in the adult. Decreased synthesis of bile acids and pancreatic lipase and decreased efficiency of ileal absorption are contributing factors. Fat digestion in the neonate is facilitated by lingual and gastric lipases. Bile salt-stimulated lipase in human milk augments the action of pancreatic lipase. Infants with malabsorption of fat are usually fed with formulas that have a greater percentage of medium-chain triglycerides, which are absorbed independently of bile salts.

The colon is a 75- to 100-cm sacculated tube formed by three strips of longitudinal muscle called *taenia coli* that traverse its length and fold the mucosa into haustra. Haustra and taenia appear by the 12th week of gestation. The most common motor activity in the colon is nonpropulsive rhythmic segmentation that acts to mix the chyme and expose the contents to the colonic mucosa. Mass movement within the colon typically occurs after a meal. The colon extracts additional water and electrolytes from the luminal contents to render the stools partially or completely solid. The colon also acts to scavenge by-products of bacterial degradation of carbohydrates. Stool is stored in the rectum until distention triggers a defecation reflex that, when assisted by voluntary relaxation of the external sphincter, permits evacuation.

### THE GASTROINTESTINAL MICROBIOTA

The term “microbiome” refers to organisms and their genomes/functions, whereas “microbiota” refers to the organisms themselves. The difference is very subtle, and sometimes they are used interchangeably.

The gastrointestinal microbiota composition develops early in life; it is influenced by environmental exposures, including specifically exposure to maternal flora (via vaginal delivery vs C-section), birth location (hospital vs at home, suburban vs rural), antibiotic use, and prominently are related to diet and infant feeding practices (breastfed vs formula fed, food supplementation). The richness and diversity of gastrointestinal microbiota developed early, as does gastrointestinal immunotolerance to it. Microbiota concentration and complexity increase from proximal to distal throughout the gastrointestinal tract.

This microflora has implications on human health and disease. There is a symbiotic relationship between the host of the gastrointestinal tract and the commensal microflora. These microorganisms are involved in the fermentation of undigestible carbohydrates (in particular, fiber), resulting in short-chain fatty acids, the preferred fuel for colonic tissues. Additionally, the microbiota is involved in the metabolism of intraluminal conjugated bile acids, and the synthesis of vitamins (vitamin K), and in the degradation of other compounds. The metabolome specifically refers to the collection of metabolites that organisms produce.

The composition of the intestinal microbiota may render individuals at risk for noncommunicable diseases, including obesity. The intestinal microbiota may have implications for vaccine efficacy. Perturbations in the intestinal microbiota composition may increase risk for gastrointestinal inflammatory conditions and disorders, including inflammatory bowel disease.

## Chapter 375

# Pyloric Stenosis and Other Congenital Anomalies of the Stomach

### 375.1 Hypertrophic Pyloric Stenosis

Arunjot Singh and Chris A. Liacouras

Hypertrophic pyloric stenosis occurs in 2-5/1,000 infants in the United States. It is common in White people, particularly of northern European ancestry, and less frequent in Black and Asian populations. Males (especially firstborns) are affected approximately 4 times as often as females. There is a familial link with an increased risk in offspring of parent(s) with pyloric stenosis. Pyloric stenosis develops in approximately 20% of the male and 10% of the female descendants of a mother who had pyloric stenosis. Pyloric stenosis has also been associated with other congenital defects, including tracheoesophageal fistula and hypoplasia or agenesis of the inferior labial frenulum.

#### Etiology

The etiology of infantile hypertrophic pyloric stenosis is unknown, although many genetic and environmental factors have been implicated. Development of pyloric stenosis is likely postnatal, given that it is unusual in stillbirths. Genetic predisposition, a well-established risk of pyloric stenosis, is more concordant in monozygotic than dizygotic twins. Pyloric stenosis has been associated with eosinophilic gastroenteritis, Apert syndrome, Zellweger syndrome, trisomy 18, Smith-Lemli-Opitz syndrome, and Cornelia de Lange syndrome (Table 375.1). An association has been seen with the use of macrolide antibiotics, particularly erythromycin in neonates, if given within the first 2 weeks of life. There have also been reports of a higher incidence of pyloric stenosis among mostly female infants of mothers treated with macrolide antibiotics during pregnancy and breastfeeding. Other risk factors may include formula feeding and a maternal history of smoking during pregnancy. Abnormal muscle innervation, elevated serum levels of prostaglandins, and infant hypergastrinemia have also been

implicated. Multiple genetic susceptibility loci have been identified including *IHPS* genes on chromosomes 12q, 16p13 and 11q14, and Xq23. The etiologic role of nitric oxide synthase gene (*NOS1*) is also apparent with reduced levels of neuronal nitric oxide found via altered expression of the neuronal nitric oxide synthase exon 1c regulatory region.

#### CLINICAL MANIFESTATIONS

Nonbilious vomiting is the initial symptom of pyloric stenosis. The vomiting may or may not be projectile initially but is usually progressive, occurring immediately after a feeding. Emesis might follow each feeding, or it may be intermittent. The vomiting usually starts after 3 weeks of age, but symptoms can develop as early as the first week of life and as late as 5 months of age. On rare occasions, late-onset pyloric stenosis may develop between 2 and 8 years of life. Approximately 20% have intermittent emesis from birth that then progresses to the classic picture. After vomiting, the infant is hungry and wants to feed again. As vomiting continues, a progressive loss of fluid, hydrogen ion, and chloride leads to *hypochloremic metabolic alkalosis*. Awareness of pyloric stenosis has led to earlier identification of patients with fewer instances of chronic malnutrition and severe dehydration and at times a subclinical self-resolving hypertrophy.

Hyperbilirubinemia is the most common clinical association of pyloric stenosis, also known as *icteropyloric syndrome*. Unconjugated hyperbilirubinemia is more common than the conjugated type and usually resolves with surgical correction of the pyloric stenosis. It may be associated with a decreased level of glucuronyl transferase as seen in approximately 5% of affected infants. Pathogenic gene variants in the bilirubin uridine diphosphate glucuronosyltransferase gene (*UGT1A1*) have also been implicated, supporting the notion that Gilbert syndrome may be linked in pathogenesis. If conjugated hyperbilirubinemia is a part of the presentation, other etiologies need to be investigated including eosinophilic gastroenteritis, hiatal hernia, peptic ulcer, congenital nephrotic syndrome, congenital heart disease, and congenital hypothyroidism.

The diagnosis has clinically been established by palpating a pyloric mass. The mass is firm, movable, approximately 2 cm in length, olive shaped, and best palpated when the patient is lying on the left side. The mass is located above and to the right of the umbilicus in the midepigastrium beneath the liver edge. The olive is easiest palpated after an episode of vomiting. After feeding, there may be a visible gastric peristaltic wave that progresses across the abdomen (Fig. 375.1). *Earlier imaging diagnosis has made the palpable olive a less common physical finding.*

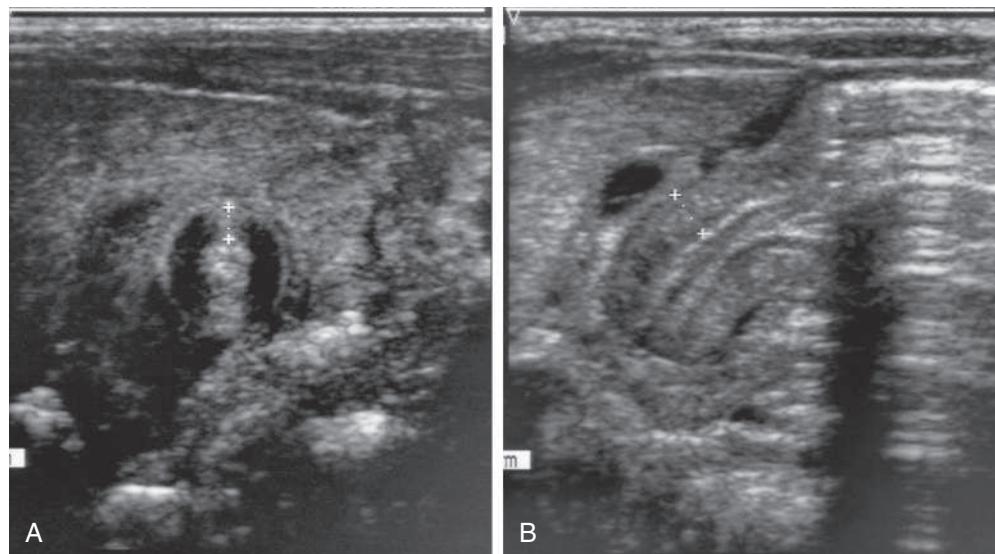
Two imaging studies are used to establish the diagnosis. Ultrasound examination confirms the diagnosis in the majority of cases. Criteria for diagnosis include pyloric thickness 3-4 mm, an overall pyloric

**Table 375.1** Etiology of Gastric Outlet Obstruction

CONGENITAL	
Aplasia	
Atresia	
Diaphragms, webs, valves	
Ectopic pancreatic rests	
Gastric duplication	
Associated with epidermolysis bullosa	
IDIOPATHIC HYPERTROPHIC PYLORIC STENOSIS	
Infantile-onset pyloric stenosis	
Late onset	
Associated with medications: erythromycin, prostaglandin E1	
ACQUIRED	
Peptic ulcer disease	
Caustic chemical injury	
Bezoars: lacto-, phyo-, tricho-, medications	
Associated with Crohn disease	
Associated with chronic granulomatous disease	
Associated with eosinophilic gastroenteritis	
Tumor	
Gastric volvulus	



**Fig. 375.1** Gastric peristaltic wave in an infant with pyloric stenosis.



**Fig. 375.2** A, Transverse sonogram demonstrating a pyloric muscle wall thickness of >4 mm (distance between crosses). B, Horizontal image demonstrating a pyloric channel length >14 mm (wall thickness outlined between crosses) in an infant with pyloric stenosis.



**Fig. 375.3** Barium in the stomach of an infant with projectile vomiting. The attenuated pyloric canal is typical of congenital hypertrophic pyloric stenosis.

length 15–19 mm, and pyloric diameter of 10–14 mm (Fig. 375.2). Ultrasonography has a sensitivity of approximately 95%. Less commonly, an upper gastrointestinal (GI) contrast study is used. Contrast studies demonstrate an elongated pyloric channel (string sign), a bulge of the pyloric muscle into the antrum (shoulder sign), and parallel streaks of barium seen in the narrowed channel, producing a “double tract sign” (Fig. 375.3).

#### DIFFERENTIAL DIAGNOSIS

Pyloric stenosis must be differentiated from other causes that present with vomiting, irritability, and dehydration in the infant. Gastroesophageal reflux is one of the most common etiologies of vomiting. In contrast to pyloric stenosis, reflux is typically a self-limiting condition that manifests with frequent effortless regurgitation and vomiting and usually does not cause abnormal chemistries. If symptoms are significant, reflux can be differentiated from pyloric stenosis by radiographic studies. Adrenogenital syndrome can also simulate

pyloric stenosis; however, abnormalities including metabolic acidosis and elevated serum potassium and urinary sodium concentrations of adrenal insufficiency aid in differentiation. Inborn errors of metabolism can also cause recurrent emesis and are manifested by alkalosis (urea cycle) or acidosis (organic aciduria) with lethargy, coma, or seizures. Metabolic disorders and adrenogenital syndrome may first be identified on the newborn screening test. Vomiting may also be a presentation of an infection such as urinary tract infection or gastroenteritis, although these are usually accompanied by fever or diarrhea. Rarely, a pyloric membrane or pyloric duplication results in projectile vomiting, visible peristalsis, and, in the case of a duplication, a palpable mass (Table 375.2). Duodenal stenosis proximal to the ampulla of Vater results in the clinical features of pyloric stenosis but can be differentiated by the presence of a pyloric mass on physical examination or ultrasonography.

#### TREATMENT

The treatment of pyloric stenosis requires surgery in most patients. The preoperative treatment is directed toward **correcting the fluid and electrolyte losses, as well as the acid-base disturbance**. Correction of the alkalosis is essential to prevent postoperative apnea, which may be associated with anesthesia. Most infants can be successfully rehydrated within 24 hours. Vomiting usually stops when the stomach is empty, and only an occasional infant requires nasogastric suction.

Surgical treatment of pyloric stenosis is by open or laparoscopic pyloromyotomy. This procedure is safe and cost-effective. Treatment is curative, with an operative mortality of 0–0.5%. The traditional Ramstedt procedure had been performed through a short transverse skin incision in the right upper quadrant of the abdomen followed by a longitudinal cut of the pyloric mass to the layer of the submucosa. Laparoscopic pyloromyotomy has become the procedure of choice given improved laparoscopic instrumentation and potential of shorter recovery times.

Postoperative vomiting occurs in half the infants and is thought to be secondary to edema of the pylorus at the incision site. In most infants, feedings can be initiated within 12–24 hours after surgery and advanced to maintenance oral feedings within 36–48 hours. Persistent vomiting suggests an incomplete pyloromyotomy, gastritis, gastroesophageal reflux disease, or another cause of the obstruction. Endoscopic balloon dilation has been successful in infants with persistent vomiting secondary to incomplete pyloromyotomy.

Conservative management with nasoduodenal feedings is a rare treatment choice, advisable only in rare patients who are not good surgical candidates. Oral and intravenous atropine sulfate (pyloric muscle relaxant) has also been described when surgical expertise is

**Table 375.2** Anomalies of the Stomach

ANOMALY	INCIDENCE	AGE AT PRESENTATION	SYMPTOMS AND SIGNS	TREATMENT
Gastric, antral, or pyloric atresia	3/100,000, when combined with webs	Infancy	Nonbilious emesis	Gastroduodenostomy, gastrojejunostomy
Pyloric or antral membrane (web)	As above	Any age	Failure to thrive, emesis	Incision or excision, pyloroplasty
Microgastria	Rare	Infancy	Emesis, malnutrition	Continuous-drip feedings or jejunal reservoir pouch
Gastric diverticulum	Rare	Any age	Usually asymptomatic	Usually unnecessary
Gastric duplication	Rare; male:female, 1:2	Any age	Abdominal mass, emesis, hematemesis; peritonitis if ruptured	Excision or partial gastrectomy
Gastric teratoma	Rare	Any age	Upper abdominal mass	Resection
Gastric volvulus	Rare	Any age	Emesis, refusal to feed	Reduction of volvulus, anterior gastropexy
Pyloric stenosis (infantile hypertrophic and adult forms)	United States, 3/1,000 (range, 1-8/1,000 in various regions); male:female, 4:1	Infancy	Nonbilious emesis	Pyloromyotomy
Congenital absence of the pylorus	Rare	Childhood, adulthood	Dyspepsia, if symptomatic	Usually unnecessary

Modified from Semrin MG, Russo MA. Anatomy, histology, and developmental anomalies of the stomach and duodenum. In Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 10th ed. Philadelphia: Elsevier; 2016; Table 48.1.

not available with 80% success rate described in some studies. Because conservative management takes longer and oral feedings may not be well tolerated, worsening of the nutritional status can occur in these patients and total parenteral nutrition may be required.

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## 375.2 Congenital Gastric Outlet Obstruction

Arunjot Singh and Chris A. Liacouras

Gastric outlet obstruction resulting from pyloric atresia and antral webs is uncommon and accounts for <1% of all GI atresias of the alimentary tract (see Tables 375.1 and 375.2). The exact cause of the defect is unknown but is hypothesized to be secondary to incomplete recanalization of the foregut or an intrauterine vascular accident. Pyloric atresia has been associated with **epidermolysis bullosa** and usually presents in early infancy. The gender distribution is equal.

### CLINICAL MANIFESTATIONS

Infants with pyloric atresia present with nonbilious vomiting, feeding difficulties, and abdominal distension during the first day of life. Low birthweight is also common. **Polyhydramnios** is a feature seen on prenatal ultrasonography in most cases. The gastric aspirate at birth is large (>20 mL fluid) and should be removed to prevent aspiration. Rupture of the stomach may occur as early as the first 12 hours of life. Infants with an antral web may present with less dramatic symptoms, depending on the degree of obstruction. Older children with antral webs present with nausea, vomiting, abdominal pain, and weight loss.

### DIAGNOSIS

The diagnosis of congenital gastric outlet obstruction is suggested by the finding of a large, dilated stomach on abdominal plain radiographs or in utero ultrasonography. Upper GI contrast series is usually

diagnostic and demonstrates a pyloric dimple. When contrast studies are performed, care must be taken to avoid possible aspiration. An antral web may appear as a thin septum near the pyloric channel. In older children, endoscopy has been helpful in identifying antral webs.

### TREATMENT

The treatment of all causes of gastric outlet obstruction in neonates starts with the correction of dehydration and hypochloremic alkalosis. Persistent vomiting should be relieved with nasogastric decompression. Surgical or endoscopic repair is then required when the patient is medically stable.

## 375.3 Gastric Duplication

Arunjot Singh and Chris A. Liacouras

Gastric duplications are rare cystic or tubular malformations that usually occur within the wall of the stomach. With an incidence of 1.7 per 100,000, gastric duplications account for 2–9% of all congenital duplications in the alimentary tract. The cystic type is most common and involves the greater curvature of the stomach (see Table 375.2). Most are less than 12 cm in diameter and do not usually communicate with the stomach lumen; however, they do have a common blood supply. Associated anomalies occur in as many as 35% of patients. Several hypotheses for the etiology of gastric duplication have been developed including the splitting notochord theory, diverticulation, canalization defects, and caudal twinning.

### CLINICAL MANIFESTATIONS

The most common clinical manifestations are associated with partial or complete gastric outlet obstruction. Presentation can also be complicated by intussusception, volvulus of the small bowel, and bleeding secondary to ulceration of ectopic mucosa. In 33% of patients, the duplication cyst may be palpable. Communicating duplications can cause gastric ulceration and be associated with hematemesis or melena.

## DIAGNOSIS

Radiographic studies usually show a paragastric mass displacing the stomach. Ultrasound can show the inner hyperechoic mucosal and outer hypoechoic muscle layers that are typical of gastric duplications. CT and MRI are diagnostic in cases where ultrasound remains unclear, although these should be used judiciously given risk associated with radiation and sedation.

## TREATMENT

Surgical treatment for symptomatic gastric duplications with complete resection of the duplication cyst is the gold standard. Avoiding incision into the gastric lumen is preferred whenever possible. Recently laparoscopic resection has shown successful outcomes. For communicating types of duplication, the marsupialization and drainage procedure may also be used.

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## 375.4 Gastric Volvulus

Arunjot Singh and Chris A. Liacouras

The stomach is tethered longitudinally by the gastrohepatic, gastrosplenic, and gastrocolic ligaments. In the transverse axis, it is tethered by the gastrophrenic ligament and the retroperitoneal attachment of the duodenum. A volvulus occurs when one of these attachments is absent or elongated, allowing the stomach to rotate around itself. In some children, other associated defects are present, including intestinal malrotation, diaphragmatic defects, hiatal hernia, or adjacent organ abnormalities such as asplenia. Volvulus can occur along the longitudinal axis, producing organo-axial volvulus, or along the transverse axis, producing mesentero-axial volvulus. Combined volvulus occurs if the stomach rotates around both organo-axial and mesentero-axial axes.

### CLINICAL MANIFESTATIONS

Gastric volvulus in infancy is usually associated with nonbilious vomiting and abdominal distention. It has also been associated with episodes of dyspnea and apnea in this age group. Acute volvulus can advance rapidly to strangulation and perforation. Chronic gastric volvulus is more common in older children who present with a history of emesis, abdominal pain, distention, early satiety, and failure to thrive.

## DIAGNOSIS

The diagnosis is suggested in plain abdominal radiographs by the presence of a dilated stomach. Erect abdominal films demonstrate a double fluid level with a characteristic “beak” near the lower esophageal junction in mesentero-axial volvulus. The stomach tends to lie in a vertical plane. In organo-axial volvulus, a single air-fluid level is seen without the characteristic beak with stomach lying in a horizontal plane. Upper GI series is the more definitive test as it reveals gastric rotation and estimates the degree of obstruction.

## TREATMENT

Treatment of acute gastric volvulus requires prompt management given the increased mortality risk. Following immediate stabilization, emergent surgery via laparoscopic gastropexy is the most common surgical approach. Open thoracotomies are also a treatment modality with gastropexy, gastrostomy, and partial/total gastric resection potentially being required. Endoscopic reduction has also been reported in select

cases, although gastropexy may ultimately be needed. Chronic gastric volvulus may be treated with conservative measures, including dietary modification, positioning, prokinetics, and antisecretory agents.

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## 375.5 Hypertrophic Gastropathy

Arunjot Singh and Chris A. Liacouras

Hypertrophic gastropathy in children is uncommon and usually a transient, benign, and self-limited condition. The mean age at diagnosis is 5 years (range: 2 days to 17 years).

### PATHOGENESIS

The condition is often secondary to cytomegalovirus (CMV) infection, but other agents, including herpes simplex virus, *Giardia*, and *Helicobacter pylori* have also been implicated. The pathophysiologic mechanisms underlying the clinical picture are not completely understood but might involve widening of gap junctions between gastric epithelial cells with resultant fluid and protein losses. There is an association with increased expression of transforming growth factor- $\alpha$  in gastric mucosal tissue shown in CMV-induced gastropathy. *H. pylori* infection can cause the elevation of serum glucagon-like peptide-2 levels, a mucosal growth-inducing gut hormone.

### CLINICAL MANIFESTATIONS

Clinical manifestations include epigastric abdominal pain, fatigue, vomiting, anorexia, and edema (protein-losing enteropathy). Other symptoms of nausea, diarrhea, and GI bleeding via hematemesis may arise due to gastric erosion or ulceration. In children, disease is typically of acute onset and spontaneously resolves within a few weeks (range: 2-14 weeks).

### DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Diagnostic imaging such as upper GI series and ultrasound show thickened gastric mucosa, although endoscopy and biopsy is essential for diagnosis. Endoscopy visualizes the enlargement of gastric folds and rugae typically in the fundus or body of the stomach. Histopathology shows characteristic foveolar hyperplasia, reduction in parietal cells, and hyperplasia of smooth muscle, whereas *H. pylori* staining and tissue CMV polymerase chain reaction can identify infectious etiology. The differential diagnosis includes different forms of hyperplastic and nonhyperplastic gastropathy such as Menetrier disease, Zollinger-Ellison syndrome, eosinophilic gastroenteritis, gastric lymphoma, Crohn disease, and inflammatory pseudotumor.

### TREATMENT

Therapy is supportive and should include adequate hydration, antisecretory agents ( $H_2$ -receptor blockade, proton pump inhibitors), and albumin replacement if hypoalbuminemia is symptomatic. When *H. pylori* are detected, appropriate treatment is recommended. Ganciclovir in CMV-positive gastropathy is indicated only in severe cases. There are no official guidelines as far as the length of treatment. In practice, IV therapy is initiated for the first 24-48 hours. Treatment is continued with oral valganciclovir for a total of 3 weeks. Octreotide therapy has been of benefit in some case reports. Complete recovery is the rule.

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## Chapter 376

# Intestinal Atresia, Stenosis, and Malrotation

Christina B. Bales and Chris A. Liacouras

Approximately 1 in 2,000 children is born with intestinal obstruction. Obstruction may be partial or complete, and it may be characterized as simple or strangulating. Luminal contents fail to progress in an aboral direction in simple obstruction, whereas blood flow to the intestine is also impaired in strangulating obstruction. If strangulating obstruction is not promptly relieved, it can lead to bowel infarction and perforation.

Intestinal obstruction can be further classified as either intrinsic or extrinsic based on underlying etiology. Intrinsic causes include inherent abnormalities of intestinal innervation, mucus production, or tubular anatomy. Among these, congenital disruption of the tubular structure is most common and can manifest as obliteration (atresia) or narrowing (stenosis) of the intestinal lumen. More than 90% of intestinal stenosis and atresia occurs in the duodenum, jejunum, and ileum. Rare cases occur in the colon, and these may be associated with more proximal atresias.

Extrinsic causes of congenital intestinal obstruction involve compression of the bowel by vessels (e.g., preduodenal portal vein), organs (e.g., annular pancreas), and cysts (e.g., duplication, mesenteric). Abnormalities in intestinal rotation during fetal development also represent a unique extrinsic cause of congenital intestinal obstruction. Malrotation is associated with inadequate mesenteric attachment of the intestine to the posterior abdominal wall, which leaves the bowel vulnerable to auto obstruction as a result of intestinal twisting or volvulus. Malrotation is commonly accompanied by congenital adhesions that can compress and obstruct the duodenum as they extend from the cecum to the right upper quadrant.

Obstruction is typically associated with bowel distention, which is caused by an accumulation of ingested food, gas, and intestinal secretions proximal to the point of obstruction. As the bowel dilates, absorption of intestinal fluid is decreased and secretion of fluid and electrolytes is increased. This shift results in isotonic intravascular depletion, which is usually associated with hypokalemia. Bowel distention also results in a decrease in blood flow to the obstructed bowel. As blood flow is shifted away from the intestinal mucosa, there is loss of mucosal integrity. Bacteria proliferate in the stagnant bowel, with a predominance of coliforms and anaerobes. This rapid proliferation of bacteria, coupled with the loss of mucosal integrity, allows bacteria to translocate across the bowel wall and potentially lead to endotoxemia, bacteremia, and sepsis.

The clinical presentation of intestinal obstruction varies with the cause, level of obstruction, vascular compromise, and time between the obstructing event and the patient's evaluation. Classic symptoms of obstruction in the neonate include vomiting, abdominal distention, and obstipation. Obstruction high in the intestinal tract results in large-volume, frequent, bilious emesis with little or no abdominal distention. Pain is intermittent and is usually relieved by vomiting. Obstruction in the distal small bowel leads to moderate or marked abdominal distention with emesis that is progressively feculent. Both proximal and distal obstructions are eventually associated with obstipation. However, meconium stools can be passed initially if the obstruction is in the upper part of the intestinal tract or if the obstruction developed late in intrauterine life.

The diagnosis of congenital bowel obstruction relies on a combination of history, physical examination, and radiologic findings. In certain cases, the diagnosis is suggested in the prenatal period. Routine prenatal ultrasound can detect polyhydramnios, which often accompanies high intestinal obstruction. The presence of polyhydramnios

should prompt aspiration of the infant's stomach immediately after birth. Aspiration of more than 15–20 mL of fluid, particularly if it is bile stained, is highly indicative of intestinal obstruction.

In the postnatal period, a plain radiograph is the initial diagnostic study and can provide valuable information about potential associated complications. With completely obstructing lesions, plain radiographs reveal bowel distention proximal to the point of obstruction. Upright or cross-table lateral views typically demonstrate a series of air-fluid levels in the distended loops. Caution must be exercised in using plain films to determine the location of intestinal obstruction. Because colonic haustra are not fully developed in the neonate, small and large bowel obstructions may be difficult to distinguish with plain films. In these cases, contrast studies of the bowel or computed tomography images may be indicated. Oral or nasogastric contrast medium may be used to identify obstructing lesions in the proximal bowel, and contrast enemas may be used to diagnose more-distal entities. Indeed, enemas may also play a therapeutic role in relieving distal obstruction caused by meconium ileus or meconium plug syndrome.

Initial treatment of infants and children with bowel obstruction must be directed at fluid resuscitation and stabilizing the patient. Nasogastric decompression usually relieves pain and vomiting. After appropriate cultures, broad-spectrum antibiotics are usually started in ill-appearing neonates with bowel obstruction and those with suspected strangulating infarction. Patients with strangulation must have immediate surgical relief before the bowel infarcts, resulting in gangrene and intestinal perforation. Extensive intestinal necrosis results in short bowel syndrome (see Chapter 385.6). Nonoperative conservative management is usually limited to children with suspected adhesions or inflammatory strictures that might resolve with nasogastric decompression or antiinflammatory medications. If clinical signs of improvement are not evident within 12–24 hours, then operative intervention is usually indicated.

## 376.1 Duodenal Obstruction

Christina B. Bales and Chris A. Liacouras

Congenital duodenal obstruction occurs in 2.5–10/100,000 live births. In most cases, it is caused by atresia, an intrinsic defect of bowel formation. It can also result from extrinsic compression by abnormal neighboring structures (e.g., annular pancreas, preduodenal portal vein), duplication cysts, or congenital bands associated with malrotation. Although intrinsic and extrinsic causes of duodenal obstruction occur independently, they can also coexist. Thus a high index of suspicion for more than one underlying etiology may be critical to avoiding unnecessary reoperations in these infants.

Duodenal atresia complicates 1/5–10,000 live births and accounts for up to 60% of all intestinal atresias. In contrast to more distal atresias, which likely arise from prenatal vascular accidents, duodenal atresia results from failed recanalization of the intestinal lumen during gestation. Throughout the fourth and fifth week of normal fetal development, the duodenal mucosa exhibits rapid proliferation of epithelial cells. Persistence of these cells, which should degenerate after the seventh week of gestation, leads to occlusion of the lumen (atresia) in approximately two thirds of cases and narrowing (stenosis) in the remaining one third. Duodenal atresia can take several forms, including a thin membrane that occludes the lumen, a short fibrous cord that connects two blind duodenal pouches, or a gap that spans two nonconnecting ends of the duodenum. The membranous form is most common, and it almost invariably occurs near the ampulla of Vater. In rare cases, the membrane is distensible and is referred to as a *windsock web*. This unusual form of duodenal atresia causes obstruction several centimeters distal to the origin of the membrane.

Approximately 50% of infants with duodenal atresia are premature. Concomitant congenital anomalies are common and include congenital heart disease (30%), malrotation (10–30%), annular pancreas (30%), renal anomalies (5–15%), esophageal atresia with or without tracheoesophageal fistula (5–10%), skeletal malformations (5%), and

anorectal anomalies (5%). Of these anomalies, only complex congenital heart disease is associated with increased mortality. Annular pancreas is associated with increased late complications, including gastroesophageal reflux disease, peptic ulcer disease, pancreatitis, gastric outlet and recurrent duodenal obstruction, and gastric cancer. Thus long-term follow-up of these patients into adulthood is warranted. Nearly half of patients with duodenal atresia have chromosome abnormalities; trisomy 21 is identified in up to 40% of patients.

### CLINICAL MANIFESTATIONS AND DIAGNOSIS

The hallmark of duodenal obstruction is bilious vomiting without abdominal distention, which is usually noted on the first day of life. Peristaltic waves may be visualized early in the disease process. A history of polyhydramnios is present in up to 80% of pregnancies and is caused by inadequate absorption of amniotic fluid in the distal intestine. This fluid may be bile stained because of intrauterine vomiting. Jaundice is present in one third of the infants.

The diagnosis is suggested by the presence of a *double-bubble* sign on a plain abdominal radiograph (Fig. 376.1). The appearance is caused by a distended and gas-filled stomach and proximal duodenum, which are invariably connected. Contrast studies are occasionally needed to exclude malrotation and volvulus because intestinal infarction can occur within 6–12 hours if the volvulus is not relieved. Contrast studies are generally not necessary and may be associated with aspiration. Prenatal diagnosis of duodenal atresia is readily made by fetal ultrasonography, which reveals a sonographic double-bubble. Prenatal identification of duodenal atresia is associated with decreased morbidity and fewer hospitalization days.

### TREATMENT

The initial treatment of infants with duodenal atresia includes nasogastric or orogastric decompression and intravenous fluid replacement. Echocardiography, renal ultrasound, and radiology of the chest and

spine should be performed to evaluate for associated anomalies. Definitive correction of the atresia is usually postponed until life-threatening anomalies are evaluated and treated.

The typical surgical repair for duodenal atresia is duodenoduodenostomy. This procedure is also preferred in cases of concomitant or isolated annular pancreas. In these instances, the duodenoduodenostomy is performed without dividing the pancreas. The dilated proximal bowel might have to be tapered to improve peristalsis. Postoperatively, a gastrostomy tube can be placed to drain the stomach and protect the airway. Intravenous nutritional support or a transanastomotic jejunal tube is needed until the infant starts to feed orally. Long-term prognosis is excellent, approaching 90% survival in most series.

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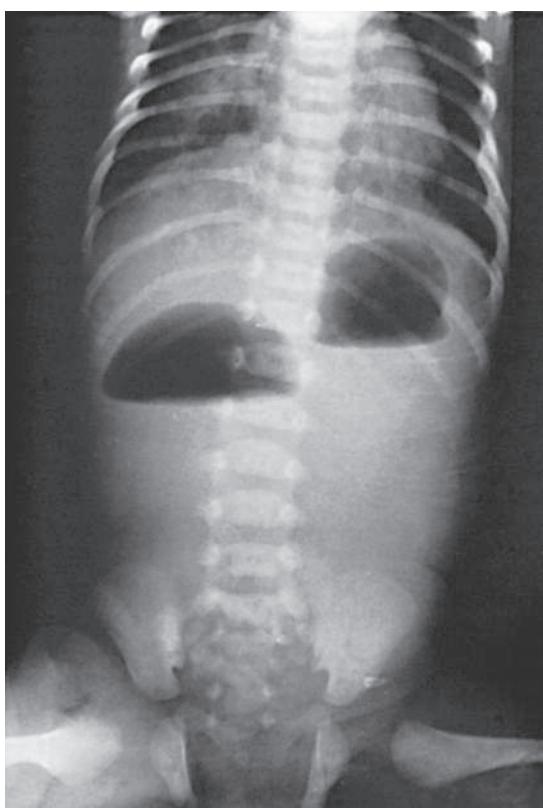
## 376.2 Jejunal and Ileal Atresia and Obstruction

Christina B. Bales and Chris A. Liacouras

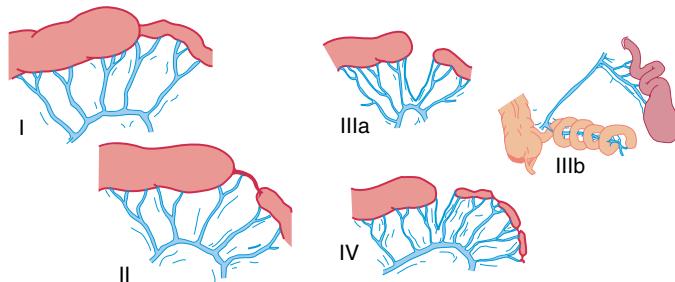
The primary etiologies of congenital small bowel obstruction involve intrinsic abnormalities in anatomic development (jejunoileal stenosis and atresia), mucus secretion (meconium ileus), and bowel wall innervation (long-segment Hirschsprung disease).

**Jejunoileal atresias** are generally attributed to intrauterine vascular accidents, which result in segmental infarction and resorption of the fetal intestine. Underlying events that potentiate vascular compromise include intestinal volvulus, intussusception, meconium ileus, and strangulating herniation through an abdominal wall defect associated with gastroschisis or omphalocele. Maternal behaviors that promote vasoconstriction, such as cigarette smoking and cocaine use, can also have a role. Only a few cases of familial inheritance have been reported. In these families, multiple intestinal atresias have occurred in an autosomal recessive pattern. Jejunoileal atresias have been linked with multiparity, low birthweight, and prematurity. Unlike atresia in the duodenum, they are not commonly associated with extraintestinal anomalies.

Five types of jejunal and ileal atresias are encountered (Fig. 376.2), with a relatively even distribution among the five types. In type I, a mucosal web occludes the lumen, but continuity is maintained between the proximal and distal bowel. Type II involves a small-diameter solid cord that connects the proximal and distal bowel. Type III is divided into two subtypes. Type IIIa occurs when both ends of the bowel end in blind loops, accompanied by a small mesenteric defect. Type IIIb is similar, but it is associated with an extensive mesenteric defect and a loss of the normal blood supply to the distal bowel. The distal ileum coils around the ileocolic artery, from which it derives its entire blood supply, producing an “apple-peel” appearance. This anomaly is



**Fig. 376.1** Abdominal radiograph of a newborn infant held upright. Note the “double-bubble” gas shadow and the absence of gas in the distal bowel in this case of congenital duodenal atresia.



**Fig. 376.2** Classification of intestinal atresia. Type I: Mucosal obstruction caused by an intraluminal membrane with intact bowel wall and mesentery. Type II: Blind ends are separated by a fibrous cord. Type IIIa: Blind ends are separated by a V-shaped mesenteric defect. Type IIIb: “Apple-peel” appearance. Type IV: Multiple atresias. (From Grosfeld J. Jejunoileal atresia and stenosis. In Welch KJ, Randolph JG, Ravitch MM, eds. Pediatric Surgery, 4th ed. Chicago: Year Book Medical Publishers; 1986.)

associated with prematurity, an unusually short distal ileum, and significant foreshortening of the bowel. Type IV involves multiple intestinal atresias. In rare cases, Type IV atresia may be associated with pathogenic variants in the *TTC7A* gene, which disrupt normal development of the thymus and intestinal epithelial lining of the intestine. This subset of patients may present with strictureing inflammatory bowel disease, severe combined immune deficiency (SCID), and associated recurrent sepsis. Thus type IV atresia uniquely warrants genetic and immunologic screening.

**Meconium ileus** occurs primarily in newborn infants with cystic fibrosis, an exocrine gland defect of chloride transport that results in abnormally viscous secretions (see Chapter 454). Approximately 80–90% of infants with meconium ileus have cystic fibrosis, but only 10–15% of infants with cystic fibrosis present with meconium ileus. Pathogenic variants in *GUCY2C* also produce meconium ileus. In simple cases of meconium ileus, the distal 20–30 cm of ileum is collapsed and filled with pellets of pale stool. The proximal bowel is dilated and filled with thick meconium that resembles sticky syrup or glue. Peristalsis fails to propel this viscid material forward, and it becomes impacted in the ileum. In complicated cases, a volvulus of the dilated proximal bowel can occur, resulting in intestinal ischemia, atresia, and/or perforation. Perforation in utero results in **meconium peritonitis**, which can lead to potentially obstructing adhesions and calcifications.

Both intestinal atresia and meconium ileus must be distinguished from long-segment Hirschsprung disease. This condition involves congenital absence of ganglion cells in the myenteric and submucosal plexuses of the bowel wall. In a small subset (5%) of patients, the aganglionic segment includes the terminal ileum in addition to the entire length of the colon. Infants with long-segment Hirschsprung disease present with a dilated small intestine that is ganglionated but has hypertrophied walls, a funnel-shaped transitional hypoganglionic zone, and a collapsed distal aganglionic bowel. Congenital pseudoobstruction syndromes may mimic long-segment Hirschsprung disease and other etiologies of intestinal obstruction (see Chapter 378).

### CLINICAL MANIFESTATION AND DIAGNOSIS

Distal intestinal obstruction is less likely than proximal obstruction to be detected in utero. Polyhydramnios is identified in 20–35% of jeunoileal atresias, and it may be the first sign of intestinal obstruction. Abdominal distention is rarely present at birth, but it develops rapidly after initiation of feeds in the first 12–24 hours. Distention is often accompanied by vomiting, which is often bilious. Up to 80% of infants fail to pass meconium in the first 24 hours of life. Jaundice is reported in 20–30% of patients.

In patients with obstruction caused by jeunoileal atresia or long-segment Hirschsprung disease, plain radiographs typically demonstrate multiple air-fluid levels proximal to the obstruction in the upright or lateral decubitus positions (Fig. 376.3). These levels may be

absent in patients with meconium ileus because the viscosity of the secretions in the proximal bowel prevents layering. Instead, a typical hazy or ground-glass appearance may be appreciated in the right lower quadrant. This haziness is caused by small bubbles of gas that become trapped in inspissated meconium in the terminal ileal region. If there is meconium peritonitis, patchy calcification may also be noted, particularly in the flanks. Plain films can reveal evidence of pneumoperitoneum due to intestinal perforation. Air may be seen in the subphrenic regions on the upright view and over the liver in the left lateral decubitus position.

Because plain radiographs do not reliably distinguish between small and large bowel in neonates, contrast studies are often required to localize the obstruction. Water-soluble enemas (Gastrografin, Hypaque) are particularly useful in differentiating atresia from meconium ileus and Hirschsprung disease. A small *microcolon* suggests disuse due to in utero obstruction proximal to the ileocecal valve. Abdominal ultrasound may be an important adjunctive study, which can help to distinguish meconium ileus from ileal atresia and identify concomitant intestinal malrotation.

### TREATMENT

Patients with small bowel obstruction should be stable and in adequate fluid and electrolyte balance before operation or radiographic attempts at disimpaction unless volvulus is suspected. Documented infections should be treated with appropriate antibiotics. Prophylactic antibiotics are usually given before surgery.

Ileal or jejunal atresia requires resection of the atretic portion of the bowel followed by end-to-end anastomosis. In select cases, proximal bowel dilation necessitates initial decompressing ostomy creation and/or bowel tapering before bowel anastomosis. If a simple mucosal diaphragm is present, jejunoplasty or ileoplasty with partial excision of the web is an acceptable alternative to resection. In uncomplicated meconium ileus, Gastrografin enemas diagnose the obstruction and wash out the inspissated material. Gastrografin is hypertonic, and care must be taken to avoid dehydration, shock, and bowel perforation. The enema may have to be repeated after 8–12 hours. Resection after reduction is not needed if there have been no ischemic complications.

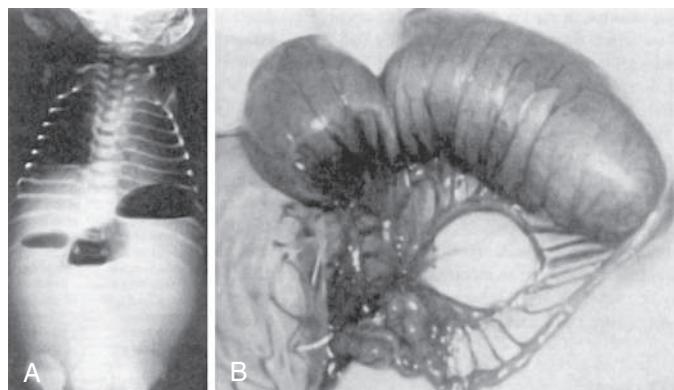
Approximately 50% of patients with simple meconium ileus do not adequately respond to water-soluble enemas and need laparotomy. Operative management is indicated when the obstruction cannot be relieved by repeated attempts at nonoperative management and for infants with complicated meconium ileus. The extent of surgical intervention depends on the degree of pathology. In simple meconium ileus, the plug can be relieved by manipulation or direct enteral irrigation with *N*-acetylcysteine following an enterotomy. In complicated cases, bowel resection, peritoneal lavage, abdominal drainage, and stoma formation may be necessary. Total parenteral nutrition is generally required.

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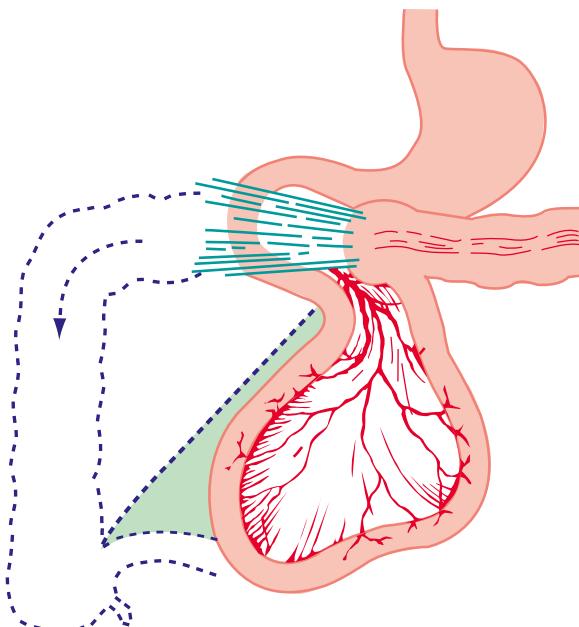
### 376.3 Malrotation

Christina B. Bales and Chris A. Liacouras

Disruptions in the normal sequential herniation, rotation, and fixation of the midgut during development give rise to a spectrum of rotational abnormalities. The gut starts as a straight tube from stomach to rectum. Intestinal rotation and attachment begin in the fifth week of gestation when the mid-bowel (distal duodenum to mid-transverse colon) elongates, gradually herniates through the umbilical ring, and then rotates in stages in a counterclockwise direction, using the superior mesenteric artery (SMA) as a rotational axis. As a 270-degree counterclockwise rotation is accomplished, the third portion of the duodenum passes posterior to the SMA and the duodenal-jejunal junction moves to the left upper quadrant and becomes suspended in the ligament of Treitz (LOT), while the cecum settles in the right lower quadrant. The ascending and descending colon subsequently become fixed in the right and



**Fig. 376.3** A, Abdominal radiograph in a neonate with bilious vomiting shows a few loops of dilated intestine with air-fluid levels. B, At laparotomy, a type I (mucosal) jejunal atresia was observed. (From O'Neill JA Jr, Grosfeld JL, Fonkalsrud EW, et al., eds. *Principles of Pediatric Surgery*, 2nd ed. St. Louis: Mosby; 2003: p 493.)



**Fig. 376.4** Mechanism of intestinal obstruction with incomplete rotation of the midgut (malrotation). The dashed lines show the course the cecum should have taken. Failure to rotate has left obstructing bands across the duodenum and a narrow pedicle for the midgut loop, making it susceptible to volvulus. (From Nixon HH, O'Donnell B. *The Essentials of Pediatric Surgery*. Philadelphia: JB Lippincott; 1961.)

left retroperitoneum, respectively. Fixation of the bowel at the LOT and in the retroperitoneum provides a broad-based support to the mesentery, thus preventing twisting of the mesenteric root and kinking of the vascular supply. Intestinal rotation and attachment are completed by the 12th week of gestation.

Nonrotation occurs when the bowel fails to rotate after it returns to the abdominal cavity. The first and second portions of the duodenum assume their normal position, but the residual small bowel remains on the right side of the abdomen and the colon resides on the left. In contrast, typical malrotation involves failure of the cecum to fully rotate into the right lower quadrant (Fig. 376.4) and form the normal broad-based adherence to the posterior abdominal wall. As a consequence of this incomplete rotation, the mesentery, including the SMA, is tethered by a narrow stalk. This configuration leaves patients with malrotation vulnerable to midgut volvulus, a life-threatening complication that occurs when the small bowel twists around the SMA, leading to vascular compromise and ischemia of the bowel. Bowel obstruction may also be caused by congenital bands of tissue (Ladd bands), which can extend from the cecum to the right upper quadrant, compress, and possibly obstruct the duodenum.

Rotational abnormalities are commonly associated with other congenital anomalies, including intestinal atresia, Hirschsprung disease and other congenital motility disorders, diaphragmatic hernia, gasteroschisis, and omphalocele. Malrotation may also be associated with heterotaxy syndrome, which is a complex of congenital anomalies including heart malformations, malrotation, biliary atresia, and asplenia or polysplenia (see Chapter 480.11).

## CLINICAL MANIFESTATIONS

Symptomatic malrotation occurs in 1 in 6,000 live births, whereas asymptomatic cases may be as frequent as 1 in 200 live births. Most symptomatic patients present in the first year of life, with approximately 50% presenting in the first week and 75% in the first month of life. Symptomatic infants typically present with bilious emesis due to bowel obstruction caused by volvulus or duodenal compression by Ladd bands or other adhesive bands that constrict the small and large bowel. Infants with volvulus may experience irritability, bloody stools, and rapid clinical deterioration with signs of sepsis. Older children with midgut volvulus may manifest similar features, though symptoms may be more subtle. Sporadic colicky pain and bilious emesis due to intermittent volvulus mandates a high level of suspicion for this entity.

## DIAGNOSIS

Upper GI series is considered the gold standard for diagnosis ( $\geq 93\%$ ) and reveals displacement of duodenojejunal junction (DJJ) from its normal position to the left of the spine, generally posterior and level or superior to the duodenal bulb. DJJ displacement may be appreciated in other conditions, including spleen or left kidney enlargement/tumor, gastric or colonic distention, and enteric feeding tubes. As fixation of the DJJ increases with age ( $>4$  years), the specificity of these findings for malrotation improves. In equivocal cases, a follow-through series or contrast enema may demonstrate malposition of the cecum, though this finding may be absent in up to 20% of patients. Ultrasonography can demonstrate the inversion of the SMA and vein, with the vein located to the left rather than to the right of the artery. In cases of midgut volvulus, the upper GI series may reveal a corkscrew appearance of the small bowel or a *bird's beak* narrowing of the duodenum, consistent with obstruction, and Doppler ultrasound may show a *whirlpool sign*.

## TREATMENT

Surgical intervention is recommended for any symptomatic patient with malrotation, regardless of age. Treatment of asymptomatic malrotation appreciated incidentally on imaging is more controversial, particularly in patients with congenital heterotaxy syndrome, who may be at higher risk for surgical complications. In asymptomatic patients careful assessment of imaging, supplemented in some cases by exploratory laparoscopy, guides selection for surgical intervention. Those patients who are older and have a broad-based mesentery may be appropriate for nonsurgical observation with careful parental counseling. If a volvulus is present, surgery is done immediately as an acute emergency. The volvulus is reduced, and a Ladd procedure is typically performed. In the Ladd procedure, the duodenum and upper jejunum are freed of any bands and remain in the right abdominal cavity. The colon is freed of adhesions and placed in the right abdomen with the cecum in the left lower quadrant, usually accompanied by incidental appendectomy. The Ladd procedure may be performed laparoscopically for malrotation without volvulus, but it is generally done as an open procedure if volvulus is present. The purpose of surgical intervention is to minimize the risk of subsequent volvulus rather than to return the bowel to a normal anatomic configuration. Extensive intestinal ischemia from volvulus can result in short bowel syndrome (see Chapter 385.6).

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## Chapter 377

# Intestinal Duplications, Meckel Diverticulum, and Other Remnants of the Omphalomesenteric Duct

### 377.1 Intestinal Duplication

Máire A. Conrad and Chris A. Liacouras

Duplications of the intestinal tract are rare anomalies that consist of well-formed tubular or spherical structures firmly attached to the intestine with a common blood supply. The lining of the duplications resembles that of the gastrointestinal (GI) tract. Duplications are located on the mesenteric border and can communicate with the intestinal lumen. Duplications can be classified into three categories: (1) localized duplications, (2) duplications associated with spinal cord defects and vertebral malformations, and (3) duplications of the colon. Occasionally (10–15% of cases), multiple duplications are found.

**Localized duplications** can occur in any area of the GI tract but are most common in the ileum and jejunum. They are usually cystic or tubular structures within the wall of the bowel. The cause is unknown, but their development has been attributed to defects in recanalization of the intestinal lumen after the solid stage of embryologic development. Duplication of the intestine occurring in association with **vertebral and spinal cord anomalies** (hemivertebra, anterior spina bifida, band connection between lesion and cervical or thoracic spine) is thought to arise from splitting of the notochord in the developing embryo. **Duplication of the colon** is usually associated with anomalies of the urinary tract and genitals. Duplication of the entire colon, rectum, anus, and terminal ileum rarely occur. The defects are thought to be secondary to caudal twinning, with duplication of the hindgut, genital, and lower urinary tracts.

### CLINICAL MANIFESTATIONS

Symptoms depend on the size, location, and type of mucosal lining. Duplications can cause bowel obstruction by compressing the adjacent intestinal lumen, or they can act as the lead point of an intussusception or a site for a volvulus. If they are lined by acid-secreting mucosa, they can cause ulceration, perforation, and hemorrhage of or into the adjacent bowel. Patients can present with abdominal pain, vomiting, palpable mass, or acute GI hemorrhage. Intestinal duplications in the thorax (**neuroenteric cysts**) can manifest as respiratory distress. Duplications of the lower bowel can cause constipation or diarrhea or be associated with recurrent prolapse of the rectum.

The diagnosis is suspected based on the history and physical examination. Radiologic studies such as barium studies, ultrasonography, CT, and MRI are helpful but usually nonspecific, demonstrating cystic structures or mass effects. Radioisotope technetium scanning can localize ectopic gastric mucosa. The treatment of duplications is surgical resection and management of associated defects.

### 377.2 Meckel Diverticulum and Other Remnants of the Omphalomesenteric Duct

Máire A. Conrad and Chris A. Liacouras

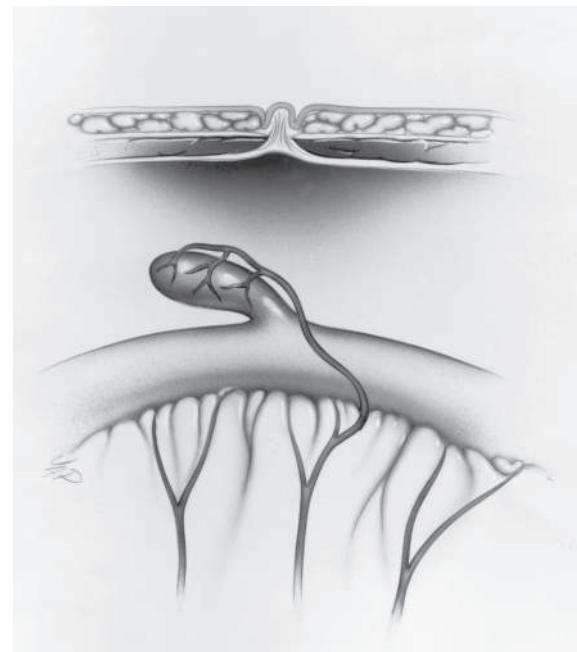
Meckel diverticulum is the most common congenital anomaly of the GI tract and is caused by the incomplete obliteration of the omphalomesenteric duct (also known as the *vitelline duct*) during the

seventh week of gestation. The omphalomesenteric duct connects the yolk sac to the gut in a developing embryo and provides nutrition until the placenta is established. Between the fifth and seventh week of gestation, the duct attenuates and separates from the intestine. Just before this involution, the epithelium of the yolk sac develops a lining similar to that of the stomach. Partial or complete failure of involution of the omphalomesenteric duct results in various residual structures. Meckel diverticulum is the most common of these structures, occurring in 2–3% of all infants. A typical Meckel diverticulum is a true diverticulum containing all layers of the small intestinal wall and is a 3- to 6-cm outpouching of the ileum along the antimesenteric border 50–75 cm (approximately 2 feet) from the ileocecal valve (Fig. 377.1). The distance from the ileocecal valve depends on the age of the patient. Meckel diverticulum has been conveniently characterized by the “rule of 2s,” which explains the classic presentation of this congenital anomaly. Meckel diverticula are found in approximately 2% of the general population, are usually located 2 feet proximal to the ileocecal valve, are approximately 2 inches in length, can contain two types of ectopic tissue (pancreatic or gastric), generally present before the age of 2 years, and are found twice as often in females. Although intraabdominal in location, a rare presentation of a Meckel diverticulum is entrapment in an inguinal, umbilical, or femoral hernia (known as a *Littre hernia*). Other omphalomesenteric duct remnants occur infrequently, including a persistently patent duct, a solid cord, or a cord with a central cyst or a diverticulum associated with a persistent cord between the diverticulum and the umbilicus.

### CLINICAL MANIFESTATIONS

Symptoms of a Meckel diverticulum usually arise in the first or second year of life (average: 2.5 years), but initial symptoms may occur in the first decade. The majority of symptomatic Meckel diverticula are lined by an ectopic mucosa, including an acid-secreting mucosa that causes intermittent painless rectal bleeding by ulceration of the adjacent normal ileal mucosa. This ectopic mucosa is most commonly of gastric origin, but it can also be pancreatic, jejunal, or a combination of these tissues. Unlike in the duodenum, the secreted acid is not neutralized by pancreatic bicarbonate.

The stool is typically described as brick colored or currant jelly colored. Bleeding can cause significant anemia but is usually self-limited because of contraction of the splanchnic vessels, as patients become



**Fig. 377.1** Typical Meckel diverticulum located on the antimesenteric border.

hypovolemic. Bleeding from a Meckel diverticulum can also be less dramatic, with melanotic stools.

Less often, a Meckel diverticulum is associated with partial or complete bowel obstruction. The most common mechanism of obstruction occurs when the diverticulum acts as the lead point of an intussusception. The mean age of onset of obstruction is younger than that for patients presenting with bleeding. Obstruction can also result from intraperitoneal bands connecting residual omphalomesenteric duct remnants to the ileum and umbilicus. These bands cause obstruction by internal herniation or volvulus of the small bowel around the band. A Meckel diverticulum occasionally becomes inflamed (**diverticulitis**) and manifests similarly to acute appendicitis. These children are older, with a mean of 8 years of age. Diverticulitis can lead to perforation and peritonitis.

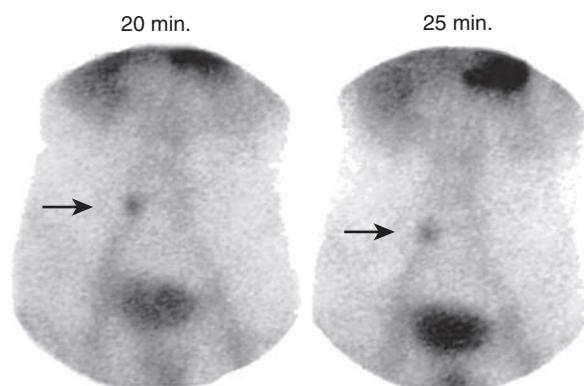
## DIAGNOSIS

The diagnosis of omphalomesenteric duct remnants depends on the clinical presentation. If an infant or child presents with significant painless rectal bleeding, the presence of a Meckel diverticulum should be suspected because Meckel diverticulum accounts for 50% of all lower GI bleeds in children younger than 2 years of age.

Confirmation of a Meckel diverticulum can be difficult. Plain abdominal radiographs are of no value, and routine barium studies rarely fill the diverticulum. The most sensitive study is a Meckel radionuclide scan, which is performed after intravenous infusion of technetium-99m pertechnetate. The mucus-secreting cells of the ectopic gastric mucosa take up pertechnetate, permitting visualization of the Meckel diverticulum (Fig. 377.2). The uptake can be enhanced with various agents, including histamine H<sub>2</sub>-blockers such as famotidine or cimetidine, glucagon, and pentagastrin. The sensitivity of the enhanced scan is approximately 85%, with a specificity of approximately 95%. A false-negative scan may be seen in anemic patients; although false-positive results are uncommon, they have been reported with intussusception, appendicitis, duplication cysts, arteriovenous malformations, and tumors. Other methods of detection include radiolabeled tagged red blood cell scan (the patient must be actively bleeding), abdominal ultrasound, superior mesenteric angiography, abdominal CT scan, or exploratory laparoscopy. In patients with omphalomesenteric duct remnants who present with intestinal obstruction or symptoms most similar to appendicitis, the diagnosis is rarely made before surgery.

The treatment of a symptomatic Meckel diverticulum is surgical excision. A diverticulectomy can be performed safely as either a laparoscopic or open procedure. There is significant debate regarding the proper management of an asymptomatic Meckel diverticulum and whether excision versus observation is appropriate. However, the risk of serious complications does seem to exceed the operative risk in children younger than 8 years old.

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**Fig. 377.2** Meckel scan demonstrating accumulation of technetium in the stomach (superior), bladder (inferior) and in the acid-secreting mucosa of a Meckel diverticulum (arrows).

## Chapter 378

# Motility Disorders and Hirschsprung Disease

### 378.1 Chronic Intestinal Pseudoobstruction

Jennifer Webster, Kristin N. Fiorino, and Chris A. Liacouras

Chronic intestinal pseudoobstruction (CIPO) comprises a group of primary and secondary disorders characterized as a motility disorder with the dominant defect of impaired peristalsis; symptoms are consistent with intestinal obstruction in the absence of mechanical obstruction (Tables 378.1 and 378.2). It has been suggested that pseudoobstruction in the pediatric population should be referred to as pediatric intestinal pseudoobstruction (PIPO) as it is a distinct entity from adult CIPO (Table 378.3). The natural history of primary pseudoobstruction is that of a progressive disorder, although there are occasional cases of secondary pseudoobstruction caused by conditions that can transiently or permanently alter bowel motility. The most common cause of acute

**Table 378.1** Classification of Pediatric Intestinal Pseudoobstruction

#### PRIMARY PIPO

- Sporadic or familial forms of myopathy and/or neuropathy and/or mesenchymopathy (abnormal ICC development) that relate to disordered development, degeneration, or inflammation.
- Inflammatory (including autoimmune) conditions include lymphocytic and eosinophilic ganglionitis and/or leiomyositis
- Mitochondrial neuro-gastrointestinal-encephalomyopathy (MNGIE) and other mitochondrial diseases
- Neuropathy associated with multiple endocrine neoplasia type IIB
- Hirschsprung disease, for example, total intestinal aganglionosis\*
- MMIHS

#### SECONDARY PIPO

- Conditions affecting GI smooth muscle:
  - Rheumatologic conditions (dermatomyositis/polymyositis, scleroderma, systematic lupus erythematosus, Ehlers-Danlos syndrome)
  - Other (Duchenne muscular dystrophy, myotonic dystrophy, amyloidosis, ceroidosis or alternatively reported as brown bowel syndrome)
- Pathologies affecting the enteric nervous system (familial dysautonomia, primary dysfunction of the autonomic nervous system, neurofibromatosis, diabetic neuropathy, fetal alcohol syndrome, postviral-related inflammatory neuropathy, e.g., cytomegalovirus, Epstein-Barr virus, varicella zoster virus, JC virus)
- Endocrinologic disorders (hypothyroidism, diabetes, hypoparathyroidism, pheochromocytoma)
- Metabolic conditions (uremia, porphyria, electrolyte imbalances, e.g., potassium, magnesium, calcium)
- Gastroschisis
- Neuropathy post neonatal necrotizing enterocolitis
- Other: celiac disease, eosinophilic gastroenteritis, Crohn disease, radiation injury, Chagas disease, Kawasaki disease, angioedema, drugs (e.g., opiates, anthraquinone laxatives, calcium channel blockers, antidepressants, antineoplastic agents like vinca alkaloids), paraneoplastic CIPO, major trauma/surgery, chromosome abnormalities

**Idiopathic** (i.e., where forms of primary or secondary PIPO classified earlier do not, as yet, have a defined etiopathogenesis)

\*Needs to be excluded in all cases of PIPO.

PIPO, Pediatric intestinal pseudoobstruction; ICC, interstitial cells of Cajal; GI, gastrointestinal; MMIHS, megacystis microcolon intestinal hypoperistalsis syndrome. From Thapar N, Saliakellis E, Benninga M, et al. Paediatric Intestinal Pseudoobstruction: Evidence and Consensus-based Recommendations From an ESPGHAN-Led Expert Group. *J Pediatr Gastroenterol Nutr.* 2018;66(6):991–1019. Table 3.

hypovolemic. Bleeding from a Meckel diverticulum can also be less dramatic, with melanotic stools.

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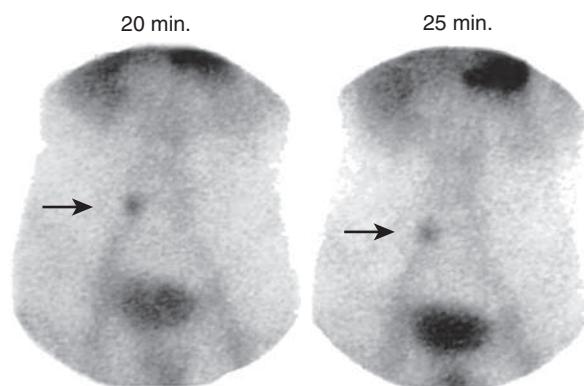
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  - Other (Duchenne muscular dystrophy, myotonic dystrophy, amyloidosis, ceroidosis or alternatively reported as brown bowel syndrome)
- Pathologies affecting the enteric nervous system (familial dysautonomia, primary dysfunction of the autonomic nervous system, neurofibromatosis, diabetic neuropathy, fetal alcohol syndrome, postviral-related inflammatory neuropathy, e.g., cytomegalovirus, Epstein-Barr virus, varicella zoster virus, JC virus)
- Endocrinologic disorders (hypothyroidism, diabetes, hypoparathyroidism, pheochromocytoma)
- Metabolic conditions (uremia, porphyria, electrolyte imbalances, e.g., potassium, magnesium, calcium)
- Gastroschisis
- Neuropathy post neonatal necrotizing enterocolitis
- Other: celiac disease, eosinophilic gastroenteritis, Crohn disease, radiation injury, Chagas disease, Kawasaki disease, angioedema, drugs (e.g., opiates, anthraquinone laxatives, calcium channel blockers, antidepressants, antineoplastic agents like vinca alkaloids), paraneoplastic CIPO, major trauma/surgery, chromosome abnormalities

**Idiopathic** (i.e., where forms of primary or secondary PIPO classified earlier do not, as yet, have a defined etiopathogenesis)

\*Needs to be excluded in all cases of PIPO.

PIPO, Pediatric intestinal pseudoobstruction; ICC, interstitial cells of Cajal; GI, gastrointestinal; MMIHS, megacystis microcolon intestinal hypoperistalsis syndrome. From Thapar N, Saliakellis E, Benninga M, et al. Paediatric Intestinal Pseudoobstruction: Evidence and Consensus-based Recommendations From an ESPGHAN-Led Expert Group. *J Pediatr Gastroenterol Nutr.* 2018;66(6):991–1019. Table 3.

**Table 378.2** Primary Pediatric Intestinal Pseudoobstruction with Identified Genetic Pathogenic Variants

GENE	SYNDROME	INHERITANCE	PHENOTYPE	AGE OF ONSET
Sox 10	Type IV Waardenburg syndrome	Autosomal dominant	Peripheral neuropathy with hypomyelination, sensorineural deafness and pseudoobstruction	Neonatal period
POLG1 (DNA-polymerase gamma)	Congenital myopathy and gastrointestinal pseudoobstruction	Autosomal recessive	Associated with mitochondrial depletion and deletions. Severe hypotonia and generalized muscle weakness, severe abdominal distension and hypoactive bowel	Neonatal period
FLNA (filamin A)	Chronic idiopathic intestinal pseudoobstruction (CIIPX)	X-linked recessive	Abnormal filamin A leads to cytoskeletal abnormalities and potentially disrupts enteric-neuron structure and function. Seizures and progressive abdominal distension and obstruction	Neonatal period
L1CAM (L1 cell adhesion molecule)	Hydrocephalus with stenosis of the aqueduct of Sylvius (HSAS) and congenital idiopathic intestinal pseudoobstruction	Autosomal recessive	Defect in the differentiation of the interstitial cells of Cajal leading to progressive distension and intermittent episodes of obstruction	Neonatal period
ACTG2 (enteric smooth muscle actin-gamma 2)	Familial visceral myopathy; megacystis-microcolon-intestinal hypoperistalsis syndrome	Autosomal dominant, sporadic	Altered ACTG2 protein in the muscularis propria leads to impaired contractility	Neonatal to third decade in life
MYH11 (myosin heavy chain 11)	Megacystis-microcolon-intestinal hypoperistalsis syndrome	Autosomal recessive	Abnormal MYH11 in smooth muscle myosin leads to impaired contractility	Neonatal to third decade in life
MYLK (myosin light chain kinase)	Megacystis-microcolon-intestinal hypoperistalsis syndrome	Autosomal recessive	Abnormal MYLK leads to impaired smooth muscle cell contraction	Neonatal to third decade in life
LMOD1 (leiomodin 1)	Megacystis-microcolon-intestinal hypoperistalsis syndrome	Sporadic	Abnormal LMOD1 leads to impaired intestinal smooth muscle contractility	Neonatal to third decade in life
MYL9 (myosin regulatory light chain 9)	Megacystis-microcolon-intestinal hypoperistalsis syndrome	Autosomal recessive	Abnormal MYL9 leads to impaired intestinal smooth muscle contractility	Neonatal to third decade in life
RET protooncogene (receptor tyrosine kinase)	MEN2B	Autosomal dominant	Gain-in-function mutation associated with intestinal ganglioneuromas leading to increased cell number in the myenteric plexus and dysmotility	Infancy to third decade of life
TYMP (thymidine phosphorylase)	Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)	Autosomal recessive	Accumulation of thymidine in mitochondrial DNA leads to impaired function. Multisystem mitochondrial disease with progressive gastrointestinal dysmotility	Infancy to third decade of life
RAD21	Mungan syndrome	Autosomal recessive	Pseudoobstruction, megaduodenum, long segment Barrett esophagus and cardiac abnormalities	First to second decade of life
SGOL1	Chronic atrial and intestinal dysrhythmia (CAID)	Autosomal recessive	Accelerated cell cycle progression and enhanced activation of transforming growth factor-β signaling leading to changes in both the enteric nervous system and smooth muscle	First to fourth decade of life
ACTA2	Megacystitis-microcolon-intestinal hypoperistalsis	Autosomal dominant	Smooth muscle dysfunction, congenital mydriasis	Neonatal period

Modified from Gamboa H, Sood M. Pediatric intestinal pseudo-obstruction in the era of genetic sequencing. *Curr Gastroenterol Rep.* 2019;21:1–12. Table 1.

**Table 378.3** Common and Distinctive Features of Pediatric Chronic Intestinal Pseudoobstruction

	CHILDREN	ADOLESCENTS AND YOUNG ADULTS
Etiology	Majority of cases appear to be congenital (up to 80%) and primary. Secondary forms rare (<10%)	Secondary forms (mostly to systemic disease) common and account for up to 50% of cases
Disease subtype	Neuropathies more common (~70%) with myopathic forms seen in ~30%	Predominantly neuropathies (majority inflammatory) (~45%) with myopathies accounting for (~30%)
Symptom onset	In utero, from birth or early infancy (65–80% of patients by 12 mo of age)	Median age of onset is 20–40 yr
Clinical features	Recurrent or continuous episodes of intestinal pseudoobstruction with symptoms present from birth/early life Pain infrequently seen (approximately 30%) Urologic involvement common (36–100%) Intestinal malrotation in about 30% of cases High risk of colonic and small bowel volvulus	Chronic abdominal pain and distension with superimposed acute episodes of pseudoobstruction Pain is a cardinal symptom present in at least 80% of patients Urologic involvement rare Intestinal malrotation rarely seen Low risk of colonic and small bowel volvulus
Natural history	Poor outcome predicted by myopathic forms of PIPO; urinary involvement; concurrent intestinal malrotation; and inability to tolerate enteral feeds Risk of mortality in approximately 20% of cases	Low mortality if ability to restore oral feeding and the presence of symptoms <20 yr of age High mortality if systemic sclerosis or paraneoplasia and severe/diffuse esophageal and intestinal dysmotility
Diagnostic approach	Diagnosis relies on clinical picture and radiology together with specialized tests (e.g., intestinal manometry, histopathology) Dilated bowel loops with fluid levels commonly absent (~40%) in patients presenting in the neonatal period Histopathology yield high and used to inform management, for example, use of parenteral nutrition in intestinal myopathies and prokinetics in intestinal neuropathies Apart from specific indications little yield from investigating for secondary PIPO Need to differentiate from feeding problems and fabricated or induced illness.	Diagnosis made on clinical picture and radiology with variable use of intestinal manometry On radiology defined by the presence of dilated loops of bowel with fluid levels Histopathology has a positive yield in the majority of patients but guides treatment only in minority May help support a diagnosis of secondary CIPO with other clinical findings/investigations
Nutritional therapy	Significant number (~80%) require parenteral nutrition to maintain normal growth and development. Specialized feeds (e.g., hydrolyzed protein feeds) and feeding routes (e.g., jejunal) used to promote enteral feed tolerance	Approximately 20–50% need home parenteral nutrition to prevent malnutrition
Pharmacologic therapy	Virtually no evidence base from controlled trials. Use of medication mostly anecdotal, case reports or drawn from adult literature	Few controlled trials, often small studies; few conclusions can be drawn
Surgical therapy	Venting ostomies very commonly used to decompress and reduce pseudoobstructive events; Surgery as a "bridge" to transplantation may be indicated in highly selected cases	Venting or defunctioning ostomies may help some patients. Little role for surgical resection

PIPO, Pediatric intestinal pseudoobstruction.

Modified from Thapar N, Saliakellis E, Benninga M, et al. Paediatric Intestinal Pseudo-obstruction: Evidence and Consensus-based Recommendations From an ESPGHAN-Led Expert Group. *J Pediatr Gastroenterol Nutr.* 2018;66(6):991–1019. Table 2.

pseudoobstruction is Ogilvie syndrome (acute pseudoobstruction of the colon). Pseudoobstruction represents a wide spectrum of pathologic disorders from abnormal myoelectric activity to abnormalities of the nerves (intestinal neuropathy) or musculature (intestinal myopathy) of the gut. The organs involved can include the entire gastrointestinal tract or be limited to certain components, although almost always include the small bowel. The distinctive pathologic abnormalities are considered together because of their clinical similarities. For these reasons, CIPO may be thought of more as a clinical syndrome at times.

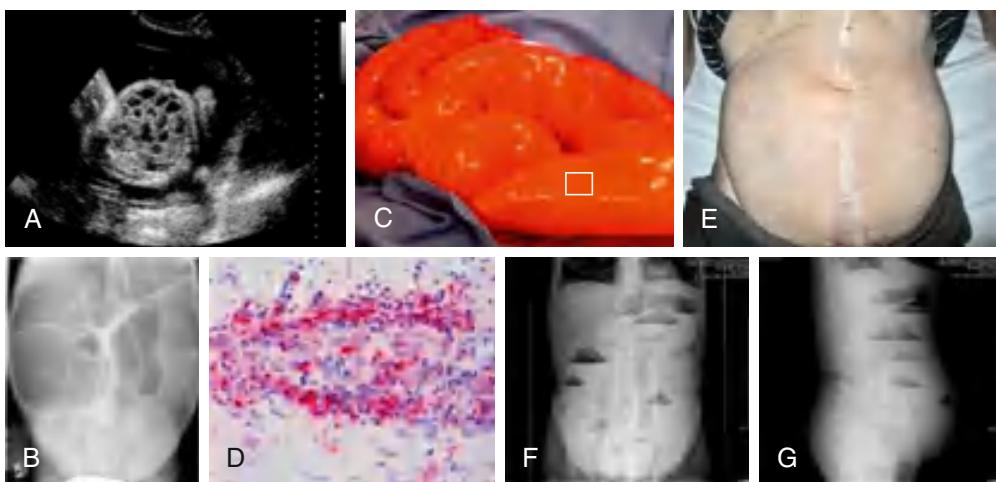
Most congenital forms of primary pseudoobstruction occur sporadically, although autosomal dominant (*SOX10*, *ACTG2*, *RET*), autosomal recessive (*RAD21*, *SGOL1*, *TYMP*, *POLG*), X-linked (*FLNA*, *L1CAM*), and familial patterns of inheritance have been identified (see Table 378.2). Patients with autosomal dominant forms of pseudoobstruction have variable expressions of the disease. Patients with pathogenic variants in *TYMP* and *POLG* genes present with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) syndrome; mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is another mitochondrial disorder associated with CIPO. MNGIE is characterized by intestinal dysmotility, abdominal pain and distention, emesis,

cachexia, ptosis, leukoencephalopathy, peripheral neuropathy (paresthesia, pain), and myopathy. Sixty percent have symptoms (often subtle) before age 20 years (see Chapter 378.2). Megacystis microcolon intestinal hypoperistalsis (MMIHS) syndrome includes pseudoobstruction plus bladder dysfunction and is due to pathogenic variants in *ACTG2* and other genes (Table 378.2). Acquired pseudoobstruction can follow episodes of acute gastroenteritis, presumably resulting in injury to the myenteric plexus.

In congenital pseudoobstruction, abnormalities of the muscle or nerves can be demonstrated in most cases. In myopathies, the smooth muscle is involved, in which the outer longitudinal muscle layer is replaced by fibrous material. These manifestations of visceral myopathies may be a primary or secondary phenomenon. The enteric nervous system is usually altered in neuropathies and may involve disorganized ganglia, hypoganglionosis, or hyperganglionosis. Abnormalities in the interstitial cells of Cajal, the intestinal pacemaker, are classified as mesenchymopathies. In others, mitochondrial defects have been identified.

## CLINICAL MANIFESTATIONS

More than half the children with congenital pseudoobstruction experience symptoms in the neonatal period (see Table 378.3). Two thirds of the



**Fig. 378.1** Synoptic view of the chronic intestinal pseudoobstruction (CIPO) spectrum. A and B, The most severe pediatric cases with antenatal (in utero) evidence of multivisceral dilation, often gut (B) and urinary system, commonly associated with an extremely poor prognosis. C and D, CIPO phenotype with rapid progression to intestinal dilation ( $\pm$  ureter/bladder) and failure, often occurring as a result of an anamnestically reported gastroenteritis. Massive bowel dilation (C) and associated histopathology (D; corresponds to white squared area in C) revealed an intense inflammatory (mainly lymphocytic) neuropathy (hence, myenteric ganglionitis). Alkaline phosphatase anti-alkaline phosphatase immunohistochemical technique using specific anti-CD8 monoclonal antibodies was used to identify a subset of T lymphocytes. E and G, Examples of another phenotype of the syndrome that may be seen in patients who have more insidious mild and nonspecific symptoms progressing to a classic CIPO over time. E, Markedly distended abdomen of a 32-yr-old man who presented with subocclusive episodes after years of unspecific (dyspeptic-like/irritable bowel syndrome-like) symptoms. Note the evident air-fluid levels detectable in upright position in anteroposterior (F) and laterolateral (G) plain abdominal radiographs. (A from Shen O, Schimmel MS, Eitan R, et al. Prenatal diagnosis of intestinal pseudo-obstruction. Ultrasound Obstet Gynecol. 2007;29:229-231; B-G from Di Nardo G, Di Lorenzo C, Lauro A, et al. Chronic intestinal pseudo-obstruction in children and adults: diagnosis and therapeutic options. Neurogastroenterol Motil. 2017;29:e12945.)

infants presenting in the first few days of life are born prematurely, and approximately 40% have malrotation of the intestine. In 75% of all affected children, symptoms occur in the first year of life, whereas the remainder are usually symptomatic within the next several years. Females present with CIPO more than males during the first year of life, with equal sex distribution in older children. The most common symptoms are abdominal distention (85–95% of patients) and vomiting (55–90%). Constipation, growth failure, and abdominal pain occur in approximately 60% of patients and diarrhea in 25–30%. The symptoms wax and wane in most patients; poor nutrition, psychologic stress, and intercurrent illness tend to exacerbate symptoms. Urinary tract and bladder involvement occurs in 80% of children with myopathic pseudoobstruction and in 20% of those with neuropathic disease. Symptoms can manifest as recurrent urinary tract infection, megacystis, or obstructive symptoms. Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) is a prenatal or neonatal manifestation of CIPO.

The clinical manifestations depend in large part on the areas of the gastrointestinal tract that are involved, with milder forms more common in older children. Although counterintuitive, older children with CIPO may present with both abdominal distention and diarrhea, related to *small bowel bacterial overgrowth* because of altered motility. Other presentations may include constipation and bilious emesis, as well as failure to thrive, as a consequence of decreased enteral feeding tolerance.

## DIAGNOSIS

The diagnosis of pseudoobstruction is based on the presence of compatible symptoms in the absence of mechanical obstruction (Fig. 378.1). If CIPO is considered, diagnosis should start with exclusion of mechanical obstruction, exclusion of alternative diagnoses, and confirmation of impaired motility. Plain abdominal radiographs demonstrate air-fluid levels in the intestine. Contrast studies are integral to rule out mechanical obstruction and often demonstrate slow passage of barium; water-soluble agents should be considered. Gastric emptying scintigraphy can be used to evaluate upper GI dysmotility. Antroduodenal (small intestinal) manometry is integral to

**Table 378.4** Findings in Pseudoobstruction

GI SEGMENT	FINDINGS*
Esophageal motility	Abnormalities in approximately half of CIPO, although in some series up to 85% demonstrate abnormalities Decreased LES pressure Failure of LES relaxation Esophageal body: low-amplitude waves, poor propagation, tertiary waves, retrograde peristalsis, occasionally aperistalsis
Gastric emptying	May be delayed
EGG	Tachygastria or bradygastria may be seen
ADM	Postprandial antral hypomotility is seen and correlates with delayed gastric emptying Myopathic subtype: low-amplitude contractions, <10–20 mm Hg Neuropathic subtype: contractions are uncoordinated, disorganized Absence of fed response Fasting MMC is absent, or MMC is abnormally propagated
Colonic	Absence of gastrocolic reflex because there is no increased motility in response to a meal
ARM	Normal rectoanal inhibitory reflex

\*Findings can vary according to the segment(s) of the GI tract that are involved.

ADM, Antroduodenal manometry; ARM, anorectal manometry; CIPO, chronic intestinal pseudoobstruction; EGG, electrogastrography; GI, gastrointestinal; LES, lower esophageal sphincter; MMC, migrating motor complex.

From Steffen R: Gastrointestinal motility. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*, 3rd ed. Philadelphia: WB Saunders; 2006: p 66.

diagnosis with a normal study conclusively ruling out a diagnosis of CIPO (Table 378.4). Manometric evidence of a normal migrating motor complex and postprandial activity should redirect the diagnostic evaluation. CIPO due to an intestinal myopathy may demonstrate manometry evidence of low-amplitude contractions, whereas CIPO due to enteric neuropathy demonstrates normal amplitude but poorly organized contractions (nonperistaltic or tonic). Anorectal motility is normal and differentiates pseudoobstruction from Hirschsprung disease. Full-thickness intestinal biopsy might show involvement of the muscle layers or abnormalities of the intrinsic intestinal nervous system. *Gene panels or whole exome sequencing helps define the genetic etiology of CIPO.*

The differential diagnosis is broad and includes such etiologies as Hirschsprung disease, MNGIE, mechanical obstruction, psychogenic constipation, neurogenic bladder, and superior mesenteric artery syndrome. Secondary causes of ileus or pseudoobstruction that should be considered include medication side effects, infectious etiologies, metabolic disturbances, immunologic disorders, oncologic processes, vasculitides, neuropathies, and myopathies (see Table 378.1). Examples include use of opiates, hypokalemia, hypothyroidism, hypokalemia, diabetic neuropathy, porphyria, amyloidosis, Chagas disease, scleroderma, hereditary angioedema, mitochondrial disorders, and radiation, and these must be excluded. Other causes of abdominal distention such as small bowel bacterial overgrowth and aerophagia may present similarly and should be considered. *Small bowel bacterial overgrowth is a complication of CIPO.*

## TREATMENT

Nutritional support is the mainstay of treatment for pseudoobstruction. Thirty to 50% of patients require partial or complete parenteral nutrition. Some patients can be treated with intermittent enteral supplementation, whereas others can maintain themselves on selective oral diets. Prokinetic drugs are generally used, although studies have not shown definitive evidence of their efficacy. Isolated gastroparesis can follow episodes of viral gastroenteritis and spontaneously resolves, usually in 6–24 months. Erythromycin, a motilin receptor agonist, and cisapride, a serotonin 5-HT<sub>4</sub> receptor agonist, may enhance gastric emptying and proximal small bowel motility and may be useful in this select group of patients. Metoclopramide, a prokinetic and antinausea agent, is effective in gastroparesis, although side effects, such as tardive dyskinesia, limit its use. Domperidone, an antidopaminergic agent, is a prokinetic agent that can be considered. Pain management is difficult and requires a multidisciplinary approach. Intravenous immunoglobulin (IVIG) may be beneficial in immune mediated CIPO.

Symptomatic small bowel bacterial overgrowth is usually treated with rotated nonabsorbable oral antibiotics and/or probiotics. Bacterial overgrowth can be associated with steatorrhea and malabsorption. Octreotide, a long-acting somatostatin analog, has been used in low doses to treat small bowel bacterial overgrowth. Patients with acid peptic symptoms are generally treated with acid suppression. Many patients with CIPO benefit from a gastrostomy for decompression, and some benefit from decompressive enterostomies (Fig. 378.2). Colectomy with ileorectal anastomosis is beneficial if the large bowel is the primary site of the motility abnormality. Bowel transplantation may benefit selected patients with CIPO. The prognosis is better for patients without urinary tract involvement and for those with neuropathic etiologies over myopathic disorders.



**Fig. 378.2** Photograph of a child with chronic intestinal pseudoobstruction who improved clinically after ileostomy creation. He receives enteral feeding through his jejunal feeding tube, whereas his gastrostomy tube remains to straight drain. (From Bitton S, Markowitz JF. *Ulcerative colitis in children and adolescents*. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*, 5th ed. Philadelphia: Elsevier; 2016: Fig. 44.3.)

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## 378.2 Mitochondrial Neurogastrointestinal Encephalomyopathy

Jennifer Webster, Kristin N. Fiorino, and Chris A. Liacouras

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a multisystem autosomal recessive disease that initially presents with severe gastrointestinal disturbances; the neurologic manifestations usually occur later in the illness and may initially be subtle or asymptomatic.

MNGIE is caused by a pathogenic variant in the nuclear DNA *TYMP* gene encoding thymidine phosphorylase that results in abnormalities in intergenomic communication with resulting instability of mitochondrial DNA (some patients have pathogenic variants in *POLG1*). There are at least 50 individual variants with a poor genotype-phenotype correlation and varying manifestations within each family. Consanguinity is present in 30% of families.

MNGIE affects both males and females and is usually diagnosed in the second and third decade (average age: 18 years; range: 5 months to 35 years). Onset is usually around age 12 years, but there is often a 5- to 10-year delay in the diagnosis. The disease is progressive with an overall survival of <5% after 50 years of age.

MNGIE *initially* presents with gastrointestinal symptoms. Severe intestinal dysmotility and gastroparesis are associated with early satiety, postprandial emesis, episodic pseudoobstruction, diarrhea, constipation, and abdominal pain and cramping, which leads to significant cachexia. Because of the age of onset, emesis, early satiety, and cachexia

patients are often misdiagnosed with an eating disorder. Radiologic studies may find small bowel diverticulosis or GI dilation.

Most often, neurologic symptoms follow the onset of gastrointestinal manifestations, which include ptosis, progressive external ophthalmoplegia, hearing loss, myopathy, and peripheral neuropathy. The neuropathy is either demyelinating or a mixed axonal demyelinating type and manifests as weakness, decreased or absent deep tendon reflexes, and paresthesias. Leukoencephalopathy is initially asymptomatic and noted on MRI as patchy lesions predominantly in the cortex but also in the basal ganglia and brainstem. Eventually the central nervous system lesions become diffuse and confluent. A small number of patients develop cognitive impairment or dementia.

The diagnosis is suggested by the constellation of gastrointestinal and neurologic symptoms, lactic acidosis, ragged red fibers, and cytochrome C oxidase-deficient fibers seen in most patients on muscle biopsy. Reduced activity of thymidine phosphorylase enzyme and elevated plasma levels of thymidine and deoxyuridine are often diagnostic; genetic testing for the *TYMP* pathogenic variant or other genes (*POLG1*) is recommended.

Treatment is focused on providing sufficient nutritional support and avoidance of infectious complications and of nutritional deficiencies. Hemodialysis, continuous ambulatory peritoneal dialysis, and platelet infusions have been effective in achieving temporary improvement and can be used while waiting for a permanent treatment option or as compassionate care. Domperidone has been used for nausea and emesis, antibiotics for small bowel bacterial overgrowth, amitriptyline or gabapentin for neuropathic pain, and parenteral alimentation for nutritional support. Opiates and any medications that affect intestinal motility or mitochondrial function must be avoided. Stem cell transplantation and liver transplantation have been successful in a small number of patients, although they are limited by posttreatment mortality rates.

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### 378.3 Encopresis and Functional Constipation

Jennifer Webster, Kristin N. Fiorino, and Chris A. Liacouras

Constipation is defined as a delay or difficulty in defecation present for >1 month and significant enough to cause distress to the patient. Another approach to the definition is the Rome criteria, outlined in Tables 378.5 and 378.6. Functional constipation, also known as idiopathic constipation or fecal withholding, can usually be differentiated from constipation secondary to organic causes based on a history and physical examination. Unlike anorectal malformations and Hirschsprung disease, functional constipation typically starts *after* the neonatal period. Usually there is an intentional or subconscious withholding of stool. An acute episode usually precedes the chronic course. This acute event could include changes in diet such as transition to formula or addition of pureed/solid foods and can also include a social stressor such as initiation of toilet training, birth of a sibling, starting daycare/school, or abuse. The stool becomes firm, smaller, and difficult to pass, resulting in anal irritation and often an anal fissure. In toddlers, coercive or inappropriately early toilet training is a factor that can initiate a pattern of stool retention. In older children, retentive constipation can develop after entering a situation that makes stooling inconvenient, such as school. Because the passage of bowel movements is painful, voluntary or subconscious withholding of feces to avoid the painful stimulus develops.

#### CLINICAL MANIFESTATIONS

When children have the urge to defecate, typical behaviors include contracting the gluteal muscles by stiffening the legs while lying down,

**Table 378.5** Rome IV Diagnostic Criteria for Defecatory Disorders in Neonates and Toddlers

FGID	AGE RANGE	CRITERIA REQUIREMENTS	CRITERIA ELEMENTS
Functional constipation	All pediatric age groups	Must include 1 month of ≥2 of the criteria elements in infants up to 4 mo of age  In toilet-trained children, the following additional criteria elements may be used	<ul style="list-style-type: none"> <li>• 2 or fewer defecations weekly</li> <li>• History of excessive stool retention</li> <li>• History of hard/painful bowel movements</li> <li>• History of large-diameter stools</li> <li>• Presence of a large fecal mass in the rectum</li> <li>• At least 1 weekly episode of incontinence after being toilet trained</li> <li>• History of large-diameter stools that may clog the toilet</li> </ul>

FGID, Functional gastrointestinal disorders.

Modified from Benninga MA, Faure C, Hyman PE, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology*. 2016;150:1443–1455.

**Table 378.6** Rome IV Diagnostic Criteria for Defecatory Disorders in Children and Adolescents

	AGE RANGE	CRITERIA REQUIREMENTS	CRITERIA ELEMENTS
Functional constipation	Developmental age ≥4yr	Must include ≥2 of the criteria elements for ≥2 months with insufficient criteria to diagnose irritable bowel syndrome	<ul style="list-style-type: none"> <li>• ≤2 defecations in the toilet per week</li> <li>• ≥1 episode of fecal incontinence per week</li> <li>• History of retentive posturing or excessive volitional stool retention</li> <li>• History of painful or hard bowel movements</li> <li>• Presence of a large fecal mass in the rectum</li> <li>• History of large-diameter stools that can obstruct the toilet</li> </ul>
Nonretentive fecal Incontinence	Developmental age ≥4yr	History of symptoms (criteria elements) for ≥1 month	<ul style="list-style-type: none"> <li>• Defecation into places inappropriate to the sociocultural context</li> <li>• No evidence of fecal retention</li> <li>• After appropriate evaluation, symptoms cannot be fully explained by another medical condition</li> </ul>

Modified from Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2016;150:1456–1468.

holding onto furniture while standing, or squatting quietly in corners, waiting for the urge to stool to pass. The urge to defecate passes as the rectum accommodates to its contents. A vicious cycle of retention develops, as increasingly larger volumes of stool need to be expelled. Caregivers may misinterpret these withholding behaviors as straining or pain. There is often a history of blood in the stool noted with the passage of a large bowel movement. Findings suggestive of underlying pathology include failure to thrive, weight loss, abdominal pain, significant abdominal distention, vomiting, or persistent anal fissure or fistula.

In functional constipation, encopresis is common. **Encopresis** is defined as voluntary or involuntary passage of feces into inappropriate places at least once a month for 3 consecutive months once a chronological or developmental age of 4 year has been reached. Encopresis is not diagnosed when the behavior is exclusively the result of the direct effects of a substance (e.g., laxatives) or a general medical condition (except through a mechanism involving constipation). Subtypes include retentive encopresis (with constipation and overflow incontinence), representing 65–95% of cases, and nonretentive encopresis (without constipation and overflow incontinence). **Nonretentive fecal incontinence** is defined as no evidence of fecal retention (impaction), ≥1 episodes per week in the previous 1 month, or defecation in places inappropriate to the social context in a child who has been previously toilet trained and without evidence of anatomic, inflammatory, metabolic, endocrine, or neoplastic process that could explain the symptoms. Encopresis can persist from infancy onward (primary) or can appear after successful toilet training (secondary). The updated Rome criteria (IV) differentiate between infants/toddlers and older children who have been toilet trained versus not toilet trained, for practical assessment purposes.

## DIAGNOSIS

The physical examination often demonstrates a large volume of stool palpated in the suprapubic area; rectal examination demonstrates a dilated rectal vault filled with guaiac-negative stool. Children with encopresis often present with reports of underwear soiling, and many parents initially presume that diarrhea, rather than constipation, is the cause. In **retentive encopresis**, associated complaints of difficulty with defecation, abdominal or rectal pain, impaired appetite with poor growth, and urinary (day and/or night) incontinence are common. Children often have large bowel movements that obstruct the toilet. There may also be retentive posturing or recurrent urinary tract infections. **Nonretentive encopresis** is more likely to occur as a solitary symptom and have an associated primary underlying psychologic etiology. Children with encopresis can present with poor school performance and attendance that is triggered by the scorn and derision from schoolmates because of the child's offensive odor.

The location of the anus relative to perineal anatomic landmarks by sex also needs to be considered. This is expressed as the **anogenital index**, and it can be calculated when necessary. This is determined by the distance in centimeters from the vagina or scrotum to the anus, divided by the distance from the vagina or scrotum to the coccyx. The normal anogenital index in females is  $0.39 \pm 0.09$ , whereas  $0.56 \pm 0.2$  is normal for males.

The presence of a hair tuft over the spine or spinal dimple, or failure to elicit a cremasteric reflex or anal wink suggests spinal pathology. A tethered cord is suggested by decreased or absent lower leg reflexes. **Spinal cord lesions** can occur with overlying skin anomalies. Urinary tract symptoms include recurrent urinary tract infection and enuresis. Children with no evidence of abnormalities on physical examination rarely require radiologic evaluation.

In refractory patients (intractable constipation), specialized testing should be considered to rule out conditions such as hypothyroidism, hypocalcemia, lead toxicity, celiac disease, and disorders of neuromuscular gastrointestinal pathology (Table 378.7). Colonic transit studies using radiopaque markers or scintigraphy techniques may be useful. Selected children can benefit from MRI of the spine to identify an intraspinal process, motility studies to identify underlying myopathic or neuropathic bowel abnormalities, or a contrast enema to identify structural abnormalities. In patients with severe functional

Table 378.7 London Classification of Gastrointestinal Neuromuscular Pathology	
1. Neuropathies	
1.1 Absent neurons	
1.1.1 Aganglionosis*	
1.2 Decreased numbers of neurons	
1.2.1 Hypoganglionosis	
1.3 Increased numbers of neurons	
1.3.1 Ganglioneuromatosis†	
1.3.2 IND, type B‡	
1.4 Degenerative neuropathy§	
1.5 Inflammatory neuropathies	
1.5.1 Lymphocytic ganglionitis¶	
1.5.2 Eosinophilic ganglionitis	
1.6 Abnormal content in neurons	
1.6.1 Intraneuronal nuclear inclusions	
1.6.2 Megamitochondria	
1.7 Abnormal neurochemical coding**	
1.8 Relative immaturity of neurons	
1.9 Abnormal enteric glia	
1.9.1 Increased numbers of enteric glia	
2. Myopathies	
2.1 Muscularis propria malformations††	
2.2 Muscle cell degeneration	
2.2.1 Degenerative leiomyopathy/‡‡	
2.2.2 Inflammatory leiomyopathy	
2.2.2.1 Lymphocytic leiomysitis	
2.2.2.2 Eosinophilic leiomysitis	
2.3 Muscle hyperplasia/hypertrophy	
2.3.1 Muscularis mucosae hyperplasia	
2.4 Abnormal content in myocytes	
2.4.1 Filament protein abnormalities	
2.4.1.1 Alpha-actin myopathy§§	
2.4.1.2 Desmin myopathy	
2.4.2 Inclusion bodies	
2.4.2.1 Polyglucosan bodies	
2.4.2.2 Amphophilic	
2.4.2.3 Megamitochondria¶¶	
2.5 Abnormal supportive tissue	
2.5.1 Atrophic desmosis***	
3. ICC abnormalities (enteric mesenchymopathy)	
3.1 Abnormal ICC networks†††	

\*Can include rare cases of non-Hirschsprung disease severe hypoplastic hypoganglionosis with long interganglionic intervals (zonal aganglionosis).

†Although neurons have not been formally quantified, gross increases of disorganized neurons are evident.

‡Can include retarded neuronal maturation.

§May occur with or without neuronal loss but is best regarded as a separate entity.

¶May occur with neuronal degeneration and/or loss; lymphocytic epithelioganglionitis is a variant.

\*\*Includes neurotransmitter loss (e.g., reduced or absent expression) or loss of a neurochemically defined functional subset of nerves (see text).

††Includes absence, fusion, or additional muscle coats.

‡‡Hollow visceral myopathy may be diagnosed in familial cases with other characteristic phenotypic features; myopathy with autophagic activity and pink blush myopathy with nuclear crowding are rare variants in which degenerative findings are less overt.

§§Smooth muscle alpha-actin deficiency is best described, although deficiencies of other proteins related to the contractile apparatus of myocytes have been reported.

¶¶Mitochondrial neurogastrointestinal encephalomyopathy causes a degenerative appearance predominantly in the longitudinal muscle.

\*\*\*Absent connective tissue scaffold has been almost exclusively described in the colon.

†††Generally reduced or absent ICC, although abnormal morphology also reported.

ICC, Interstitial cells of Cajal; IND, intestinal neuronal dysplasia.

From Knowles CH, De Giorgio R, Kapur RP, et al. The London classification of gastrointestinal neuromuscular pathology: report on behalf of the Gastro 2009 International Working Group. Gut. 2010;59:882–887. Table 1.

constipation, water-soluble contrast enema reveals the presence of a mega rectosigmoid (Fig. 378.3). Anorectal motility studies can demonstrate a pattern of paradoxical contraction of the external anal sphincter during defecation, which can be treated by behavior modification, biofeedback, and pelvic floor physical therapy. Colonic motility can guide therapy in refractory cases, demonstrating segmental problems that might require surgical intervention.



**Fig. 378.3** Barium enema in a 14-yr-old boy with severe constipation. The enormous dilation of the rectum and distal colon is typical of acquired functional megacolon.

Complications of retentive encopresis include day and night urinary incontinence, urinary retention, urinary tract infection, megacystis, and rarely toxic megacolon.

### TREATMENT

Therapy for functional constipation and encopresis includes patient education, behavioral interventions, relief of impaction, and softening of the stool. Caregivers must understand that soiling associated with overflow incontinence is associated with loss of normal sensation and not a willful act. There needs to be a focus on adherence with regular postprandial toilet sitting and adoption of a balanced diet. In addition, caregivers should be instructed not to respond to soiling with retaliatory or punitive measures, because children are likely to become angry, ashamed, and resistant to intervention. From the outset, parents should be actively encouraged to reward the child for adherence to a healthy bowel regimen and to avoid power struggles.

If an impaction is present on the initial physical examination, an enema is usually required to clear the impaction while stool softeners are started as maintenance medications. Typical regimens include the use of polyethylene glycol preparations, lactulose, magnesium, or mineral oil (Tables 378.8 and 378.9). Stimulant laxatives such as senna and bisacodyl can also be helpful.

Compliance can wane, and failure of this standard treatment approach sometimes requires more intensive intervention. In cases where behavioral or psychiatric problems are evident, involvement of a psychologist or behavioral management (e.g., behavior programs and/or biofeedback) is recommended. Maintenance therapy is generally continued until a regular bowel pattern has been established and the association of pain with the passage of stool is abolished.

For children with chronic diarrhea and/or irritable bowel syndrome where stress and anxiety play a major role, stress reduction and learning effective coping strategies can play an important role

**Table 378.8** Suggested Medications and Dosages for Disimpaction

MEDICATION	AGE	DOSAGE
<b>RAPID RECTAL DISIMPACTION</b>		
Glycerin suppositories	Infants and toddlers	
Phosphate enema	6 mo-2 yr	66 mL
	≥3 yr	133 mL
<b>SLOW ORAL DISIMPACTION IN OLDER CHILDREN</b>		
<i>Over 2-3 Days</i>		
Polyethylene glycol with electrolytes		25 mL/kg body weight/hr, up to 1,000 mL/hr until clear fluid comes from the anus
<i>Over 5-7 Days</i>		
Polyethylene without electrolytes		1.5 g/kg body weight/day for 3 days
Milk of magnesia		2 mL/kg body weight twice/day for 7 days
Mineral oil		3 mL/kg body weight twice/day for 7 days
Lactulose or sorbitol		2 mL/kg body weight twice/day for 7 days

From Loening-Baucke V. Functional constipation with encopresis. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*, 3rd ed. Philadelphia: WB Saunders; 2006: p 183.

**Table 378.9** Suggested Medications and Dosages for Maintenance Therapy of Constipation

MEDICATION	AGE	DOSE
<b>TYPICAL DOSES FOR LONG-TERM TREATMENT (YR)</b>		
Milk of magnesia	>1 mo	1-3 mL/kg body weight/day, divided into 1-2 doses
Mineral oil	>12 mo	1-3 mL/kg body weight/day, divided into 1-2 doses
Lactulose or sorbitol	>1 mo	1-3 mL/kg body weight/day, divided into 1-2 doses
Polyethylene glycol 3350 (MiraLAX)	>1 yr	0.7 g/kg body weight/day
<b>FOR SHORT-TERM TREATMENT (MO)</b>		
Senna (Senokot) syrup, tablets	1-5 yr	5 mL (1 tablet) with breakfast, max 15 mL daily
	5-15 yr	2 tablets with breakfast, maximum 3 tablets daily

From Loening-Baucke V. Functional constipation with encopresis. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*, 3rd ed. Philadelphia: WB Saunders; 2006: p 183.

in responding to the encopresis. Relaxation training, stress inoculation, assertiveness training, and/or general stress management procedures can be helpful, and the participation of behavioral health specialists is valuable.

Neurostimulation (transcutaneous or sacral implantation) and pelvic physiotherapy are novel approaches used in patients with medication refractory constipation. Surgical interventions such as rectal Botox, cecostomy, and colostomy may be considered for severe cases.

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## 378.4 Congenital Aganglionic Megacolon (Hirschsprung Disease)

Prasanna K. Kapavarapu, Kristin N. Fiorino, and Chris A. Liacouras

Hirschsprung disease, or congenital aganglionic megacolon, is a developmental disorder (neurocristopathy) of the enteric nervous system, characterized by the absence of ganglion cells in the submucosal and myenteric plexus. It is the most common cause of lower intestinal obstruction in neonates, with an overall incidence of 1 in 5,000 live births. The male:female ratio for Hirschsprung disease is 4:1 for short-segment disease and approximately 2:1 with total colonic aganglionosis. Prematurity is uncommon.

There is an increased familial incidence in long-segment disease. Hirschsprung disease may be associated with other congenital defects, including trisomy 21, Joubert syndrome, Goldberg-Shprintzen syndrome, Smith-Lemli-Opitz syndrome, Shah-Waardenburg syndrome, cartilage-hair hypoplasia, multiple endocrine neoplasm 2 syndrome, neurofibromatosis, neuroblastoma, congenital hypoventilation (Ondine's curse), and urogenital or cardiovascular abnormalities. Hirschsprung disease has been seen in association with microcephaly, intellectual disability, abnormal facies, autism, cleft palate, hydrocephalus, and micrognathia.

### PATHOLOGY

Hirschsprung disease is the result of an absence of ganglion cells in the bowel wall, extending proximally from the anus for a variable distance. The absence of neural innervation is a consequence of an arrest of neuroblast migration from the proximal to distal bowel. Without the myenteric and submucosal plexus, there is inadequate relaxation of the bowel wall and bowel wall hypertonicity, which can lead to intestinal obstruction.

Hirschsprung disease is usually sporadic, although dominant and recessive patterns of inheritance have been demonstrated in family groups. Genetic variants have been identified in multiple genes that encode proteins of the RET signaling pathway (*RET*, *GDNF*, *NTN*, *ARTN*, and *PSPN*) and involved in the endothelin (EDN) type B receptor pathway (*EDNRB*, *EDN3*, and *ECE-1*). **Syndromic forms** of Hirschsprung disease have been associated with the *L1CAM*, *SOX10*, *PHOX2B*, *KIAA1279*, and *ZFHX1B* (formerly *SIP1*) genes.

The aganglionic segment is limited to the rectosigmoid in 80% of patients. Approximately 10–15% of patients have long-segment disease, defined as disease proximal to the sigmoid colon. Total bowel aganglionosis is rare and accounts for approximately 5% of cases. Observed histologically is an absence of Meissner's and Auerbach's plexuses and hypertrophied nerve bundles with high concentrations of acetylcholinesterase between the muscular layers and in the submucosa.

### CLINICAL MANIFESTATIONS

Hirschsprung disease is usually diagnosed in the neonatal period secondary to a distended abdomen, failure to pass meconium, and/or bilious emesis or aspirates with feeding intolerance. In 99% of healthy full-term infants, meconium is passed within 48 hours of birth. Hirschsprung disease should be suspected in any full-term infant (the disease is unusual in preterm infants) with delayed passage of stool. Some neonates pass meconium normally but subsequently present with a history of chronic constipation. Failure to thrive with hypoproteinemia from protein-losing enteropathy is a less common presentation because Hirschsprung disease is usually recognized early in the course of the illness but has been known to occur. Breastfed infants might not present as severely as formula-fed infants.

Failure to pass stool leads to dilation of the proximal bowel and abdominal distention. As the bowel dilates, intraluminal pressure increases, resulting in decreased blood flow and deterioration of the mucosal barrier. Stasis allows proliferation of bacteria, which can lead to **enterocolitis** (*Clostridium difficile*, *Staphylococcus aureus*, anaerobes, coliforms) with associated diarrhea, abdominal tenderness, sepsis, and signs of bowel obstruction. **Red flags** in the neonatal period then include neonatal intestinal obstruction, bowel perforation, delayed passage of meconium, abdominal distention relieved by digital

rectal stimulation or enemas, chronic severe constipation, and enterocolitis. Early recognition of Hirschsprung disease before the onset of enterocolitis is essential in reducing morbidity and mortality.

Hirschsprung disease in older patients must be distinguished from other causes of abdominal distention and chronic constipation (see Tables 378.7; Table 378.10 and Figs. 378.4 and 378.5). The history often reveals constipation starting in infancy that has responded poorly to medical management. Failure to thrive is not uncommon. Fecal incontinence, fecal urgency, and stool-withholding behaviors are usually not present. Significant abdominal distention is unusual in non-Hirschsprung-related constipation, as is emesis. The abdomen is tympanic and distended, with a large fecal mass palpable in the left lower abdomen. Rectal examination demonstrates a normally placed anus that easily allows entry of the finger but feels snug. The rectum is usually empty of feces, and when the finger is removed, there may be an explosive discharge of foul-smelling feces and gas. The stools, when passed, can consist of small pellets, be ribbon-like, or have a fluid consistency, unlike the large stools seen in patients with functional constipation. Intermittent attacks of intestinal obstruction from retained feces may be associated with pain and fever. Urinary retention with enlarged bladder or hydronephrosis can occur secondary to urinary compression.

In neonates, Hirschsprung disease must be differentiated from meconium plug syndrome, meconium ileus, and intestinal atresia. In older patients, the ***Currarino triad*** must be considered, which includes anorectal malformations (ectopic anus, anal stenosis, imperforate anus), sacral bone anomalies (hypoplasia, poor segmentation), and presacral anomaly (anterior meningoceles, teratoma, cyst). Mimics of Hirschsprung disease include intestinal neuronal dysplasia (IND), hypoganglionosis, absence of argyrophil plexus, and **megacystis**.

**Table 378.10** Distinguishing Features of Hirschsprung Disease and Functional Constipation

VARIABLE	FUNCTIONAL	HIRSCHSPRUNG DISEASE
<b>HISTORY</b>		
Onset of constipation	After 2 yr of age	At birth
Encopresis	Common	Very rare
Failure to thrive	Uncommon	Possible
Enterocolitis	None	Possible
Forced bowel training	Usual	None
<b>EXAMINATION</b>		
Abdominal distention	Uncommon	Common
Poor weight gain	Rare	Common
Rectum	Filled with stool	Empty
Rectal examination	Stool in rectum	Explosive passage of stool
Malnutrition	None	Possible
<b>INVESTIGATIONS</b>		
Anorectal manometry	Relaxation of internal anal sphincter	Failure of internal anal sphincter relaxation
Rectal biopsy	Normal	No ganglion cells, increased acetylcholinesterase staining
Barium enema	Massive amounts of stool, no transition zone	Transition zone, delayed evacuation (>24 hr)

From Imseis E, Gariepy C. Hirschsprung disease. In: Walker WA, Goulet OJ, Kleinman RE, et al., eds. *Pediatric Gastrointestinal Disease*, 4th ed. Hamilton, ON: BC Decker; 2004: p 1035.



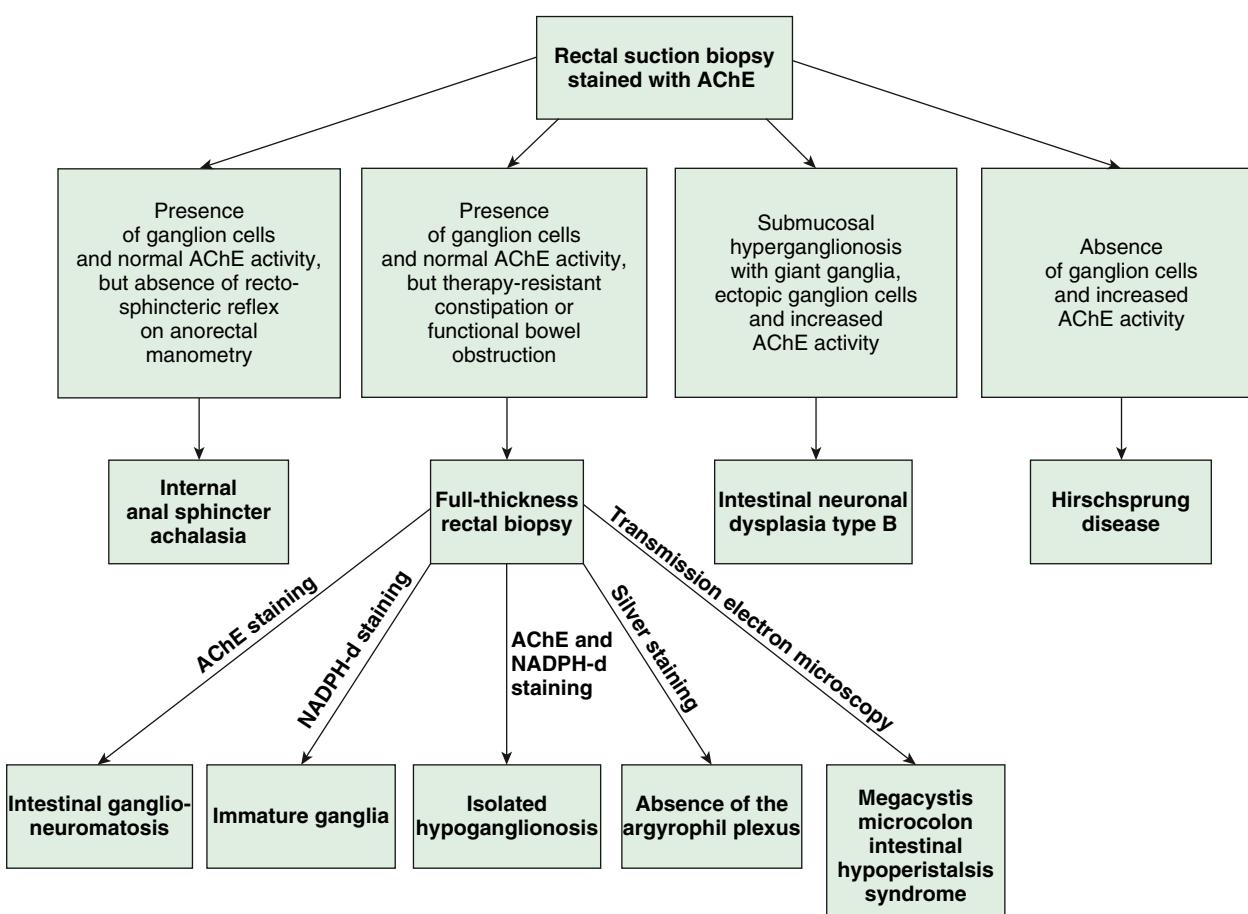
**Fig. 378.4** Lateral view of a barium enema in a 3-yr-old with Hirschsprung disease. The aganglionic distal segment is narrow, with distended normal ganglionic bowel above it.

**microcolon intestinal hypoperistalsis syndrome (MMIHS).** MMIH demonstrates an enlarged bladder and intestinal obstruction with microcolon (Fig. 378.6 and Fig. 378.7); involved genes are noted in Table 378.11.

### DIAGNOSIS

Rectal suction biopsy is the “gold standard” for diagnosing Hirschsprung disease (see Fig. 378.5). The biopsy material should contain an adequate amount of submucosa to evaluate for the presence of ganglion cells. To avoid obtaining biopsies in the normal area of hypoganglionosis, which ranges from 3 to 17 mm in length, the suction rectal biopsy should be obtained no closer than 2 cm above the dentate line. The biopsy specimen should be stained for acetylcholinesterase to facilitate interpretation. Patients with aganglionosis demonstrate a large number of hypertrophied nerve bundles that stain positively for acetylcholinesterase with an absence of ganglion cells. Calretinin is a calcium binding protein expressed in ganglion cells in submucosa and myenteric plexus; hence, calretinin staining may provide a diagnosis of Hirschsprung disease when acetylcholinesterase staining may not be sufficient. In Hirschsprung disease, on the hematoxylin and eosin staining there is absence of ganglion cells in the submucosa with abundance of hypertrophic nerves; on acetylcholinesterase staining there is abnormal accumulation of acetylcholinesterase-positive hypertrophied nerve bundles in muscularis mucosa and lamina propria; and on calretinin staining there is paucity of calretinin-immunoreactive nerves in muscularis mucosa and lamina propria.

Anorectal manometry evaluates the internal anal sphincter while a balloon is distended in the rectum. In healthy individuals, rectal distention initiates relaxation of the internal anal sphincter in response to rectal distention (known as the rectoanal inhibitory reflex [RAIR]). In patients with Hirschsprung disease, the internal



**Fig. 378.5** Diagnostic algorithm for investigating chronic constipation and functional bowel obstruction in newborn infants and young children. AChE, Acetylcholinesterase; NADPH-d, nicotinamide adenine dinucleotide phosphate diaphorase. (From Friedmacher F, Puri P. Classification and diagnostic criteria of variants of Hirschsprung's disease. *Pediatr Surg Int*. 2013;29:855–872. Fig. 1.)



**Fig. 378.6** Voiding cystourethrogram showing massively enlarged bladder in an MMIHS patient. (Modified from Puri P, Gosemann JH. Variants of Hirschsprung disease. *Semin Pediatr Surg.* 2012;21:310–318. Fig. 5A.)



**Fig. 378.7** Megacystis-microcolon-intestinal hypoperistalsis syndrome. Single frontal view of newborn female reveals the microcolon characteristic of this entity. Note the malposition of the cecum, consistent with the malrotation that is common in these patients. Soft tissue density in the pelvis is consistent with a distended urinary bladder. (From Hernanz-Schulman M. *Congenital and neonatal disorders*. In Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*, 13th ed. Philadelphia: Elsevier; 2019: Fig. 105.16, p. 1019.)

anal sphincter fails to relax in response to rectal distention, and there is absence of the RAIR. Although the sensitivity and specificity can vary widely, in experienced hands, the test can be quite sensitive. However, the test can be technically difficult to perform

in young infants. A normal response in the course of manometric evaluation precludes a diagnosis of Hirschsprung disease; an equivocal or paradoxical response requires a repeat anorectal manometry or rectal suction biopsy. The sensitivity and specificity of anorectal manometry are both >90%.

An unprepared contrast enema is most likely to aid in the diagnosis in children older than 1 month of age because the proximal ganglionic segment might not be significantly dilated in the first few weeks of life. Classic findings are based on the presence of an abrupt narrow transition zone between the normal dilated proximal colon and a smaller-caliber obstructed distal aganglionic segment. In the absence of this finding, it is imperative to compare the diameter of the rectum with that of the sigmoid colon, because a rectal diameter that is the same as or smaller than the sigmoid colon suggests Hirschsprung disease. Radiologic evaluation should be performed without prior preparation (i.e., *unprep contrast enema study*) to prevent transient dilation of the aganglionic segment. As many as 10% of newborns with Hirschsprung disease have a normal contrast study. This diagnostic test is most valuable in the disease that involves the distal colon, and specifically, the rectosigmoid. A transition zone may not be readily identifiable in total bowel aganglionosis. The 24-hour delayed films are helpful in showing retained contrast (see Fig. 378.4). If significant barium is still present in the colon, it increases the suspicion of Hirschsprung disease even if a transition zone is not identified. Barium enema examination is useful in determining the extent of aganglionosis before surgery and in evaluating other diseases that manifest as lower bowel obstruction in a neonate. The sensitivity (~70%) and specificity (50–80%) of barium enema studies diagnosing Hirschsprung disease is lower than other methodologies. Full-thickness rectal biopsies can be performed at the time of surgery to confirm the diagnosis, level of involvement, and to differentiate other disorders (see Fig. 378.5).

## TREATMENT

Once the diagnosis is established, the definitive treatment is operative intervention. Previously, a temporary ostomy was placed, and definitive surgery was delayed until the child was older. Currently, many infants undergo a primary pull-through procedure unless there is associated enterocolitis or other complications, when a decompressing ostomy is usually required.

There are essentially two surgical options. One procedure creates a neorectum, bringing down normally innervated bowel behind the aganglionic rectum. The neorectum created in this procedure has an anterior aganglionic segment with normal sensation and a posterior ganglionic segment with normal propulsion. The **endorectal pull-through procedure** involves stripping the mucosa from the aganglionic rectum and bringing normally innervated colon through the residual muscular cuff, thus bypassing the abnormal bowel from within. Advances in techniques have led to successful laparoscopic single-stage endorectal pull-through procedures, which are the treatment of choice.

In **ultrashort-segment Hirschsprung disease**, also known as **anal achalasia**, the aganglionic segment is limited to the internal sphincter. The clinical symptoms are similar to those of children with functional constipation. Ganglion cells are present on rectal suction biopsy, but the anorectal manometry is abnormal, with failure of relaxation of the internal anal sphincter in response to rectal distention. Current treatment, although controversial, includes anal botulism injection to relax the anal sphincter and anorectal myectomy if indicated.

Long-segment Hirschsprung disease involving the entire colon and, at times, part of the small bowel presents a difficult problem. Anorectal manometry and rectal suction biopsy demonstrate findings of Hirschsprung disease, but radiologic studies are difficult to interpret because a colonic transition zone cannot be identified. The extent of aganglionosis can be determined accurately by biopsy at the time of laparotomy. When the entire colon is aganglionic, often together with a length of terminal ileum, ileal-anal anastomosis is the treatment of choice, preserving part of the aganglionic colon to facilitate water absorption, which helps the stools to become firm.

Table 378.11 Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome: Genes and Distinguishing Clinical Features				
GENE*	% OF ALL MMIHS	MOI	DISTINGUISHING CLINICAL FEATURES	OTHER
ACTG2	44.1%	AD	Classic features of MMIHS (e.g., megacystis, microcolon, intestinal dysmotility)	Greater disease severity reported in probands with <i>de novo</i> (vs inherited) pathogenic variant Parental somatic and germline mosaicism reported
LMOD1	1 person	AR	Classic features of MMIHS	Large deletions/duplications not reported to date
MYH11	2 persons	AR	Overlapping features of MMIHS and prune-belly sequence (one person) Overlapping features of MMIHS and MSMDS (1 person)	Large del/dups not associated with MMIHS to date
MYL9	1 person	AR	Mydriasis No vascular smooth muscle dysfunction <sup>†</sup>	Homozygous partial-gene deletion reported
MYLK	2 families	AR	No vascular smooth muscle dysfunction <sup>†</sup>	Large deletions/duplications not associated with MMIHS to date
Unknown	~55%			

\*Genes are listed alphabetically.

<sup>†</sup>Vascular smooth muscle dysfunction including aortic aneurysms or dissection has not been reported.

AD, Autosomal dominant; AR, autosomal recessive; MMIHS, megacystis-microcolon-intestinal hypoperistalsis syndrome; MOI, mode of inheritance; MSMDS, multisystemic smooth muscle dysfunction syndrome.

Modified from Ambartsumyan L. Megacystis-microcolon-intestinal hypoperistalsis syndrome overview. NIH National Library of Medicine. GeneRev. 2019.

The prognosis of surgically treated Hirschsprung disease is generally satisfactory independent of the kind of surgical procedure, about 15–60% experience bowel problems ranging from constipation and/or fecal incontinence and enterocolitis episodes, but these symptoms diminish with age. Children presenting with persistent bowel problems after surgery often need additional diagnostics (contrast enema, three-dimensional [3D] high-definition anorectal manometry, rectal suction biopsy, and colon manometry), advanced bowel regimen (stool softeners, stimulant laxatives, medicated enemas, pelvic floor therapy), and additional surgical procedures (anal dilation, anal myectomy, re-do pull-through corrective surgery, appendicostomy or cecostomy, colostomy, ileostomy). Recent advances in the field of motility include usage of 3D high-definition anorectal manometry to assess the anorectal function of the post-surgical anal sphincter and high-resolution colon manometry to assess and characterize the motility function of the residual colon after Hirschsprung surgery.

Hirschsprung disease-associated **enterocolitis** can occur at any time before or after surgery and is the leading cause of death in these patients. Dysmotility related to partial obstruction, underlying disease, impaired immune function, and the intestinal microbiome may all contribute to this pathophysiologic process. Explosive, foul-smelling and/or bloody diarrhea, abdominal distention, explosive discharge of rectal contents on digital examination, diminished peripheral perfusion, lethargy, and fever are all ominous signs. Management principles include hydration, decompression from above and below (nasogastric Salem Sump, rectal tube, rectal irrigation), and the use of broad-spectrum antibiotics.

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## 378.5 Intestinal Neuronal Dysplasia

Prasanna K. Kapavarapu, Kristin N. Fiorino, and Chris A. Liacouras

IND describes different quantitative (hypoganglionosis or hyperganglionosis) and qualitative (immature or heterotropic ganglion cells) abnormalities of the submucosal plexus. The typical histology is that of hyperganglionosis and giant ganglia. **Type A** occurs very rarely and is characterized by congenital aplasia or hypoplasia of the sympathetic innervation. Patients present early in the neonatal period with episodes of intestinal obstruction, diarrhea, and bloody stools. **Type B** accounts for more than 95% of cases. Biopsies for diagnosis of IND type B have to be taken 8 cm proximal to the dentate line with sufficient submucosa and should be cut rectangular to the surface mucosa to avoid false-positive results. Qualitative criteria include hypoganglionosis and hypertrophy of nerve trunks. Quantitative criteria include presence of at least 20% submucosal giant ganglia in 30 serial sections examined, 8 (10 ± 2) nerve cells per ganglion, and children >1 year of age. IND type B mimics Hirschsprung disease, and patients present with chronic constipation (see Table 378.7 and Fig. 378.5). Clinical manifestations include abdominal distention, constipation, and enterocolitis. Various lengths of bowel may be affected from segmental to the entire intestinal tract. IND has been observed in an isolated form and proximal to an aganglionic segment. Other intraintestinal and extraintestinal manifestations are present in patients with IND. It has been reported in all age groups, most commonly in infancy, but is also seen in adults who have had constipation not dating back to childhood.

Associated diseases and conditions include Hirschsprung disease, prematurity, small left colon syndrome, and meconium plug syndrome. Studies have identified a deficiency in substance P in patients with IND. Type A IND may be inherited in a familial, autosomal recessive pattern. Most cases of IND type B are sporadic, with few familial clusters, suggesting autosomal dominant inheritance.

Management includes that for functional constipation, and, if unsuccessful, surgery is indicated including emergency surgeries for acute obstruction.

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### **378.6 Superior Mesenteric Artery Syndrome (Wilkie Syndrome, Cast Syndrome, Arteriomesenteric Duodenal Compression Syndrome)**

Prasanna K. Kapavarapu, Kristin N. Fiorino, and Chris A. Liacouras

Superior mesenteric artery syndrome results from compression of the third duodenal segment by the superior mesenteric artery against the aorta. Malnutrition or catabolic states may cause mesenteric fat depletion, which collapses the duodenum within a narrowed aortomesenteric angle. Other etiologies include extraabdominal compression (e.g., body cast) and mesenteric tension, as can occur from ileoanal pouch anastomosis. Rapid weight loss and immobilization are risk factors.

Symptoms include intermittent epigastric pain, anorexia, nausea, and vomiting. Risk factors include thin body habitus, prolonged bed rest, abdominal surgery, and exaggerated lumbar lordosis. Onset can be within weeks of a trigger, but some patients have chronic symptoms that evade diagnosis. A classic example is an underweight adolescent who begins vomiting 1-2 weeks after scoliosis surgery or spinal fusion. Recognition may be delayed in the context of an eating disorder. Superior mesenteric artery syndrome can not only simulate anorexia nervosa, but also precipitate and sometimes even complicate anorexia nervosa.

The diagnosis is established radiologically by demonstrating a duodenal cutoff just right of midline along with proximal duodenal dilation, with or without gastric dilation. Although the upper gastrointestinal series remains a mainstay, modalities including abdominal CT or CT/MR angiography, or ultrasound may be more appropriate if there is concern for other etiologies such as malignancy. Upper endoscopy should be considered to rule out intraluminal pathology.

Treatment focuses on obstructive relief, nutritional rehabilitation, and correction of associated fluid and electrolyte abnormalities. Lateral or prone positioning can shift the duodenum away from obstructing structures and allow resumption of oral intake. If repositioning is unsuccessful, patients require nasojejunal enteral nutrition past the obstruction or parenteral nutrition if this is not tolerated. This management is successful in the vast majority of cases, with eventual withdrawal of tube feeding once weight has been regained and enteral feeding tolerance orally has been gradually and fully restored. Patients with refractory courses may require surgery to bypass the obstruction.

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## Chapter 379

# Ileus, Adhesions, Intussusception, and Closed-Loop Obstructions

### **379.1 Ileus**

Elizabeth C. Maxwell and Chris A. Liacouras

Ileus is the failure of intestinal peristalsis caused by loss of coordinated gut motility without evidence of mechanical obstruction. In children, it is most often associated with abdominal surgery or infection (gastroenteritis, pneumonia, peritonitis). Ileus also accompanies metabolic abnormalities (e.g., uremia, hypokalemia, hypercalcemia, hypermagnesemia, acidosis) or administration of certain drugs, such as opiates, vincristine, and antimotility agents such as loperamide when given during gastroenteritis.

Ileus manifests with nausea, vomiting, feeding intolerance, abdominal distention with associated pain, and delayed passage of stool and bowel gas. Bowel sounds are minimal or absent, in contrast to early mechanical obstruction, when they are hyperactive. Abdominal radiographs demonstrate multiple air-fluid levels throughout the abdomen. Serial radiographs usually do not show progressive distention as they do in mechanical obstruction. Contrast radiographs, if performed, demonstrate slow movement of barium through a patent lumen. Ileus after abdominal surgery generally resolves within 72 hours.

Treatment involves correcting the underlying abnormality, supportive care of comorbidities, and mitigation of iatrogenic contributions. Electrolyte abnormalities should be identified and corrected, and narcotic agents, when used, should be weaned as tolerated. Nasogastric decompression can relieve recurrent vomiting or abdominal distention associated with pain; resultant fluid losses should be corrected with isotonic crystalloid solution. Prokinetic agents such as erythromycin are not routinely recommended. Selective peripheral opioid antagonists such as methylnaltrexone hold promise in decreasing postoperative ileus, but pediatric data are lacking.

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### **379.2 Adhesions**

Elizabeth C. Maxwell and Chris A. Liacouras

Adhesions are fibrous tissue bands that result from peritoneal injury. Their formation is a complex process involving inflammation, hypoxia, and the extracellular matrix. They can constrict hollow organs and are a major cause of postoperative small bowel obstruction. Most remain asymptomatic, but problems can arise any time after the second postoperative week to years after abdominal surgery, regardless of surgical extent. In one large meta-analysis, the incidence of bowel obstruction

secondary to adhesive formation (ASBO) was between 1 and 12.6% in children. ASBO is an important cause of pediatric surgical emergency.

The diagnosis is suspected in patients with colicky abdominal pain, constipation, anorexia, emesis, and a history of intraperitoneal surgery. Nausea and vomiting quickly follow onset of pain. Initially, bowel sounds are hyperactive, and the abdomen is flat. Subsequently, bowel sounds disappear, and bowel dilation can cause abdominal distention. Fever and leukocytosis suggest bowel necrosis and peritonitis. Plain radiographs demonstrate obstructive features, and a CT scan or contrast studies may be needed to define the etiology.

Management includes nasogastric decompression, intravenous fluid resuscitation, and broad-spectrum antibiotics in preparation for surgery. The laparoscopic approach is used with increased frequency now compared to open laparotomy. Nonoperative intervention is contraindicated unless a patient is stable with obvious clinical improvement. Gastrografin (diatrizoate meglumine), typically used as an oral contrast agent for radiologic studies, may be a useful nonoperative management tool. A few small pediatric studies have shown promise, including decreased surgical requirement, decreased time to feed after admission, decreased hospital length of stay, and decreased healthcare costs with its use. Long-term complications include formation of new adhesions from surgery to relieve the obstruction, female infertility, failure to thrive, and chronic abdominal and/or pelvic pain.

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### 379.3 Intussusception

Elizabeth C. Maxwell and Chris A. Liacouras

Intussusception occurs when a portion of the alimentary tract is telescoped into an adjacent segment. It is the most common cause of intestinal obstruction between 5 months and 3 years of age and the most common abdominal emergency in children younger than 2 years of age. Sixty percent of patients are younger than 1 year of age and 80% of the cases occur before age 24 months; it is rare in neonates. The incidence varies from 1 to 4 per 1,000 live births. The male:female ratio is 3:1. Many small bowel–small bowel and a few small bowel–colon intussusceptions reduce spontaneously; if left untreated, ileal–colonic intussusception may lead to intestinal infarction, perforation, peritonitis, and death.

#### Etiology and Epidemiology

Approximately 90% of cases of intussusception in children are idiopathic. The seasonal incidence has peaks in fall and winter. Correlation with prior or concurrent respiratory adenovirus (type C) infection has been noted, and the condition can complicate otitis media, gastroenteritis, Henoch-Schönlein purpura, COVID-19, or upper respiratory tract infections. A slight increase in intussusception has been noted to occur within 3 weeks of the rotavirus vaccine (especially after the first dose), but this is a very rare side effect.

It is postulated that gastrointestinal infection or the introduction of new food proteins results in swollen Peyer patches in the terminal ileum. Lymphoid nodular hyperplasia is another related risk factor. Prominent mounds of lymph tissue lead to mucosal prolapse of the ileum into the colon, thus causing an intussusception. In 2–8% of patients, **recognizable lead points** for the intussusception are found, such as a Meckel diverticulum, intestinal polyp, neurofibroma, intestinal duplication cysts, inverted appendix stump, leiomyomas, hamartomas, ectopic pancreatic tissue, anastomotic suture line, enterostomy tube, posttransplant lymphoproliferative disease, hemangioma, or malignant conditions such as lymphoma or Kaposi sarcoma. Gastrojejunostomy and jejunostomy tubes can also serve as lead points for intussusception. Lead points are more common in children older than 2 years of age; the older the child, the higher the risk of a lead point. In adults, lead points are present



**Fig. 379.1** Transverse image of an ileocolic intussusception. Note the loops within the loops of bowel.

in 90%. Intussusception can complicate mucosal hemorrhage, as in Henoch-Schönlein purpura, idiopathic thrombocytopenic purpura, or hemophilia. Cystic fibrosis, celiac disease, and Crohn disease are other risk factors. Postoperative intussusception is ileoileal and usually occurs within several days of an abdominal operation. Anterograde intussusception may occur rarely following bariatric surgery with a Roux-en-Y gastric bypass and is noteworthy that there does not seem to be a lead point in these cases. Intussusception occurring during development in utero may be associated with the development of intestinal atresia. Intussusception in premature infants is rare.

Ileo-ileal (as compared to ileo-colonic) intussusception may be more common than previously believed, is often idiopathic or associated with Henoch-Schönlein purpura, and usually resolves spontaneously.

#### Pathology

Symptomatic intussusceptions are most often ileocolic, less commonly cecocolic, and occasionally ileal. Very rarely, the appendix forms the apex of an intussusception. The upper portion of bowel, the **intussusceptum**, invaginates into the lower, the **intussuscipiens**, pulling its mesentery along with it into the enveloping loop. Constriction of the mesentery obstructs venous return; engorgement of the intussusceptum follows, with edema, and bleeding from the mucosa leads to a bloody stool, sometimes containing mucus. The apex of the intussusception can extend into the transverse, descending, or sigmoid colon, even to and through the anus in neglected cases. This presentation must be distinguished from rectal prolapse. Most intussusceptions do not strangulate the bowel within the first 24 hours but can eventuate in intestinal gangrene and shock.



**Fig. 379.2** Intussusception in an infant. The obstruction is evident in the proximal transverse colon. Contrast material between the intussusceptum and the intussuscipiens (arrows) is responsible for the coiled-spring appearance.

### CLINICAL MANIFESTATIONS

In typical cases, there is sudden onset, in a previously well child, of severe paroxysmal colicky pain that recurs at frequent intervals and is accompanied by straining efforts with legs and knees flexed and loud cries. The child may initially be comfortable and play normally between the paroxysms of pain, but if the intussusception is not reduced, the child becomes progressively weaker and lethargic. At times, the **lethargy** is often disproportionate to the abdominal signs. With progression, a shocklike state, with fever and peritonitis, can develop. The pulse becomes weak and thready, the respirations become shallow and grunting, and the pain may be manifested only by moaning sounds. Vomiting occurs in most cases and is usually more frequent in the early phase. In the later phase, the vomitus becomes bile stained. Stools of normal appearance may be evacuated in the first few hours of symptoms. After this time, fecal excretions are small or more often do not occur, and little or no flatus is passed. Blood is generally passed in the first 12 hours but at times not for 1–2 days and infrequently not at all; 60% of infants pass a stool containing red blood and mucus, the commonly described **currant jelly stool**. Some patients have only irritability and alternating or progressive lethargy. *The classic triad of pain, a palpable sausage-shaped abdominal mass, and bloody or currant jelly stool is seen in <30% of patients with intussusception.* The combination of paroxysmal pain, vomiting, and a palpable abdominal mass has a positive predictive value of >90%; the presence of rectal bleeding increases this to approximately 100%.

Palpation of the abdomen usually reveals a slightly tender sausage-shaped mass, sometimes ill defined, which might increase in size and firmness during a paroxysm of pain and is most often in the right upper abdomen, with its long axis cephalocaudal. If it is felt in the epigastrium, the long axis is transverse. Approximately 30% of patients do not have a palpable mass. The presence of bloody mucus on rectal examination supports the diagnosis of intussusception. Abdominal distention and tenderness develop as intestinal obstruction becomes more acute. On rare occasions, the advancing intestine prolapses through the anus. *This prolapse can be distinguished from prolapse of the rectum by the separation between*

*the protruding intestine and the rectal wall, which does not exist in prolapse of the rectum.*

Ileoileal intussusception in children younger than 2 years can have a less typical clinical picture, and the symptoms and signs are chiefly those of small intestinal obstruction. These often resolve without treatment. **Recurrent intussusception** is noted in 5–8% and is more common after hydrostatic than surgical reduction. Chronic intussusception, in which the symptoms exist in milder form at recurrent intervals, is more likely to occur with or after acute enteritis and can arise in older children as well as in infants.

### DIAGNOSIS

When the clinical history and physical findings suggest intussusception, an abdominal ultrasound is typically performed. A plain abdominal radiograph might show a density in the area of the intussusception. Screening ultrasounds for suspected intussusception increases the yield of diagnostic or therapeutic enemas and reduces unnecessary radiation exposure in children with negative ultrasound examinations. The diagnostic findings of intussusception on ultrasound include a tubular mass in longitudinal views and a doughnut or target appearance in transverse images (Fig. 379.1). Ultrasound has a sensitivity of approximately 98–100% and a specificity of approximately 98% in diagnosing intussusception. Air, hydrostatic (saline), and, less often, water-soluble contrast enemas have replaced barium examinations. Contrast enemas demonstrate a filling defect or cupping in the head of the contrast media where its advance is obstructed by the intussusceptum (Fig. 379.2). A central linear column of contrast media may be visible in the compressed lumen of the intussusceptum, and a thin rim of contrast may be seen trapped around the invaginating intestine in the folds of mucosa within the intussuscipiens (coiled-spring sign), especially after evacuation. Retrogression of the intussusceptum under pressure and visualized on x-ray or ultrasound documents successful reduction. Air reduction is associated with fewer complications and lower radiation exposure than traditional contrast hydrostatic techniques.

### DIFFERENTIAL DIAGNOSIS

It may be particularly difficult to diagnose intussusception in a child who already has gastroenteritis; a change in the pattern of illness, in the character of pain, or in the nature of vomiting or the onset of rectal bleeding should alert the physician. The bloody stools and abdominal cramps that accompany enterocolitis can usually be differentiated from intussusception because in enterocolitis the pain is less severe and less regular, there is diarrhea, and the infant is recognizably ill between painful episodes. Bleeding from a Meckel diverticulum is usually painless. Joint symptoms, purpura, or hematuria usually but not invariably accompany the intestinal hemorrhage of Henoch-Schönlein purpura. Because intussusception can be a complication of this disorder, ultrasonography may be needed to distinguish the conditions.

It is important in patients with cystic fibrosis to distinguish intussusception from distal intestinal obstruction syndrome. Distal intestinal obstruction syndrome requires antegrade treatment, which would be harmful if there was an intussusception.

### TREATMENT

Reduction of an acute intussusception is an emergency procedure and should be performed immediately after diagnosis in preparation for possible surgery. In patients with prolonged intussusception and signs of shock, peritoneal irritation, intestinal perforation, or pneumatisis intestinalis, hydrostatic reduction should not be attempted.

The success rate of radiologic hydrostatic reduction under fluoroscopic or ultrasonic guidance is approximately 80–95% in patients with ileocolic intussusception. Spontaneous reduction of

intussusception occurs in approximately 4–10% of patients. Bowel perforations occur in 0.5–2.5% of attempted barium and hydrostatic (saline) reductions. The perforation rate with air reduction is 0.1–0.2%. Surgical reduction is indicated in the presence of refractory shock, suspected bowel necrosis or perforation, peritonitis, and multiple recurrences (suspected lead point).

An *ileoileal intussusception* is best demonstrated by abdominal ultrasonography. Reduction by instillation of contrast agents, saline, or air might not be possible. Such intussusceptions can develop insidiously after bowel surgery and require reoperation if they do not spontaneously reduce. Ileoileal disease is common with Henoch-Schönlein purpura and other unidentifiable disorders and usually resolves without the need for any specific treatment. If manual operative reduction is impossible or the bowel is not viable, resection of the intussusception is necessary, with end-to-end anastomosis.

## PROGNOSIS

Untreated ileal-colonic intussusception in infants is usually fatal; the chances of recovery are directly related to the duration of intussusception before reduction. Most infants recover if the intussusception is reduced in the first 24 hours, but the mortality rate rises rapidly after this time, especially after the second day. Spontaneous reduction during preparation for operation is not uncommon.

The **recurrence rate** after nonsurgical reduction of intussusceptions is approximately 10%, and after surgical reduction it is 2–5%; none has recurred after surgical resection. Most recurrences occur within 72 hours of reduction. Corticosteroids may reduce the frequency of recurrent intussusception but are rarely used for this purpose. Repeated reducible episodes caused by lymphonodular hyperplasia may respond to treatment of identifiable food allergies if present. A single recurrence of intussusception can usually be reduced radiologically. In patients with multiple ileal-colonic recurrences, a lead point should be suspected and laparoscopic surgery considered. It is unlikely that an intussusception caused by a lesion such as lymphosarcoma, polyp, or Meckel diverticulum will be successfully reduced by radiologic intervention. With adequate surgical management, laparoscopic reduction carries a very low mortality.

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## 379.4 Closed-Loop Obstructions

Elizabeth C. Maxwell and Chris A. Liacouras

Closed-loop obstructions (i.e., **internal hernia**) result from bowel loops that enter windows created by mesenteric defects or adhesions and become trapped, with the entrapped segment of bowel becoming obstructed at two points. Vascular engorgement of the strangulated bowel results in intestinal ischemia and necrosis unless promptly relieved. Prior abdominal surgery is an important risk factor. Symptoms include abdominal pain, distention, and bilious emesis. Symptoms can be intermittent if the herniated bowel slides in and out of the defect. Peritoneal signs suggest ischemic bowel. Plain radiographs demonstrate signs of small bowel obstruction or free air if the bowel has perforated. CT scan can identify and delineate internal hernias. Supportive management includes intravenous fluids, antibiotics, and nasogastric decompression. Prompt surgical relief of the obstruction is indicated to prevent bowel necrosis.

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## Chapter 380

# Foreign Bodies and Bezoars

## 380.1 Foreign Bodies in the Stomach and Intestine

Trusha Patel, Petar Mamula, and Chris A. Liacouras

Foreign body (FB) ingestions are common in children, with most ingestions occurring between 6 months and 3 years of age. Generally, FB ingestions in young children are unintentional and involve small household objects (coins, toys, jewelry, magnets, batteries, etc.). Although children may present with symptoms of abdominal pain or chest pain, stridor, drooling, respiratory distress, fever, dysphagia, or inability to tolerate oral intake after FB ingestions, up to 50% of children may be asymptomatic at the time of presentation. A thorough history and clinical examination is required, including evaluation for respiratory distress, oropharyngeal injury, and signs of perforation such as subcutaneous emphysema or peritoneal signs. When determining the appropriate management of a child after FB ingestion, clinicians must consider patient age and anatomy; object type, location, and size; timing of ingestion; presence or absence of symptoms; nil per os (NPO) status; and logistical factors (availability of necessary staff, social factors that may impact timely follow-up). In addition to history and clinical examination, anteroposterior and lateral radiographs of the neck, chest, and/or abdomen are useful to confirm the presence and determine the location of radiopaque foreign bodies. Object location is particularly important to consider in the context of the most common sites of potential FB impaction, obstruction, or retention, which include multiple locations in the esophagus, pylorus, duodenal sweep, ligament of Treitz, ileocecal valve, rectosigmoid colon, and anus.

Otolaryngologists, gastroenterologists, and general surgeons are all trained in the management of FB ingestions and center-specific availability and expertise should guide consultation with the appropriate specialist. The management of esophageal foreign bodies is reviewed elsewhere (Chapter 373.1). Considerations for management of gastrointestinal foreign bodies in the stomach and intestine are based on object type, along with recommendations regarding timing of potential endoscopic removal as being emergent (<2 hours, regardless of NPO status), urgent (<24 hours, following usual NPO guidelines), or elective (>24 hours from presentation, following usual NPO guidelines). It should be noted, however, that given the great variability in patient and object size, the management of pediatric FB ingestions is case dependent, and clinicians must use their judgment when determining appropriate management.

### BUTTON BATTERIES

Button battery ingestion in a child of any age requires emergent evaluation, given the potential for rapid, severe caustic injury and associated complications. For children ≥1 year of age with suspected lithium button battery ingestion in the prior 12 hours or confirmed location in the esophagus, current recommendations are to administer honey 10 mL every 10 minutes (or sucralfate if available) and proceed to the emergency department as soon as possible.

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## Chapter 380

# Foreign Bodies and Bezoars

## 380.1 Foreign Bodies in the Stomach and Intestine

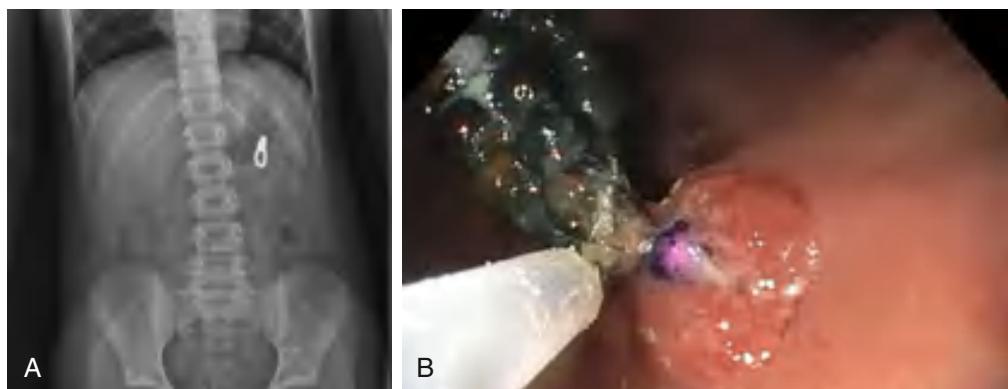
Trusha Patel, Petar Mamula, and Chris A. Liacouras

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**Fig. 380.1** A, Supine abdominal radiograph of 8-yr-old girl with history of ingestion of 23 Buckyball-type magnets over preceding 3-mo period demonstrating loop of magnets. B, Endoscopic image of magnets during retrieval from lesser curvature of the stomach, with additional finding of magnet penetrating the wall of stomach. Subsequent surgical exploration demonstrated fistula between stomach and jejunum, which was repaired.

Immediate two-view radiograph is indicated to determine battery location and negative pole orientation; direct notification of otolaryngology, gastroenterology, and/or general surgery is indicated pending results of this radiograph. Although removal of esophageal button batteries is emergent, management of button batteries in the stomach and more distally depends on the presence of symptoms and whether a single battery or multiple objects have been ingested. If symptoms of anorexia, vomiting, abdominal pain, or fever are present or if there is co-ingestion of a magnet, then urgent endoscopic removal is indicated if the button battery is in the stomach or proximal small intestine. If the patient is asymptomatic after the ingestion of a single button battery  $\geq 15$  mm that has passed beyond the esophagus, esophagram should still be considered (particularly in children  $< 6$  years of age) to evaluate for esophageal injury. If esophagram is normal, observant management may be appropriate, with repeat abdominal x-ray (AXR) in 2-3 days and consideration of button battery removal if it still has not passed the stomach within 4 days. However, if the esophagram is abnormal or if patient size or other factors make it unlikely that the battery will pass spontaneously, hospital admission for observation, endoscopic evaluation, and potential battery removal is indicated. If the patient is asymptomatic and only a single button battery  $< 15$  mm has been ingested and is in the stomach or more distal, observant management is appropriate. AXR should be considered if an ingested button battery has not passed in the stool within 10-14 days.

### COINS/BLUNT OBJECTS

Although coins are the most frequently ingested FB, when coin ingestion is reported or identified on imaging, it is important to confirm that the ingested object could not potentially be a button battery (on imaging, it is important to make sure there is no “step-off” sign on lateral view or “double halo” sign on anteroposterior views). Generally, endoscopic removal of coins and other small, blunt objects in the stomach and more distally is only necessary if the patient is symptomatic or if the object is unlikely to pass (child  $< 2$  years old and object dimensions of width  $> 2$  cm or length  $> 5$  cm). Repeat abdominal radiography may be considered in 2-3 weeks if a child under 2 years of age swallowed a quarter or another object that may not pass in a timely fashion.

### MAGNETS

In the case of a suspected or confirmed magnet ingestion, two-view radiographs should be obtained to confirm whether a single magnet



**Fig. 380.2** Abdominal radiograph of a 3-yr-old boy, noting three attached magnets that resulted in volvulus (i.e., twisting of the bowel) and multiple bowel perforations. (Courtesy U.S. Consumer Product Safety Commission. From Centers for Disease Control and Prevention: Gastrointestinal injuries from magnet ingestion in children—United States, 2003–2006. MMWR Morb Mortal Wkly Rep. 2006;55:1296–1300.)

or multiple magnets have been ingested, as multiple magnet ingestion places the patient at risk for entero-enteric fistula formation between magnets in adjacent loops of bowel, which can lead to perforation, peritonitis, and bowel ischemia/necrosis. If a single magnet has been ingested and is in the stomach or intestine and the patient is asymptomatic, with low risk for ingestion of additional magnets and with good follow-up, allowing spontaneous passage is appropriate. In that case, precautions that should be taken include removing all magnets and metallic objects from the patient's environment (including patient's clothing) and preventing any risk of additional magnet ingestion until the magnet has passed. In the case of multiple magnet ingestion, urgent endoscopic removal is indicated if the magnets are in the stomach to prevent further passage or complications (Fig. 380.1). If multiple magnets are beyond the stomach, consultation with a general surgeon is recommended and magnet removal should be pursued if the patient is symptomatic (either with enteroscopy, laparoscopy or laparotomy, depending on center expertise) (Fig. 380.2). If the patient is asymptomatic, hospital admission for laxative therapy, serial abdominal exams and x-rays (every 4-6 hours) and consideration of later removal if not passing is appropriate.

## SHARP OBJECTS

The management of ingested sharp objects depends on size and shape of the object. Radiographic evaluation is key in identifying size, location, and orientation of radiopaque sharp objects, although it will not be beneficial for radiolucent objects. Generally, urgent endoscopic removal is indicated for sharp objects in the stomach or duodenum if the patient is symptomatic, the object is likely to cause perforation if allowed to pass spontaneously, or if the object is unlikely to pass due to large size ( $>5\text{-}6$  cm long in teenagers/adults or  $\geq 2\text{-}3$  cm long in a younger child). If a large, sharp object is beyond the duodenum, consultation with general surgery is recommended, as removal is indicated if the patient is symptomatic. Even if the patient is asymptomatic, serial radiographs are indicated and removal with enteroscopy or surgery may be needed if symptoms develop or if the object does not pass after 3 days. Otherwise, if the patient is asymptomatic and the object is smaller than the aforementioned dimensions, particularly with the sharp end of the object trailing behind a heavier blunt end, allowing spontaneous passage is reasonable. For reported ingestion of sharp, radiolucent objects, urgent endoscopic evaluation and potential removal is indicated if the patient is asymptomatic. If the patient is symptomatic, alternate imaging (CT, ultrasound, MRI, fluoroscopy) may be utilized for assessment and removal may be considered if the object is identified.

## SPECIAL CONSIDERATIONS

Other foreign bodies that may require special considerations include those with the potential to cause obstruction or toxicity based on object characteristics. Super-absorbent objects (including expanding children's spongelike toys, tampons) may expand rapidly within the GI tract and cause gastric outlet or bowel obstruction. If not yet expanded and accessible via endoscope, removal should be considered. Lead-containing foreign bodies should be removed promptly if endoscopically accessible, as they have the potential to cause lead toxicity. Consultation with toxicology is recommended and obtaining baseline serum lead level is suggested. If the lead-containing FB is beyond the stomach, bowel irrigation and monitoring of blood lead levels may be appropriate to minimize and monitor toxicity. In the case of ingestion of narcotic packets, endoscopic removal should be avoided to prevent packet rupture and severe toxicity and consultation with Poison Control Center is recommended.

Children occasionally place objects in their rectum. Small blunt objects usually pass spontaneously, but large or sharp objects typically need to be retrieved. Adequate sedation is essential to relax the anal sphincter before attempting endoscopic or speculum removal. If the object is proximal to the rectum, observation for 12-24 hours usually allows the object to descend into the rectum.

## IMPORTANT NUMBERS

National Battery Ingestion Hotline: 800-498-8666

Poison Control: 800-222-1222

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## 380.2 Bezoars

Trusha Patel, Petar Mamula, and Chris A. Liacouras

A bezoar is an accumulation of exogenous matter in the stomach or intestine. Risk factors for development of a bezoar include anatomic abnormalities (congenital or due to prior gastrointestinal surgery), gastric dysmotility, and medical and psychiatric conditions that lead to consumption of nonfood materials. Bezoars are often incidental findings on imaging or endoscopy in an asymptomatic patient. When they cause symptoms, abdominal pain, nausea, vomiting, decreased appetite, and halitosis are most common. An



**Fig. 380.3** Large trichobezoar in the shape of the stomach, duodenum, and proximal jejunum after surgical removal. (Courtesy Dr. Michael L. Nance, Division of Pediatric General, Thoracic and Fetal Surgery, Children's Hospital of Philadelphia.)

abdominal plain film can suggest the presence of a bezoar, which can be confirmed on ultrasound, fluoroscopy, or CT examination. On fluoroscopy or CT scan, a bezoar appears as a nonhomogeneous, nonenhancing mass within the lumen of the stomach or intestine. Oral contrast circumscribes the mass.

Bezoars are classified on the basis of their composition. **Phytobezoars** are the most common type of bezoar and are composed of undigestible vegetable/fruit matter. Carbonated soda has been demonstrated to help dissolve phytobezoars and should be considered as a first-line option for management. When available, cellulase can also be used for chemical dissolution. Given the risk of gastric ulcer or perforation, the use of papain (meat tenderizer) is not recommended. If endoscopic removal is needed, endotracheal intubation is required and use of an overtube may be considered. In addition to chemical dissolution and endoscopic or removal, prokinetic agents may be used for adjuvant medical therapy as well. **Trichobezoars** are composed of hair and are most frequently a complication of the psychiatric disorder trichotillomania, and the most severe form is known as Rapunzel syndrome (hair bezoar extending beyond the stomach to the small intestine). Large trichobezoars require surgical removal; endoscopic removal is not recommended (Fig. 380.3). **Lactobezoars** are uncommon and are most frequently seen in premature infants and can be attributed to the high casein or calcium content of some premature formulas. These bezoars generally resolve when feedings are withheld for 24-48 hours. **Pharmacobezoars** (composed of ingested medications) and other bezoars composed of various other objects (vinyl gloves, cement, Styrofoam, etc.) may also be seen and management is case-dependent.

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## Chapter 381

# Peptic Ulcer Disease in Children

Samra S. Blanchard and Steven J. Czinn

Peptic ulcer disease, the end result of inflammation caused by an imbalance between cytoprotective and cytotoxic factors in the stomach and duodenum, manifests with varying degrees of gastritis or frank ulceration. The pathogenesis of peptic ulcer disease is multifactorial, but the final common pathway for the development of ulcers is the action of acid and pepsin-laden contents of the stomach on the gastric and duodenal mucosa and the inability of mucosal defense mechanisms to allay those effects. Abnormalities in the gastric and duodenal mucosa can be visualized on endoscopy, with or without histologic changes. Deep mucosal lesions that disrupt the muscularis mucosa of the gastric or duodenal wall define **peptic ulcers**. Gastric ulcers are generally located on the lesser curvature of the stomach, and 90% of duodenal ulcers are found in the duodenal bulb. Rates of peptic ulcer disease in childhood appear to be low. Large pediatric centers anecdotally report an incidence of 5-7 children with gastric or duodenal ulcers per 2,500 hospital admissions each year.

Ulcers in children can be classified as **primary** peptic ulcers, which are chronic and more often duodenal, or **secondary**, which are usually more acute in onset and are more often gastric (Table 381.1). Primary ulcers are most often associated with *Helicobacter pylori* infection. Secondary peptic ulcers can result from stress caused by sepsis, shock, or an intracranial lesion (Cushing ulcer), or in response to a severe burn injury (Curling ulcer). Secondary ulcers can also occur as the result of using drugs (nonsteroidal antiinflammatory drugs [NSAIDs], corticosteroids, sodium valproate, iron, potassium supplements, theophylline), hypersecretory states like Zollinger-Ellison syndrome (see Chapter 381.1), G-cell hyperplasia, short bowel syndrome, and hyperparathyroidism. Infections with cytomegalovirus, herpes simplex virus, and tuberculosis and systemic inflammatory diseases like Crohn disease, sarcoidosis, mastocytosis, and eosinophilic gastroenteritis can also cause ulcers.

## PATHOGENESIS

### Acid Secretion

By 3-4 years of age, gastric acid secretion approximates adult values. Acid initially secreted by the oxytic cells of the stomach has a pH

**Table 381.1** Etiologic Classification of Peptic Ulcers

Positive for <i>Helicobacter pylori</i> infection
Drug (NSAID)-induced
<i>H. pylori</i> and NSAID-positive
<i>H. pylori</i> and NSAID-negative*
Acid hypersecretory state (Zollinger-Ellison syndrome)
Anastomosis ulcer after subtotal gastric resection
Tumors (cancer, lymphoma, carcinoid syndrome)
Crohn disease of the stomach or duodenum
Eosinophilic gastroduodenitis
Systemic mastocytosis
Radiation damage
Viral infections (cytomegalovirus or herpes simplex infection, particularly in immunocompromised patients)
Colonization of stomach with <i>Helicobacter heilmannii</i>
Severe systemic disease
Cameron ulcer (gastric ulcer where a hiatal hernia passes through the diaphragmatic hiatus)
True idiopathic ulcer

\*Requires search for other specific causes.

NSAID, Nonsteroidal antiinflammatory drug.

From Vakil N, Megraud F. Eradication therapy for *Helicobacter pylori*. *Gastroenterology*. 2007;133:985-1001.

of approximately 0.8, whereas the pH of the stomach contents is 1-2. Excessive acid secretion is associated with a large parietal cell mass, hypersecretion by antral G cells, and increased vagal tone, resulting in increased or sustained acid secretion in response to meals and increased secretion during the night. The secretagogues that promote gastric acid production include acetylcholine released by the vagus nerve, histamine secreted by enterochromaffin cells, and gastrin released by the G cells of the antrum. Mediators that decrease gastric acid secretion and enhance protective mucin production include prostaglandins.

### Mucosal Defense

A continuous layer of mucous gel that serves as a diffusion barrier to hydrogen ions and other chemicals covers the gastrointestinal (GI) mucosa. Mucus production and secretion are stimulated by prostaglandin E<sub>2</sub>. Underlying the mucous coat, the epithelium forms a second-line barrier, the characteristics of which are determined by the biology of the epithelial cells and their tight junctions. Another important function of epithelial cells is to secrete chemokines when threatened by microbial attack. Secretion of bicarbonate into the mucous coat, which is regulated by prostaglandins, is important for neutralization of hydrogen ions. If mucosal injury occurs, active proliferation and migration of mucosal cells occurs rapidly, driven by epithelial growth factor, transforming growth factor- $\alpha$ , insulin-like growth factor, gastrin, and bombesin, and covers the area of epithelial damage.

### CLINICAL MANIFESTATIONS

The presenting symptoms of peptic ulcer disease vary with the age of the patient. Hematemesis or melena is reported in up to half of the patients with peptic ulcer disease. School-age children and adolescents more commonly present with epigastric pain and nausea, presentations generally seen in adults. Dyspepsia, epigastric abdominal pain or fullness, is seen in older children. Infants and younger children usually present with feeding difficulty, vomiting, crying episodes, hematemesis, or melena. In the neonatal period, gastric perforation can be the initial presentation.

The classic symptom of peptic ulceration, epigastric pain alleviated by the ingestion of food, is present only in a minority of children. Many pediatric patients present with poorly localized abdominal pain, which may be perumbilical. The vast majority of patients with perumbilical or epigastric pain or discomfort do not have a peptic ulcer, but rather a functional GI disorder, such as irritable bowel syndrome or nonulcer (functional) dyspepsia (see Chapter 389). Patients with peptic ulceration rarely present with acute abdominal pain from perforation or symptoms and signs of pancreatitis from a posterior penetrating ulcer. Occasionally, bright red blood per rectum may be seen if the rate of bleeding is brisk and the intestinal transit time is short. Vomiting can be a sign of gastric outlet obstruction.

The pain is often described as dull or aching, rather than sharp or burning, as in adults. It can last from minutes to hours; patients have frequent exacerbations and remissions lasting from weeks to months. Nocturnal pain waking the child is common in older children. A history of typical ulcer pain with prompt relief after taking antacids is found in <33% of children. Rarely, in patients with acute or chronic blood loss, penetration of the ulcer into the abdominal cavity or adjacent organs produces shock, anemia, peritonitis, or pancreatitis. If inflammation and edema are extensive, acute or chronic gastric outlet obstruction can occur.

### DIAGNOSIS

Esophagogastroduodenoscopy is the method of choice to establish the diagnosis of peptic ulcer disease. Endoscopy allows the direct visualization of esophagus, stomach, and duodenum, identifying the specific lesions. Biopsy specimens must be obtained from the esophagus, stomach, and duodenum for histologic assessment as well as to screen for the presence of *H. pylori* infection. Endoscopy also provides the opportunity for hemostatic therapy including clipping, injection, and the use of thermal coagulation.

## PRIMARY ULCERS

### *Helicobacter pylori* Gastritis

*H. pylori* is among the most common bacterial infections in humans. It is a gram-negative, S-shaped rod that produces urease, catalase, and oxidase; these enzymes might play a role in the pathogenesis of peptic ulcer disease. The mechanism of acquisition and transmission of *H. pylori* is unclear, although the most likely mode of transmission is fecal-oral or oral-oral. Viable *H. pylori* organisms can be cultured from the stool or vomitus of infected patients. Risk factors such as low socioeconomic status in childhood or affected family members also influence the prevalence. All children infected with *H. pylori* develop histologic chronic active gastritis but are often asymptomatic. In children, *H. pylori* infection can manifest with abdominal pain or vomiting and, less often, refractory iron-deficiency anemia or poor growth. *H. pylori* can be associated, though rarely, with chronic autoimmune thrombocytopenia. Chronic colonization with *H. pylori* can predispose children to a significantly increased risk of developing a duodenal ulcer, gastric cancer such as adenocarcinoma, or mucosa-associated lymphoid tissue lymphomas. The relative risk of gastric carcinoma is 2.3–8.7 times greater in infected adults compared with uninfected subjects. *H. pylori* is classified by the World Health Organization as a group I carcinogen.

Anemia, idiopathic thrombocytopenic purpura, short stature, and sudden unexplained infant death (SUID) have also been reported as extragastric manifestations of *H. pylori* infection. In one published study, *H. pylori* infection has been correlated with cases of SUID, but there is no evidence to suggest that *H. pylori* plays a role in the pathogenesis of SUID.

The diagnosis of *H. pylori* infection is made histologically by demonstrating the organism in the biopsy specimens. The current consensus report does not recommend using antibody-based tests (IgG, IgA) for *H. pylori* in serum, whole blood, urine, and saliva in the clinical setting. <sup>13</sup>C-urea breath tests and stool antigen tests are reliable non-invasive methods of detecting *H. pylori* infection in patients who do not require endoscopic evaluation. Patients should stop proton pump inhibitor (PPI) therapy 2 weeks before testing as they can cause false-negative results. Nonetheless, for symptomatic children with suspected *H. pylori* infection, an initial upper endoscopy is recommended to evaluate and confirm *H. pylori* disease. The range of endoscopic findings in children with *H. pylori* infection varies from being grossly normal to the presence of nonspecific gastritis with prominent rugal folds, nodularity (Fig. 381.1), or ulcers. Because the antral mucosa appears to be *endoscopically normal* in a significant number of children with primary *H. pylori* gastritis, gastric biopsies should always be obtained from the body and antrum of the stomach regardless of the endoscopic appearance. If *H. pylori* is identified, even in a child with no symptoms, eradication therapy should be offered (Tables 381.2 and 381.3). Successful *H. pylori* eradication is associated with cure of peptic ulcer disease and very low risk of relapse. Therefore monitoring the success of therapy is mandatory in these patients 4–6 weeks after stopping antibiotics and at least 2 weeks after stopping PPI therapy. Eradication must be tested with the <sup>13</sup>C-urea breath test or stool antigen test. If there is an eradication failure, the patient should receive rescue therapy.

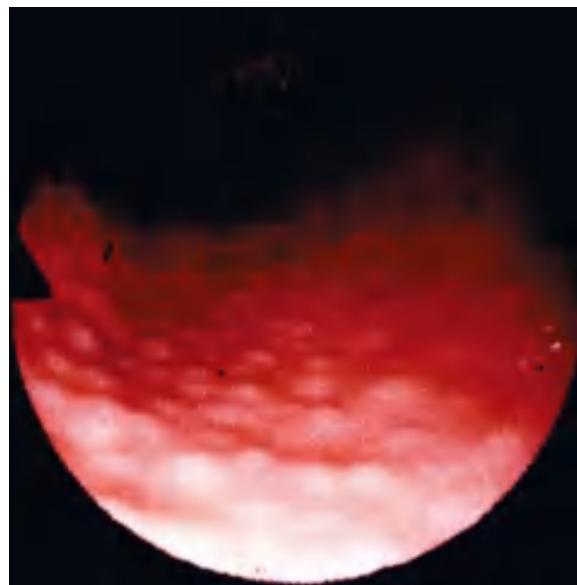
### IDIOPATHIC ULCERS

*H. pylori*-negative peptic ulcers in children who have no history of taking NSAIDs represent 15–20% of pediatric peptic ulcers. The pathogenesis of idiopathic ulcer remains uncertain. These patients do not have nodularity in the gastric antrum or histologic evidence of gastritis. In idiopathic ulcers, acid suppression alone is the preferred effective treatment. Either PPIs or H<sub>2</sub>-receptor antagonists may be used. Idiopathic ulcers have a high recurrence rate after discontinuing antisecretory therapy. These children should be followed closely, and if symptoms recur, antisecretory therapy should be restarted. It is also important to consider uncommon but possible conditions like Crohn disease, cytomegalovirus, and Zollinger-Ellison syndrome.

### SECONDARY ULCERS

#### Aspirin and Other Nonsteroidal Antiinflammatory Drugs

NSAIDs produce mucosal injury by direct local irritation and by inhibiting cyclooxygenase (COX) and prostaglandin



**Fig. 381.1** Endoscopic view of lymphoid modular hyperplasia of the gastric antrum. Endoscopic hemostatic therapy is indicated for ulcers with active spurting, active oozing, and nonbleeding but visible vessels. Hemostatic therapy may include bipolar electrocoagulation or heater probe, or injectable soluble alcohol. (From Campbell DI, Thomas JE. *Helicobacter pylori infection in paediatric practice*. Arch Dis Child Educ Pract Ed. 2005;90:ep25–ep30.)

formation. Prostaglandins enhance mucosal resistance to injury; therefore a decrease in prostaglandin production increases the risk of mucosal injury. The severe erosive gastropathy produced by NSAIDs can ultimately result in bleeding ulcers or gastric perforations. The location of these ulcers is more common in the stomach than in the duodenum, and usually in the antrum. The discovery of two isoforms of COX-1 and COX-2 has led to the development of COX-2-selective NSAIDs, but they can still cause ulcerations in the GI tract.

### STRESS ULCERATION

Stress ulceration usually occurs within 24 hours of onset of a critical illness in which physiologic stress is present. In many cases, the patients bleed from gastric erosions, rather than ulcers. Approximately 25% of the critically ill children in a pediatric intensive care unit have macroscopic evidence of gastric bleeding. Preterm and term infants in the neonatal intensive care unit can also develop gastric mucosal lesions and can present with upper GI bleeding or perforated ulcers. Although prophylactic measures to prevent stress ulcers in children are not standardized, drugs that inhibit gastric acid production (PPIs) are often used in the pediatric intensive care unit to reduce the rate of gastric erosions or ulcers. There is a concern that prophylactic PPI therapy increases the risk of ventilator-associated pneumonia and possibly *Clostridium difficile*-associated disease.

### TREATMENT

The management of acute hemorrhage includes serial monitoring of pulse, blood pressure, and hematocrit to ensure hemodynamic stability and avoid significant hypovolemia and anemia. Normal saline can be used to resuscitate a patient who has poor intravascular volume status. This can be followed by packed red blood cell transfusions for significant symptomatic anemia. The patient's blood should be typed and cross matched, and a large-bore catheter should be placed for fluid or blood replacement. A nasogastric tube should be placed to determine whether the bleeding has stopped. Significant anemia can occur after fluid resuscitation as a consequence of equilibration or continued blood loss (which can also cause shock). In adults, a conservative threshold for transfusion (<7 g/dL vs 9 g hemoglobin) resulted in improved survival and fewer episodes of rebleeding. Fortunately, most acute peptic ulcer bleeding stops spontaneously.

<b>Table 381.2</b> Recommended Eradication Therapies for <i>Helicobacter pylori</i> -Associated Disease in Children			
<b>MEDICATIONS</b>	<b>DOSE</b>	<b>DURATION OF TREATMENT</b>	
Proton pump inhibitor	1 mg/kg/dose twice a day	1 mo	
<b>ANTIBIOTICS</b>	<b>WEIGHT</b>	<b>DOSE</b>	<b>DURATION OF TREATMENT</b>
Amoxicillin	15-24 kg	500 mg twice a day	14 days
	25-34 kg	750 mg twice a day	
	>35 kg	1,000 mg twice a day	
Clarithromycin	15-24 kg	250 mg twice a day	14 days
	25-34 kg	500 mg in a.m., 250 mg in p.m.	
	>35 kg	500 mg twice a day	
Metronidazole	15-24 kg	250 mg twice a day	14 days
	25-34 kg	500 mg in a.m., 250 mg in p.m.	
	>35 kg	500 mg twice a day	

Depending on previous antibiotic use history, recommended combinations are amoxicillin + clarithromycin + PPI OR amoxicillin + metronidazole + PPI OR clarithromycin + metronidazole + PPI. Adapted from Jones NL, Koletzko S, Goodman K, et al. Joint ESPGHAN/NASPGHAN Guidelines for the Management of Helicobacter pylori in Children and Adolescents. *J Pediatr Gastroenterol Nutr*. 2017;64(6):991–1003.

<b>Table 381.3</b> Antisecretory Therapy with Pediatric Dosages		
<b>MEDICATION</b>	<b>PEDIATRIC DOSE</b>	<b>HOW SUPPLIED</b>
<b>H<sub>2</sub>-RECEPTOR ANTAGONISTS</b>		
Ranitidine	4-10 mg/kg/day divided 2 or 3 × a day	Pulled from market
Famotidine	1-2 mg/kg/day divided twice a day	Syrup: 40 mg/5 mL Tablets: 20, 40 mg
Nizatidine	5-10 mg/kg/day divided twice a day Older than 12 yr: 150 mg twice a day	Pulled from market
<b>PROTON PUMP INHIBITORS</b>		
Omeprazole	1.0-3.3 mg/kg/day weigh <20 kg: 10 mg/day weigh >20 kg: 20 mg/day Approved for use in those older than 1 month	Capsules: 10, 20, 40 mg
Lansoprazole	0.8-4 mg/kg/day weigh <30 kg: 15 mg/day weigh >30 kg: 30 mg/day Approved for use in those older than 1 yr	Capsules: 15, 30 mg Powder packet: 15, 30 mg SoluTab: 15, 30 mg
Rabeprazole	1-11 yr (weigh <15 kg): 5 mg/day 1-11 yr (weigh >15 kg): 10 mg/day >12 yr: 20 mg tablet Approved for use in those older than 1 yr	Delayed release capsule: 5, 10 mg Delayed release tablet: 20 mg
Pantoprazole	1-5 yr: 0.3-1.2 mg/kg/day (limited data) >5 yr of age: weigh >15 kg to <40 kg: 20 mg/day weigh >40 kg: 40 mg/day Approved for use in those older than 1 yr	Tablet: 20, 40 mg Powder pack: 40 mg
Esomeprazole	1 mo - < 1 yr old weigh 3 kg to 5 kg: 2.5 mg weigh >5 kg to 7.5 kg: 5 mg weigh >7.5 kg to 12 kg: 10 mg 1-11 yr old weigh <20 kg: 10 mg weigh >20 kg: 20 mg Approved for use 1 mo and older	Capsules: 20, 40 Delayed-release single-dose packs: 2.5, 5, 10, 20 mg
Dexlansoprazole	12-17 yr: 30-60 mg Approved for use in those older than 12 yr	Capsules: 30, 60
Omeprazole sodium bicarbonate	Safety and efficacy have not been established for those under 18 yr	Capsules: 20, 40 Powder for oral suspension: 20 mg, 40 mg
<b>CYTOPROTECTIVE AGENTS</b>		
Sucralfate	40-80 mg/kg/day	Suspension: 1,000 mg/5 mL Tablet: 1,000 mg

Patients with suspected peptic ulcer hemorrhage should receive high-dose intravenous (IV) PPI therapy, which lowers the risk of rebleeding. Some centers also use octreotide, which lowers splanchnic blood flow and gastric acid production.

Once the patient is hemodynamically stable, endoscopy is indicated to identify the source of bleeding and to treat a potential bleeding site (Fig. 381.2). Methods used to achieve hemostasis include mechanical devices (clipping), injection therapy (diluted epinephrine 1:100,000), and thermal therapy (heater probe). Ulcer therapy has two goals, ulcer healing and elimination of the primary cause. Other important considerations are relief of symptoms and prevention of complications. The **first-line drugs** for the treatment of gastritis and peptic ulcer disease in children are PPIs and H<sub>2</sub>-receptor antagonists (see Table 381.3). PPIs are more potent in ulcer healing. Cytoprotective agents can also be used as adjunct therapy if mucosal lesions are present. Antibiotics in combination with a PPI must be used for the treatment of *H. pylori*-associated ulcers (see Table 381.2).

H<sub>2</sub>-receptor antagonists (cimetidine, ranitidine, famotidine, nizatidine) competitively inhibit the binding of histamine at the H<sub>2</sub> subtype receptor of the gastric parietal cell. PPIs block the gastric parietal cell H<sup>+</sup>/K<sup>+</sup>-adenosine triphosphatase pump in a dose-dependent fashion, reducing basal and stimulated gastric acid secretion. Ranitidine and nizatidine were pulled out of the market in April 2020 due to unacceptable levels of N-nitrosodimethylamine (NDMA), a probable human carcinogen. NDMA impurities have been introduced during the manufacturing processes and as the result of product degradation during storage. Currently, seven PPIs are available in the United States: omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole, dexlansoprazole, and omeprazole/sodium bicarbonate. Apart from the last two, they are all approved in children and adolescents. They are well tolerated with only minor adverse effects, such as diarrhea (1–4%), headache (1–3%), and nausea (1%). When one considers therapeutic efficacy, the evidence suggests that all PPIs have comparable efficacy in treatment of peptic ulcer disease using standard doses and are superior to H<sub>2</sub>-receptor antagonists. PPIs have their greatest effect when given before a meal. Pantoprazole and esomeprazole are the only PPI available in IV form in United States. IV PPI should be used in acute upper GI bleeding. Studies in adults have demonstrated that twice a day IV PPI is as effective as continuous infusion, and the current recommendation is to start with IV PPI and change to the oral form after evaluating their rebleeding risk at the time of endoscopy.

### Treatment of *Helicobacter pylori*-Related Peptic Ulcer Disease

In pediatrics, antibiotics and bismuth salts have been used in combination with PPIs to treat *H. pylori* infection (see Table 381.2). Eradication rates in children range from 68–92% when the dual or triple therapy is used for 14 days. The ulcer healing rate ranges from 91–100%. Triple therapy yields a higher cure rate than dual therapy. The optimal regimen for the

eradication of *H. pylori* infection in children has yet to be established, but the use of a PPI in combination with clarithromycin and amoxicillin or metronidazole for 2 weeks is a well-tolerated and recommended triple therapy (see Table 381.2). Although children younger than 5 years of age can become reinfected, the most common reason for treatment failure is poor compliance or antibiotic resistance. *H. pylori* has become more resistant to clarithromycin or metronidazole as a consequence of the extensive use of these antibiotics for other infections. In the case of resistant *H. pylori* infection, *bismuth-based quadruple therapy* or *sequential treatment* with different antibiotics or rescue therapy are acceptable options. The sequential treatment regimen is a 10-day treatment consisting of a PPI and amoxicillin (both twice daily) administered for the first 5 days followed by triple therapy consisting of a PPI, clarithromycin, and metronidazole for the remaining 5 days. Levofloxacin, rifabutin, or furazolidone can be used with amoxicillin and bismuth as a rescue therapy depending on the age of the patient. Fidaxomicin has equivalent efficacy to vancomycin in adults. Knowledge of the community's *H. pylori* resistance pattern to clarithromycin or metronidazole might help choose the initial or rescue therapy. In adults with persistent *H. pylori* infection, a combination of rifabutin with amoxicillin and esomeprazole was effective in eradicating *H. pylori*.

### Surgical Therapy

Since the discovery of *H. pylori* and the availability of modern medical management, peptic ulcer disease requiring surgical treatment has become extremely rare. The indications for surgery remain uncontrolled bleeding, perforation, and obstruction.

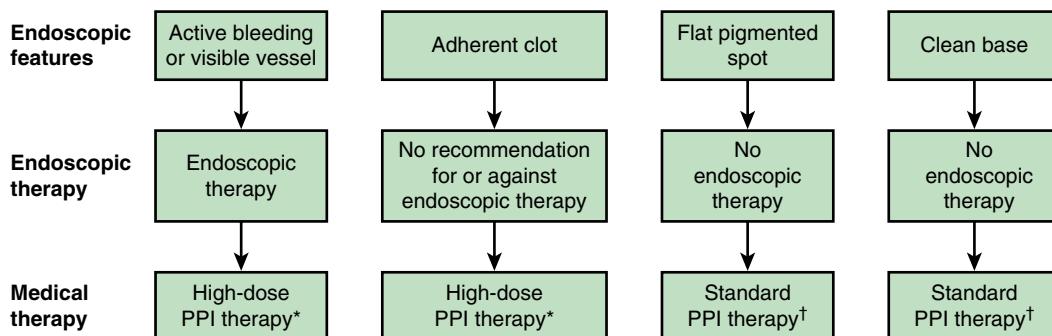
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## 381.1 Zollinger-Ellison Syndrome

Samra S. Blanchard and Steven J. Czinn

Zollinger-Ellison syndrome is a rare syndrome characterized by refractory, severe peptic ulcer disease caused by gastric hypersecretion due to the autonomous secretion of gastrin by a neuroendocrine tumor (gastrinoma). Clinical presentations are similar to those of peptic ulcer disease with the addition of diarrhea. The diagnosis is suspected by the presence of recurrent, multiple, or atypically located ulcers. More than 98% of patients have elevated fasting gastrin levels. Zollinger-Ellison syndrome is common in patients with **multiple endocrine neoplasia 1** and rare with **neurofibromatosis** and **tuberous sclerosis**. Prompt and effective management of increased gastric acid secretion is essential in the management. PPIs are the drug of choice due to their long duration of action and potency. H<sub>2</sub>-receptor antagonists are also effective, but higher doses are required than those used in peptic ulcer disease.

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**Fig. 381.2** Endoscopic and medical therapy algorithm for ulcer bleeding based on endoscopic features of ulcer. \*For continuous regimen, 80-mg bolus followed by 8-mg/min infusion for 3 days is recommended. For intermittent regimens, doses of 40 mg 2 to 4 times daily for 3 days are suggested, given orally if feasible, and an initial bolus of 80 mg may be appropriate. †Standard PPI therapy (e.g., oral PPI once daily) has been recommended by previous guidelines. PPI, Proton pump inhibitor. (From Laine L, Barkun AN, Saltzman JR, et al. ACG clinical guideline: upper gastrointestinal and ulcer bleeding. Am J Gastroenterol. 2021;116:899–917. Fig. 3.)

## Chapter 382

# Inflammatory Bowel Disease

Ronen E. Stein, Sudha A. Anupindi, and Robert N. Baldassano

The term *inflammatory bowel disease* (IBD) is used to represent two distinctive disorders of idiopathic chronic intestinal inflammation: Crohn disease and ulcerative colitis. Their respective etiologies are poorly understood, and both disorders are characterized by unpredictable exacerbations and remissions. The most common time of onset of IBD is during the preadolescent/adolescent era and young adulthood. A bimodal distribution has been shown with an early onset at 10–20 years of age and a second, smaller peak at 50–80 years of age. Approximately 25% of patients present before 20 years of age. IBD may begin as early as the first year of life, and an increased incidence among young children has been observed since the turn of the 20th century. Children with *early-onset* IBD are more likely to have colonic involvement. In developed countries, these disorders are the major causes of chronic intestinal inflammation in children beyond the first few years of life. A third, less-common category, *indeterminate colitis*, represents approximately 10% of pediatric patients.

Genetic and environmental influences are involved in the pathogenesis of IBD. The risk of IBD in family members of an affected person has been reported in the range of 7–30%; a child whose parents both have IBD has a >35% chance of acquiring the disorder. Relatives of a patient with ulcerative colitis have a greater risk of acquiring ulcerative colitis than Crohn disease, whereas relatives of a patient with Crohn disease have a greater risk of acquiring this disorder; the two diseases can occur in the same family. The risk of occurrence of IBD among relatives of patients with Crohn disease is somewhat greater than for patients with ulcerative colitis.

The importance of genetic factors in the development of IBD is noted by a higher chance that both twins will be affected if they are monozygotic rather than dizygotic. The concordance rate in twins is higher in Crohn disease (36%) than in ulcerative colitis (16%). Genetic disorders that have been associated with IBD include Turner syndrome, Hermansky-Pudlak syndrome, glycogen storage disease type Ib, and various immunodeficiency disorders. The first IBD gene, *NOD2*, was identified through association mapping; an IBD5 risk haplotype was also identified. There has been an exponential growth in the set of validated genetic risk factors for IBD (Table 382.1).

A perinuclear antineutrophil cytoplasmic antibody is found in approximately 70% of patients with ulcerative colitis compared with <20% of those with Crohn disease and is believed to represent a marker of genetically controlled immunoregulatory disturbance. Approximately 55% of those with Crohn disease are positive for anti-*Saccharomyces cerevisiae* antibody. Since the importance of these were first described, multiple other serologic and immune markers of Crohn disease and ulcerative colitis have been recognized.

IBD is caused by dysregulated or inappropriate immune response to environmental factors in a genetically susceptible host. An abnormality in intestinal mucosal immunoregulation may be of primary importance in the pathogenesis of IBD, involving activation of cytokines, triggering a cascade of reactions that results in bowel inflammation. These cytokines are recognized as known or potential targets for IBD therapies.

Multiple environmental factors are recognized to be involved in the pathogenesis of IBD, none more critical than the gut microbiota. The increasing incidence of IBD over time is likely in part attributable to alterations in the microbiome. Evidence includes association between IBD and residence in or immigration to industrialized nations, a

*Western diet*, increased use of antibiotics at a younger age, high rates of vaccination, and less exposure to microbes at a young age. Although gut microbes likely play an important role in the pathogenesis of IBD, the exact mechanism needs to be elucidated further. Some environmental factors are disease specific; for example, cigarette smoking is a risk factor for Crohn disease but paradoxically protects against ulcerative colitis.

It is usually possible to distinguish between ulcerative colitis and Crohn disease by the clinical presentation and radiologic, endoscopic, and histopathologic findings (Table 382.2). It is not possible to make a definitive diagnosis in approximately 10% of patients with chronic colitis; this disorder is called *indeterminate colitis*. Occasionally, a child initially believed to have ulcerative colitis on the basis of clinical findings is subsequently found to have Crohn colitis. This is particularly true for the youngest patients, because Crohn disease in this patient population can more often manifest as exclusively colonic inflammation, mimicking ulcerative colitis. The medical treatments of Crohn disease and ulcerative colitis overlap.

**Extraintestinal manifestations** occur slightly more commonly with Crohn disease than with ulcerative colitis (Table 382.3). Poor growth is seen in 15–40% of children with Crohn disease at diagnosis. Decrease in height velocity occurs in nearly 90% of patients with Crohn disease diagnosed in childhood or adolescence. Of the extraintestinal manifestations that occur with IBD, joint, skin, eye, mouth, and hepatobiliary involvement tend to be associated with colitis, whether ulcerative or Crohn. The presence of some manifestations, such as peripheral arthritis, erythema nodosum, and anemia, correlates with activity of the bowel disease. Activity of pyoderma gangrenosum correlates less well with activity of the bowel disease, whereas sclerosing cholangitis, ankylosing spondylitis, and sacroiliitis do not correlate with intestinal disease. Arthritis occurs in three patterns: migratory peripheral arthritis involving primarily large joints, ankylosing spondylitis, and sacroiliitis. The peripheral arthritis of IBD tends to be nondestructive. Ankylosing spondylitis begins in the third decade and occurs most commonly in patients with ulcerative colitis who have the human leukocyte antigen B27 phenotype. Symptoms include low back pain and morning stiffness; back, hips, shoulders, and sacroiliac joints are typically affected. Isolated sacroiliitis is usually asymptomatic but is common when a careful search is performed. Among the skin manifestations, erythema nodosum is most common. Patients with erythema nodosum or pyoderma gangrenosum have a high likelihood of having arthritis as well. Glomerulonephritis, uveitis, and a hypercoagulable state are other rare manifestations that occur in childhood. Cerebral thromboembolic disease has been described in children with IBD.

## 382.1 Chronic Ulcerative Colitis

Ronen E. Stein, Sudha A. Anupindi, and Robert N. Baldassano

Ulcerative colitis, an idiopathic chronic inflammatory disorder, is localized to the colon and spares the upper gastrointestinal (GI) tract. Disease usually begins in the rectum and extends proximally for a variable distance. When it is localized to the rectum, the disease is ulcerative proctitis, whereas disease involving the entire colon is pancolitis. Approximately 50–80% of pediatric patients have extensive colitis; adults more commonly have distal disease. Ulcerative proctitis is less likely to be associated with systemic manifestations, although it may be less responsive to treatment than more diffuse disease. Approximately 30% of children who present with ulcerative proctitis experience proximal spread of the disease. Ulcerative colitis has rarely been noted to present in infancy. Dietary protein intolerance can easily be misdiagnosed as ulcerative colitis in this age-group. Dietary protein intolerance (cow's milk protein) is a transient disorder; symptoms are directly associated with the intake of the offending antigen.

The incidence of ulcerative colitis has increased but not to the extent of the increase in Crohn disease; incidence varies with country of origin. The age-specific incidence rates of pediatric ulcerative colitis in

**Table 382.1** Selection of Most Important Genes Associated with Inflammatory Bowel Disease and the Most Commonly Associated Physiologic Functions and Pathways

	GENE NAME	ASSOCIATED DISEASE	GENE FUNCTION AND ASSOCIATED PATHWAYS	PHYSIOLOGIC FUNCTION
NOD2	Nucleotide-binding oligomerization domain-containing protein 2	Crohn disease	Bacterial recognition and response, NFκB activation and autophagy and apoptosis	Innate mucosal defense
IL10	IL-10	Crohn disease	Antiinflammatory cytokine, NFκB inhibition, JAK-STAT regulation	Immune tolerance
IL10RA	IL-10 receptor A	Crohn disease	Antiinflammatory cytokine receptor, NFκB inhibition, JAK-STAT regulation	Immune tolerance
IL10RB	IL-10 receptor B	Crohn disease	Antiinflammatory cytokine receptor, NFκB inhibition, JAK-STAT regulation	Immune tolerance
IL23R	IL-23 receptor	Crohn disease and ulcerative colitis	Immune regulation, proinflammatory pathways—JAK-STAT regulation	IL-23/T helper 17
TKY2	Tyrosine kinase 2	Crohn disease and ulcerative colitis	Inflammatory pathway signaling (IL-10 and -6, etc.) through intracellular activity	IL-23/T helper 17
IRGM	Immunity-related GTPase M	Crohn disease	Autophagy and apoptosis in cells infected with bacteria	Autophagy
ATG16L1	Autophagy-related 16 like 1	Crohn disease	Autophagy and apoptotic pathways	Autophagy
SLC22A4	Solute carrier family 22 member 4	Crohn disease	Cellular antioxidant transporter	Solute transporters
CCL2	C-C motif chemokine ligand 2	Crohn disease	Cytokine involved in chemotaxis for monocytes	Immune cell recruitment
CARD9	Caspase recruitment domain family member 9	Crohn disease and ulcerative colitis	Apoptosis regulation and NFκB pathway activation	Oxidative stress
IL2	IL-2	Ulcerative colitis	Cytokine involved in immune cell activation	T-cell regulation
MUC19	Mucin 19	Crohn disease and ulcerative colitis	Gel-forming mucin protein	Epithelial barrier

IL, Interleukin; JAK-STAT, Janus kinase-signal transducers and activators of transcription; NFκB, nuclear factor κ-light chain enhancer of activated B cells.

From Ashton JJ, Ennis S, Beattie RM. Early-onset paediatric inflammatory bowel disease. *Lancet*. 2017;1:147–158. Table 1.

**Table 382.2** Comparison of Crohn Disease and Ulcerative Colitis

FEATURE	CROHN DISEASE	ULCERATIVE COLITIS	FEATURE	CROHN DISEASE	ULCERATIVE COLITIS
Rectal bleeding	Sometimes	Common	Strictures	Common	Rare
Diarrhea, mucus, pus	Variable	Common	Fissures	Common	Rare
Abdominal pain	Common	Variable	Fistulas	Common	Rare
Abdominal mass	Common	Not present	Toxic megacolon	None	Present
Growth failure	Common	Variable	Sclerosing cholangitis	Less common	Present
Perianal disease	Common	Rare	Risk for intestinal cancers	Increased	Greatly increased
Rectal involvement	Occasional	Universal	Discontinuous (skip) lesions	Common	Not present
Pyoderma gangrenosum	Rare	Present	Transmural involvement	Common	Unusual
Erythema nodosum	Common	Less common	Crypt abscesses	Less common	Common
Mouth ulceration	Common	Rare	Granulomas	Common	None
Thrombosis	Less common	Present	Linear ulcerations	Uncommon	Common
Colonic disease	50–75%	100%	Perinuclear antineutrophil cytoplasmic antibody-positive	<20%	70%
Ileal disease	Common	None except backwash ileitis			
Stomach–esophageal disease	More common	Chronic gastritis can be seen			

**Table 382.3** Extraintestinal Complications of Inflammatory Bowel Disease

<b>MUSCULOSKELETAL</b>	<b>HEMATOLOGIC/ONCOLOGIC</b>
Peripheral arthritis	Anemia: iron deficiency (blood loss)
Granulomatous monoarthritis	Vitamin B <sub>12</sub> (ileal disease or resection, bacterial overgrowth, folate deficiency)
Granulomatous synovitis	Anemia of chronic inflammation
Rheumatoid arthritis	Anaphylactoid purpura (Crohn disease)
Sacroilitis	Hyposplenism
Ankylosing spondylitis	Autoimmune hemolytic anemia
Digital clubbing and hypertrophic osteoarthropathy	Coagulation abnormalities
Periostitis	Increased activation of coagulation factors
Osteoporosis, osteomalacia	Activated fibrinolysis
Rhabdomyolysis	Anticardiolipin antibody
Pelvic osteomyelitis	Increased risk of arterial and venous thrombosis with cerebrovascular stroke, myocardial infarction, peripheral arterial, and venous occlusions and pulmonary embolism
Chronic recurrent multifocal osteomyelitis (CRMO)	Systemic lymphoma (nonenteric)
Relapsing polychondritis	
<b>SKIN AND MUCOUS MEMBRANES</b>	<b>RENAL AND GENITOURINARY</b>
Oral lesions	Metabolic
Orofacial granulomatosis	<ul style="list-style-type: none"> <li>Urinary crystal formation (nephrolithiasis, uric acid, oxalate)</li> </ul>
Cheilitis	Hypokalemic nephropathy
Aphthous stomatitis, glossitis	Inflammation
Granulomatous oral Crohn disease	<ul style="list-style-type: none"> <li>Retroperitoneal abscess</li> <li>Fibrosis with ureteral obstruction</li> <li>Fistula formation</li> </ul>
Inflammatory hyperplasia fissures and cobblestone mucosa	Glomerulitis
Peristomatitis vegetans	Membrane nephritis
	Renal amyloidosis, nephrotic syndrome
<b>DERMATOLOGIC</b>	<b>PANCREATITIS</b>
Erythema nodosum	Secondary to medications (sulfasalazine, 6-mercaptopurine, azathioprine, parenteral nutrition)
Pyoderma gangrenosum	Ampullary Crohn disease
Sweet syndrome	Granulomatous pancreatitis
Metastatic Crohn disease	Decreased pancreatic exocrine function
Psoriasis	Sclerosing cholangitis with pancreatitis
Epidermolysis bullosa acquisita	
Perianal skin tags	<b>HEPATOBILIARY</b>
Polyarteritis nodosa	Primary sclerosing cholangitis
Melanoma and nonmelanoma skin cancers	Small duct primary sclerosing cholangitis (pericholangitis)
	Carcinoma of the bile ducts
<b>OCULAR</b>	Fatty infiltration of the liver
Conjunctivitis	Cholelithiasis
Uveitis, iritis	Autoimmune hepatitis
Episcleritis	
Scleritis	<b>ENDOCRINE AND METABOLIC</b>
Retrobulbar neuritis	Growth failure, delayed sexual maturation
Chorioretinitis with retinal detachment	Thyroiditis
Crohn keratopathy	Osteoporosis, osteomalacia
Posterior segment abnormalities	
Retinal vascular disease	<b>NEUROLOGIC</b>
Idiopathic orbital inflammation (orbital pseudotumor)	Peripheral neuropathy
	Meningitis
<b>BRONCHOPULMONARY</b>	Vestibular dysfunction
Chronic bronchitis with bronchiectasis	Idiopathic intracranial hypertension (Pseudotumor cerebri)
Chronic bronchitis with neutrophilic infiltrates	Cerebral vasculitis
Fibrosing alveolitis	Migraine
Pulmonary vasculitis	
Small airway disease and bronchiolitis obliterans	
Eosinophilic lung disease	
Granulomatous lung disease	
Tracheal obstruction	
<b>CARDIAC</b>	
Pleuropericarditis	
Cardiomyopathy	
Endocarditis	
Myocarditis	
<b>MALNUTRITION</b>	
Decreased intake of food	
<ul style="list-style-type: none"> <li>Inflammatory bowel disease</li> <li>Dietary restriction</li> </ul>	
Malabsorption	
<ul style="list-style-type: none"> <li>Inflammatory bowel disease</li> <li>Bowel resection</li> <li>Bile salt depletion</li> <li>Bacterial overgrowth</li> </ul>	
Intestinal losses	
<ul style="list-style-type: none"> <li>Electrolytes</li> <li>Minerals</li> <li>Nutrients</li> </ul>	
Increased caloric needs	
<ul style="list-style-type: none"> <li>Inflammation</li> <li>Fever</li> </ul>	

Modified from Kugathasan S. Diarrhea. In Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy*, 2nd ed. Philadelphia: Elsevier; 2004.p. 285.

North America is 2/100,000 population. The prevalence of ulcerative colitis in northern European countries and the United States varies from 100 to 200/100,000 population. Men are slightly more likely to acquire ulcerative colitis than are women; the reverse is true for Crohn disease.

### CLINICAL MANIFESTATIONS

Blood, mucus, and pus in the stool as well as diarrhea are the typical presentation of ulcerative colitis. Constipation may be observed in those with proctitis. Symptoms such as tenesmus, urgency, cramping abdominal pain (especially with bowel movements), and nocturnal bowel movements are common. The mode of onset ranges from insidious with gradual progression of symptoms to acute and fulminant (Table 382.4; Figs. 382.1 and 382.2). Fever, severe anemia, hypoalbuminemia, leukocytosis, and more than five bloody stools per day for 5 days define **fulminant colitis**. Chronicity is an important part of the diagnosis; it is difficult to know if a patient has a subacute, transient infectious colitis or ulcerative colitis when a child has had 1–2 weeks of symptoms. Symptoms beyond this duration often prove to be secondary to IBD. Anorexia, weight loss, and growth failure may be present, although these complications are more typical of Crohn disease.

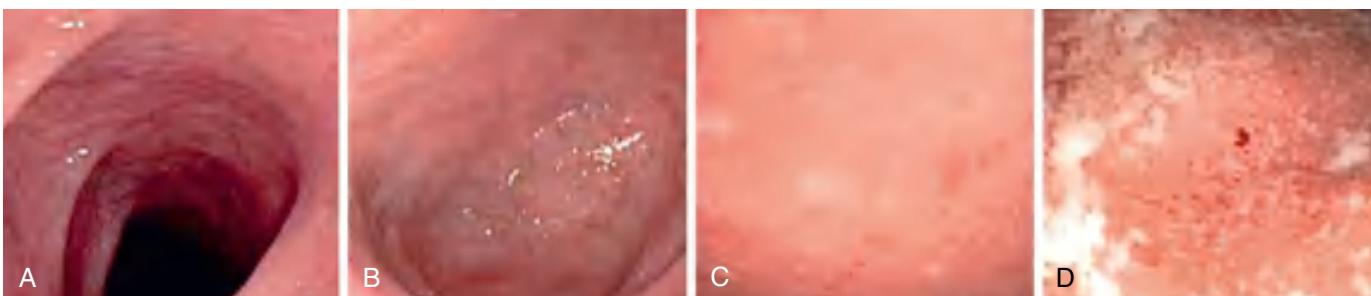
**Extraintestinal manifestations** that tend to occur more commonly with ulcerative colitis than with Crohn disease include pyoderma gangrenosum, sclerosing cholangitis, chronic active hepatitis, and ankylosing spondylitis. Iron deficiency can result from chronic blood loss as well as decreased intake. Folate deficiency is unusual but may be accentuated in children treated with sulfasalazine, which interferes with folate absorption. Chronic inflammation and the elaboration of a variety of inflammatory cytokines can interfere with erythropoiesis and result in the anemia of chronic disease. Secondary amenorrhea is common during periods of active disease.

**Table 382.4** Montreal Classification of Extent and Severity of Ulcerative Colitis

- E1 (proctitis): inflammation limited to the rectum
- E2 (left-sided; distal): inflammation limited to the splenic flexure
- E3 (pancolitis): inflammation extends to the proximal splenic flexure
- S0 (remission): no symptoms
- S1 (mild): four or less stools per day (with or without blood), absence of systemic symptoms, normal inflammatory markers
- S2 (moderate): four stools per day, minimum signs of systemic symptoms
- S3 (severe): six or more bloody stools per day, pulse rate of ≥90 beats/min, temperature ≥37.5°C (99.5°F), hemoglobin concentration <105 g/L, erythrocyte sedimentation rate ≥30 mm/hr

E, Extent; S, severity.

From Ordàs I, Eckmann L, Talamini M, et al. Ulcerative colitis. *Lancet*. 2012;380:1606–1616. Panel 2.



**Fig. 382.1** Mayo endoscopic score for ulcerative colitis. A, Score 0 = normal; endoscopic remission. B, Score 1 = mild; erythema, decreased vascular pattern, mild friability. C, Score 2 = moderate; marked erythema, absent vascular pattern, friability, erosions. D, Score 3 = severe; spontaneous bleeding, ulceration. (Images courtesy Elena Ricart. From Ordàs I, Eckmann L, Talamini M, et al. Ulcerative colitis. *Lancet*. 2012;380:1606–1616. Fig. 2, p. 1610.)

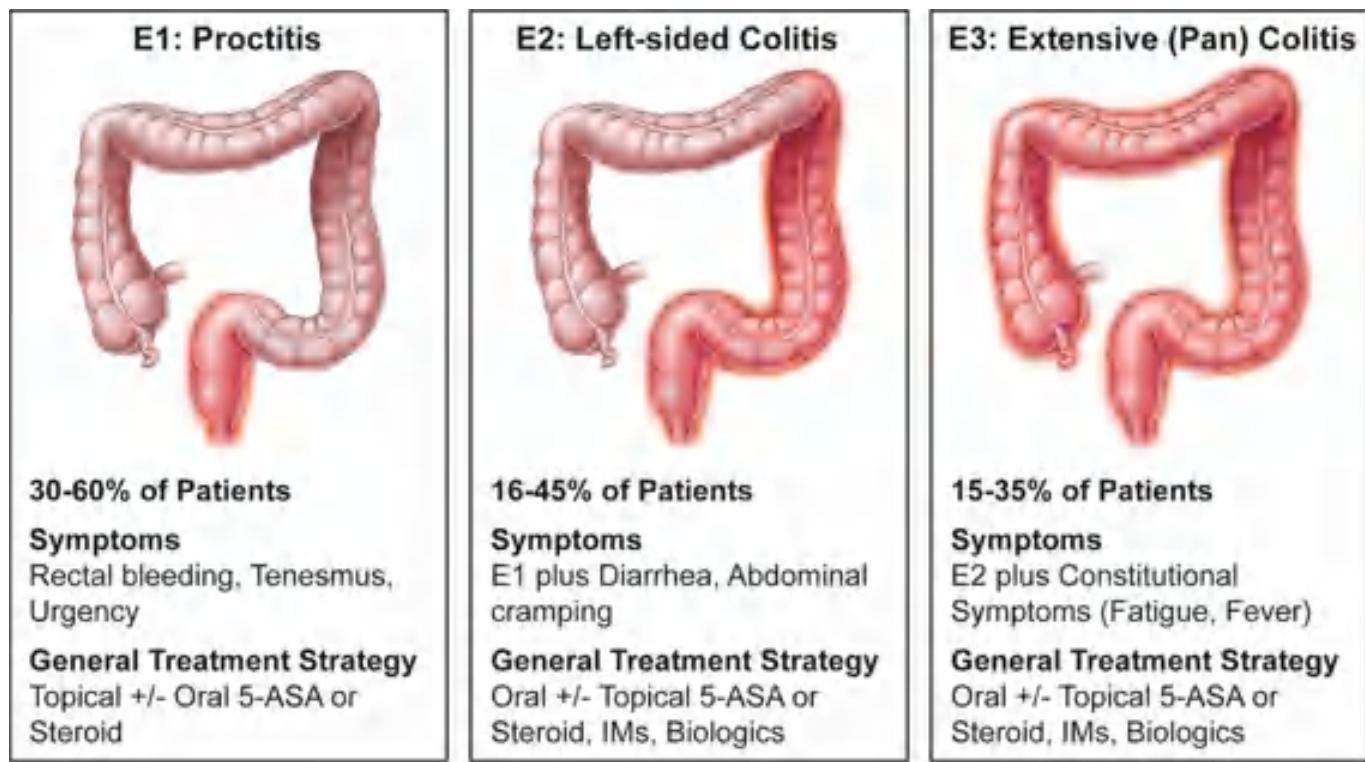
The clinical course of ulcerative colitis is marked by remission and relapse, often without apparent explanation. After treatment of initial symptoms, approximately 5% of children with ulcerative colitis have a prolonged remission (longer than 3 years). Approximately 25% of children presenting with severe ulcerative colitis require colectomy within 5 years of diagnosis, compared with only 5% of those presenting with mild disease. It is important to consider the possibility of enteric infection with recurrent symptoms, specifically *Clostridium difficile*; these infections can mimic a flare-up or actually provoke a recurrence. The use of nonsteroidal antiinflammatory drugs is considered by some to predispose to exacerbation.

It is generally believed that the risk of colon cancer begins to increase after 8–10 years of disease and can then increase by 0.5–1% per year. The risk is delayed by approximately 10 years in patients with colitis limited to the descending colon. Proctitis alone is associated with virtually no increase in risk over the general population. Because colon cancer is usually preceded by changes of mucosal dysplasia, it is recommended that patients who have had ulcerative colitis for longer than 8–10 years be screened with colonoscopy and biopsies every 1–2 years. Although this is the current standard of practice, it is not clear if morbidity and mortality are changed by this approach. Two competing concerns about this plan of management remain unresolved. The original studies may have overestimated the risk of colon cancer; therefore the need for surveillance has been overemphasized, and screening for dysplasia might not be adequate for preventing colon cancer in ulcerative colitis if some cancers are not preceded by dysplasia.

### DIFFERENTIAL DIAGNOSIS

The major conditions to exclude are infectious colitis, allergic colitis, and Crohn colitis. Every child with a new diagnosis of ulcerative colitis should have stool cultured for enteric pathogens, stool evaluation for *C. difficile*, ova and parasites, and perhaps serologic studies for amebae (Table 382.5). Cytomegalovirus infection can mimic ulcerative colitis or be associated with an exacerbation of existing disease, usually in immunocompromised patients. The most difficult distinction is from Crohn disease because the colitis of Crohn disease can initially appear identical to that of ulcerative colitis, particularly in younger children. The gross appearance of the colitis or development of small bowel disease eventually leads to the correct diagnosis; this can occur years after the initial presentation.

At the onset, the colitis of hemolytic uremic syndrome may be identical to that of early ulcerative colitis. Ultimately, signs of microangiopathic hemolysis (the presence of schistocytes on blood smear), thrombocytopenia, and subsequent renal failure should confirm the diagnosis of hemolytic-uremic syndrome. Although IgA vasculitis (Henoch-Schönlein purpura) can manifest as abdominal pain and bloody stools, it is not usually associated with colitis. Behcet disease can be distinguished by its typical features (see Chapter 202). Other considerations are radiation proctitis, viral colitis in immunocompromised patients, and ischemic colitis (Table 382.6). In infancy, dietary protein intolerance can be confused with ulcerative colitis, although the former is a transient problem that resolves on removal of the offending



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**Fig. 382.2** Ulcerative colitis phenotypes by Montreal Classification. Symptoms and treatment strategy can differ based on extent of disease. 5-ASA, 5-Aminosalicylate; IM, immunomodulator. (Illustration by Jill Gregory. Printed with permission of Mount Sinai Health System.)

protein, and ulcerative colitis is extremely rare in this age-group. Very early onset monogenic disorders should be considered in infants (see Chapter 382.3 and Table 382.6). Hirschsprung disease can produce an enterocolitis before or within months after surgical correction; this is unlikely to be confused with ulcerative colitis.

## DIAGNOSIS

The diagnosis of ulcerative colitis or ulcerative proctitis requires a typical presentation in the absence of an identifiable specific cause (see Tables 382.5 and 382.6) and typical endoscopic and histologic findings (see Tables 382.2 and 382.4). One should be hesitant to make a diagnosis of ulcerative colitis in a child who has experienced symptoms for <2-3 weeks until infection has been excluded. When the diagnosis is suspected in a child with subacute symptoms, the physician should make a firm diagnosis only when there is evidence of chronicity on colonic biopsy. Laboratory studies can demonstrate evidence of anemia (either iron deficiency or the anemia of chronic disease) or hypoalbuminemia. Although the sedimentation rate and C-reactive protein are often elevated, they may be normal even with fulminant colitis. An elevated white blood cell count is usually seen only with more severe colitis. Fecal calprotectin levels are usually elevated and are increasingly recognized to be a more sensitive and specific marker of GI inflammation than typical laboratory parameters. Barium enema is suggestive but not diagnostic of acute (Fig. 382.3) or chronic burned-out disease (Fig. 382.4).

The diagnosis of ulcerative colitis must be confirmed by endoscopic and histologic examination of the colon (see Fig. 382.1). Classically, disease starts in the rectum with a gross appearance characterized by erythema, edema, loss of vascular pattern, granularity, and friability. There may be a *cutoff* demarcating the margin between inflammation and normal colon, or the entire colon may be involved. There may be some variability in the intensity of inflammation even in those areas involved. Flexible sigmoidoscopy can confirm the diagnosis; colonoscopy can evaluate the extent of disease and rule out Crohn colitis. A colonoscopy should not be performed when fulminant colitis is suspected because of the risk of provoking *toxic megacolon* or causing a perforation during the

procedure. The degree of colitis can be evaluated by the gross appearance of the mucosa. One does not generally see discrete ulcers, which would be more suggestive of Crohn colitis. The endoscopic findings of ulcerative colitis result from microulcers, which give the appearance of a diffuse abnormality. With very severe chronic colitis, pseudopolyps may be seen. Biopsy of involved bowel demonstrates evidence of acute and chronic mucosal inflammation. Typical histologic findings are cryptitis, crypt abscesses, separation of crypts by inflammatory cells, foci of acute inflammatory cells, edema, mucus depletion, and branching of crypts. The last finding is not seen in infectious colitis. Granulomas, fissures, or full-thickness involvement of the bowel wall (usually on surgical rather than endoscopic biopsy) suggest Crohn disease.

**Perianal disease**, except for mild local irritation or anal fissures associated with diarrhea, should make the clinician think of Crohn disease. Plain radiographs of the abdomen might demonstrate loss of haustral markings in an air-filled colon or marked dilation with toxic megacolon. With severe colitis, the colon may become dilated; a diameter of >6 cm, determined radiographically, in an adult suggests toxic megacolon. If it is necessary to examine the colon radiologically in a child with severe colitis (to evaluate the extent of involvement or to try to rule out Crohn disease), it is sometimes helpful to perform an upper GI contrast series with small bowel follow-through and then look at delayed films of the colon. Small bowel ultrasonography is another option for evaluation of small intestinal inflammation. CT and MR enterography allow for even higher resolution images of the small intestine. A barium enema is contraindicated in the setting of a potential toxic megacolon.

## TREATMENT

### Medical

A medical *cure* for ulcerative colitis is not available; treatment is aimed at controlling symptoms and reducing the risk of recurrence, with a secondary goal of minimizing steroid exposure. The intensity of treatment varies with the severity of the symptoms.

The first drug class to be used with mild or mild to moderate colitis is an aminosalicylate. Sulfasalazine is composed of a sulfur moiety linked

**Table 382.5** Infectious Agents Mimicking Inflammatory Bowel Disease

AGENT	MANIFESTATIONS	DIAGNOSIS	COMMENTS
<b>BACTERIAL</b>			
<i>Campylobacter jejuni</i>	Acute diarrhea, fever, fecal blood, and leukocytes	Culture	Common in adolescents, may relapse
<i>Yersinia enterocolitica</i>	Acute → chronic diarrhea, right lower quadrant pain, mesenteric adenitis–pseudoappendicitis, fecal blood, and leukocytes Extraintestinal manifestations, mimics Crohn disease	Culture	Common in adolescents as fever of unknown origin, weight loss, abdominal pain
<i>Clostridium difficile</i>	Postantibiotic onset, watery → bloody diarrhea, pseudomembrane on sigmoidoscopy	Cytotoxin assay	May be nosocomial Toxic megacolon possible
<i>Escherichia coli</i> O157:H7	Colitis, fecal blood, abdominal pain	Culture and typing	Hemolytic uremic syndrome
<i>Salmonella</i>	Watery → bloody diarrhea, food-borne, fecal leukocytes, fever, pain, cramps	Culture	Usually acute
<i>Shigella</i>	Watery → bloody diarrhea, fecal leukocytes, fever, pain, cramps	Culture	Dysentery symptoms
<i>Edwardsiella tarda</i>	Bloody diarrhea, cramps	Culture	Ulceration on endoscopy
<i>Aeromonas hydrophila</i>	Cramps, diarrhea, fecal blood	Culture	May be chronic Contaminated drinking water
<i>Plesiomonas shigelloides</i>	Diarrhea, cramps	Culture	Shellfish source
Tuberculosis	Rarely bovine, now <i>Mycobacterium tuberculosis</i> Ileocecal area, fistula formation	Culture, purified protein derivative, biopsy	Can mimic Crohn disease
<b>PARASITES</b>			
<i>Entamoeba histolytica</i>	Acute bloody diarrhea and liver abscess, colic	Trophozoite in stool, colonic mucosal flask ulceration, serologic tests	Travel to endemic area
<i>Giardia lamblia</i>	Foul-smelling, watery diarrhea, cramps, flatulence, weight loss; no colonic involvement	"Owl"-like trophozoite and cysts in stool; rarely duodenal intubation	May be chronic
<b>AIDS-ASSOCIATED ENTEROPATHY</b>			
<i>Cryptosporidium</i>	Chronic diarrhea, weight loss	Stool microscopy	Mucosal findings not like inflammatory bowel disease
<i>Isospora belli</i>	As in <i>Cryptosporidium</i>		Tropical location
Cytomegalovirus	Colonic ulceration, pain, bloody diarrhea	Culture, biopsy	More common when on immunosuppressive medications

to the active ingredient 5-aminosalicylate (5-ASA). This linkage prevents the absorption of the medication in the upper GI tract, allowing it to reach the colon, where the two components are separated by bacterial cleavage. The dose of sulfasalazine is 30-100 mg/kg/24 hr (divided into two to four doses). Generally, the dose is not more than 2-4 g/24 hr. Hypersensitivity to the sulfa component is the major side effect of sulfasalazine and occurs in 10-20% of patients. Because of poor tolerance, sulfasalazine is used less commonly than other, better tolerated 5-ASA preparations (mesalamine, 50-100 mg/kg/day; balsalazide 2.25-6.75 g/day). Sulfasalazine and the 5-ASA preparations effectively treat active ulcerative colitis and prevent recurrence. It is recommended that the medication be continued even when the disorder is in remission. These medications might also modestly decrease the lifetime risk of colon cancer.

Approximately 5% of patients have an *allergic reaction* to 5-ASA, manifesting as rash, fever, and bloody diarrhea, which can be difficult to distinguish from symptoms of a flare of ulcerative colitis. 5-ASA can also be given in enema or suppository form and is especially useful for proctitis. Hydrocortisone enemas are used to treat proctitis as well, but they are probably not as effective. A combination of oral and rectal 5-ASA as well as monotherapy with rectal preparation has been shown to be more effective than just oral 5-ASA for distal colitis. Extended release budesonide may also induce remission in patients with mild to moderate ulcerative colitis. Rectal preparations of budesonide are also available.

Probiotics are effective in adults for maintenance of remission for ulcerative colitis, although they do not induce remission during an active flare. The most promising role for probiotics has been to prevent *pouchitis*, a common complication following colectomy and ileal-pouch anal anastomosis surgery.

Children with moderate to severe pancolitis or colitis that is unresponsive to 5-ASA therapy should be treated with corticosteroids, most commonly oral prednisone. The usual starting dose of prednisone is 1-2 mg/kg/24 hr (40-60 mg maximum dose). This medication can be given once daily. With severe colitis, the dose can be divided twice daily and can be given intravenously. Steroids are considered an effective medication for acute flares, but they are not appropriate maintenance medications because of loss of effect and side effects, including poor growth, adrenal suppression, cataracts, osteopenia, aseptic necrosis of the head of the femur, glucose intolerance, risk of infection, mood disturbance, and cosmetic effects.

For a hospitalized patient with persistence of symptoms despite intravenous steroid treatment for 3-5 days, escalation of therapy or surgical options should be considered. The validated pediatric ulcerative colitis activity index can be used to help determine current disease severity based on clinical factors and help determine who is more likely to respond to steroids and those who will likely require escalation of therapy (Table 382.7).

With medical management, most children are in remission within 3 months; however, 5-10% continue to have symptoms unresponsive

**Table 382.6** Chronic Inflammatory Bowel-Like Intestinal Disorders Including Monogenic Diseases

INFECTION (SEE TABLE 382.5)

AIDS-Associated

Toxin

Immune-Inflammatory

Severe combined immunodeficiency diseases

Agammaglobulinemia

Chronic granulomatous disease

Wiskott-Aldrich syndrome

Common variable immunodeficiency diseases

Acquired immunodeficiency states

Dietary protein enterocolitis

Autoimmune polyendocrine syndrome type 1

Behcet disease

Lymphoid nodular hyperplasia

Eosinophilic gastroenteritis

Omenn syndrome

Graft-versus-host disease

IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked) syndromes

Interleukin-10 signaling defects

Autoimmune enteropathy\*

Microscopic colitis

Hyperimmunoglobulin M syndrome

Hyperimmunoglobulin E syndromes

Mevalonate kinase deficiency

Familial Mediterranean fever

Phospholipase C $\gamma$ 2 defects

IL10RA pathogenic variant

Familial hemophagocytic lymphohistiocytosis type 5

X-linked lymphoproliferative syndromes types 1, 2 (XIAP gene)

Congenital neutropenia

TRIM22 pathogenic variant

Leukocyte adhesion deficiency 1

NLRC4 pathogenic variants

VASCULAR-ISCHEMIC DISORDERS

Systemic vasculitis (systemic lupus erythematosus, dermatomyositis)

Henoch-Schönlein purpura

Hemolytic uremic syndrome

Granulomatosis with angiitis

OTHER

Glycogen storage disease type 1b

Dystrophic epidermolysis bullosa

X-linked ectodermal dysplasia and immunodeficiency

Dyskeratosis congenita

ADAM-17 deficiency

Prestenotic colitis

Diversion colitis

Kindler syndrome

Radiation colitis

Neonatal necrotizing enterocolitis

Typhlitis

Sarcoidosis

Hirschsprung colitis

Intestinal lymphoma

Laxative abuse

Endometriosis

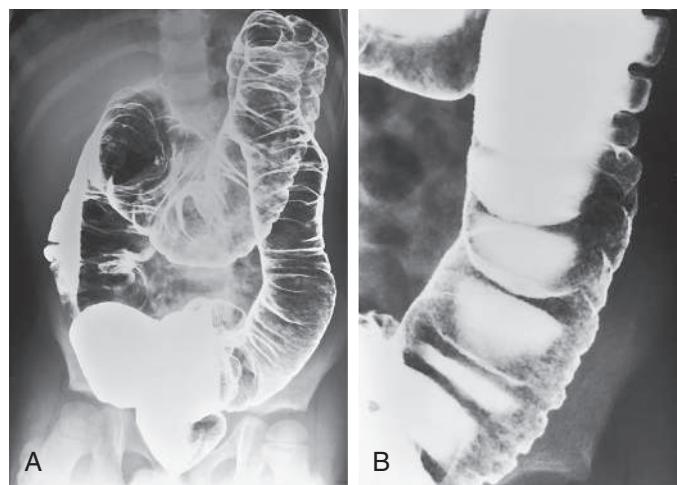
Hermansky-Pudlak syndrome

Trichohepatoenteric syndrome

Phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome

\*May be the same as IPEX.

to treatment beyond 6 months. Many children with disease requiring frequent corticosteroid therapy are started on immunomodulators such as azathioprine (2.0–2.5 mg/kg/day) or 6-mercaptopurine (1–1.5 mg/kg/day). Uncontrolled data suggest a corticosteroid-sparing effect in many treated patients. This is not an appropriate choice in a patient who is non-responsive to steroids with acute severe colitis because of longer onset of action. Lymphoproliferative disorders are associated with thiopurine



**Fig. 382.3** Ulcerative colitis. Double-contrast barium enema in a 5-yr-old child who had had intermittent intestinal and extraintestinal symptoms since the age of 3 yr. A, Small ulcerations are distributed uniformly about the colonic circumference and continuously from the rectum to the proximal transverse colon. This pattern of involvement is typical of ulcerative colitis. B, In this coned view of the sigmoid in the same patient, small ulcerations are represented by fine stippling of the colonic contour in tangent and by fine stippling of the colon surface en face. (From Hoffman AD. The child with diarrhea. In Hilton SW, Edwards DK, eds. Practical Pediatric Radiology, 2nd ed. Philadelphia: WB Saunders; 1994. p. 260.)



**Fig. 382.4** Ulcerative colitis: late changes. This single-contrast barium enema shows the late changes of ulcerative colitis in a 15-yr-old child. The colon is featureless, reduced in caliber, and shortened. Dilatation of the terminal ileum (backwash ileitis) is present. (From Hoffman AD. The child with diarrhea. In Hilton SW, Edwards DK, eds. Practical Pediatric Radiology, 2nd ed. Philadelphia: WB Saunders; 1994. p. 262.)

use. Infliximab and adalimumab, which are a fully human monoclonal antibody to tumor necrosis factor (TNF)- $\alpha$ , are effective for induction and maintenance therapy in children and adults with moderate to severe disease. TNF blocking agents are associated with an increased risk of infection (particularly tuberculosis) and malignancies (lymphoma, leukemia). There are a number of other agents that are approved for treatment of refractory ulcerative colitis in adults, but are often used

**Table 382.7** Pediatric Ulcerative Colitis Activity Index

ITEM	POINTS
(1) ABDOMINAL PAIN	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
(2) RECTAL BLEEDING	
None	0
Small amount only, in <50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
(3) STOOL CONSISTENCY OF MOST STOOLS	
Formed	0
Partially formed	5
Completely unformed	10
(4) NUMBER OF STOOLS PER 24 HR	
0-2	0
3-5	5
6-8	10
>8	15
(5) NOCTURNAL STOOLS (ANY EPISODE CAUSING WAKENING)	
No	0
Yes	10
(6) ACTIVITY LEVEL	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of Index (0-85)	

delicate anastomosis between the sleeve of the pouch and the rectum. The ileostomy is usually closed within several months, restoring bowel continuity. At that time, stool frequency is often increased but may be improved with loperamide. The major complication of this operation is *pouchitis*, which is a chronic inflammatory reaction in the pouch, leading to bloody diarrhea, abdominal pain, and, occasionally, low-grade fever. The cause of this complication is unknown, although it is more common when the ileal pouch has been constructed for ulcerative colitis than for other indications (e.g., familial polyposis coli). Pouchitis is seen in 30–40% of patients who had ulcerative colitis. It commonly responds to treatment with oral metronidazole or ciprofloxacin. Probiotics have also been shown to decrease the rate of pouchitis as well as the recurrence of pouchitis following antibiotic therapy.

### Support

Psychosocial support is an important part of therapy for this disorder. This may include adequate discussion of the disease manifestations and management between patient and physician, psychologic counseling for the child when necessary, and family support from a social worker or family counselor. Patient support groups have proved helpful for some families. Children with ulcerative colitis should be encouraged to participate fully in age-appropriate activities; however, activity may need to be reduced during periods of disease exacerbation.

### PROGNOSIS

The course of ulcerative colitis is marked by remissions and exacerbations. Most children with this disorder respond initially to medical management. Many children with mild manifestations continue to respond well to medical management and may stay in remission on a prophylactic 5-ASA preparation for long periods. An occasional child with mild onset, however, experiences intractable symptoms later. Beyond the first decade of disease, the risk of development of colon cancer begins to increase rapidly. The risk of colon cancer may be diminished with surveillance colonoscopies beginning after 8–10 years of disease. Detection of significant dysplasia on biopsy would prompt colectomy.

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## 382.2 Crohn Disease (Regional Enteritis, Regional Ileitis, Granulomatous Colitis)

Ronen E. Stein, Sudha A. Anupindi, and Robert N. Baldassano

Crohn disease, an idiopathic, chronic inflammatory disorder of the bowel, involves any region of the alimentary tract from the mouth to the anus. Although there are many similarities between ulcerative colitis and Crohn disease, there are also major differences in the clinical course and distribution of the disease in the GI tract (see Table 382.2). The inflammatory process tends to be eccentric and segmental, often with skip areas (normal regions of bowel between inflamed areas). Although inflammation in ulcerative colitis is limited to the mucosa (except in toxic megacolon), GI involvement in Crohn disease is often *transmural*.

Compared to adult-onset disease, pediatric Crohn disease is more likely to have extensive anatomic involvement. At initial presentation, more than 50% of patients have disease that involves ileum and colon (ileocolitis), 20% have exclusively colonic disease, and upper GI involvement (esophagus, stomach, duodenum) is seen in up to 30% of children. Isolated small bowel disease is much less common in the pediatric population compared to adults. Isolated colonic disease is common in children younger than 8 years of age and may be indistinguishable from ulcerative colitis. Anatomic location of disease tends to extend over time in children.

Crohn disease tends to have a bimodal age distribution, with the first peak beginning in the teenage years. The incidence of Crohn disease has been increasing. In the United States, the reported incidence of

off-label in children, including vedolizumab, a humanized monoclonal antibody that inhibits adhesion and migration of leukocytes into the GI tract, and ustekinumab, a monoclonal antibody against interleukins (ILs) 12 and 23. Small molecule agents are another class of medications to be approved for adults with moderate to severe ulcerative colitis in adults, including tofacitinib and upadacitinib; oral Janus kinase inhibitors; and ozanimod, a sphingosine 1-phosphate receptor modulator that leads to peripheral lymphocyte sequestration. A specific combination of three to four broad-spectrum oral antibiotics given over 2–3 weeks may be effective in treating severe pediatric ulcerative colitis refractory to other therapies, but it is being further studied in children.

### Surgical

Colectomy is performed for intractable disease, complications of therapy, and fulminant disease that is unresponsive to medical management. No clear benefit of the use of total parenteral nutrition or a continuous enteral elemental diet in the treatment of severe ulcerative colitis has been noted. Nevertheless, parenteral nutrition is used if oral intake is insufficient so that the patient will be nutritionally ready for surgery if medical management fails. With any medical treatment for ulcerative colitis, the clinician should always weigh the risk of the medication or therapy against the fact that colitis can be successfully treated surgically.

Surgical treatment for intractable or fulminant colitis is total colectomy. The optimal approach is to combine colectomy with an endorectal pull-through, where a segment of distal rectum is retained and the mucosa is stripped from this region. The distal ileum is pulled down and sutured at the internal anus with a J pouch created from ileum immediately above the rectal cuff. This procedure allows the child to maintain continence. Commonly, a temporary ileostomy is created to protect the

pediatric Crohn disease is 4.56/100,000 and the pediatric prevalence is 43/100,000 children.

## CLINICAL MANIFESTATIONS

Crohn disease can be characterized as inflammatory, stricturing, or penetrating. Patients with small bowel disease are more likely to have an obstructive pattern (most commonly with right lower quadrant pain) characterized by fibrostenosis, and those with colonic disease are more likely to have symptoms resulting from inflammation (diarrhea, bleeding, cramping). Disease phenotypes often change as duration of disease lengthens (inflammatory becomes structuring and/or penetrating) (Figs. 382.5 and 382.6).

Systemic signs and symptoms are more common in Crohn disease than in ulcerative colitis. Fever, malaise, and easy fatigability are common. Growth failure with delayed bone maturation and delayed sexual development can precede other symptoms by 1 or 2 years and is at least twice as likely to occur with Crohn disease as with ulcerative colitis. Children can present with growth failure as the only manifestation of Crohn disease. Decreased height velocity occurs in about 88% of prepubertal patients diagnosed with Crohn disease, and this often precedes GI symptoms. Causes of growth failure include inadequate caloric intake (anorexia, partial obstruction-related pain), suboptimal absorption or excessive loss of nutrients, the effects of chronic inflammation on bone metabolism and appetite, and the use of corticosteroids during treatment. Primary or secondary amenorrhea and pubertal delay are common. In contrast to ulcerative colitis, perianal disease is common (tag, fistula, deep fissure, abscess). Gastric or duodenal involvement may be associated with recurrent vomiting and epigastric pain. **Partial small bowel obstruction**, usually secondary to narrowing of the bowel lumen from *inflammation or stricture*, can cause symptoms of cramping abdominal pain (especially with meals), borborygmus, and intermittent abdominal distention (Fig. 382.7). Stricture should be suspected if the child notes relief of symptoms in association with a sudden sensation of gurgling of intestinal contents through a localized region of the abdomen.

**Penetrating disease** is demonstrated by fistula formation. Enterointeric or enterocolonic fistulas (between segments of bowel) are often asymptomatic but can contribute to malabsorption if they have high output or result in bacterial overgrowth. Enterovesical fistulas (between bowel and urinary bladder) originate from ileum or sigmoid colon and appear as signs of urinary infection, pneumaturia, or fecaluria. Enterovaginal fistulas originate from the rectum, cause feculent vaginal drainage, and are difficult to manage. Enterocutaneous fistulas (between bowel and abdominal skin) often are caused by prior surgical

anastomoses with leakage. Intraabdominal abscess may be associated with fever and pain but might have relatively few symptoms. Hepatic or splenic abscess can occur with or without a local fistula. Anorectal abscesses often originate immediately above the anus at the crypts of Morgagni. The patterns of perianal fistulas are complex because of the different tissue planes. Perianal abscess is usually painful, but perianal fistulas tend to produce fewer symptoms than anticipated. Purulent drainage is commonly associated with perianal fistulas. Psoas abscess secondary to intestinal fistula can present as hip pain, decreased hip extension (psoas sign), and fever.

**Extraintestinal** manifestations occur more commonly with Crohn disease than with ulcerative colitis; those that are especially associated with Crohn disease include oral aphthous ulcers, peripheral arthritis, erythema nodosum, digital clubbing, episcleritis, venous thrombosis, pulmonary disease, renal stones (uric acid, oxalate), and gallstones. Any of the extraintestinal disorders described in the section on IBD can occur with Crohn disease (see Table 382.3). The peripheral arthritis is nondeforming. The occurrence of extraintestinal manifestations usually correlates with the presence of colitis. Metastatic Crohn disease is most often cutaneous, presenting with noncaseating granulomas in a location that is not contiguous with an active penetrating lesion; it may resemble erythema nodosum.

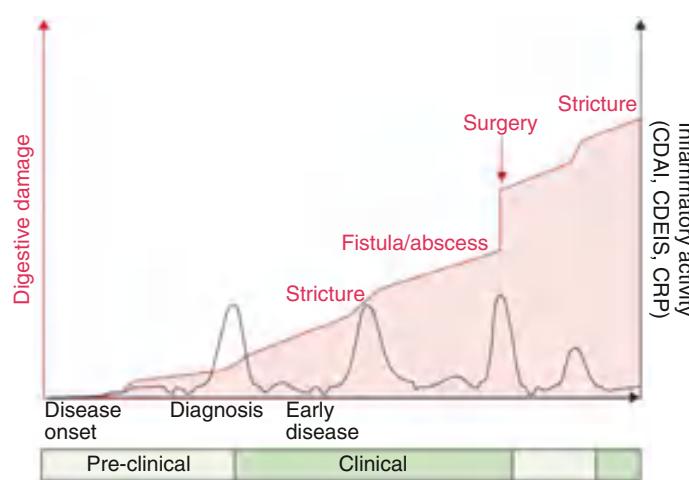
Extensive involvement of small bowel, especially in association with surgical resection, can lead to short bowel syndrome, which is rare in children. Complications of terminal ileal dysfunction or resection include bile acid malabsorption with secondary diarrhea and vitamin B<sub>12</sub> malabsorption, with possible resultant deficiency. Chronic steatorrhea can lead to oxaluria with secondary renal stones. Increasing calcium intake can actually decrease the risk of renal stones secondary to ileal inflammation. The risk of cholelithiasis is also increased secondary to bile acid depletion.

A disorder with this diversity of manifestations can have a major impact on an affected child's lifestyle. Fortunately, the majority of children with Crohn disease are able to continue with their normal activities, having to limit activity only during periods of increased symptoms.

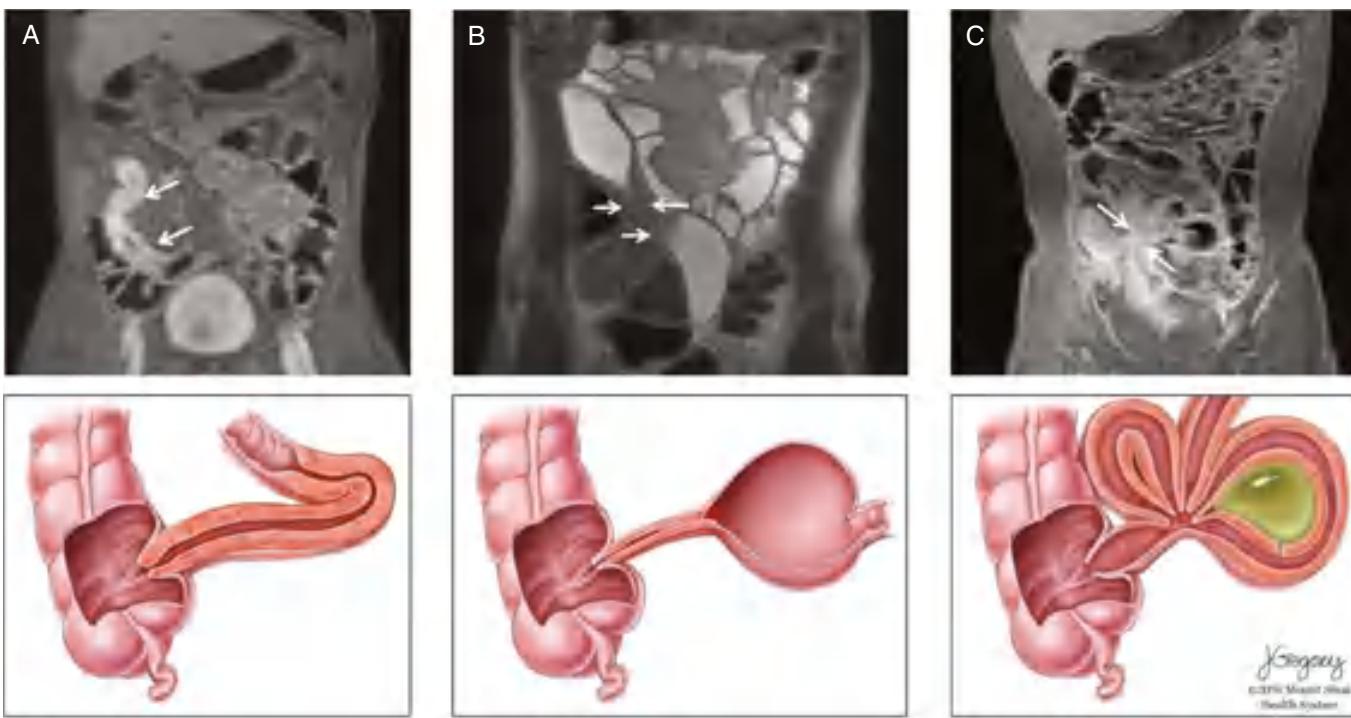
## DIFFERENTIAL DIAGNOSIS

The most common diagnoses to be distinguished from Crohn disease are the infectious enteropathies (in the case of Crohn disease: acute terminal ileitis, infectious colitis, enteric parasites, and periappendiceal abscess) (see Tables 382.5 and 382.6; Table 382.8). *Yersinia* can cause many of the radiologic and endoscopic findings in the distal small bowel that are seen in Crohn disease. The symptoms of bacterial dysentery are more likely to be mistaken for ulcerative colitis than for Crohn disease. Celiac disease and *Giardia* infection have been noted to produce a Crohn-like presentation including diarrhea, weight loss, and protein-losing enteropathy. GI tuberculosis is rare but can mimic Crohn disease. Foreign-body perforation of the bowel (toothpick) can mimic a localized region with Crohn disease. Small bowel lymphoma can mimic Crohn disease but tends to be associated with nodular filling defects of the bowel without ulceration or narrowing of the lumen. Bowel lymphoma is much less common in children than is Crohn disease. Recurrent functional abdominal pain can mimic the pain of small bowel Crohn disease. *Lymphoid nodular hyperplasia* of the terminal ileum (a normal finding) may be mistaken for Crohn ileitis. Right lower quadrant pain or mass with fever can be the result of periappendiceal abscess. This entity is occasionally associated with diarrhea as well.

Growth failure may be the only manifestation of Crohn disease; other disorders such as growth hormone deficiency, gluten-sensitive enteropathy (celiac disease), Turner syndrome, or anorexia nervosa must be considered. If arthritis precedes the bowel manifestations, an initial diagnosis of juvenile idiopathic arthritis may be made. Refractory anemia may be the presenting feature and may be mistaken for a primary hematologic disorder. Chronic granulomatous disease of childhood can cause inflammatory changes in the bowel as well as perianal disease. Antral narrowing in this disorder may be mistaken for a stricture secondary to Crohn disease. Other immunodeficiencies or autoinflammatory conditions and monogenetic disorders may



**Fig. 382.5** The Lémann Score. Exemplary visualization of the Lémann score, a new technique to score and study intestinal damage in Crohn disease. CDAI, Crohn disease activity index; CDEIS, Crohn disease of endoscopic severity; CRP, C-reactive protein. (From Baumgart DC, Sandborn WJ. Crohn's disease. Lancet. 2012;380:1590–1602. Fig. 5, p. 1596.)

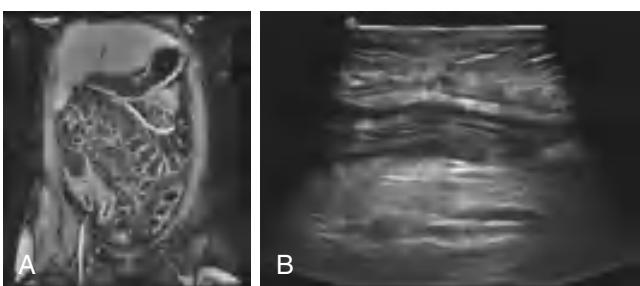


- Diarrhea
- Abdominal pain
- Weight loss
- Low-grade fever
- Fatigue
- Growth retardation
- Malnourishment

- Postprandial pain
- Bloating
- Nausea and vomiting
- Occlusion/subocclusion

- Symptoms depend on the location of fistulae
- Enterourinary fistula: fecaluria, pneumaturia, recurrent UTI
- Rectovaginal fistula: dispareunia, stool discharge through the vagina
- Enteroenteric fistula: asymptomatic, abdominal abscesses

**Fig. 382.6** Behavior of Crohn disease (CD) as per Montreal classification represented in MR enterography (MRE) and illustrated with typical symptoms. A, T1 weighted MRE imaging with fat saturation after injection of gadolinium chelates shows mural thickening and enhancement in the distal ileum (arrows) in a patient with active CD. B, T2 weighted MRE imaging shows a narrowed luminal segment with thickened wall and upstream dilation (arrows), suggesting the presence of a stricture. C, T1 weighted MRE imaging with fat saturation after injection of gadolinium chelates shows multiple converging enhancing loops of small bowel suggestive of enterointeric fistulas (arrows). Lower illustration shows a deep and transmural fissure or ulcer leading to the formation of an abscess. UTI, Urinary tract infection. (Illustration by Jill Gregory. Printed with permission of Mount Sinai Health System.)



**Fig. 382.7** Stenosis in Crohn disease. A, MR enterography of Crohn disease restricted to the terminal ileum (Montreal category L1) with inflammatory stenosis. B, Ultrasound image of an intestinal stenosis in Crohn disease. (From Baumgart DC, Sandborn WJ. Crohn's disease. Lancet. 2012;380:1590–1602. Fig. 4.)

present with GI symptoms suggestive of IBD, particularly in very early or infant/toddler onset of disease (see Table 382.6).

## DIAGNOSIS

Crohn disease can manifest as a variety of symptom combinations (see Fig. 382.6). At the onset, symptoms may be subtle (growth failure,

abdominal pain alone); this explains why the diagnosis might not be made until 1 or 2 years after the start of symptoms. The diagnosis of Crohn disease depends on finding typical clinical features of the disorder (history, physical examination, laboratory studies, and endoscopic or radiologic findings), ruling out specific entities that mimic Crohn disease, and demonstrating chronicity. The history can include any combination of abdominal pain (especially right lower quadrant), diarrhea, vomiting, anorexia, weight loss, growth retardation, and extraintestinal manifestations. Only 25% initially have the triad of diarrhea, weight loss, and abdominal pain. Most do not have diarrhea, and only 25% have GI bleeding.

Children with Crohn disease often appear chronically ill. They commonly have weight loss and growth failure, and they are often malnourished. The earliest sign of growth failure is decreased height velocity, which can be present in up to 88% of prepubertal patients with Crohn disease and typically precedes symptoms. Children with Crohn disease often appear pale, with decreased energy level and poor appetite; the latter finding sometimes results from an association between meals and abdominal pain or diarrhea. There may be abdominal tenderness that is either diffuse or localized to the right lower quadrant. A tender mass or fullness may be palpable in the right lower quadrant. Perianal disease, when present, may be characteristic. Large anal skin tags (1-3 cm in diameter) or perianal fistulas with purulent drainage suggest Crohn disease. Digital clubbing, findings of arthritis, and skin manifestations may be present.

A complete blood cell count commonly demonstrates anemia, often with a component of iron deficiency, as well as thrombocytosis. Although the erythrocyte sedimentation rate and C-reactive protein are often elevated, they may be unremarkable. The serum albumin level may be low, indicating small bowel inflammation or protein-losing enteropathy. Fecal calprotectin and lactoferrin are more sensitive and specific markers of bowel inflammation as compared to serologic parameters, and these are often elevated. Multiple serologic, immune, and genetic markers can also be abnormal, although the best utilization of these remains to be determined.

The small and large bowel and the upper GI tract should be examined by both endoscopic and radiologic studies in the child with suspected Crohn disease. Esophagogastroduodenoscopy and ileocolonoscopy should be performed to properly assess the upper GI tract, terminal ileum, and entire colon. Findings on colonoscopy can include patchy, nonspecific inflammatory changes (erythema, friability, loss of vascular pattern), aphthous ulcers, linear ulcers, nodularity, and strictures. Findings on biopsy may be only nonspecific chronic inflammatory changes. Noncaseating granulomas, similar to those of sarcoidosis, are the most characteristic histologic findings, although often they are not present. Transmural inflammation is also characteristic but can be identified only in surgical specimens.

Radiologic studies are necessary to assess the entire small bowel and investigate for evidence of structuring or penetrating disease. A variety of findings may be apparent on radiologic studies. Plain films of the abdomen may be normal or might demonstrate findings of partial small bowel obstruction or thumbprinting of the colon wall (Fig. 382.8). An upper GI contrast study with small bowel follow-through might show aphthous ulceration and thickened, nodular folds as well as narrowing or stricturing of the lumen. Linear ulcers can give a cobblestone appearance to the mucosal surface. Bowel loops are often separated as a result of thickening of bowel wall and mesentery (Fig. 382.9). Other manifestations on radiographic studies that suggest more severe Crohn disease are fistulas between bowel (enteroenteric or enterocolonic), sinus tracts, and strictures (see Fig. 382.7).

An upper GI contrast examination with small bowel follow-through has typically been the study of choice for imaging of the small bowel, but CT and MR enterography as well as small bowel ultrasonography are more often performed (Fig. 382.10). MR and ultrasound have the advantage of not exposing the patient to ionizing radiation. CT and MR enterography can also assess for extraluminal findings such as intraabdominal abscess. MR of the pelvis is also useful for delineating the extent of perianal involvement. PET/MRI studies are also helpful in identifying areas of active intestinal and extraintestinal inflammation (Fig. 382.11).

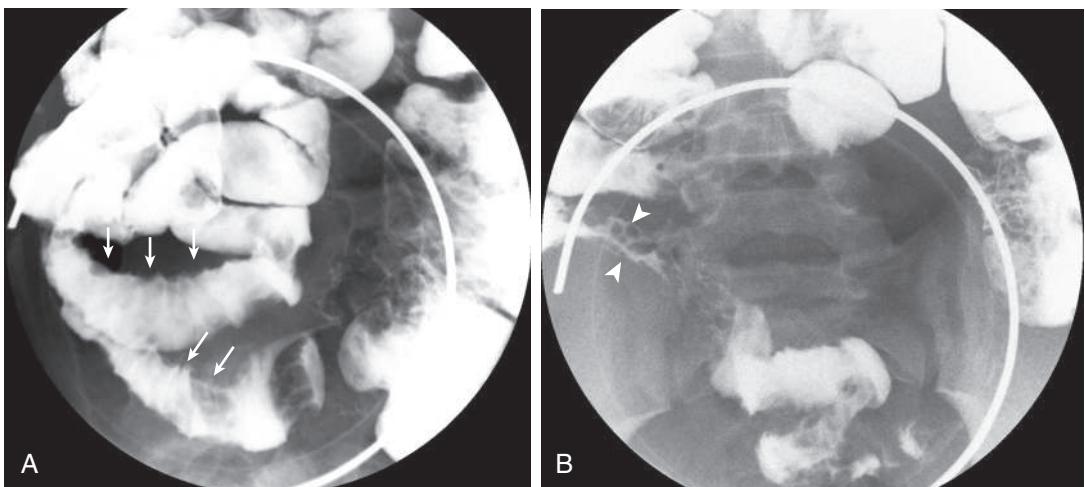
Video capsule endoscopy is another modality that allows for evaluation of the small bowel. This study can uncover mucosal inflammation or ulceration that might not have been detected by traditional imaging. However, video capsule endoscopy is contraindicated in the presence of stricturing disease, as surgical intervention would be required to remove a video capsule that is unable to pass through the bowel because a stricture. If there is concern for stricturing disease, a patency capsule can be swallowed before video capsule endoscopy to assess for passage through the GI tract.



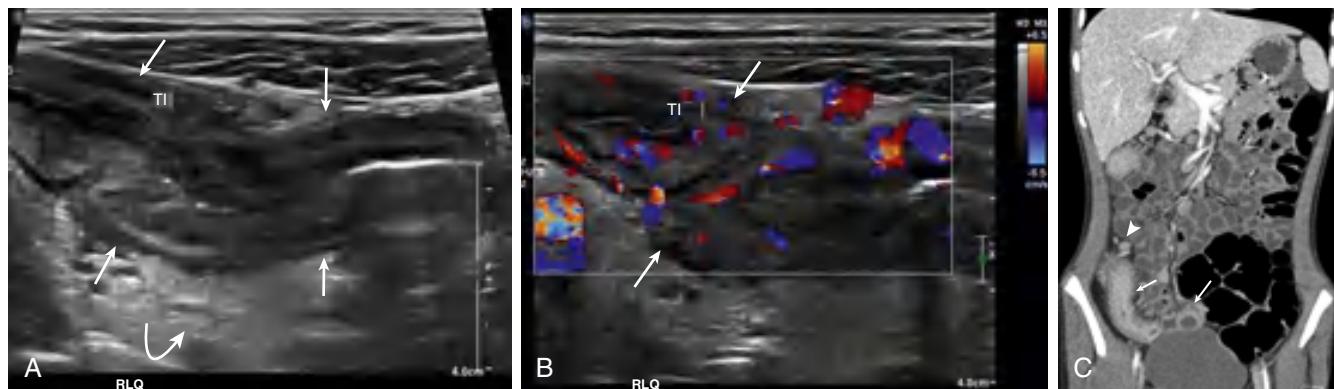
**Fig. 382.8** A 19-yr-old patient who presented with bloody stools and later diagnosed with inflammatory bowel disease. Abdominal radiograph at presentation showed classic thumbprinting involving the distal transverse colon, splenic flexure, and descending colon (arrows) representing submucosal edema seen in colitis. (Images from Department of Radiology, Children's Hospital of Philadelphia.)

**Table 382.8** Differential Diagnosis of Presenting Symptoms of Crohn Disease

PRIMARY PRESENTING SYMPTOM	DIAGNOSTIC CONSIDERATIONS
Right lower quadrant abdominal pain, with or without mass	Appendicitis, infection (e.g., <i>Campylobacter</i> , <i>Yersinia</i> spp.), lymphoma, intussusception, mesenteric adenitis, Meckel diverticulum, ovarian cyst
Chronic periumbilical or epigastric abdominal pain	Irritable bowel syndrome, constipation, lactose intolerance, peptic disease
Rectal bleeding, no diarrhea	Fissure, polyp, Meckel diverticulum, rectal ulcer syndrome
Bloody diarrhea	Infection, hemolytic-uremic syndrome, Henoch-Schönlein purpura, ischemic bowel, radiation colitis
Watery diarrhea	Irritable bowel syndrome, lactose intolerance, giardiasis, <i>Cryptosporidium</i> infection, sorbitol, laxatives
Perirectal disease	Fissure, hemorrhoid (rare), streptococcal infection, condyloma (rare)
Growth delay	Endocrinopathy
Anorexia, weight loss	Anorexia nervosa
Arthritis	Collagen vascular disease, infection
Liver abnormalities	Chronic hepatitis



**Fig. 382.9** A 12-yr-old child with weight loss and bloody stools diagnosed with Crohn disease. Small bowel follow-through barium examination showed the classic features of Crohn disease. **A**, Mucosal thickening, irregularity (arrows). **B**, Nodularity, "cobblestoning" (arrowheads) of the terminal ileum and distal ileal loops. There was also separation of the bowel loops due to fatty proliferation of the mesentery. (Images from Department of Radiology, Children's Hospital of Philadelphia.)



**Fig. 382.10** An 11-yr-old child who presented with abdominal pain, weight loss, leukocytosis, and elevated erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP). The patient underwent an initial bowel ultrasound and then CT enterography with assistance from Child Life mitigating use of sedation. Sagittal (A) grayscale and color Doppler (B) ultrasound images showed markedly thickened abnormal hyperemic terminal ileum (straight arrows) and surrounding thickened echogenic mesentery (curved arrow) indicative of active inflammation. C, Coronal image from a contrast-enhanced CT enterography showed correlating abnormal enhancing and thickened distal and terminal ileum (arrows) with enlarged reactive adjacent lymph nodes (arrowhead). (Images from Department of Radiology, Children's Hospital of Philadelphia.)

## TREATMENT

Crohn disease cannot be *cured* by medical or surgical therapy. The aim of treatment is to relieve symptoms and prevent complications of chronic inflammation (anemia, growth failure), prevent relapse, minimize corticosteroid exposure, and, if possible, effect mucosal healing.

### Medical

The specific therapeutic modalities used depend on geographic localization of disease, severity of inflammation, age of the patient, and the presence of complications (abscess). Traditionally, a *step-up* treatment paradigm has been used in the treatment of pediatric Crohn disease, whereby early disease is treated with steroids and less immunosuppressive medications. Escalation of therapy would occur if disease severity increased, the patient was refractory to current medications, or for steroid dependence. A *top-down* approach has also been espoused, particularly in adults after multiple studies demonstrated superior efficacy. With this approach, patients with moderate to severe Crohn disease are treated initially with stronger, disease-modifying agents, with the goal of achieving mucosal healing, or deep remission, early in the disease course. This is thought to increase the likelihood of long-term remission while decreasing corticosteroid exposure. Improvements in

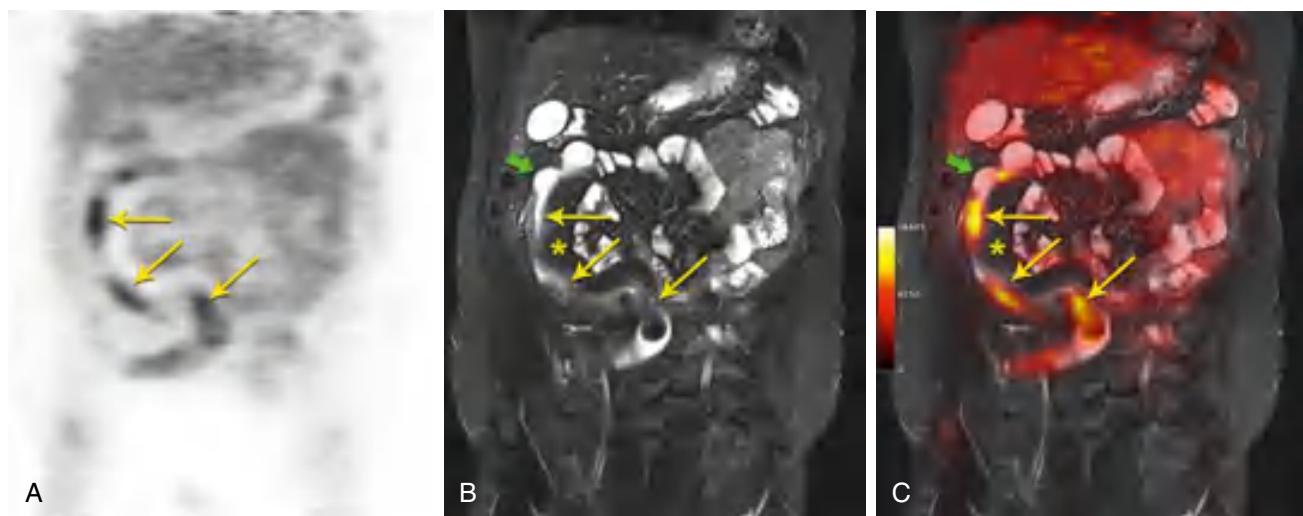
remission and growth have been shown using a top-down approach in pediatrics, and this treatment approach is being increasingly used among children.

### 5-Aminosalicylates

For mild terminal ileal disease or mild Crohn disease of the colon, an initial trial of mesalamine (50–100 mg/kg/day, maximum 3–4 g) may be attempted. Specific pharmaceutical preparations have been formulated to release the active 5-ASA compound throughout the small bowel, in the ileum and colon, or exclusively in the colon. Rectal preparations are used for distal colonic inflammation.

### Antibiotics/Probiotics

Antibiotics such as metronidazole (5 mg/kg/dose three times per day, up to 250 mg three times per day) are used for infectious complications and are first-line therapy for perianal disease (although perianal disease usually recurs when antibiotic is discontinued). Additionally, at low doses antibiotics may be effective for treatment of mild to moderate Crohn disease. To date, probiotics have not been shown to be effective in induction or maintenance of remission for pediatric Crohn disease.



**Fig. 382.11** Crohn disease, coexistence of active and chronic changes. Coronal PET (A), coronal STIR MRI (B), and fused PET/MRI (C). Discontinuous areas of active inflammation (arrows) demonstrate increased focal FDG uptake, bowel wall thickening, and edema. Note adjacent fibrofatty proliferation (asterisk) and pseudosacculations indicative of the chronicity of the process. (From Furtado FS, Suarez-Weiss KE, Amorim BJ, et al. *Gastrointestinal imaging*. In Catalano A (ed). *Clinical PET/MRI*. London: Elsevier, 2023. Fig 14.15.)

### Corticosteroids

Corticosteroids are used for acute exacerbations of pediatric Crohn disease because they effectively suppress acute inflammation, rapidly relieving symptoms (prednisone, 1–2 mg/kg/day, by mouth [PO], maximum 40–60 mg). The goal is to taper dosing as soon as the disease becomes quiescent. Clinicians vary in their tapering schedules, and the disease can flare during this process. There is no role for continuing corticosteroids as maintenance therapy because, in addition to their side effects, tolerance develops, and steroids do not change disease course or promote healing of mucosa. A special controlled ileal-release formulation of budesonide, a corticosteroid with local antiinflammatory activity on the bowel mucosa and high hepatic first-pass metabolism, is also used for mild to moderate ileal or ileocecal disease (adult dose: 9 mg daily). Ileal-release budesonide appears to be more effective than mesalamine in the treatment of active ileocolonic disease but is less effective than prednisone. Although less effective than traditional corticosteroids, budesonide does cause fewer steroid-related side effects.

### Immunomodulators

Approximately 70% of patients require escalation of medical therapy within the first year of pediatric Crohn disease diagnosis. Immunomodulators such as azathioprine (2.0–2.5 mg/kg/day) or 6-mercaptopurine (1.0–1.5 mg/kg/day) may be effective in some children who have a poor response to prednisone or who are steroid dependent. Because a beneficial effect of these drugs can be delayed for 3–4 months after starting therapy, they are not helpful acutely. The early use of these agents can decrease cumulative prednisone dosages over the first 1–2 years of therapy. Genetic variations in an enzyme system responsible for metabolism of these agents (thiopurine S-methyltransferase) can affect response rates and potential toxicity. Lymphoproliferative disorders have developed from thiopurine use in patients with IBD. Other common toxicities include hepatitis, pancreatitis, increased risk of skin cancer, increased risk of infection, and slightly increased risk of lymphoma.

Methotrexate is another immunomodulator that is effective in the treatment of Crohn disease and has been shown to improve height velocity in the first year of administration. The advantages of this medication include once-weekly dosing by either a subcutaneous or oral

route (15 mg/m<sup>2</sup>, adult dose 25 mg weekly) and a more rapid onset of action (6–8 weeks) than azathioprine or 6-mercaptopurine. Folic acid is usually administered concomitantly to decrease medication side effects. Administration of ondansetron before methotrexate has been shown to diminish the risk of the most common side effect of nausea. The most common toxicity is hepatitis. The immunomodulators are effective for the treatment of perianal fistulas.

### Biologic Therapy

*Therapy with antibodies directed against mediators of inflammation is used for patients with Crohn disease.* Infliximab, a chimeric monoclonal antibody to TNF- $\alpha$ , is effective for the induction and maintenance of remission and mucosal healing in chronically active moderate to severe Crohn disease, healing of perianal fistulas, steroid sparing, and preventing postoperative recurrence. Pediatric data additionally support improved growth with the administration of this medication. The onset of action of infliximab is quite rapid, and it is initially given as three infusions over a 6-week period (0, 2, and 6 weeks), followed by maintenance dosing beginning every 8 weeks. The durability of response to infliximab is variable, and dose escalation (higher dose and/or decreased interval) is often necessary. Measurement of serum trough infliximab level before an infusion can help guide dosing decisions. Side effects include infusion reactions, increased incidence of infections (especially reactivation of latent tuberculosis), increased risk of lymphoma, and the development of autoantibodies. The development of antibodies to infliximab is associated with an increased incidence of infusion reactions and decreased durability of response. Regularly scheduled dosing of infliximab, as opposed to episodic dosing on an as-needed basis, is associated with decreased levels of antibodies to infliximab. A purified protein derivative test or gamma interferon test for tuberculosis should be done before starting infliximab.

Adalimumab, a subcutaneously administered, fully humanized monoclonal antibody against TNF- $\alpha$ , is effective for the treatment of chronically active moderate to severe Crohn disease in adults and children. After a loading dose, this is typically administered once every 2 weeks, although dose escalation is sometimes required with this medication. Vedolizumab, a humanized monoclonal antibody that inhibits adhesion and migration of leukocytes into the GI tract, is approved for

the treatment of Crohn disease in adults. Like infliximab, vedolizumab is initially given as three infusions over a 6-week period followed by maintenance dosing beginning every 8 weeks. However, the onset of action for vedolizumab is slower compared to infliximab and adalimumab. Therefore concomitant therapies may be needed until response is demonstrated. Dose escalation to every 4 weeks may be necessary in some patients with loss of response, but it is being further studied. Ustekinumab, a monoclonal antibody against both IL-12 and IL-23, is also approved for treatment of chronically active moderate to severe Crohn disease in adults. A loading dose is given intravenously followed by maintenance dosing administered subcutaneously every 8 weeks. Risankizumab, a monoclonal antibody against IL-23A, has demonstrated efficacy for induction and remission maintenance in adults.

### **Enteral Nutritional Therapy**

Exclusive enteral nutritional therapy, whereby all of a patient's calories are delivered via formula, is an effective primary as well as adjunctive treatment. The enteral nutritional approach is as rapid in onset and as effective as the other treatments. Pediatric studies have suggested similar efficacy to prednisone for improvement in clinical symptoms, but enteral nutritional therapy is superior to steroids for actual healing of mucosa. Because affected patients have poor appetite and these formulas are relatively unpalatable, they are often administered via a nasogastric or gastrostomy infusion, usually overnight. The advantages are that it is relatively free of side effects, avoids the problems associated with corticosteroid therapy, and simultaneously addresses the nutritional rehabilitation. Children can participate in normal daytime activities. A major disadvantage of this approach is that patients are not able to eat a regular diet because they are receiving all of their calories from formula. A novel approach where 80–90% of caloric needs are provided by formula, allowing children to have some food intake, has been successful. For children with growth failure, this approach may be ideal.

High-calorie oral supplements, although effective, are often not tolerated because of early satiety or exacerbation of symptoms (abdominal pain, vomiting, or diarrhea). Nonetheless, they should be offered to children whose weight gain is suboptimal even if they are not candidates for exclusive enteral nutritional therapy. The continuous administration of nocturnal nasogastric feedings for chronic malnutrition and growth failure has been effective with a much lower risk of complications than parenteral hyperalimentation.

### **Surgical**

Surgical therapy should be reserved for very specific indications. Recurrence rate after bowel resection is high (>50% by 5 years); the risk of requiring additional surgery increases with each operation. Potential complications of surgery include development of fistula or stricture, anastomotic leak, postoperative partial small bowel obstruction secondary to adhesions, and short bowel syndrome. Surgery is the treatment of choice for localized disease of small bowel or colon that is unresponsive to medical treatment, bowel perforation, fibrosed stricture with symptomatic partial small bowel obstruction, and intractable bleeding. Intraabdominal or liver abscess sometimes is successfully treated by ultrasonographic or CT-guided catheter drainage and concomitant intravenous antibiotic treatment. Open surgical drainage is necessary if this approach is not successful.

Perianal abscess often requires drainage unless it drains spontaneously. In general, perianal fistulas should be managed by a combined medical and surgical approach. Often, the surgeon places a seton through the fistula to keep the tract open and actively draining while medical therapy is administered, to help prevent the formation of a perianal abscess. A severely symptomatic perianal fistula can require fistulotomy, but this procedure should be considered only if the location allows the sphincter to remain undamaged.

The surgical approach for Crohn disease is to remove as limited a length of bowel as possible. There is no evidence that removing bowel up to margins that are free of histologic disease has a better outcome

than removing only grossly involved areas. The latter approach reduces the risk of short bowel syndrome. Laparoscopic approach is increasingly being used, with decreased postoperative recovery time. One approach to symptomatic small bowel stricture has been to perform a strictureplasty rather than resection. The surgeon makes a longitudinal incision across the stricture but then closes the incision with sutures in a transverse fashion. This is ideal for short strictures without active disease. The reoperation rate is no higher with this approach than with resection, whereas bowel length is preserved. Postoperative medical therapy with agents, such as mesalamine, metronidazole, azathioprine, and, more recently, infliximab, is often given to decrease the likelihood of postoperative recurrence.

Severe perianal disease can be incapacitating and difficult to treat if unresponsive to medical management. Diversion of fecal stream can allow the area to be less active, but on reconnection of the colon, disease activity usually recurs.

### **Support**

Psychosocial issues for the child with Crohn disease include a sense of being different, concerns about body image, difficulty in not participating fully in age-appropriate activities, and family conflict brought on by the added stress of this disease. Social support is an important component of the management of Crohn disease. Parents are often interested in learning about other children with similar problems, but children may be hesitant to participate. Social support and individual psychologic counseling are important in the adjustment to a difficult problem at an age that by itself often has difficult adjustment issues. Patients who are socially "connected" fare better. Ongoing education about the disease is an important aspect of management because children generally fare better if they understand and anticipate problems. The Crohn and Colitis Foundation has local chapters throughout the United States and supports several regional camps for children with Crohn disease.

### **PROGNOSIS**

Crohn disease is a chronic disorder that is associated with high morbidity but low mortality. Symptoms tend to recur despite treatment and often without apparent explanation. Weight loss and growth failure can usually be improved with treatment and attention to nutritional needs. Up to 15% of patients with early growth retardation secondary to Crohn disease have a permanent decrease in linear growth. Osteopenia is particularly common in those with chronic poor nutrition and frequent exposure to high doses of corticosteroids. Dual-energy x-ray absorptiometry can help identify patients at risk for developing osteopenia. Steroid-sparing agents, weight-bearing exercise, and improved nutrition, including supplementation with vitamin D and calcium, can improve bone mineralization. Some of the extraintestinal manifestations can, in themselves, be major causes of morbidity, including sclerosing cholangitis, chronic active hepatitis, pyoderma gangrenosum, and ankylosing spondylitis.

The region of bowel involved and complications of the inflammatory process tend to increase with time and include bowel strictures, fistulas, perianal disease, and intraabdominal or retroperitoneal abscess. Most patients with Crohn disease eventually require surgery for one of its many complications; the rate of reoperation is high. Surgery is unlikely to be curative and should be avoided except for the specific indications noted previously. An earlier, most aggressive medical treatment approach, with the goal of exacting mucosal healing may improve long-term prognosis, and this is an active area of investigation. The risk of colon cancer in patients with long-standing Crohn colitis approaches that associated with ulcerative colitis, and screening colonoscopy after 8–10 years of colonic disease is indicated.

Despite these complications, most children with Crohn disease lead active, full lives with intermittent flare-up in symptoms.

### 382.3 Very Early Onset Inflammatory Bowel Disease

Ronen E. Stein, Sudha A. Anupindi, and Robert N. Baldassano

IBD may be classified according to age at onset: pediatric onset (<17 years), early onset (<10 years), very early onset (<6 years), infant/toddler onset (0-2 years), and neonatal onset IBD (<28 days). The incidence of pediatric IBD is rising with the greatest rates of increase occurring among young children. Very early onset IBD (VEO-IBD) accounts for up to 15% of pediatric-onset IBD with an estimated prevalence of 14/100,000 children. Approximately 1% of children with IBD are diagnosed before the age of 2 years.

Although IBD is a complex disorder with genetics, the immune system, the microbiome, and environmental factors each contributing to its development, children with VEO-IBD are more likely to have a *monogenic* cause for their disease. Genetic testing has led to the identification of novel genetic pathways linked to the development of

VEO-IBD. Many of these pathways contain genes associated with primary immunodeficiencies (see Tables 382.1 and 382.6; Table 382.9). Family history of IBD among first-degree relatives occurs more frequently in children diagnosed at a younger age. Approximately 44% of children diagnosed with ulcerative colitis under the age of 2 years will have a first-degree relative with IBD compared with 19% of older children with IBD.

VEO-IBD has a distinct clinical phenotype characterized by a higher likelihood for extensive colonic involvement and a greater tendency for a more aggressive disease course that is refractory to conventional therapies. However, there is a spectrum of clinical presentations within this population, including patients with milder forms of the disease and a more traditional disease course. Younger patients with IBD can present with any combination of diarrhea, abdominal pain, vomiting, and growth failure. Severe perirectal disease can be present and is often associated with monogenic forms of VEO-IBD, including those caused by IL-10 receptor pathogenic variants. In addition to intestinal symptoms, there may be associated manifestations of the specific monogenic disorder (Fig. 382.12).

**Table 382.9** Known Defects Associated with Very Early Onset Inflammatory Bowel Disease and Its Associated Extraintestinal Manifestations and Laboratory Findings

DEFECTS	GENE DEFECT	EXTRAINTESTINAL IMMUNE, HEMATOLOGIC, OR SOMATIC MANIFESTATIONS	LABORATORY FINDINGS AND FUNCTIONAL EVALUATION
<b>IPEX AND IPEX-LIKE DISORDERS</b>			
IPEX	FOXP3	Autoimmune endocrinopathy, cytopenia, hepatitis and kidney disease, eczema, food allergy, eosinophilia	Decrease in Treg cells number and function Decreased Foxp3 expression
CD25 deficiency	CD25	Autoimmune endocrinopathy, cytopenia, eczema, gingivitis, alopecia universalis, bullous pemphigoid, CMV, EBV disease	Absent CD25 expression
STAT5b deficiency	STAT5B	Autoimmune endocrinopathy, eczema, short stature, interstitial pneumonitis, alopecia universalis, bullous pemphigoid, varicella and herpes zoster infections	Variable immune abnormality Normal to low T, B, and NK cells
STAT1 GOF mutation	STAT1	Mucocutaneous candidiasis, short stature, eczema, autoimmune endocrinopathy, sinopulmonary infection, hypertension, aneurysm	Most have normal Treg cell number and Foxp3 expression, abnormal STAT1 phosphorylation studies
STAT3 GOF mutation	STAT3	Multisystem autoimmunity, variable short stature, lymphoproliferation	Hypogammaglobulinemia Decreased class switched memory B cells
LRBA deficiency	LRBA	Multisystem autoimmunity, cytopenia, arthritis, recurrent sinopulmonary infection, granuloma, hypogammaglobulinemia	Hypogammaglobulinemia Decreased class switched memory B cells
CTLA4 haploinsufficiency	CTLA4	Diarrhea, enteropathy, hypogammaglobulinemia, granulomatous lymphocytic interstitial lung disease, multisystem autoimmunity	Hypogammaglobulinemia Decreased class switched memory B cells
<b>DEFECTS IN IL-10 SIGNALING</b>			
Defects in IL-10 and IL-10R	IL-10RA IL-10RB IL-10	Perianal fistula, folliculitis, arthritis, abscess, lymphoma	STAT3 phosphorylation by IL-6 and IL-10 studies*
<b>DEFECTS IN NEUTROPHIL FUNCTION</b>			
CGD	CYBB CYBA NCF1 NCF2 NCF4	Perianal fistula, recurrent cold abscess from catalase positive organisms, <sup>†</sup> gastric outlet obstruction	Decreased neutrophil oxidative burst study Elevated IgG
Glycogen storage disease 1b	SLC37A4	Recurrent bacterial infections, hypoglycemic seizures, hepatomegaly	Neutropenia, hypoglycemia, hyperuricemia, hyperlipidemia
Leukocyte adhesion defect	ITGB2	Neutrophilia, recurrent bacterial infections, delayed separation of umbilical cord, poor wound healing	Leukocytosis Absent CD18 expression
Congenital neutropenia	G6PC3	Cutaneous vascular malformation and cardiac defect	Severe neutropenia

*Continued*

**Table 382.9** Known Defects Associated with Very Early Onset Inflammatory Bowel Disease and Its Associated Extraintestinal Manifestations and Laboratory Findings—cont'd

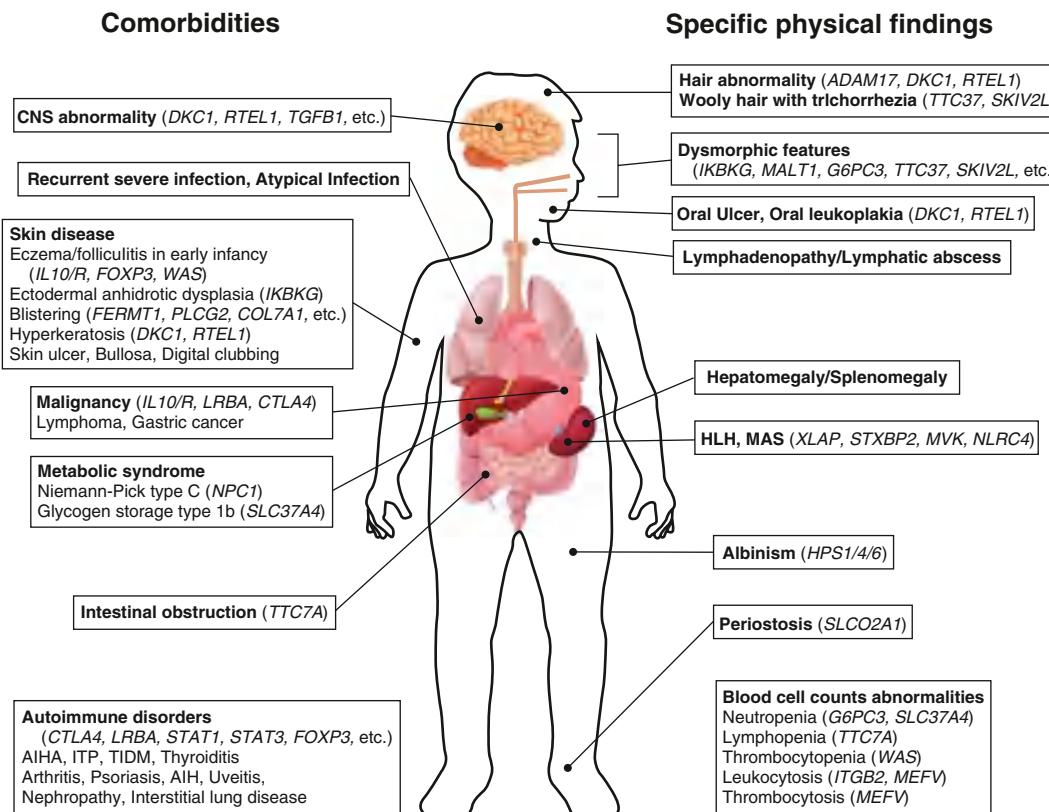
DEFECTS	GENE DEFECT	EXTRAINTESTINAL IMMUNE, HEMATOLOGIC, OR SOMATIC MANIFESTATIONS	LABORATORY FINDINGS AND FUNCTIONAL EVALUATION
<b>HYPERINFLAMMATORY DISORDERS</b>			
XIAP	BIRC4	Perianal fistula, recurrent HLH, EBV, and CMV infections, hypogammaglobinemia	Markedly elevated IL-18 Decreased or absent XIAP protein expression by flow
NLRC4 GOF variant	NLRC4	Recurrent macrophage activation, rash	Markedly elevated IL-18
Mevalonate kinase deficiency	MVK	Recurrent fever, rash, abdominal pain and emesis	Elevated inflammatory markers Elevated IgD Elevated urine mevalonate
Familial Mediterranean fever	MEFV	Recurrent fever, abdominal pain, arthralgia, peritonitis	Elevated inflammatory markers
Familial HLH type 5	STXBP2	HLH, hypogammaglobinemia, sensorineural hearing loss	Marked elevated ferritin and sIL-2R Decreased CD107a degranulation
Hermansky-Pudlak syndrome	HPS1 HPS4 HPS6	Partial albinism, bleeding tendency, recurrent infection and immunodeficiency	Decreased CD107a degranulation
<b>DEFECTS IN EPITHELIAL BARRIER FUNCTION</b>			
TTC7A deficiency	TTC7A	Varying degree of intestinal atresia, T-cell immune defect and recurrent infections	Mild to severe T-cell immune deficiency Hypogammaglobinemia
X-linked ectodermal immunodeficiency (NEMO deficiency)	IKBKG	Varying degree of ectodermal dysplasia, conical teeth, sparse and brittle hair, recurrent bacterial, viral and mycobacterial infections	Hypogammaglobinemia Decreased class switched memory B cells
ADAM17 deficiency	ADAM17	Neonatal inflammatory skin and bowel disease, generalized pustular rash	Normal T-cell and B-cell numbers
Dystrophic epidermolysis bullosa	COL7A1	Blistering disorder primarily affect the hands, feet, knees, and elbows	Unremarkable immune findings
Kindler syndrome	FERMT1	Acral skin blistering, photosensitivity, progressive poikiloderma, and diffuse cutaneous atrophy	Eosinophilia
<b>ISOLATED OR COMBINED T-CELL AND B-CELL IMMUNE DEFECTS</b>			
X-linked agammaglobulinemia	BTK	Recurrent sinopulmonary infection	Absent B cells in peripheral blood Absent plasma cells in tissue Decreased class switched memory B cells
Common variable immune defect (CVID)		Heterogeneous group of defects with sinopulmonary infections, autoimmunity, lymphoproliferation, and variable T-cell immune defect	Hypogammaglobinemia Variable T-cell lymphopenia
X-linked hyper IgM (CD40L)	CD40L	Sclerosing cholangitis, Cryptosporidium diarrhea and Pneumocystis infection	Elevated or normal IgM, neutropenia Absent class switched memory B cells
Wiskott-Aldrich syndrome	WAS	Eczema, recurrent infection, autoimmunity, vasculitis	Microthrombocytopenia Variable lymphopenia, low IgM Decreased WAS protein
Leaky SCID or Omenn	RAG1, RAG2 IL-7Ra IL-2RG	Generalized erythroderma, hepatosplenomegaly, lymphadenopathy	Eosinophilia T-cell lymphopenia Decreased naïve T cells

\*STAT3 signaling following IL-6 and IL-10 will only identify IL-10R A and B defects; it will not identify IL-10 deficiency.

<sup>†</sup>*Staphylococcus aureus*, *Serratia marcescens*, *Burkholderia cepacia*, *Aspergillus*, and *Candida*.

IPEX, Immune dysfunction, polyendocrinopathy, enteropathy, X-linked; Treg, regulatory T cell; CMV, cytomegalovirus; EBV, Epstein-Barr virus; NK, natural killer; GOF, gain of function; IL, interleukin; CGD, chronic granulomatous disease; HLH, hemophagocytic lymphohistiocytosis; SCID, severe combined immune deficiency.

From Chandrasekaran S, Venkateswaran S, Kugathasan S. Nonclassic inflammatory bowel disease in young infants – immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, and other disorders. *Pediatr Clin N Am*. 2017;64:139–160. Table 2.



**Fig. 382.12** Key indicators of monogenic IBD in clinical practice. Showing physical findings and comorbidities of which physicians should be aware at the initial physical examination and during follow-up. (Modified from Nambu R, Muise AM. Advanced understanding of monogenic inflammatory bowel disease. *Front Pediatr.* 2021;8:Article 618918. Fig. 1C.)

Diagnosis of IBD is ultimately confirmed by upper endoscopy and ileocolonoscopy. Classic histologic findings of IBD can be seen, although atypical findings, such as the presence of extensive epithelial apoptosis, could indicate the presence of monogenic disease. Most children with VEO-IBD will have isolated colonic inflammation on ileocolonoscopy. However, the inflammation can be extensive and involve the entire colon making it challenging to differentiate between Crohn disease and ulcerative colitis; 11–22% of patients with VEO-IBD are diagnosed with *indeterminate colitis* at diagnosis. Additionally, an initial diagnosis of ulcerative colitis occurs in approximately 60% of VEO-IBD patients. However, because children with VEO-IBD are more likely to have disease extension over time, a number of patients felt to have indeterminate colitis or ulcerative colitis at diagnosis may eventually be reclassified as having Crohn disease later in life. As small bowel imaging using CT or MR enterography may not be tolerated in a young child, small bowel ultrasonography is an alternative imaging modality in VEO-IBD.

The differential diagnosis of VEO-IBD is similar to older children and adults including infectious and allergic colitis (see Table 382.5). However, primary immunodeficiencies, such as chronic granulomatous disease, common variable immunodeficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome and immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, are higher on the differential (see Tables 382.6 and 382.9). Therefore immunologic evaluation is a critical component of diagnosis and management (Table 382.10). History of autoimmunity, atypical infections,

recurrent infections, skin disorders, and/or hair abnormalities could indicate an underlying immunodeficiency. Laboratory evaluation could include dihydrorhodamine cytometric testing, quantitative immunoglobulins, vaccine titers, as well as testing of B- and T-cell function. More targeted immunologic testing is guided by clinical history. Genetic testing modalities, such as whole exome sequencing, are helpful in identifying rare monogenic pathways responsible for development of the disease.

A multidisciplinary team approach at a center experienced in VEO-IBD can be helpful in formulating an individualized treatment plan. Younger children are more likely to fail conventional therapies, such as 5-ASA, immunomodulators, and biologics, and require surgical intervention. Surgical decisions must be made with caution in very young children as disease extension from the colon to the small intestine can occur with time. More extensive and severe disease at presentation could explain the higher rates of treatment failure among younger children. However, other children may fail conventional therapies if the inflammation is being driven by a monogenic disease process that is not targeted by conventional therapies. Therefore for children with an underlying primary immunodeficiency or a novel monogenic disease process, the specific disease pathway involved may influence treatment choices. In some cases, bone marrow transplantation may be a necessary treatment for the underlying disease process.

**Table 382.10** Functional Analysis

## FUNCTIONAL SCREENING CONSIDERED

- Immunoglobulins (IgG, IgM, IgA, IgD, IgE)
- Lymphocyte subsets by flow
- Antibody to vaccines
- TREC
- DHR-123
- Cytokine assay (serum cytokine level during flare)

## TARGETED FUNCTIONAL ANALYSIS (RECOMMENDED)

GENE	FUNCTIONAL ANALYSIS
IL10RA	IL-10-induced STAT3 phosphorylation by flow cytometry or immunoblotting
IL10RB	
NCF1	Neutrophil oxidative burst study, DHR-123 test
NCF2	
CYBA	
CYBB	
NCF4*	Neutrophil oxidative burst study
CYBC1	
TTC7A	Immunohistochemistry-TTC7A, apoptosis
WAS	WASP expression by flow cytometry
XIAP	XIAP expression by flow cytometry TNF, IL-8, and MCP-1 expression in response to MDP stimulation
SLCO2A1	Immunohistochemistry-SLCO2A1
NPC1	Filipin staining of cultured skin fibroblasts
SLC37A4	G6Pase enzyme activity in Liver tissue (non-frozen)
MVK	Increased urine mevalonic acid when fever
TNFAIP3	A20 expression by immunoblotting RT-PCR using total RNA
CTLA4	CTLA-4 expression within stimulated Treg cells by flow cytometry
LRBA	LRBA expression in response to PHA stimulation by flow cytometry
FOXP3	FOXP3 expression by flow cytometry
STAT1(GOF)	CD25 expression by flow cytometry
STAT3(GOF)	STAT3 reporter luciferase assay under basal or stimulated condition (IL-6/growth hormone) in cell lines SOCS3 expression levels under basal or stimulated condition (IL-21) in EBV-transformed patient cell lines

\*The production of ROS in phagocyte is normal and need to examine the bacterial killing activity.

TREC, T-cell receptor excision circles; DHR-123, dihydrorhodamine 123; WASP, Wiskott-Aldrich syndrome protein; IL-8, interleukin-8; MCP-1, monocyte chemoattractant protein; MDP, muramyl dipeptide; RT-PCR, real-time reverse transcription polymerase chain reaction; TNF, tumor necrosis factor; Treg, regulatory T cell; PHA, phytohemagglutinin; SOCS3, suppressor of cytokine signaling 3; EBV, Epstein-Barr virus; ROS, reactive oxygen species.

From Nambu R, Muise AM. Advanced understanding of monogenic inflammatory bowel disease. *Front Pediatr.* 2021;8:Article 618918. Table 1A.

## Chapter 383

**Eosinophilic Gastroenteritis**

Ronen E. Stein and Robert N. Baldassano

Eosinophilic gastroenteritis consists of a group of rare and poorly understood disorders that have in common gastric and small intestine infiltration with eosinophils and peripheral eosinophilia. The esophagus and large intestine may also be involved. Tissue eosinophilic infiltration can be seen in mucosa, muscularis, or serosa. The mucosal form is most common and is diagnosed by identifying large numbers of eosinophils in biopsy specimens of gastric antrum or small bowel. Endoscopy may reveal gastritis or colitis, ulceration, and thickened mucosal folds, as well as nodules. This condition clinically overlaps the dietary protein hypersensitivity disorders of the small bowel and colon. Peripheral eosinophilia may be absent. The differential diagnosis also includes celiac disease, chronic granulomatous disease, connective tissue disorders and vasculitides (eosinophilic granulomatosis with polyangiitis), multiple infections (particularly parasites), hypereosinophilic syndrome, early inflammatory bowel disease, medications (tacrolimus, enalapril, naproxen, interferon, rifampicin, azathioprine), and rarely malignancy. Many patients have allergies to multiple foods, seasonal allergies, atopy, eczema, and asthma. Serum immunoglobulin E is commonly elevated. Laboratory abnormalities may include hypoalbuminemia, iron-deficiency anemia, and elevated liver enzymes. Medications have been associated with eosinophilic gastroenteritis including gold, enalapril, and carbamazepine.

The presentation of eosinophilic gastroenteritis is nonspecific. Clinical symptoms often correlate with which layers of the gastrointestinal tract are affected. Mucosal involvement can produce nausea, vomiting, diarrhea, abdominal pain, gastrointestinal bleeding, protein-losing enteropathy, or malabsorption. Involvement of the muscularis can produce obstruction (especially of the pylorus) or intussusception, whereas serosal activity produces abdominal distention and eosinophilic ascites. Presentation in infants can be similar to pyloric stenosis. Laboratory testing often reveals peripheral eosinophilia, elevated serum immunoglobulin E levels, hypoalbuminemia, and anemia.

The disease usually runs a chronic, debilitating course with sporadic severe exacerbations. Although usually effective for the treatment of isolated eosinophilic esophagitis (see Chapter 370), elemental diets are not always successful for the treatment of eosinophilic gastroenteritis. Orally administered cromolyn sodium and montelukast are sometimes successful. There have been case reports of clinical improvement using ketotifen, an antihistamine and mast cell stabilizer. Many patients require treatment for acute disease exacerbations with systemic corticosteroids, which are often effective. Systemic corticosteroids may also be needed long term. Oral budesonide, a corticosteroid with local antiinflammatory activity on the bowel mucosa and limited systemic absorption due to high hepatic first-pass metabolism, can be attempted for long-term therapy. In adults, biologic agents (e.g., omalizumab) have been used.

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## Chapter 384

# Celiac Disease

Ankur A. Chugh

### ETIOLOGY AND EPIDEMIOLOGY

Celiac disease (CD) is an immune-mediated systemic disorder elicited by gluten in wheat and related prolamins from rye and barley in genetically susceptible individuals, and is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, human leukocyte antigen (HLA)-DQ2 or DQ8 haplotypes, and enteropathy. CD-specific antibodies comprise autoantibodies against tissue transglutaminase (TG2) including endomysial antibodies (EMAs), and antibodies against forms of deamidated gliadin peptides (DGPs).

CD is a common disorder with 1.4% global prevalence of positive serologies and 0.7% of biopsy-proven disease, with variability across countries. CD affects both children and adults (second to third decade of life). Although CD develops in genetically susceptible individuals, environmental factors might affect the risk of developing CD or the timing of its presentation. Neither breastfeeding during gluten introduction nor any breastfeeding has been shown to reduce the risk of CD. The impact of *early* gluten introduction (age 4 months) on the risk of developing CD is contradictory. Large amounts of gluten at a young age (6 months) may convey risk of earlier development of CD autoimmunity (positive serology) and CD, whereas *lower* amounts of gluten in the first 2 years of life may convey lower risk of CD. Infectious agents have been hypothesized to play a causative role, as frequent rotavirus infections were shown to be associated with an increased risk of developing CD. It is plausible that the contact with gliadin at a time when there is an ongoing intestinal inflammation alters intestinal permeability, and the enhanced antigen presentation can increase the risk of developing CD, at least in a subset of persons. The mode of delivery, socioeconomic status, season of birth, and the use of drugs have been associated with the risk of developing CD, but the evidence is contradictory.

### GENETICS AND PATHOGENESIS

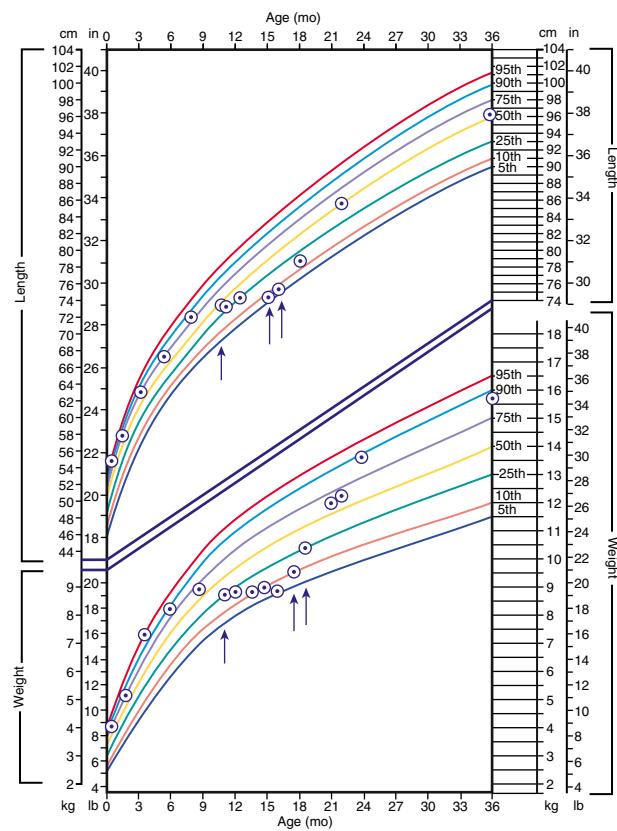
A genetic predisposition is suggested by the family aggregation and the concordance in monozygotic twins, which approaches 100%. The strongest association is with HLA-DQ2.5 (one or two copies encoded by DQA1\*05 [for the alpha] and DQB1\*02 genes [for the beta chain]). Such a DQ molecule has been found to be present in more than 90% of CD patients. The highly homologous DQ2.2 molecule confers a much lower risk, whereas the data available on DQ2-negative CD patients indicate that they almost invariably are HLA-DQ8 positive (DQA1\*0301/DQB1\*0302). A gene dosage effect has been proved in prospective studies, and a molecular hypothesis for such a phenomenon has been proposed, based on the impact of the number and quality of the HLA-DQ2 molecules on gluten peptide presentation to T cells. The HLA locus is the most significant and dominant gene associated with CD; however, other loci known to contribute to CD have been documented. Most have been found to be associated with other autoimmune diseases such as type 1 diabetes. Interestingly, very few polymorphisms associated with CD are in coding regions, as they often are in binding sites for transcription factors, where they then affect gene expression.

CD is a T-cell-mediated chronic inflammatory disorder with an autoimmune component. Altered processing by intraluminal enzymes, changes in intestinal permeability, and activation of innate immunity mechanisms precede the activation of the adaptive immune response. Immunodominant epitopes from gliadin are highly resistant to intraluminal and mucosal digestion; incomplete degradation favors the immunostimulatory and toxic effects of these sequences. Some gliadin peptides activate innate immunity, in particular they induce interleukin (IL)-15. The latter, but also type 1 interferons, may alter the tolerogenic phenotype of dendritic cells, resulting in lamina propria T-cell activation by other peptides presented in the context of HLA-DQ2 or HLA-DQ8 molecules. Gliadin-specific T-cell responses are enhanced by the

action of TG2: the enzyme converts particular glutamine residues into glutamic acid, which results in higher affinity of these gliadin peptides for HLA-DQ2 or HLA-DQ8. The pattern of cytokines produced following gliadin activation is dominated by interferon- $\gamma$  (T-helper type 1 skewed); IL-21 is also upregulated. In downstream T-cell activation a complex remodeling of the mucosa takes place involving increased levels of metalloproteinases and growth factors, which leads to the classical histologic finding of a flat mucosa. A severe impairment of intraepithelial lymphocyte (IEL) homeostasis is present in CD. IL-15 is implicated in the expression of natural killer receptors CD94 and NKG2D, as well as in epithelial expression of stress molecules, thus enhancing cytotoxicity, cell apoptosis, and villous atrophy. The most evident expression of autoimmunity is the presence of serum antibodies to TG2. However, the mechanisms leading to autoimmunity are largely unknown, as well as their pathogenetic significance. Potential CD, in which TG2 antibodies can be detected *in situ* without any histologic abnormality, shows that the production of antibodies does not necessarily lead to intestinal damage. The finding that IgA deposits on extracellular TG2 are not limited to the intestine but can be found in the liver, lymph nodes, and muscles indicates that TG2 is accessible to the gut-derived autoantibodies, turning CD into a systemic disease.

### CLINICAL PRESENTATION AND ASSOCIATED DISORDERS

Clinical features of CD vary considerably. Intestinal symptoms are more common in children whose disease is diagnosed *within the first 2 years of life*; failure to thrive, chronic diarrhea, vomiting, abdominal distension, muscle wasting, anorexia, and irritability are present in most cases (Fig. 384.1). Occasionally there is constipation, with cases presenting with intussusception. As the age at presentation of the disease shifts to later in childhood, and with the more extensive use of serologic screening tests, extraintestinal manifestations, without any accompanying digestive symptoms, have increasingly become recognized, affecting



**Fig. 384.1** Gluten-sensitive enteropathy. Growth curve demonstrates initial normal growth from 0 to 9 mo, followed by onset of poor appetite with intermittent vomiting and diarrhea after initiation of gluten-containing diet (single arrow). After biopsy confirmed diagnosis and treatment with gluten-free diet (double arrow), growth improves.

almost all organs (Table 384.1). One of the most common extraintestinal manifestation of CD is iron-deficiency anemia, which is usually unresponsive to iron therapy. Osteoporosis may be present; in contrast to adults, it can be reversed by a gluten-free diet in children, with restoration of normal peak bone densitometric values. Other extraintestinal manifestations include short stature, delayed puberty, arthritis and arthralgia, epilepsy with bilateral occipital calcifications, peripheral neuropathies, isolated hypertransaminasemia, dental enamel hypoplasia, and aphthous stomatitis. The mechanisms responsible for the severity and the variety of clinical presentations remain obscure. Nutritional deficiencies or abnormal immune responses have been suggested. Silent CD is recognized, mainly in asymptomatic first-degree

relatives of CD patients and in subjects affected by diseases associated with CD (Table 384.2). Small bowel biopsy in silent/subclinical CD reveals severe mucosal damage consistent with CD. Potential CD is defined when patients have positive CD-specific antibodies, but without documented small bowel damage (Table 384.3).

Some diseases, many with an autoimmune pathogenesis, are found with a higher than normal incidence in CD patients. Among these are type 1 diabetes, autoimmune thyroid disease, Addison disease, Sjögren syndrome, rheumatoid arthritis, autoimmune cholangitis, autoimmune hepatitis, primary biliary cholangitis, and juvenile idiopathic arthritis. Such associations have been interpreted as a consequence of the sharing of identical HLA haplotypes, but a direct role of

**Table 384.1** Extraintestinal Manifestations of Celiac Disease

MANIFESTATION	PROBABLE CAUSE(S)
<b>CUTANEOUS</b>	
Eccymoses and petechiae	Vitamin K deficiency; rarely, thrombocytopenia
Edema	Hypoproteinemia
Dermatitis herpetiformis	Epidermal (type 3) tTG autoimmunity
Follicular hyperkeratosis and dermatitis	Vitamin A malabsorption, vitamin B complex malabsorption
<b>ENDOCRINOLOGIC</b>	
Amenorrhea, infertility, impotence, delayed puberty, short stature, type 1 diabetes, thyroiditis, Addison disease, Graves disease	Malnutrition, hypothalamic-pituitary dysfunction, immune dysfunction
Secondary hyperparathyroidism	Calcium and/or vitamin D malabsorption with hypocalcemia
<b>HEMATOLOGIC</b>	
Anemia	Iron, folate, vitamin B <sub>12</sub> , or pyridoxine deficiency
Hemorrhage	Vitamin K deficiency; rarely, thrombocytopenia due to folate deficiency
Thrombocytosis, Howell-Jolly bodies	Hyposplenism; splenic atrophy; autoantibodies
Pancytopenia	Vitamin B <sub>12</sub> deficiency; immune medicated
Thrombosis	Venous and arterial, including portal vein
Malignancies	Enteropathy-type T-cell lymphoma, B-cell gut lymphoma, adenocarcinoma of small intestine
<b>HEPATIC</b>	
Elevated liver biochemical test levels	Lymphocytic celiac hepatitis, NAFLD
Autoimmune hepatitis	Associated autoimmune hepatitis
<b>MUSCULAR</b>	
Atrophy	Malnutrition due to malabsorption
Tetany	Calcium, vitamin D, and/or magnesium malabsorption
Weakness	Generalized muscle atrophy, hypokalemia
<b>NEUROLOGIC</b>	
Peripheral neuropathy	Deficiencies of vitamin B <sub>12</sub> and thiamine; immune-based neurologic dysfunction
Ataxia	Cerebellar and/or posterior column damage
Demyelinating central nervous system lesions	Immune-based neurologic dysfunction
Seizures (difficult to treat)	Unknown; associated occipital calcifications
<b>SKELETAL</b>	
Osteopenia, osteomalacia, and osteoporosis	Malabsorption of calcium and vitamin D, secondary hyperparathyroidism, chronic inflammation
Osteoarthropathy	Unknown
Pathologic fractures	Osteopenia and osteoporosis
<b>OTHER</b>	
Enamel hypoplasia	Vitamin D, calcium malabsorption
Anxiety, schizophrenia	Unknown, uncertain
Pulmonary hemosiderosis	Unknown, uncertain
Aphthous stomatitis	Unknown
Benign inflammatory mass	Granulomatous self-resolving process with treatment

tTG, Tissue transglutaminase; NAFLD, nonalcoholic fatty liver disease.

Modified from Kelly CP. Celiac disease. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 10th ed. Philadelphia: Elsevier; 2016: Table 107.1.

**Table 384.2** National Institute for Health and Care Excellence Guidelines on the Indications That Should Prompt Testing for Celiac Disease

**CELIAC TESTING RECOMMENDED**

- Persistent unexplained abdominal or gastrointestinal symptoms
- Faltering growth
- Prolonged fatigue
- Unexpected weight loss
- Severe or persistent mouth ulcers
- Unexplained iron, vitamin B<sub>12</sub>, or folate deficiency
- Type 1 diabetes
- Autoimmune thyroid disease
- Irritable bowel syndrome
- First degree relatives of people with celiac disease
- Dermatitis herpetiformis

**CELIAC TESTING SHOULD BE CONSIDERED**

- Metabolic bone disorders (reduced bone mineral density or osteomalacia)
- Unexplained neurologic symptoms (particularly peripheral neuropathy or ataxia)
- Unexplained subfertility or recurrent miscarriage
- Persistently increased concentrations of liver enzymes with unknown cause
- Dental enamel defects
- Down syndrome
- Turner syndrome
- William syndrome
- Selective IgA deficiency

IgA, Immunoglobulin A.

From Downey L, Houten R, Murch S, Longson D for the Guideline Development Group. Recognition, assessment, and management of coeliac disease: summary of updated NICE guidance. *BMJ*. 2015;351:h4513.

**Table 384.3** Clinical Spectrum of Celiac Disease

**SYMPTOMATIC**

Frank malabsorption symptoms and signs (e.g., chronic diarrhea, failure to thrive, weight loss)

Extraintestinal symptoms and signs (e.g., anemia, fatigue, hypertransaminasemia, neurologic disorders, short stature, dental enamel defects, arthralgia, aphthous stomatitis)

**SILENT**

No apparent symptoms in spite of histologic evidence of villous atrophy

In most cases identified by serologic screening in at-risk groups (see Table 384.1)

**LATENT**

Subjects who have a normal intestinal histology, but at some other time have shown a gluten-dependent enteropathy

**POTENTIAL**

Subjects with positive celiac disease serology but without evidence of altered intestinal histology. Patients may or may not have symptoms and signs of disease and may or may not develop a gluten-dependent enteropathy later

gluten in promoting autoimmunity cannot be excluded. The relation between CD and other autoimmune diseases is poorly defined; once those diseases are established, they are not influenced by a gluten-free diet. Other associated conditions include selective IgA deficiency and Down, Turner, and Williams syndromes (see Table 384.2).

**DIAGNOSIS**

The diagnosis of CD is based on a combination of symptoms, antibodies, and duodenal histology. The initial approach to symptomatic patients is to test for anti-TG2 IgA antibodies and for total IgA in serum to exclude IgA deficiency. If IgA anti-TG2 antibodies are negative, and serum total IgA is normal for age, CD is unlikely to be the

cause of the symptoms. If anti-TG2 antibody testing is positive, the patients should be referred to a pediatric gastroenterologist for further diagnostic workup, which depends on the serum antibody levels.

In patients with selective IgA deficiency, testing is recommended with IgG antibodies to TG2. Patients with positive anti-TG2 antibody levels <10 times the upper limit of normal should undergo upper endoscopy with multiple biopsies. In patients with positive anti-TG2 antibody levels at or >10 times the upper limit of normal, EMA titers should be obtained in a second blood draw (to prevent mislabeling). If the patient has positive antibodies, the diagnosis of CD is essentially confirmed, a lifelong gluten-free diet is started, and the patient is followed for the improvement of symptoms and the decline of antibodies. In the rare case of negative anti-EMA in a child with TG2 antibody titers >10 times the upper limits of normal, the diagnostic workup should be extended, and duodenal biopsies obtained (Fig. 384.2). In asymptomatic persons belonging to high-risk groups with anti-TG2 levels >10 times the upper limit of normal, the decision to utilize the nonbiopsy approach should be a shared decision with the patient/family. When biopsies are indicated, at least four fragments should be obtained from the descending part of the duodenum and at least one from the duodenal bulb. The diagnosis is confirmed by an antibody decline and preferably a clinical response to a gluten-free diet. CD is not the only cause for lymphocytic infiltration or villous atrophy (Table 384.4). HLA testing is helpful for diagnostic uncertainty, patients already on a gluten free diet, and in screening of high-risk individuals. The benefit of obtaining additional DGP antibodies in patients <2 years of age is no longer favored.

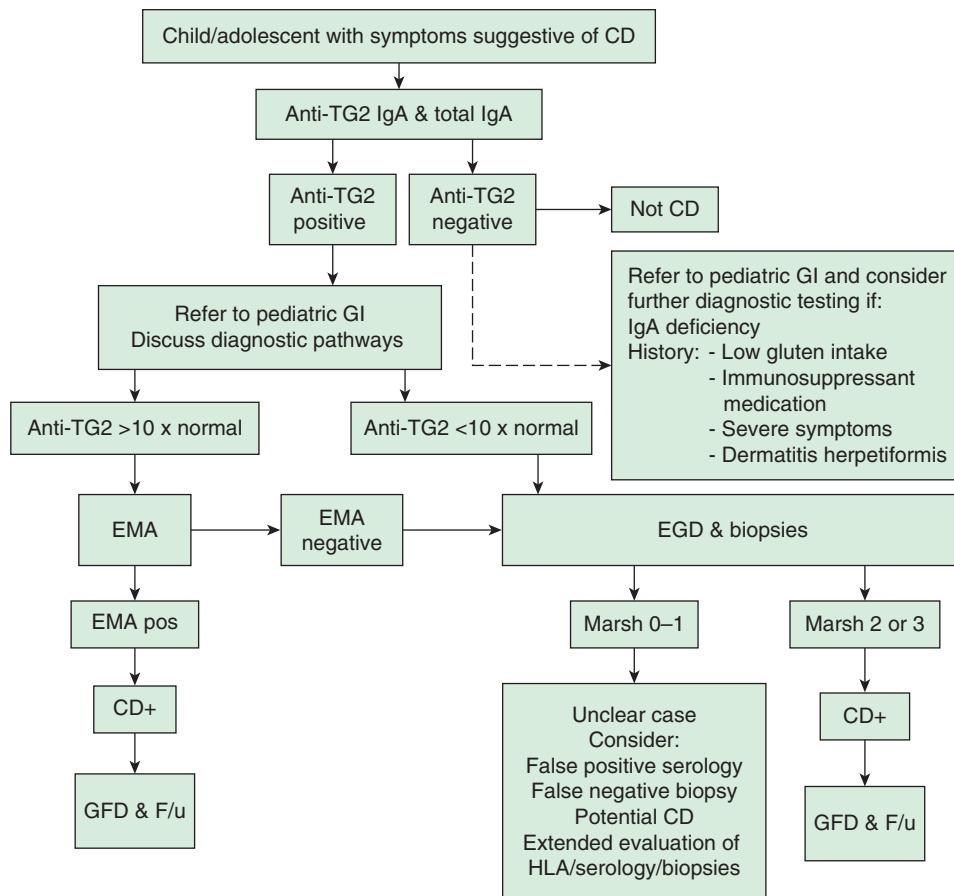
**TREATMENT**

The only treatment for CD is lifelong, strict adherence to a gluten-free diet. This requires a wheat-, barley-, and rye-free diet (Tables 384.5 and 384.6). Despite evidence that oats are safe for most patients with CD, there is concern regarding the possibility of contamination of oats with gluten during harvesting, milling, and shipping. Nevertheless, it seems wise to add oats to the gluten-free diet only when the latter is well established, so that possible adverse reactions can be readily identified. There is a consensus that all CD patients should be treated with a gluten-free diet regardless of the presence of symptoms. However, whereas it is relatively easy to assess the health improvement after treatment of CD in patients with clinical symptoms of the disease, it proves difficult in persons with *asymptomatic* CD. The nutritional risks, particularly osteopenia and increased risk for other autoimmune disorders, along with the increased but rare risk of intestinal lymphoma, are those mainly feared for subjects who have silent CD and continue on a gluten-containing diet. Little is known about the health risks in untreated patients with potential CD. For these patients, adequate gluten intake should be confirmed, the biopsy orientation should be checked, and monitoring should occur at a tertiary medical center, given the potential for serologies to both normalize or progress to villous atrophy.

Some older patients do not respond to a gluten free diet; *refractory* or *nonresponsive* CD requires a systematic approach to determine the correct diagnosis, compliance, and therapeutic options (Fig. 384.3).

The Codex Alimentarius Guidelines define gluten-free food item for food containing <20 parts per million (ppm; equivalent to 20 mg gluten in 1 kg of product). However, despite analytical methods for gluten detection reaching a satisfactory degree of sensitivity, more information is needed on the daily gluten amount that may be tolerated by CD patients. The data available so far seem to suggest that the threshold should be set to <50 mg/day, although individual variability makes it difficult to set a universal threshold.

It is important that an experienced dietitian with specific expertise in CD counseling educates the family and the child about dietary restriction. Compliance with a gluten-free diet can be difficult, especially in adolescents, and patients should be monitored for signs of depression and referred to psychology or adolescent medicine as appropriate. It is recommended that children with CD be monitored with periodic visits for assessment of symptoms, growth, physical examination, and adherence to the gluten-free diet. Bloodwork, such as complete blood count, hepatic panel, thyroid function, calcium, vitamin D, iron, and ferritin have been suggested at diagnosis, with abnormal values followed until normalized. Periodic measurements of TG2 antibody levels to document reduction in antibody titers are recommended as indirect evidence of adherence to a



**Fig. 384.2** Diagnostic algorithm for celiac disease according to European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). CD, Celiac disease; EMA, endomysial antibodies; EGD, esophagogastroduodenoscopy; F/u, follow-up; GFD, gluten-free diet; GI, gastrointestinal; HLA, human leukocyte antigen; Ig, immunoglobulin; neg, negative; pos, positive; TG2, transglutaminase. (Modified from Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for Pediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease. *J Pediatr Gastroenterol Nutr*. 2020;70:13841–14157. Fig. 4.)

**Table 384.4** Conditions Other Than Celiac Disease That Can Cause Duodenal Lymphocytosis or Villous Atrophy

#### DUODENAL LYMPHOCYTOSIS

- Food allergy, non-celiac gluten sensitivity
- Infection (e.g., *Helicobacter pylori* or giardiasis)
- Drugs (e.g., nonsteroidal antiinflammatory drugs)
- Postenteritis syndrome
- Immune deficiency (e.g., selective IgA deficiency, common variable immune deficiency)
- Immune dysregulation (e.g., autoimmune thyroiditis)
- Crohn disease
- Preinfiltrative intestinal T-cell lymphoma

#### VILLOUS ATROPHY

- Environmental enteropathy (tropical sprue)
- Common variable immune deficiency
- Autoimmune enteropathy
- Drugs (e.g., olmesartan or azathioprine)
- Food allergy
- Giardiasis
- Crohn disease
- Eosinophilic enteritis
- Radiation enteritis
- Intestinal lymphoma
- HIV enteropathy
- Bacterial overgrowth
- Graft-versus-host disease
- Protein energy malnutrition

**Table 384.5** Principles of Initial Dietary Therapy for Patients with Celiac Disease

Avoid all foods containing wheat, rye, and barley gluten (pure oats usually safe).

Avoid malt unless clearly labeled as derived from corn.

Use only rice, corn, maize, buckwheat, millet, amaranth, quinoa, sorghum, potato or potato starch, soybean, tapioca, and teff, bean, and nut flours.

Wheat starch and products containing wheat starch should only be used if they contain <20 ppm gluten and are marked "gluten free."

Read all labels and study ingredients of processed foods.

Beware of gluten in medications, supplements, food additives, emulsifiers, or stabilizers.

Limit milk and milk products initially if there is evidence of lactose intolerance.

Avoid all beers, lagers, ales, and stouts (unless labeled gluten free).

Wine, most liqueurs, ciders, and spirits, including whiskey and brandy, are allowed.

ppm, Parts per million.

gluten-free diet, although they are insensitive to slight dietary transgressions and can take up to 2-3 years to normalize. The TG2 antibody levels can be checked every 1-2 years after they normalize, or sooner if symptoms or concerns for compliance arise. Commercial tests are available to monitor for compliance and transgressions via the detection of gluten peptides in the urine and stool, but remain under investigation for validation. If compliance is uncertain or body mass index (BMI) z scores are low, bone health should be assessed. Therapeutic treatments, such as those that target IL-15, IL-21, and gluten degradation, remain in clinical trials.

**Table 384.6** Some Potential Sources of Hidden Gluten

- Beers, ales, other fermented beverages (distilled beverages acceptable)
- Bouillon and soups
- Candy
- Communion wafers
- Drink mixes
- Gravy and sauces
- Herbal tea
- Imitation meat and seafood
- Nutritional supplements
- Play-Doh
- Salad dressings and marinades
- Self-basting turkeys
- Soy sauce

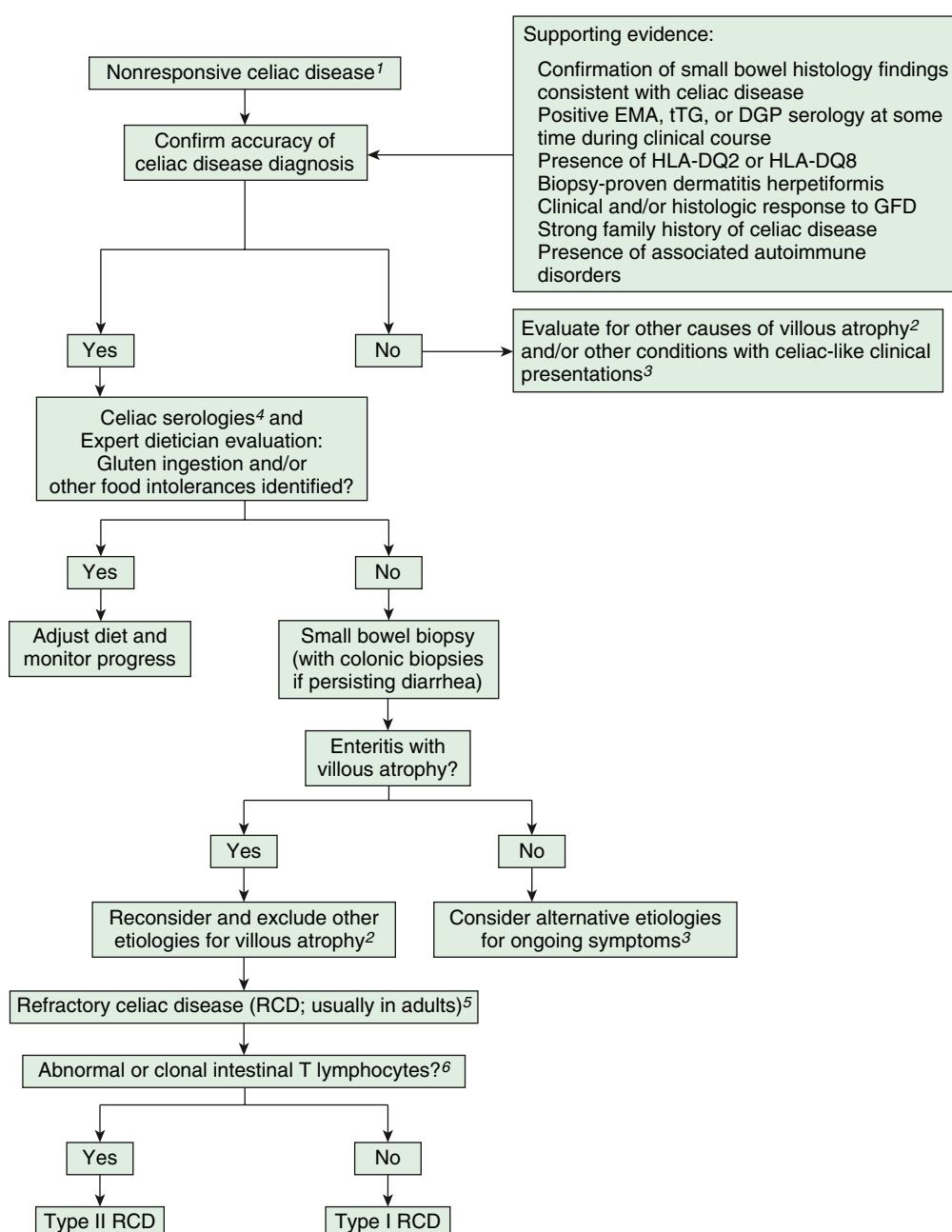
From Kelly CP. Celiac disease. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 10th ed. Philadelphia: Elsevier; 2016: Box 107.3.

## THE SPECTRUM OF GLUTEN-RELATED DISORDERS

CD is not the only disorder related to gluten ingestion. Symptoms in IgE-mediated wheat allergy are usually immediate (urticaria, angioedema, asthma, exercise-induced anaphylaxis). Diagnosis is based on dietary challenge, in vitro assay for specific IgE, and skin testing.

**Nonceliac gluten sensitivity (NCGS)** is a poorly understood condition. Diagnosis is suspected in patients who do not have CD or wheat allergy, and yet show GI and non-GI symptoms upon ingestion of gluten- or wheat-containing food. In the general population, the incidence of self-reported gluten avoidance varies from 0.5% to 13%. Similar symptoms are often experienced by patients with irritable bowel syndrome (IBS), and some patients with IBS respond positively to a gluten-free diet or a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP diet).

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**Fig. 384.3** Diagnostic algorithm for the approach to patients with nonresponsive celiac disease. <sup>1</sup>Nonresponsive celiac disease may be defined as persistent symptoms and signs despite 6–12 mo of dietary gluten avoidance. Abnormal tissue transglutaminase (tTG) can last even 2–3 yr. <sup>2</sup>Causes of nonceliac small intestinal villous atrophy that may be misdiagnosed as celiac disease include autoimmune enteropathy, tropical sprue, medication induced enteropathy, hypogammaglobulinemia, combined variable immunodeficiency, collagenous sprue, Crohn disease, and peptic duodenitis. <sup>3</sup>Conditions that present clinically in a fashion similar to celiac disease but where villous atrophy is not evident include irritable bowel syndrome (IBS), carbohydrate malabsorption, small intestinal bacterial overgrowth, Crohn's disease, and microscopic colitis. <sup>4</sup>Positive serologic testing for celiac disease despite 12 mo of treatment with a gluten-free diet (GFD) suggest that there may be ongoing gluten ingestion. <sup>5</sup>Refractory celiac disease (RCD) is defined as persistent or recurrent malabsorptive symptoms and signs, with small intestinal villous atrophy despite a strict GFD for more than 12 mo and in the absence of other disorders including overt lymphoma. <sup>6</sup>Abnormal intestinal lymphocytes may be identified by immunohistochemistry of intraepithelial lymphocytes or by flow cytometry showing an increased number of CD3-positive cells that lack CD8 or by the identification of clonal T-cell receptor gene rearrangement by molecular analysis. EMA, Endomysial antibody; DGP, deamidated gliadin peptide; HLA, human leukocyte antigen. (Adapted from Green PHR, Paski S, Ko CW, Rubio-Tapia A. AGA clinical practice update on management of refractory celiac disease: expert review. *Gastroenterology* 2022;163(5):1461–1469.)

## Chapter 385

# Disorders of Malabsorption

Abdul-Aziz K. Elkadri

Malabsorption is defined as a decreased intestinal absorption of one or more dietary elements. The intestinal tract requires several components to properly absorb the required elements from our diet, and the absence or improper **digestion** within the lumen or diminished or dysfunctional mucosal **absorption** is due to the lack of presence or function of these components. Due to the change in composition or volume of luminal contents, many if not all malabsorptive disorders result in diarrhea. Chronic ongoing losses further worsen the malabsorption, resulting in chronic diarrhea (see Chapter 388). Malabsorption can be categorized based on mucosal defects resulting in a more generalized malabsorption with multiple nutrient defects (Table 385.1), or due to the malabsorption of specific components such as carbohydrates, proteins, lipids, vitamins, minerals, and trace elements (Table 385.2).

### CLINICAL APPROACH

Because malnutrition leads to the loss of typically absorbed components in stool, the presentation of a patient will differ depending upon the length of time with malabsorption, the extent of losses, and the phase of growth and magnitude of required nutrients. With proper follow-up, the clinical features tend to be growth related, with failure to gain weight and a stagnation of linear growth percentiles. Physical exam findings tend to be subtle, with abdominal distension, diarrhea, and even constipation as presenting features depending on the malabsorbed component. With more extensive losses or delay in presentation, the clinical features become more pronounced. Findings can include muscle wasting, loss of subcutaneous fat, and loose skinfolds (Fig. 385.1). Because toddlers have increased energy requirements, presentation in this age-group can be dramatic and more acute. In older children and adolescents, the presentation may be more subtle, with suboptimal weight gain or weight loss as a more common presentation. Height stunting tends to lag behind weight parameters. In developing areas of the world where access to health resources including enteral and parenteral nutrition (PN) continues to be limited, prolonged malabsorption may lead to death (see Chapter 64). This outcome is uncommon in the developed world, where access to healthcare leads to improved outcomes. Nonetheless, monogenetic causes of malabsorption often produce failure to thrive in any region of the world. Specific findings on examination can guide toward a specific disorder; edema is usually associated with protein-losing enteropathy (PLE), digital clubbing with conditions including cystic fibrosis and celiac disease, perianal excoriation and gaseous abdominal distention with carbohydrate malabsorption, perianal and circumoral rash with acrodermatitis enteropathica, abnormal hair with Menkes syndrome (ATP7A defects), tricho-hepato-enteric syndrome (THE), and the typical facial features diagnostic of the Johanson-Blizzard syndrome.

To compensate for the fecal losses of nutrients and calories, many children present with a history of a good appetite. In exocrine pancreatic insufficiency, fecal losses of up to 40% of ingested protein and energy do not lead to malnutrition, as long as they are compensated by an increased appetite. In conditions associated with villous atrophy or inflammation (Celiac disease, postinfectious enteropathy or Crohn disease), fecal protein and energy losses are usually modest, but associated anorexia and thus reduced food intake results in malnutrition.

The nutritional assessment is an important part of clinical evaluation in children with malabsorptive disorders (see Chapter 60). Long-term calcium and vitamin D malabsorption can lead to reduced bone mineral density and metabolic bone disease (often resistant to oral vitamin

D), with increased risk of bone fractures. Vitamin K malabsorption, irrespective of the underlying mechanism (fat malabsorption, mucosal atrophy), can result in coagulopathy. Severe PLE is often associated with malabsorption syndromes (celiac disease, Crohn disease, congenital disorders of glycosylation, intestinal lymphangiectasia [IL]) and causes hypoalbuminemia and edema. Other nutrient deficiencies include iron malabsorption causing microcytic anemia and low reticulocyte count, low serum folate levels in conditions associated with mucosal atrophy, especially in the proximal part of the small intestinal tract, and low serum vitamin A and vitamin E concentrations in fat malabsorption.

Diarrhea is the main clinical expression of malabsorption. Early presentation of diarrhea in early infancy suggests a congenital defect (Table 385.3). In congenital disorders of diarrhea such as microvillus inclusion disease (MVID) and congenital sodium or chloride diarrhea, higher volume fluid losses within the stool lead to watery like diarrhea, often mistaken for urine (see Chapter 388). The onset of symptoms after the introduction of a particular food into a child's diet can provide diagnostic clues, such as with sucrose in sucrase-isomaltase (SI) deficiency. The nature of the diarrhea may be helpful: explosive watery diarrhea suggests carbohydrate malabsorption; loose, bulky stools are associated with celiac disease; and pasty, yellowish, and offensive smelling stools suggest fat malabsorption and an exocrine pancreatic insufficiency. Stool color is usually not helpful, though it may suggest blood loss if red or melena. Green stool with undigested foods can suggest rapid intestinal transit in toddler's diarrhea, which by itself is a self-limiting condition unassociated with failure to thrive.

Following medical history, physical examination, and laboratory testing (see Chapter 385.1), intestinal biopsies may assist in the diagnosis. This is usually done for chronic rather than acute diseases which are typically self-limited. Generalized mucosal villous atrophy (flat mucosa) may be associated with malabsorption of multiple *macronutrients* and *micronutrients* and has a wide range of differential diagnoses (see Chapters 384 and 385.2).

### 385.1 Evaluation of Children with Suspected Intestinal Malabsorption

Abdul-Aziz K. Elkadri

In a child presenting with chronic or recurrent diarrhea, the initial workup should include nucleic acid amplification tests (NAATs) (viruses, bacteria) and, when not available, by stool cultures and antibody (or antigen testing) tests for parasites. Stool microscopy for ova and parasites can look for parasites such as *Giardia*. Fecal leukocytes and calprotectin and/or lactoferrin may suggest inflammatory disorders. Acidic stool pH and positive reducing substances suggest a component of carbohydrate malabsorption. Stool osmolality helps differentiate between osmotic and secretory diarrhea. Along with a careful diet history focusing on fat intake, quantitative stool fat examination helps determine whether there is fat malabsorption. Elevated fecal  $\alpha_1$ -antitrypsin and a low serum albumin (in the absence of hepatic or renal disease) can suggest enteral protein loss. Fecal stool elastase-1 can assess for exocrine pancreatic insufficiency.

A complete blood count, including peripheral smear for microcytic anemia, lymphopenia (lymphangiectasia), neutropenia (Shwachman-Diamond syndrome), and acanthocytosis (abetalipoproteinemia), is useful. If celiac disease is suspected, serum immunoglobulin IgA and anti-tissue transglutaminase IgA (anti-TTG IgA) antibody levels should be determined (see Chapter 384). If inflammation is suspected, CRP and ESR can be drawn. Depending on the initial test results, more specific investigations can be planned.

### INVESTIGATIONS FOR CARBOHYDRATE MALABSORPTION

The measurement of acidic stool pH and the amount of reducing substances are simple screening tests for carbohydrate malabsorption. An acidic stool with a pH <5 and >2+ reducing substance suggests carbohydrate malabsorption. Sucrose or starch in the stool is not recognized

**Table 385.1** Malabsorption Disorders and Chronic Diarrhea Associated with Generalized Mucosal Defect

**ACQUIRED AUTOIMMUNITY**

- Celiac disease (Gluten sensitive enteropathy)
  - Cow's milk and other protein intolerance enteropathy
  - Eosinophilic enteropathy
  - Crohn disease
- Immune Dysregulation**
- Congenital immunodeficiency disorders
  - Selective immunoglobulin A deficiency (associated with celiac disease)
  - Severe combined immunodeficiency
  - Agammaglobulinemia
  - X-linked hypogammaglobulinemia
  - Wiskott-Aldrich syndrome
  - Common variable immunodeficiency disease
  - Chronic granulomatous disease
  - IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked inheritance) and IPEX-like syndromes (tregopathies)
  - Autoimmune polyendocrine candidiasis ectodermal dystrophy syndrome type 1 (APECED)

**CONGENITAL BOWEL MUCOSAL DEFECTS**

- Microvillus inclusion disease
- Tufting enteropathy
- Carbohydrate-deficient glycoprotein syndrome
- Enterocyte heparan sulfate deficiency
- Tricho-hepatic-enteric syndrome

**Enterocytic Cell Dysfunction**

- Enteric anendocrinosis (NEUROG3)
- Protein convertase 1/3 deficiency (PCSK1)

**ACQUIRED IMMUNE DEFICIENCY**

- HIV infection
- Immunosuppressive therapy and post bone marrow transplantation

**Mechanical Defects**

- Short bowel syndrome
- Blind loop syndrome
- Pseudoobstruction

**MISCELLANEOUS**

- Lymphangiectasia
- Immunoproliferative small intestinal disease
- Radiation enteritis
- Protein-calorie malnutrition

as a reducing sugar until after hydrolysis with hydrochloric acid, which converts them to reducing sugars.

**Breath hydrogen test** is used to identify the specific carbohydrate that is malabsorbed. After an overnight fast, the suspected sugar (lactose, sucrose, fructose, or glucose) is administered as an oral solution (carbohydrate load up to 2 g/kg, maximum total of 25 g, depending on the specific carbohydrate type). In malabsorption, the sugar is not digested or absorbed in the small bowel; it passes on to the colon and is metabolized by the normal gut microflora. One of the products of this process is hydrogen gas, which is absorbed through the colon mucosa and excreted in the breath. Because human cells are incapable of producing hydrogen, increased hydrogen concentration in the breath samples suggests carbohydrate malabsorption. A rise in breath hydrogen of 20 parts per million (ppm) above the baseline, preferably with associated symptoms, is considered a positive test. The child should not be on antibiotics at the time of the test because antibiotics may suppress the colonic flora, which is essential for fermenting the sugar. Care should be taken in the interpretation of these results as small intestinal bacterial overgrowth can lead to an early elevation of hydrogen.

**Small bowel mucosal biopsies** can directly measure mucosal disaccharidase (lactase, sucrase, maltase, palatinase) concentrations. In primary enzyme deficiencies the mucosal enzyme levels are low and small bowel

**Table 385.2** Classification of Malabsorption Disorders and Chronic Diarrhea Based on the Predominant Nutrient Malabsorbed

**CARBOHYDRATE MALABSORPTION**

- Lactose malabsorption
- Congenital lactase deficiency
- Hypolactasia (adult type)
- Secondary lactase deficiency
- Congenital sucrase isomaltase deficiency
- Glucose galactose malabsorption

**FAT MALABSORPTION**

- Exocrine pancreatic insufficiency
  - Cystic fibrosis
  - Shwachman-Diamond syndrome
  - Johanson-Blizzard syndrome
  - Pearson syndrome
- Secondary exocrine pancreatic insufficiency
  - Chronic pancreatitis
  - Severe protein-calorie malnutrition
  - Decreased pancreatic lipase/cholecystokinin secretion
- Isolated enzyme deficiency
  - Enterokinase deficiency
  - Trypsinogen deficiency
  - Lipase/colipase deficiency
  - Disrupted enterohepatic circulation of bile salts
  - Cholestatic liver disease
  - Bile acid synthetic defects
  - Deconjugation of bile acids (bacterial overgrowth)
  - Bile acid malabsorption (terminal ileal disease or resection)
- Intestinal brush border disorders
  - Allergic enteropathy
  - Autoimmune enteropathy
  - Disorders in formation and transport of chylomicrons by enterocytes to the lymphatics
- Abetalipoproteinemia
- Homozygous hypobetalipoproteinemia
- Chylomicron retention disease (Anderson disease)
- Disorders of lymph flow
  - Primary or secondary lymphangiectasia

**PROTEIN/AMINO ACID MALABSORPTION**

- Lysinuric protein intolerance (defect in dibasic amino acid transport)
- Hartnup disease (defect in free neutral amino acids)
- Blue diaper syndrome (isolated tryptophan malabsorption)
- Oasthouse urine disease (defect in methionine absorption)
- Lowe syndrome (lysine and arginine malabsorption)
- Enterokinase deficiency
- Protein-losing enteropathy
  - Congenital disorders of glycosylation
  - CD55 deficiency

**MINERAL AND VITAMIN MALABSORPTION**

- Congenital chloride diarrhea
- Congenital sodium diarrhea
- Acrodermatitis enteropathica (zinc malabsorption)
- Menkes disease (copper malabsorption)
- Vitamin D-dependent rickets
- Folate malabsorption
- Secondary to chronic mucosal damage
- Vitamin B<sub>12</sub> malabsorption
- Autoimmune pernicious anemia
- Decreased gastric acid (H<sub>2</sub> blockers or proton pump inhibitors)
- Terminal ileal disease (e.g., Crohn disease) or resection
- Inborn errors of vitamin B<sub>12</sub> transport and metabolism
- Primary hypomagnesemia

**DRUG INDUCED**

- Sulfasalazine: folic acid malabsorption
- Cholestyramine: calcium and fat malabsorption
- Anticonvulsant drugs such as phenytoin (causing vitamin D deficiency and folic acid and calcium malabsorption)
- Gastric acid suppression: vitamin B<sub>12</sub>
- Methotrexate: mucosal injury

mucosal morphology is normal. Primary enzymatic deficiencies can also be diagnosed by genetic testing (see Chapters 385.8–385.10 and 388). Partial or total villous atrophy due to autoimmune disorders such as celiac

disease or Crohn disease or following acute rotavirus gastroenteritis can result in secondary disaccharidase deficiency and transient lactose intolerance (see Chapters 384 and 385.2 for differential diagnosis of villous atrophy). The disaccharidase levels revert to normal after mucosal healing.



**Fig. 385.1** An 18-month-old male with active celiac disease. Note the ill appearance with loose skinfolds, marked proximal muscle wasting, and distended abdomen.

### INVESTIGATIONS FOR FAT MALABSORPTION

The presence of fat globules in the stool suggests fat malabsorption. The ability to absorb fat varies with age. While on a typical diet, a premature infant can absorb only 65–75% of dietary fat, a full-term infant absorbs almost 90%, and an older child absorbs more than 95% of fat. Quantitative determination of fat malabsorption requires a 3-day stool collection and dietary fat intake recall for evaluation of fat excretion and determination of the coefficient of fat absorption:

$$\text{Coefficient of fat absorption \%} = (\text{fat intake} - \text{fecal fat losses/fat intake}) \times 100$$

where fat intake and fat losses are in grams. Because fecal fat balance studies are cumbersome, expensive, and unpleasant to perform, simpler tests are often preferred. Among these stool tests, the acid steatorcrit test is the most reliable. When bile acid (BA) deficiency is suspected of being the cause of fat malabsorption, the evaluation of BA levels in duodenal fluid aspirate may be useful. Intestinal mucosal abnormalities may not affect only fat absorption, but shorter intestinal transit time may also result in steatorrhea. Steatorrhea from intestinal mucosal disorders such as celiac disease or cow's milk protein enteropathy are usually far less severe than in exocrine pancreatic insufficiency.

Exocrine pancreatic insufficiency and other fat malabsorption disorders (see Table 385.2) are usually associated with deficiencies of fat-soluble vitamins A, D, E, and K. Serum concentrations of vitamins A, D, and E can be measured. A prolonged prothrombin time is an indirect test to assess vitamin K malabsorption and subsequent deficiency.

### INVESTIGATIONS FOR PROTEIN-LOSING ENTEROPATHY

Dietary and endogenous proteins secreted into the bowel are usually completely absorbed; minimal amounts of protein from these sources pass into the colon. The majority of stool nitrogen is derived from gut bacterial proteins. Excessive bowel protein loss usually manifests as

**Table 385.3** Disorders Leading to Early-Onset Diarrhea

CATEGORY	DISORDER	GENE(S) INVOLVED	INHERITANCE	FEATURES
Defects in epithelial nutrient and electrolyte transport	Congenital chloride diarrhea	SLC26A3	AR	<ul style="list-style-type: none"> <li>High chloride in stools</li> <li>Founder effect from Saudi Arabia (Taif region) and Finland</li> <li>Premature with IUGR</li> <li>Absence of meconium</li> <li>Polyhydramnios and dilated loops of bowel on prenatal imaging, abdominal distension after birth</li> <li>24% had renal involvement (chronic kidney disease)</li> <li>Dental carries</li> <li>Some overlap with Bartter and Gitelman syndrome</li> </ul>
	Congenital sodium diarrhea	SLC9A3 GUCY2C	AR AD	<ul style="list-style-type: none"> <li>Increased risk of development of IBD</li> <li>Polyhydramnios and dilated loops of bowel on prenatal imaging</li> <li>High sodium in stools</li> <li>Diarrhea may improve with time</li> </ul>
	Glucose-galactose malabsorption	SLC5A1	AR	<ul style="list-style-type: none"> <li>Treatment requires avoidance of all sugars other than fructose</li> </ul>
	Primary bile acid diarrhea	SLC10A2 SLC51B	AR AR	<ul style="list-style-type: none"> <li>Associated with cholestasis, increased gamma-glutamyl transferase level, and fat-soluble vitamin deficiency</li> </ul>
	Acrodermatitis enteropathica	SLC39A4	AR	<ul style="list-style-type: none"> <li>Perioral and extremity lesions, alopecia, and diarrhea</li> <li>Recurrent infection from immune dysfunction</li> </ul>

**Table 385.3** Disorders Leading to Early-Onset Diarrhea—cont'd

Category	Disorder	Gene(s) Involved	Inheritance	Features
Defects in epithelial enzymes and metabolism	Congenital lactase deficiency	<i>LCT</i>	AR	<ul style="list-style-type: none"> <li>Rare form of inherited diarrhea</li> </ul>
	Congenital sucrase-isomaltase deficiency	<i>SI</i>	AR	<ul style="list-style-type: none"> <li>Bloating, diarrhea, and rarely associated with failure to thrive</li> <li>High prevalence in Greenland and Inuit (5%), with 0.2% prevalence in Europeans</li> <li>Variable phenotype</li> </ul>
	Trehalase deficiency	<i>TREH</i>	AR	<ul style="list-style-type: none"> <li>Up to 8% of Greenland population</li> <li>Similar to lactase deficiency</li> </ul>
	Enterokinase deficiency	<i>TMPRSS15</i>	AR	<ul style="list-style-type: none"> <li>Deficiency of activator of pancreatic enzymes</li> </ul>
	DGAT1 deficiency	<i>DGAT1</i>	AR	<ul style="list-style-type: none"> <li>Fat-soluble vitamin deficiency</li> <li>Avoidance of enteral lipids seems to help</li> </ul>
	Sieving protein-losing enteropathy	<i>PLVAP</i>	AR	<ul style="list-style-type: none"> <li>Protein loss of specific sizes</li> <li>Syndromic with hydrops, dysmorphic facies, cardiac and renal abnormalities</li> </ul>
	Abetalipoproteinemia	<i>MTTP</i>	AR	<ul style="list-style-type: none"> <li>Enterocytes show lipid-filled vacuoles</li> </ul>
	Hypobetalipoproteinemia	<i>APOB</i>	AR	<ul style="list-style-type: none"> <li>Steatorrhea and failure to thrive</li> <li>Later noted to have fat-soluble vitamin deficiency and bleeding issues</li> </ul>
	Chylomicron retention disease	<i>SAR1B</i>	AR	
	Dyskeratosis congenita	<i>DKC1</i> <i>RTEL1</i>	X AR	<ul style="list-style-type: none"> <li>Nail pitting, leukoplakia, and immune defects</li> </ul>
Defects in epithelial trafficking and polarity	Kabuki syndrome	<i>KMT2D</i>	AD	<ul style="list-style-type: none"> <li>Multiple congenital anomalies with varying phenotype</li> </ul>
	Microvillus inclusion disease	<i>MYO5B</i>	AR	<ul style="list-style-type: none"> <li>Microvilli seen on electron microscopy are periodic acid-Schiff positive</li> <li>May be associated with Fanconi syndrome</li> </ul>
		<i>STX3</i>	AR	<ul style="list-style-type: none"> <li>Rare form; may be associated with neurologic findings</li> </ul>
	Tufting enteropathy	<i>EPCAM</i>	AR	<ul style="list-style-type: none"> <li>Teardrop-shaped tufts of enterocytes throughout the intestine</li> </ul>
	Syndromic sodium-losing diarrhea	<i>SPINT2</i>	AR	<ul style="list-style-type: none"> <li>Phenotype similar to tufting enteropathy, but with sodium-losing diarrhea</li> </ul>
	Trichohepatointestinal syndrome	<i>TTC37</i>	AR	<ul style="list-style-type: none"> <li>Woolly hair, SCID-like phenotype and hepatic defects</li> </ul>
		<i>SKIV2L</i>	AR	
Enteroendocrine cell dysfunction	Familial hemophagocytic lymphohistiocytosis type 5	<i>STXBP2</i>	AR	<ul style="list-style-type: none"> <li>Recurrence after HSCT, villous blunting</li> </ul>
	Multiple intestinal atresia	<i>TTC7A</i>	AR	<ul style="list-style-type: none"> <li>Variable phenotype with multiple intestinal atresia, SCID-like phenotype, and enterocolitis</li> </ul>
	Enteric anendocrinosis	<i>NEUROG3</i>	AR	<ul style="list-style-type: none"> <li>Severe malabsorptive diarrhea, neonatal-onset diabetes mellitus, and normal intestinal biopsies</li> </ul>
	Proprotein convertase 1/3 deficiency	<i>PCSK1</i>	AR	<ul style="list-style-type: none"> <li>Age-dependent phenotype. Infants have TPN-dependent diarrhea and failure to thrive; later appear to lose intestinal phenotype and develop multiple endocrine abnormalities</li> </ul>
	X-linked lissencephaly with abnormal genitalia	<i>ARX</i>	X	<ul style="list-style-type: none"> <li>Seizures, abnormal genitalia, survival between 6 days and 6 yr</li> </ul>
	Mitchell-Riley syndrome	<i>RFX6</i>	AR	<ul style="list-style-type: none"> <li>Lack of enteroendocrine cells</li> </ul>
	Intractable congenital diarrhea in infants	<i>ICR</i>	AR	<ul style="list-style-type: none"> <li>Secretory diarrhea caused by a noncoding variant with wide-ranging effects on multiple intestinal genes</li> </ul>

Continued

**Table 385.3** Disorders Leading to Early-Onset Diarrhea—cont'd

CATEGORY	DISORDER	GENE(S) INVOLVED	INHERITANCE	FEATURES
Immune dysregulation-associated enteropathy	Immune dysregulation, polyendocrinopathy, enteropathy X-linked	FOXP3	X	<ul style="list-style-type: none"> <li>Polyendocrinopathy</li> </ul>
	Common variable immune deficiency (CVID) type 1	ICOS	AR	<ul style="list-style-type: none"> <li>Variable presentation; may have dietary-induced diarrhea</li> </ul>
	CVID type 8	LRBA	AR	
	ADAM17 deficiency	ADAM17	AR	<ul style="list-style-type: none"> <li>Fatal in most patients</li> </ul>
	EGFR deficiency	EGFR	AR	<ul style="list-style-type: none"> <li>Described in three patients</li> </ul>
	CTLA-4	CTLA-4	AD	<ul style="list-style-type: none"> <li>Similar to LRBA; may respond to abatacept</li> </ul>
	CD55 deficiency	CD55	AR	<ul style="list-style-type: none"> <li>Protein-losing enteropathy and thrombosis</li> </ul>
X-linked inhibitor of apoptosis	XIAP	X		<ul style="list-style-type: none"> <li>Responsive to HSCT</li> </ul>

AD, Autosomal dominant; AR, autosomal recessive; EGFR, epidermal growth factor receptor; HSCT, hematopoietic stem cell transplantation; IBD, inflammatory bowel disease; IUGR, intrauterine growth restriction; SCID, severe combined immunodeficiency; TPN, total parenteral nutrition; X, X-linked.

From Elkadri AA. Congenital diarrheal syndrome. *Clin Perinatol*. 2020;47:87–104. Table 2.

hypoalbuminemia. Because the most common cause of hypoalbuminemia in children is a renal disorder, urinary protein excretion must be determined. Other potential causes of hypoalbuminemia include acute infection, liver disease (reduced production), and inadequate protein intake. Very rarely hypoalbuminemia can result from an extensive skin disorder (burns) causing protein loss via the skin. Measurement of stool  $\alpha_1$ -antitrypsin is a useful screening test for PLE. This serum protein has a molecular weight similar to albumin; however, unlike albumin it is resistant to digestion in the gastrointestinal (GI) tract. Excessive  $\alpha_1$ -antitrypsin excretion in the stool should prompt further investigations to identify the specific cause of intestinal or stomach (Ménétrier disease) protein loss (Table 385.4).

### INVESTIGATIONS FOR EXOCRINE PANCREATIC FUNCTION

Cystic fibrosis (see Chapter 454) is the most common cause of exocrine pancreatic insufficiency in children; therefore a sweat chloride test must be performed before embarking on invasive tests to investigate possible exocrine pancreatic insufficiency (Fig. 385.2). Many cases of cystic fibrosis are detected by neonatal genetic screening programs; occasional rare pathogenic variants are undetected. Other etiologies are noted in Table 385.5.

Fecal elastase-1 estimation is a sensitive test to assess exocrine pancreatic function in chronic cystic fibrosis and pancreatitis. Elastase-1 is a stable endoprotease unaffected by exogenous pancreatic enzymes. One disadvantage of the fecal elastase-1 test is the lack of full differentiation between primary exocrine pancreatic insufficiency and exocrine pancreatic dysfunction secondary to intestinal villous atrophy. The proximal small bowel is the site for pancreozymin/cholecystokinin production; the latter is the hormone that stimulates enzyme secretion from the exocrine pancreas. Mucosal atrophy can lead to diminished pancreozymin/cholecystokinin secretion and subsequently to exocrine pancreatic insufficiency. Fecal elastase-1 can also give a false-positive result during acute episodes of diarrhea.

Serum trypsinogen concentration can also be used as a screening test for exocrine pancreatic insufficiency. In cystic fibrosis, the levels are greatly elevated early in life, and then they gradually fall, so that by 5–7 years of age, most patients with cystic fibrosis with pancreatic insufficiency have subnormal levels. Patients with cystic fibrosis and adequate exocrine pancreatic function tend to have normal or elevated levels. In such patients, observing the trend in serial serum trypsinogen estimation may be useful in monitoring exocrine pancreatic function. In Shwachman-Diamond syndrome, another condition associated with exocrine pancreatic insufficiency, the serum trypsinogen level is low.

Other tests for pancreatic insufficiency (nitroblue tetrazolium–para-aminobenzoic acid test and pancreolauryl test) measure urine or breath concentrations of substances released and absorbed across the mucosal surface following pancreatic digestion. These tests lack specificity and are rarely used in clinical practice.

The gold standard test for exocrine pancreatic function is direct analysis of duodenal aspirate for volume, bicarbonate, trypsin, and lipase upon secretin and pancreozymin/cholecystokinin stimulation. This involves duodenal intubation (see Chapter 396) and is technically difficult.

### INVESTIGATIONS FOR INTESTINAL MUCOSAL DISORDERS

Establishing a specific diagnosis for malabsorption often requires histologic examination of small bowel mucosal biopsies. These are obtained during endoscopy, allowing multiple biopsies to be performed. Mucosal involvement can often be patchy, especially in milder forms of celiac disease or Crohn disease. Periodic acid-Schiff (PAS) staining of mucosal biopsies collected in formalin and electron microscopy biopsies collected in fixatives such as glutaraldehyde are necessary in congenital diarrhea to assess cellular ultrastructure and diagnose disorders such as congenital microvillus inclusion disease. Bowel mucosal lesions can also be segmental in cases of intestinal lymphangiectasia. In these situations, radiographic small bowel series, repeated ultrasonographies, lymphoscintigraphy, and/or MRI lymphangiography can identify a region of thickened bowel responsible for protein loss. Intestinal biopsies can also detect infectious agents such as *Giardia lamblia*. During endoscopy, mucosal biopsies can be obtained to measure mucosal disaccharidase activities. Duodenal aspirates can be performed to measure pancreatic enzyme concentration as well as quantitative bacterial cultures.

### IMAGING PROCEDURES

Plain radiographs and barium contrast studies might suggest a site and cause of intestinal motility disorders. Although flocculations of barium and dilated bowel with thickened mucosal folds have been attributed to diffuse malabsorptive lesions such as celiac disease, these abnormalities are nonspecific. Diffuse fluid-filled bowel loops during sonography also suggest malabsorption. MRI enterography, though technically difficult in younger children due to the prolonged image acquisition time, provides information about small bowel inflammation and the extent of involvement.

**Table 385.4** Etiology of Protein-Losing Enteropathy

CATEGORIES		AGENT, DISEASES (GENE)
Gastrointestinal infections		CMV, rotavirus, HIV enteropathy <i>Salmonella</i> , <i>Shigella</i> , <i>Campylobacter</i> , <i>Clostridium difficile</i> , <i>Helicobacter pylori</i> Whipple disease Small bowel bacterial overgrowth Giardiasis <i>Strongyloides stercoralis</i> Tuberculosis
Gastrointestinal inflammatory disorders		Ménétrier disease Eosinophilic gastroenteropathy Food (milk, others)-induced enteropathy Celiac disease Crohn disease Ulcerative colitis Tropical sprue Radiation enteritis GVHD NEC Malrotation/volvulus Lymphoproliferative disorder (posttransplant)
Malignancies		Adenocarcinomas Lymphomas Kaposi sarcoma Neuroblastoma Langerhan cell histiocytosis
Vasculitic disorders		IgA vasculitis (Henoch-Schönlein purpura) Systemic lupus erythematosus
Drugs		NSAID-induced enteropathy
Metabolic/genetic		Congenital disorders of glycosylation (CDG) Variants in <i>DGAT1</i> gene Variants in <i>CD55</i> Congenital enterocyte heparan sulfate deficiency ( <i>ALG6</i> ) <i>PVLAP</i> -associated diarrhea Infantile systemic hyalinosis ( <i>ANTRX2</i> ) Familial polyposis ( <i>SMAD4</i> )
Intestinal lymphangiectasia	Congenital/primary IL Syndromal/genetic/metabolic	Turner, Noonan, Klippel-Trenaunay-Weber Hennekam ( <i>CCBE1</i> , <i>FAT4</i> ) syndromes PLE with skeletal dysplasia ( <i>FGFR3</i> ) Generalized lymphatic dysplasia ( <i>PIEZ01</i> )
	Secondary	
	Inflammation	Sarcoidosis
	Radiotherapy	Retroperitoneal fibrosis
	Neoplastic disorders	Retroperitoneal malignancies, lymphoma
	Cardiac disorders	Constrictive pericarditis, after Fontan operation, CHF
	Other	Budd-Chiari syndrome, lymphatic-enteric fistula

CHF, Congestive heart failure; CMV, cytomegalovirus; GVHD, graft-versus-host disease; IL, intestinal lymphangiectasia; NEC, necrotizing enterocolitis, NSAID, nonsteroidal antiinflammatory drug; PLE, protein-losing enteropathy.

From Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 12.10, p. 221.

## 385.2 Other Malabsorptive Syndromes

Abdul-Aziz K. Elkadri

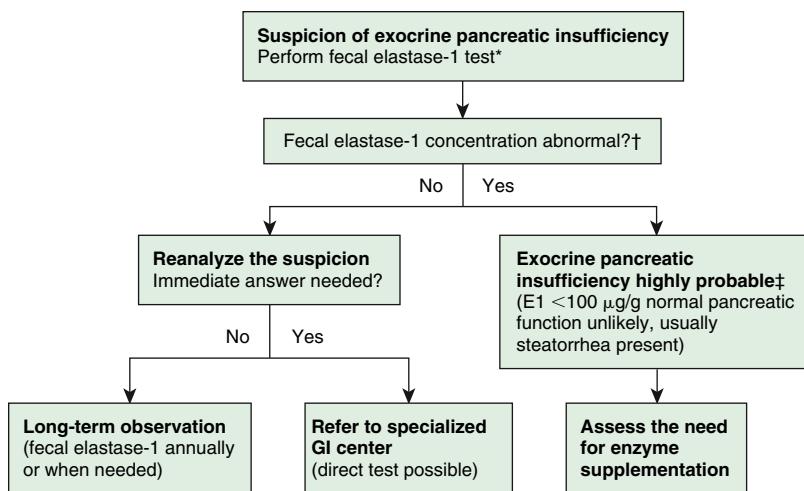
### DEFECTS OF ENTEROCYTE DIFFERENTIATION AND POLARIZATION

This group mainly includes two conditions characterized by typical histologic and ultrastructural lesions in the intestinal biopsies, microvillus inclusion disease (MVID) and congenital tufting enteropathy (CTE). Tricho-hepato-enteric syndrome (THE) or syndromic/phenotypic diarrhea is also usually classified in this group.

#### MICROVILLUS INCLUSION DISEASE (CONGENITAL MICROVILLUS ATROPHY)

MVID is an autosomal recessive disorder that manifests at birth with profuse watery *secretory diarrhea*. A late-onset variant, with onset 2–3

months postnatally, has also been described. It is the most severe cause of congenital diarrhea involving the development of the intestinal mucosa. Light microscopy of the small bowel mucosa demonstrates diffuse thinning of the mucosa, with hypoplastic villous atrophy and no inflammatory infiltrate. If MVID is suspected, electron microscopy should be performed as it shows enterocytes with electron-dense secretory granules as well as vesicles containing microvilli (Fig. 385.3). Using PAS and CD10 staining, light microscopy may show an absent or thin brush border with PAS-positive intracellular inclusions. Polyhydramnios is observed on prenatal sonography, and neonates usually present with very early onset severe watery diarrhea (up to 200–330 mL/kg/day) causing dehydration and failure to thrive. Despite parenteral nutrition, diarrhea continues; fluid management is difficult. Fanconi syndrome has been described in two unrelated patients with MVID, leading to increased renal fluid losses, aminoaciduria, renal tubular acidosis, and resulting phosphaturia with hypophosphatemic rickets. Disease causing variations of the *MYO5B* gene coding for a nonconventional motor



**Fig. 385.2** Algorithm for assessment of exocrine pancreatic function. \*If not available, use another test. Perform appropriate imaging studies of the pancreas. †In case of borderline values, consider repeating the test with three independent samples. ‡Consider differential diagnosis (especially consider mucosal villous atrophy and dilation effect of watery stool). GI, Gastrointestinal. (Modified from Walkowiak J, Nousia-Arvanitakis S, Henker J, et al. Indirect pancreatic function tests in children. *J Pediatr Gastroenterol Nutr*. 2005;40:107–114.)

**Table 385.5** Pancreatic Disorders Leading to Early-Onset Chronic Diarrhea

DISEASE	GENETICS	SYMPTOMS	DIAGNOSIS
Cystic fibrosis	<ul style="list-style-type: none"> <li>AR</li> <li>Pathogenic genetic variants involving CFTR</li> <li>More than 1,300 pathogenic genetic variants have been described</li> <li>Most common is pathogenic genetic variant ΔF508</li> </ul>	<ul style="list-style-type: none"> <li>Meconium ileus in neonate</li> <li>Megacolon</li> <li>Chronic diarrhea from pancreatic insufficiency starting from 1 mo of age</li> <li>Failure to thrive</li> <li>Conjugated hyperbilirubinemia</li> </ul>	<ul style="list-style-type: none"> <li>Low stool elastase</li> <li>High sweat chloride (&gt;60 mEq/L)</li> <li>Newborn screening</li> <li>Molecular genetic testing</li> </ul>
Shwachman-Diamond syndrome	<ul style="list-style-type: none"> <li>AR</li> <li>SBDS gene in over 90%</li> </ul>	<ul style="list-style-type: none"> <li>Chronic diarrhea from pancreatic insufficiency</li> <li>Bone marrow failure</li> <li>Skeletal changes</li> <li>Pancreatic lipomatosis on diagnostic imaging (ultrasound or computed tomography)</li> </ul>	<ul style="list-style-type: none"> <li>Clinical features</li> <li>Molecular genetic testing</li> </ul>
Johanson-Blizzard syndrome	<ul style="list-style-type: none"> <li>AR</li> <li>UBR1 gene</li> </ul>	<ul style="list-style-type: none"> <li>Chronic diarrhea from pancreatic insufficiency</li> <li>Dysmorphic features: aplastic alae nasi, extension of the hairline to the forehead with upswept frontal hair, low-set ears, large anterior fontanel, micrognathia, thin lips, microcephaly, aplasia cutis (patchy distribution of hair with areas of alopecia), dental anomalies, poor growth, and anorectal anomalies (mainly imperforate anus)</li> </ul>	<ul style="list-style-type: none"> <li>Clinical features</li> <li>Molecular genetic testing</li> </ul>
Pearson syndrome	Sporadic: caused by de novo single, large deletions of mtDNA, which can range from 1,000 to 10,000 nucleotides	<ul style="list-style-type: none"> <li>Chronic diarrhea from pancreatic insufficiency</li> <li>Sideroblastic anemia, variable neutropenia, thrombocytopenia, and vacuolization of bone marrow precursors</li> <li>Lactic acidosis and liver failure</li> </ul>	<ul style="list-style-type: none"> <li>Clinical features</li> <li>Molecular genetic testing</li> </ul>

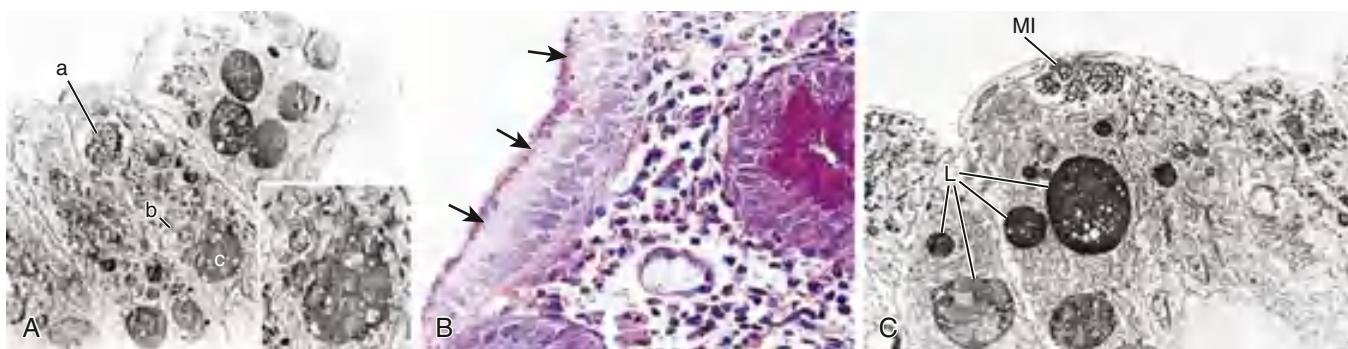
AR, Autosomal recessive; CFTR, cystic fibrosis transmembrane conductance regulator; mtDNA, mitochondrial DNA.

From Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 14.12, p. 253.

protein, myosin Vb, results in MVID as is described in a cohort of patients suffering from early-onset MVID.

*MYO5B* disease causing variants result in mislocalization of apical proteins and disrupted enterocyte polarization, leading to the visualized inclusions in MVID. Another gene, the t-SNARE syntaxin3 (*STX3*), has been described in patients with a milder form of MVID. Patients with pathologic variants in the *STX3* binding protein *STXBP2/Munc18-2*, causing **familial hemophagocytic lymphohistiocytosis type 5**, also

demonstrates microvillous atrophy and histologic findings reminiscent of MVID. Loss of *STX3* or *Munc18-2* inhibits the fusion of vesicles with the apical membrane, resulting in the intracellular retention of apical proteins. *MYO5B* disease causal variants have also been identified in several patients with **progressive familial intrahepatic cholestasis (PFIC)-like phenotype** with normal serum gamma-glutamyl transferase activity and without intestinal disease. Variants in *MYO5B* have been identified in children of Navajo descent presenting with severe infantile diarrhea.



**Fig. 385.3** Microvillus inclusion disease. A, From top to bottom: microvillus inclusion (a), a granule with few microvilli (b), and a lysosome (c) detected in the same enterocyte. Inset: Higher magnification of b and c  $\times 11,000$ , inset  $\times 21,500$ . B, Microvillus inclusion disease. Periodic acid-Schiff (PAS) staining highlights abundant PAS-positive material (arrows) in the apical part of the enterocyte cytoplasm. C, Microvillus inclusion disease. The villous enterocytes lack brush border microvilli, whereas their apical cytoplasm contains a microvillus inclusion (MI) and numerous lysosomes (L)  $\times 5,500$ . (A from Morroni M, Cangiotti AM, Guarino A, et al. Unusual ultrastructural features in microvillus inclusion disease: a report of two cases. *Virchows Arch*. 2006;448:805–810.)

Management includes parenteral nutrition and, depending upon the severity of the diarrhea, intestinal transplantation (see Chapter 386).

### TUFTING ENTEROPATHY (CONGENITAL TUFTING ENTEROPATHY)

CTE (intestinal epithelial dysplasia) manifests in the first few weeks of life with persistent watery diarrhea; it accounts for a small fraction of infants with *intractable diarrhea of infancy*. The distinctive feature on small intestinal mucosal biopsy is focal epithelial tufts (teardrop-shaped groups of closely packed enterocytes with apical rounding of the plasma membrane) involving 80–90% of the epithelial surface. The typical pathology does not appear immediately after birth; other enteropathies may show tufts on the epithelial surface.

CTE is a phenotypic and genetic heterogenous condition. Genetic studies identified causal variants in the epithelial cell adhesion molecule (*EPCAM*) gene in 73% of patients and causal variants in the serine protease inhibitor Kunitz type 2/hepatocyte growth factor activator inhibitor type 2 (*SPINT2/HAI2*) gene in 21%. A minority of patients do not carry any identifiable variants in either gene. The phenotype associated with pathologic variants of *EPCAM* is usually an isolated congenital diarrhea without associated extra digestive symptoms, except late-onset arthritis or superficial punctate keratitis. In the **syndromic** form of CTE, diarrhea is associated with one or more of these same anomalies: superficial punctate keratitis (100%), choanal atresia (50%), esophageal or intestinal atresia, anal imperforation, hair dysplasia, skin hyperlaxity, bone abnormalities, hexadactyly, and facial dysmorphism.

No specific treatment exists, and as for MVID, management requires permanent parenteral nutrition with possible intestinal transplantation (see Chapter 386).

### TRICHO-HEPATO-ENTERIC SYNDROME (SYNDROMIC DIARRHEA)

THE, also known as *syndromic diarrhea* (SD), is a congenital enteropathy manifesting with early onset of severe diarrhea. Patients are born small for gestational age and present with diarrhea starting in the first 6 months of life. They are noted to have facial dysmorphism with a prominent forehead, broad nose, and hypertelorism. Their hair is noted to have a poor pigmentation, with hair follicles showing **trichorrhexis nodosa**, a distinctly woolly, fragile, and uncombable presentation. Abnormal cutaneous lesions including café-au-lait on the lower limbs have been observed. Liver disease affects about half of the patients, with extensive fibrosis or cirrhosis observed. Cardiac abnormalities and colitis have been reported sporadically, as well as one case involving polyhydramnios, placental abnormalities, and congenital hemochromatosis. The immune phenotype is characterized by defective antibody responses to vaccination, with some patients with hypogammaglobulinemia that improves over time. Antigen-specific skin tests are defective despite positive proliferative responses in vitro. Patients with THE can also present as very early onset inflammatory bowel disease (VEO-IBD; see Chapter 382.3) with involvement of any

portion of the GI tract. Small bowel biopsies show nonspecific villous atrophy with or without mononuclear cell infiltration of the lamina propria, and without specific histologic abnormalities involving the epithelium. Causal variants in either tetratricopeptide repeat domain 37 (*TTC37*) gene (60%) or *SKIV2L* (40%) have been identified as a cause of THE syndrome. Enterocytes with *TTC37* variants show reduced expression of brush border-associated NHE-2 and -3, aquaporin-7, the  $\text{Na}^+/\text{I}^-$  symporter, and the  $\text{H}^+/\text{K}^+$ -ATPase or mislocalization relative to their normal pattern. Prognosis of this type of intractable diarrhea of infancy is noted to be poor. The long-term follow-up of these children reported that at 15 years about 50% of patients were alive or have been weaned off PN. The main complications are liver disease and infections. Most of the children achieve short final stature, and half are slightly developmentally delayed.

### DEFECTS IN ENTEROENDOCRINE CELLS DIFFERENTIATION

This class of congenital diarrhea is characterized by abnormal enteroendocrine cell development, function, or complete absence. The genes causing these disorders encode either transcription factors essential for the development of all or a subset of enteroendocrine cells, or cellular proteins/endopeptidases that are required for the production of active hormones from prohormones. These conditions manifest with osmotic diarrhea and may be associated with additional systemic endocrine disorders. The treatment is nutritional support and hormonal replacement if needed. Defects in four genes have been associated with the diseases classified in this group: *NEUROG3*, *RFX6*, *ARX*, and *PCSK1*.

### ENTERIC ANENDOCRINOSIS

*NEUROG3* is a key transcription factor that controls the fate of endocrine cells in both the pancreas and intestine. Variants of the *NEUROG3* gene produce generalized mucosal malabsorption, vomiting, diarrhea, failure to thrive, dehydration, and a hyperchlormic metabolic acidosis. Oral alimentation with anything other than water produces diarrhea. Villus-crypt architecture in small bowel biopsies is normal, but staining for neuroendocrine cells using immunohistochemistry staining for chromogranin A demonstrates a complete absence of this secretory cell lineage with the preservation of goblet cells and Paneth cells.

### PROPROTEIN CONVERTASE 1/3 DEFICIENCY

Autosomal recessive proprotein convertase 1/3 (PC1/3) deficiency, caused by variants in the *PCSK1* gene, is characterized by severe congenital malabsorptive diarrhea requiring parenteral nutrition, childhood-onset obesity, and other endocrine abnormalities. All functional hormones produced by endocrine cells, including those in the gut, are processed by a specific  $\text{Ca}^{2+}$ -dependent serine endopeptidase named proprotein convertase 1/3 (also known as neuroendocrine convertase 1). Chronic watery, neonatal-onset diarrhea is described in infants with hyperinsulinism, hypoglycemia, hypogonadism, and hypoadrenalinism. A small bowel biopsy reveals a nonspecific

enteropathy. Growth hormone deficiency, adrenal insufficiency, central diabetes insipidus, and hypogonadism are commonly observed.

### MITCHELL-RILEY SYNDROME

Mitchell-Riley syndrome is a complex clinical phenotype that includes severe intrauterine growth restriction, neonatal diabetes, multiple GI anomalies including duodenal atresia, intestinal malrotation, gallbladder agenesis, abnormal biliary tract, and an annular pancreas. They also have chronic osmotic diarrhea. Several probands previously reported with Mitchell-Riley syndrome were found to carry pathologic variants in *RFX6*. DNA-binding protein RFX6 (regulatory factor X6; encoded by *RFX6*) is a winged helix transcription factor downstream of the neurogenin-3 signal required for islet cell development and enterendocrine cell function. Immunofluorescence staining in *RFX6* knockout mice shows that pancreatic endocrine cells are present, but do not express the islet cell hormones including insulin, glucagon, somatostatin, and ghrelin.

### ARISTALESS-RELATED HOMEBOX GENE VARIANTS

Aristaless-related homeobox (*ARX*) gene encodes a homeodomain containing a transcription factor required for the normal development of mouse and human enteroendocrine cells. *ARX* expression is detected in a subset of neurogenin-3-positive endocrine progenitors and is also found in a subset of hormone-producing cells. In mice, removal of *Arx* from the developing endoderm results in a decrease of some enteroendocrine cell types, such as gastrin, glucagon/GLP-1, CCK, secretin secreting cells, and an increase of somatostatin-expressing cells. Disease causal variants in the *ARX* gene are associated with a complex X-linked disorder with a clinical phenotype of intellectual disability, seizures, lissencephaly, loss of pancreatic alpha cells, abnormal genitalia, and in approximately half of the patients, congenital malabsorptive diarrhea.

### AUTOIMMUNE ENTEROPATHY

The term autoimmune enteropathy describes a subgroup of infants with severe, protracted diarrhea, no response to dietary restriction, the presence of circulating gut autoantibodies and/or associated autoimmune diseases, and the lack of another cause of severe immunodeficiency. Symptoms of autoimmune enteropathy usually occur within the first 6 months of life, presenting with chronic diarrhea, PLE, malabsorption, and failure to thrive. The diagnosis is based on the endoscopic and histologic identification of inflammation of the GI tract, more pronounced in the small bowel. Histologic findings in the small bowel include partial or complete villous atrophy, crypt hyperplasia, and an increase in chronic inflammatory cells in the lamina propria. Marked intraepithelial lymphocytosis reminiscent of celiac disease can be present in a subset of patients. Cryptitis and crypt abscesses can also be seen and may obscure the presence of apoptosis. Immunologic analyses indicate the presence of autoantibodies including *anti-enterocyte antibodies* (present in ~85% of patients), as well as *anti-autoimmune enteropathy-related 75-kDa antigen*.

Genetic testing in patients with autoimmune enteropathy identified that the majority of patients with autoimmune enteropathy carried disease causal variants in the forkhead box P3 (*FOXP3*) gene on the X chromosome. The term *immune dysregulation*, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is used to describe these patients. Patients not found to have a causal variant in *FOXP3* had what were termed IPEX-like disorders and were found to have a variable phenotype and presented in females as well. Disease causing variants within other genes include interleukin-2 receptor A (IL2RA), LPS responsive beige-like anchor protein (LRBA), cytotoxic T-lymphocyte associated protein 4 (CTLA-4), and signal transducer and activator of transcription 1 and 3 (STAT1 and STAT3), along with others.

The differential diagnosis of pediatric autoimmune enteropathy includes other immune-mediated disorders, such as food sensitivity enteropathies (e.g., cow's milk protein intolerance and celiac disease), severe Crohn disease, and graft-versus-host disease.

Treatment options are limited and are based on nutritional support, including parenteral nutrition and glucocorticoids followed by

immunosuppressive drugs. Hematopoietic stem cell transplantation is indicated in patients with a known molecular defect.

### AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 1

See Chapter 165.

### Defects in Lipids Transport and Metabolism

See Chapter 106.3.

After uptake from the lumen, fatty acids and monoacylglycerol are transported to the endoplasmic reticulum (ER). In the ER they are converted to triglycerides in several metabolic steps, the last of which is dependent on acyl CoA:diacylglycerol acyltransferase 1 (DGAT1). Apolipoprotein B (ApoB) and microsomal triglycerides transfer protein (MTTP) act in concert to incorporate triglycerides into chylomicrons. The newly formed chylomicrons bud from the ER in a prechylomicron transport vesicle (PCTV), which subsequently fuses with the Golgi, a process that is dependent on Sar1b. The chylomicron is then transported in a vesicle to the basal membrane, where it exits the cell.

### ABETALIPOPROTEINEMIA

Abetalipoproteinemia (Bassen-Kornzweig syndrome) is a rare autosomal recessive disorder of lipoprotein metabolism associated with severe fat malabsorption and steatorrhea from birth (see Chapter 106.3). Children fail to thrive during the first year of life and have stools that are pale, foul smelling, and bulky. The abdomen is distended, and deep tendon reflexes are absent because of peripheral neuropathy secondary to vitamin E deficiency. Intellectual development tends to be delayed. After 10 years of age, intestinal symptoms are less severe, ataxia may develop, with loss of position and vibration sensation, and the onset of intention tremors. These latter symptoms reflect involvement of the posterior columns, cerebellum, and basal ganglia. In adolescence, in the absence of adequate supplement of vitamin E, atypical retinitis pigmentosa develops.

The diagnosis is suggested by the presence of acanthocytes in the peripheral blood smear and extremely low plasma levels of cholesterol (<50 mg/dL); triglycerides are also very low (<20 mg/dL). Chylomicrons and very low density lipoproteins are not detectable, and the low-density lipoprotein (LDL) fraction is virtually absent from the circulation. Marked triglyceride accumulation in villous enterocytes occurs in the duodenal mucosa. Patients with abetalipoproteinemia have pathogenic variants of the *MTTP* gene. *MTTP* catalyzes the transfer of triglycerides to nascent ApoB particles in the ER.

Specific treatment is not available. Nutritional support and large supplements of the fat-soluble vitamins A, D, E, and K should be given. High doses of vitamin E (100–300 mg/kg/24 hr) appears to arrest neurologic and retinal degeneration, with some children requiring higher doses based on serum levels. Limiting long-chain fat intake can alleviate intestinal symptoms; medium-chain triglycerides (MCTs) can be used to supplement fat intake.

### HOMOZYGOUS HYPOBETALIPOPROTEINEMIA

Homozygous hypobetalipoproteinemia (see Chapter 106.3) is a dominantly inherited condition associated with pathogenic variants in the *APOB* gene, encoding ApoB, the apolipoprotein of the nascent chylomicron. The homozygous form is indistinguishable from abetalipoproteinemia. The parents of these patients, as heterozygotes, have reduced plasma LDL and ApoB concentrations, whereas the parents of patients with abetalipoproteinemia have normal levels. On transmission electron microscopy of small bowel biopsies, the size of lipid vacuoles in enterocytes differentiates between abetalipoproteinemia and hypobetalipoproteinemia: many small vacuoles are present in hypobetalipoproteinemia, and larger vacuoles are seen in abetalipoproteinemia.

### CHYLOMICRON RETENTION DISEASE (ANDERSON DISEASE)

Chylomicron retention disease (CRD) is a rare autosomal recessive disorder caused by pathogenic variants in the *SAR1B* gene. *SAR1B* variants result in defective trafficking of nascent chylomicrons in PCTVs between the ER and the Golgi apparatus, interfering with the successful

assembly of chylomicrons and their delivery to the lamina propria. The patients with CRD have steatorrhea, chronic diarrhea, and failure to thrive. Acanthocytosis is rare, and neurologic manifestations are less severe than those observed in abetalipoproteinemia. Plasma cholesterol levels are moderately reduced (<75 mg/dL), and fasting triglycerides are normal, but the fat-soluble vitamins, particularly A and E, are very low. Treatment is early aggressive therapy with fat-soluble vitamins and modification of dietary fat intake, as in the treatment of abetalipoproteinemia.

### DGAT1 VARIANTS

*DGAT1* encodes for DGAT that converts diacylglycerides to triglycerides by adding an acyl CoA moiety. In the small intestine, DGAT1 helps to reassemble the triglycerides, whereas in the liver it produces triglycerides from fatty acids synthesized de novo or taken up from the circulation. The mechanism by which *DGAT1* disease causal variants causes diarrhea is unclear but is likely to involve the buildup of DGAT1 lipid substrates in the enterocytes or in the gut lumen. Pathogenic variants in *DGAT1* gene have been reported in patients presenting with failure to thrive, PLE, hypoalbuminemia, early-onset diarrhea, and oral vitamin D refractory rickets.

### WOLMAN DISEASE

Wolman disease is a rare, lethal lipid storage disease that leads to lipid accumulation in multiple organs, including the small intestine and liver. In addition to vomiting, severe diarrhea, and hepatosplenomegaly, patients have steatorrhea as a result of lymphatic obstruction. Insufficient free cholesterol available for steroidogenesis in adrenal glands results in adrenal insufficiency; a characteristic pattern of subcapsular adrenal calcification represents a distinctive marker of disease. Deficiency of lysosomal acid lipase (LAL) is the underlying cause of disease (see Chapter 106.4). LAL is a lysosomal enzyme that hydrolyzes cholesteryl esters and triglycerides within endolysosomes. Loss-of-function variants in the *LIPA* gene are associated with variable phenotypes. Homozygous and compound heterozygous pathogenic variations, resulting in complete LAL deficiency, cause Wolman disease. Variants associated with residual LAL activity cause cholesteryl ester storage disease, an attenuated form of Wolman disease exhibiting a variable phenotype. Common features in infants, children, and adults include elevated serum aminotransferase levels, dyslipidemia, hepatomegaly, liver fibrosis, and cirrhosis. Wolman disease may also present with neonatal cholestasis and severe liver disease as its main feature already in infancy. Hemophagocytic lymphohistiocytosis has been reported in few infants with Wolman disease. The hallmark of the disease is the presence of *adrenal calcification* seen on imaging, and definite diagnosis is done genetically.

Hematopoietic stem cell transplantation has been reported in few patients with variable outcome. A recombinant human enzyme-replacement therapy for LAL deficiency is approved for use in patients suffering from LAL deficiency. This treatment has allowed a small number of infants with Wolman disease to achieve a relatively normal growth rate and to improve survival. In older children and adults, the enzyme has corrected their dyslipidemia and produced significant improvement in markers of hepatic function.

### TANGIER DISEASE

See Chapter 106.

Cellular free cholesterol is mobilized, along with phospholipid, through the export pump ABCA1, resulting in the transfer to an extracellular ApoA-I acceptor and the formation of discoidal high-density lipoprotein (HDL) cholesterol. Loss-of-function variants in *ABCA1* genes in patients with Tangier disease cause cholesterol accumulation in the intestine, spleen, tonsils, relapsing neuropathy, orange-brown spots on the colon and ileum, and diarrhea in association with decreased plasma cholesterol levels (ApoA-I and A-II), with virtually no detectable plasma HDL. Heterozygosity of ABCA1 variants leads to low HDL levels (below the 10th percentile). Specific therapy for Tangier disease has not yet been established.

### SITOSTEROLEMIA

See Chapter 106.4.

Sitosterol and other sterols are preferentially secreted back into the intestinal lumen through the sterol pump, paired half-transporters ABCG5/G8. Pathogenic variants of the *ABCG5* (sterolin-1) and *ABCG8* (sterolin-2) transporters result in the defective efflux of sterol and leads to the increased absorption of dietary sterols. The disorder is associated with tendon xanthomas, increased atherosclerosis, and hemolytic anemia. Plasma levels of phytosterols (mainly sitosterol) are typically >10 mg/dL.

### BILE ACID MALABSORPTION

Bile acids (BAs) are detergent compounds secreted by and excreted from the liver, and are responsible for the solubilization of the dietary lipids, aiding in their digestion and absorption. Approximately 95% of BAs are reabsorbed in the terminal ileum and transported back to the liver, the enterohepatic circulation. The apical Na<sup>+</sup>-dependent bile salt transporter (ASBT) or ileal BA transporter (IBAT) is responsible for the active reuptake of BAs in the terminal ileum. Pathogenic variants in the *ASBT/SLC10A2* gene are very rare and are responsible for *primary BA malabsorption*, a disease associated with congenital diarrhea, steatorrhea, and reduced plasma cholesterol levels. Unabsorbed BAs stimulate chloride excretion in the colon, resulting in diarrhea. *Secondary BA malabsorption* can result from ileal disease, such as in Crohn disease, and following ileal resection. The diagnosis of BA malabsorption is typically based on reduced BA retention of radiolabeled <sup>75</sup>selenium-homocholic acid taurine (<sup>75</sup>SeHCAT), increased BA synthesis (serum C4), or increased fecal BA loss (measured by serum FGF-19 levels). In clinical practice, diagnosis is often based on the response to BA sequestrants (e.g., cholestyramine or colestevam), which are also the treatment of choice for this disorder.

Chronic neonatal-onset diarrhea has also been described in autosomal recessive *cerebrotendinous xanthomatosis*, which is caused by pathogenic variants in *CYP27A1* and results in an inborn error of BA synthesis due to 27-hydroxylase deficiency. These children also present with juvenile-onset cataracts and developmental delay. Neonatal cholestasis has also been described as a presenting feature. Tendon xanthomas develop in the second and third decades of life. The diagnosis is important to establish at a younger age, as treatment with oral chenodeoxycholic acid is effective at preventing irreversible neurologic damage.

### PROTEIN-LOSING ENTEROPATHY

PLE is a rare entity caused by a variety of intestinal and extraintestinal disorders and characterized by excessive enteric loss of plasma proteins. The clinical presentation of patients with PLE is variable and depends upon the underlying cause, but generally includes edema and hypoproteinemia. Impaired synthesis (malnutrition, liver disease), protein loss through other organs (kidney or skin), or redistribution (septic states) must be excluded before considering PLE. The disorders causing PLE can be divided into those due to protein loss from an inflamed or abnormal mucosal surface or from derangements in intestinal lymphatics, such as in primary or secondary IL (see Table 385.4).

Intestinal lymphangiectasia is characterized by diffuse or focal dilatation of the enteric lymphatics and is located in the mucosa, submucosa, or subserosa. Lymph rich in proteins, lipids, and lymphocytes leaks into the bowel lumen, resulting in PLE, steatorrhea, and lymphocyte depletion. Hypoalbuminemia, hypogammaglobulinemia, edema, lymphopenia, malabsorption of fat and fat-soluble vitamins, and chylous ascites often occur. IL can also manifest with ascites, peripheral edema, and a low serum albumin. The etiology of *primary IL* is unknown. Several genes, including vascular endothelial growth factor receptor 3 (*VEGFR3*), prospero-related homeobox-transcriptional factor (*PROX1*), forkhead transcriptional factor (*FOXC2*), and SRY (sex determining region Y)-box 18 (*SOX18*), are involved in the development of the lymphatic system and have been shown to have altered expression in the duodenal mucosa in patients with IL. A pathogenic variant in *CD55*, a regulator of complement activation, has also been described as a cause for primary PLE. The diagnosis of PLE is suggested

by the typical clinical and laboratory findings in association with an elevated fecal  $\alpha_1$ -antitrypsin clearance. Radiologic findings of uniform, symmetric thickening of mucosal folds throughout the small intestine are characteristic but nonspecific. Small bowel mucosal biopsy in patients with IL can show dilated lacteals with distortion of villi and no inflammatory infiltrate. A patchy distribution and deeper mucosal involvement on occasion causes false-negative results on small bowel histology. Video capsule endoscopy may reveal similar lesions (Figs. 385.4 and 385.5). Magnetic resonance lymphangiography may identify lymphatic abnormalities (Fig. 385.6).

Treatment of PLE is generally supportive and consists of a low-fat, high-protein diet. In patients with IL, a low-fat, high-protein diet supplemented with MCTs is recommended. Along with dietary adjustments, appropriate treatment for the underlying etiology is necessary, as well as supportive care to avoid complications of edema. Rarely, PN is required. If only a portion of the intestine is involved, surgical resection may be considered. A few patients with lymphatic malformation and generalized lymphatic anomalies were successfully treated with propranolol. Sirolimus, an mTOR inhibitor, has been used for primary IL and is thought to decrease lymphatic sprouting and proliferation. Everolimus use has been described in a patient with primary IL. Prognosis depends upon the severity and treatment options of the underlying disease.

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### 385.3 Intestinal Infections and Infestations Associated with Malabsorption

Abdul-Aziz K. Elkadri

Malabsorption is a rare consequence of primary intestinal infection and infestation in immunocompetent children but is relatively common in previously malnourished or immunocompromised children and is associated with significant mortality. Often malabsorption is associated with diarrhea and triggers a vicious cycle of further weight loss and growth failure. For children living in developing countries, malabsorption is associated with long-term growth failure leading to stunting within a peculiar condition defined as environmental enteropathy, in which diarrhea is not always present. Generally, malabsorption

is associated with a duration of an intestinal infection longer than expected. *Prolonged* diarrhea is an acute-onset diarrhea that lasts >7 days, whereas *chronic* diarrhea lasts >14 days, with some using 30 days as a more definitive cutoff.

### POSTINFECTIOUS DIARRHEA

Chronic diarrhea can appear following infectious enteritis, regardless of the nature of the pathogen. The pathogenesis of the diarrhea is not always clear and may be related to persistent infection or reinfection, secondary lactase deficiency, food protein allergy, antibiotic-associated diarrhea, or a combination of these. In some cases, postinfectious diarrhea may be the initial manifestation of functional diarrhea, in which case it is not associated with malabsorption.

Treatment of postinfectious diarrhea is supportive and may include a lactose-free diet in the presence of secondary lactase deficiency. Some infants might require a semi-elemental diet. The beneficial effect of specific probiotic products may be indicated in selected conditions.

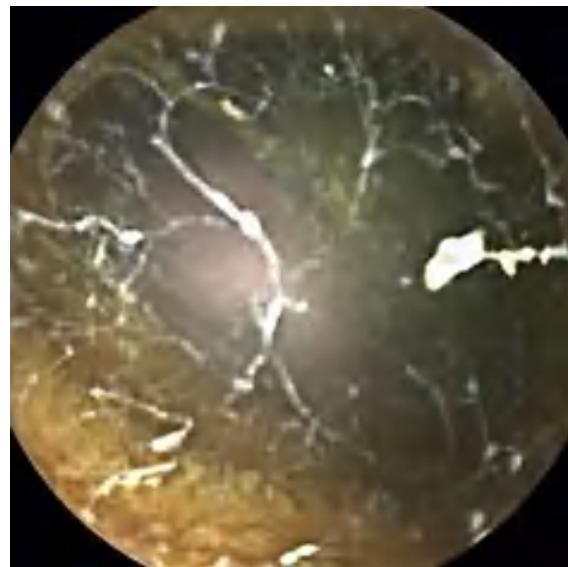
### PROXIMAL INTESTINAL BACTERIAL OVERGROWTH

Bacteria are normally present in large numbers in the colon ( $10^{11}$ - $10^{13}$  colony-forming units [CFU]/g of feces) and have a symbiotic relationship with the host, providing nutrients and protecting the host from pathogenic organisms. Within the stomach and small bowel, bacteria are usually present in much smaller numbers. Excessive numbers of bacteria in the stomach or small bowel are noted to be harmful. Bacterial overgrowth can result from clinical conditions that alter the gastric pH or small bowel motility, such as partial bowel obstruction, diverticula, intestinal failure, intestinal duplications, diabetes mellitus, idiopathic intestinal pseudoobstruction syndrome, and scleroderma, as well as proton pump inhibitor use. Prematurity, immunodeficiency, and malnutrition are other factors associated with bacterial overgrowth of the small bowel.

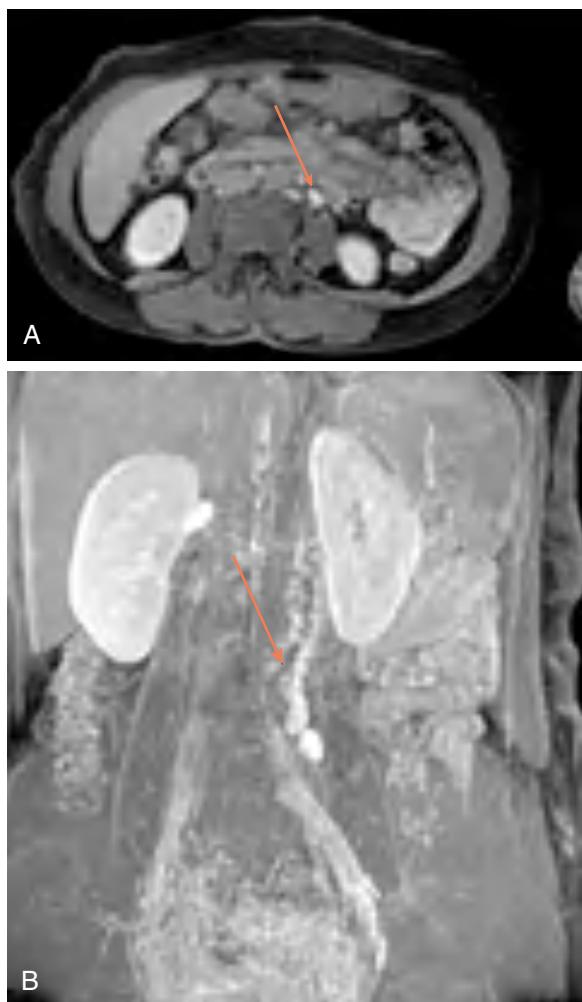
The diagnosis of bacterial overgrowth is often difficult and can be made by culturing small bowel aspirate ( $>10^5$  CFU/mL) or by a lactulose hydrogen breath test. Lactulose is a synthetic disaccharide not digested by mucosal brush border enzymes but is fermented by bacteria producing hydrogen and methane. High baseline breath hydrogen and a quick rise in hydrogen in expired breath samples support the diagnosis of bacterial overgrowth. Some individuals (up to 30%) produce methane as a predominant by-product of carbohydrate digestion. False-positive tests are common and may be due to rapid GI transit time and colonic fermentation.



**Fig. 385.4** Swollen villi detected by video capsule endoscopy in the proximal ileum. (From Gortani G, Maschio M, Ventura A. A child with edema, lower limb deformity, and recurrent diarrhea. *J Pediatr*. 2012;161:1177. Fig. 1.)



**Fig. 385.5** Protein-rich lymphatic fluid aggregates detected by video capsule endoscopy in the intestinal lumen. (From Gortani G, Maschio M, Ventura A. A child with edema, lower limb deformity, and recurrent diarrhea. *J Pediatr*. 2012;161:1177. Fig. 2.)



**Fig. 385.6** MR lymphangiogram. A, Axial T1-weighted fat-saturated MR image showing contrasted-filled dilated retroperitoneal tubular channels (arrow). B, Thick maximum intensity projection of MR lymphangiogram (T1-weighted) image showing dilated retroperitoneal channels with contrast refluxing into bowel wall (arrow) suggestive of associated intestinal lymphangiectasia. (From Valakada J, Madhusudhan KS, Ranjan G, et al. Abdominal lymphangiomatosis with intestinal lymphangiectasia diagnosed by magnetic resonance lymphangiography: a case study. *Curr Prob Diag Radiol.* 2018;47:200–202.)

Bacterial overgrowth leads to inefficient intraluminal processing of dietary fat with steatorrhea due to bacterial deconjugation of bile salts, vitamin B<sub>12</sub> malabsorption, and microvillus brush border injury with further malabsorption. Bacterial consumption of vitamin B<sub>12</sub> and enhanced synthesis of folate result in decreased vitamin B<sub>12</sub> and increased folate serum levels. Overproduction of D-lactate (the stereoisomer of L-lactate) can cause stupor, neurologic dysfunction, and shock from D-lactic acidosis. Lactic acidosis should be suspected in children at risk of bacterial overgrowth who show signs of neurologic deterioration and a high anion gap metabolic acidosis not explained by measurable acids such as L-lactate. Measurement of D-lactate is required because standard lactate assay only measures the L-isomer.

The treatment of bacterial overgrowth focuses on the correction of underlying causes such as partial obstruction. Oral metronidazole can provide relief for many months but is not always effective. The cycling of antibiotics, including azithromycin, trimethoprim-sulfamethoxazole, ciprofloxacin, and metronidazole, may be required. Other alternatives are oral nonabsorbable antibiotics such as aminoglycosides, nitazoxanide, or rifaximin. Occasionally, antifungal therapy is required to control fungal overgrowth of the bowel.

## ENVIRONMENTAL ENTEROPATHY (TROPICAL SPRUE)

In developing regions of the world, an atypical subclinical form of enteropathy has been described termed environmental enteropathy (tropical sprue). Theorized to be due to chronic fecal-oral exposure, it is thought to be the result of interactions between enteric pathogens, enteropathy, and malnutrition. There is resulting malabsorption, which may be clinically evident or subclinical, at times with or without diarrhea. It is a frequent cause of death in childhood in endemic regions, particularly in South Asian areas, African countries, and other developing regions. Selected pathogens including rotavirus, *Shigella*, *Cryptosporidium*, and enterotoxigenic *Escherichia coli* cause the majority of intestinal infections leading to moderate to severe diarrhea and often triggers a vicious circle with malnutrition. This tends to progress to wasting and stunting with or without a clear association with diarrhea.

In addition to a high risk of death, environmental enteropathy impairs normal growth and brain development and impacts productivity. There is evidence of oral vaccine failure, pointing to an alteration of the intestinal mucosal immune system. The etiology of this disorder is unclear because it follows outbreaks of acute diarrheal disease and improves with antibiotic therapy. Individuals traveling in endemic regions have developed enteropathy similar to native residents, which improves with return to nonendemic regions. Immigrants with malabsorptive diarrhea were shown to have improved absorption and jejunal biopsies with increasing periods of residence in nonendemic countries. Therefore an infectious etiology within the endemic environment is suspected. Nevertheless, environmental enteropathy includes interrelated mechanisms such as intestinal malabsorption, increased permeability, loss of intestinal mass, inflammation, increased bacterial translocation, and impairment of immune response. The incidence is decreasing worldwide, largely because of an improvement in hygiene and access to nutrients. Clinical symptoms include fever and malaise followed by diarrhea. After about a week the acute features subside, and anorexia, intermittent diarrhea, and chronic malabsorption result in severe malnutrition characterized by glossitis, stomatitis, cheilosis, night blindness, hyperpigmentation, and edema, reflecting the various nutrient deficiencies. Muscle wasting is often marked, and the abdomen is often distended. Megaloblastic anemia results from folate and vitamin B<sub>12</sub> deficiencies.

Diagnosis is made by small bowel biopsy, which shows villous flattening with crypt hyperplasia and mild intestinal inflammation, with lipid accumulation in the surface epithelium.

Treatment response with nutritional and antimicrobial interventions may be poor, with no clear improvement in weight gain. Nutritional supplementation, including supplementation of folate and vitamin B<sub>12</sub> as well as glutamine, is recommended. To prevent recurrence, 6 months of therapy with oral folic acid (5–10 mg) and antibiotics are recommended. Relapses occur in 10–20% of patients who continue to reside in an endemic tropical region. This suggests a persistent environmental factor causing recurrence, and that improved overall hygiene is key to treatment and prevention. Improvements in public health infrastructure and educational interventions are the key to prevention rather than medical interventions in individual cases.

## WHIPPLE DISEASE

Whipple disease is a rare childhood chronic systemic infectious disorder. It is caused by *Tropheryma whipplei*, which can be cultured from a lymph node in the involved tissue.

The most common symptoms in Whipple disease are diarrhea, abdominal pain, weight loss, and joint pains. Malabsorption, lymphadenopathy, skin hyperpigmentation, and neurologic symptoms are also common. Involvement of other organs, such as eyes, heart, and kidneys, has been reported.

Diagnosis requires a high index of suspicion and is made upon demonstration of PAS-positive macrophage inclusions in the biopsy material, usually a duodenal biopsy. Positive identification using polymerase chain reaction for *T. whipplei* confirms the diagnosis.

Treatment requires antibiotics, such as trimethoprim-sulfamethoxazole, for 1–2 years. A 2-week course of intravenous ceftriaxone or meropenem, followed by trimethoprim-sulfamethoxazole for 1 year, is recommended.

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## 385.4 Immunodeficiency Disorders

Abdul-Aziz K. Elkadri

Malabsorption and diarrhea are a common presentation of patients with underlying primary immune deficiencies. It is not surprising that more than half of the primary immunodeficiencies present with GI manifestations because the gut is the largest lymphoid organ in the body and represents an interface between our environment, microbiome, and immune system. Malabsorption can be due to either intestinal inflammation or infection, with chronic diarrhea and failure to thrive one of the main modes of presentation. Multiple defects of humoral and/or cellular immunity have been described, including selective IgA deficiency, agammaglobulinemia, common variable immunodeficiency disease (CVID), severe combined immunodeficiency (SCID), hyper-IgM syndrome, Wiskott-Aldrich syndrome, and chronic granulomatous disease. The most common primary immunodeficiency is selective IgA deficiency, with the majority of patients being asymptomatic. Recurrent infections with *Giardia* or nonspecific enteropathy with bacterial overgrowth can occur; celiac disease is noted to be more common in selective IgA deficiency. In CVID and X-linked agammaglobulinemia, lymphoid hyperplasia, villous atrophy, granulomas, and increased intraepithelial lymphocytes have been reported in up to 60% of children with these disorders, with relative paucity of plasma cells. Pathology is reminiscent of acute graft-versus-host disease, with the presence of apoptotic bodies in the intestinal epithelia. Malabsorption has also been reported in approximately 10% of patients with CVID or X-linked agammaglobulinemia, often secondary to noroviral infection, giardiasis, *Campylobacter*, *Salmonella*, *Cryptosporidium*, enteroviruses, or cytomegalovirus (CMV) infections, and can be hard to eradicate. *Cryptosporidium* is the most common pathogen causing diarrhea and malabsorption in hyper-IgM syndrome patients, though other infections have also been described. SCID-affected children develop severe diarrhea and malabsorption early in life involving viral and opportunistic infections, especially chronic rotavirus infection, CMV, and adenovirus. Malabsorption associated with immunodeficiency is exacerbated by villous atrophy and secondary disaccharidase deficiency. In chronic granulomatous disease, phagocytic function is impaired and granulomas develop throughout the GI tract, mimicking Crohn disease. In addition to failure to thrive, it is important to consider that malabsorption associated with immunodeficiency is often complicated by micronutrient deficiencies, including vitamins A, E, and B<sub>12</sub>, and calcium, zinc, and iron.

Acquired immunodeficiencies in children are more often secondary to other conditions such as cancer and chemotherapy. Malnutrition, diarrhea, and failure to thrive are common in untreated children with HIV infection. The risk of GI infection is related to the depression of the CD4 count. Opportunistic infections include *Cryptosporidium parvum*, CMV, *Mycobacterium avium-intracellulare*, *Isospora belli*, *Enterocytozoon bieneusi*, *Candida albicans*, astrovirus, calicivirus, adenovirus, and the usual bacterial enteropathogens. In these patients, *Cryptosporidium* can cause a chronic secretory diarrhea.

Chemotherapeutic agents can damage the bowel mucosa, leading to secondary malabsorption of disaccharides such as lactose. After bone marrow transplantation, mucosal damage from conditioning agents and graft-versus-host disease can cause diarrhea and malabsorption. Small bowel biopsies show nonspecific villous atrophy, mixed inflammatory cell infiltrates, and increased apoptosis. Cancer chemotherapy and bone marrow transplantation are associated with pancreatic damage, which may lead to exocrine pancreatic insufficiency.

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## 385.5 Immunoproliferative Small Intestinal Disease

Abdul-Aziz K. Elkadri

**Lymphoma** (see Chapter 545) is the most common small bowel malignancy in the pediatric age-group. Malignant lymphomas of the small intestine are categorized into three subtypes: Burkitt lymphoma, non-Hodgkin lymphomas, and immunoproliferative small intestinal disease (IPSID) (originally termed as Mediterranean lymphoma or α-heavy chain disease but found worldwide). Burkitt lymphoma, the most common form in children, characteristically involves the terminal ileum with extensive abdominal involvement. The relatively uncommon non-Hodgkin lymphomas (usually large B-cell type) can involve various regions of the small intestine. Inflammatory bowel disease and primary immunodeficiencies are risk factors for the development of lymphoproliferative disorders of the intestinal tract. IPSID is a rare extranodal marginal zone B-cell lymphoma occurring primarily in the proximal small intestine. It is a variant of **mucosa-associated lymphoid-tissue (MALT) lymphoma** described in young adults from the developing world and is characterized by lymphoplasmacytic intestinal infiltrates with monotypic α-heavy chain expression.

IPSID occurs most often in the proximal small intestine in older children and young adults in the Mediterranean basin, Middle East, Asia, and Africa. Poverty and frequent episodes of gastroenteritis during infancy are risk factors. The initial clinical presentation is intermittent diarrhea and abdominal pain. Later, chronic diarrhea with malabsorption, PLE, weight loss, digital clubbing, and growth failure ensue. Intestinal obstruction, abdominal masses, and ascites are common in advanced stages.

In contrast to primary nonimmunoproliferative small intestinal lymphomas, in which the pathology in the intestine is usually focal, IPSID involves specific segments of the intestine and leaves the segments between the involved areas free of disease. The pathology in IPSID is diffuse, with a mucosal cellular infiltrate involving large segments of the intestine and sometimes the entire length of the intestine, thus producing malabsorption. Molecular and immunohistochemical studies demonstrated an association with *Campylobacter jejuni* infection. The differential diagnosis includes chronic enteric infections (parasites, tropical sprue), celiac disease, and other lymphomas. Radiologic findings include multiple filling defects, ulcerations, strictures, and enlarged mesenteric lymph nodes on CT scan.

The diagnosis is usually established by endoscopic biopsies and/or laparotomy. Upper endoscopy shows thickening, erythema, and nodularity of the mucosal folds in the duodenum and proximal jejunum. Capsule endoscopy may be helpful in the diagnosis. When the disease progresses, tumors usually appear in the proximal small intestine and rarely in the stomach. The diagnosis requires multiple duodenal and jejunal mucosal biopsies showing dense mucosal infiltrates, consisting of centrocyte-like and plasma cells. Progression to higher grade large cell lymphoplasmacytic and immunoblastic lymphoma is characterized by increased plasmocytic atypia with formation of aggregates and later sheets of dystrophic plasma cells and immunoblasts invading the submucosa and muscularis propria. A serum marker of IgA, a heavy-chain paraprotein, is present in most cases.

Treatment of early-stage IPSID with antibiotics results in complete remission in 30–70% of cases (tetracycline, ampicillin, or metronidazole). Some patients achieve durable remission lasting several years but should be monitored closely for relapse. The majority of untreated IPSID cases progress to lymphoplasmacytic and immunoblastic lymphoma invading the intestinal wall and mesenteric lymph nodes, resulting in metastasis to distant organs, and requiring aggressive treatment with surgery and/or chemotherapy.

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## 385.6 Short Bowel Syndrome

Abdul-Aziz K. Elkadri

Short bowel (or short gut) syndrome is defined as a state of reduced functional intestinal mass that is lower than the required amount for the digestion and absorption of nutrients and fluids required for normal growth and survival. It results from congenital malformations or the resection of the small bowel (Table 385.6). Its incidence increases with low birthweight and earlier gestational age and is estimated at 7/1,000 live births in U.S. infants with birthweight <1,500 mg. Depending upon the area of the bowel resected or absent, loss of >50% of the small bowel, with or without a portion of the large intestine, can result in symptoms of generalized malabsorptive disorder or in specific nutrient deficiencies. At birth, the length of small bowel is 200–250 cm; by adulthood, it grows to 300–800 cm. Bowel resection is better tolerated in infants with an improved prognosis relative to adults due to the potential for intestinal growth and adaptation. An infant with as little as 15 cm of bowel with an ileocecal valve, or 20 cm without an ileocecal valve, has the potential to survive and be eventually weaned from PN.

In addition to the length of the bowel, the anatomic location of the resection is also important. The proximal 100–200 cm of jejunum is the main site for carbohydrate, protein, iron, and water-soluble vitamin absorption, whereas fat absorption occurs over a longer length of the small bowel. Depending on the region of the bowel resected, specific nutrient malabsorption can result. Vitamin B<sub>12</sub> and bile salts are only absorbed in the distal ileum (Fig. 385.7). Jejunal resections are generally tolerated better than ileal resections because the ileum, unlike the jejunum, is better able to adapt to absorb nutrients and fluids. Net sodium and water absorption is relatively higher in the ileum. Ileal resection has a profound effect on fluid and electrolyte absorption due to malabsorption of sodium and water by the remaining ileum. Ileal malabsorption of bile salts stimulates increased colonic secretion of fluid and electrolytes. The presence of a colon in continuity is better tolerated and improves absorption and enteral autonomy.

### TREATMENT

After bowel resection, treatment of short bowel syndrome is initially focused on repletion of the massive fluid and electrolyte losses while the bowel initially accommodates to absorb these losses. Proton pump inhibitors are usually added to reduce gastric secretions due to hypersecretion of gastric acids of up to 4 L per day compared to 750 mL in healthy individuals. Nutritional support is often provided via parenteral nutrition. A central venous catheter should be inserted to provide optimized and durable parenteral fluid and nutrition support. The ostomy or stool output should be measured, and fluid and electrolyte losses adequately replaced. Measurement of urinary Na<sup>+</sup> to assess whole body Na<sup>+</sup> stores is useful to prevent Na<sup>+</sup> depletion. Maintaining urinary Na<sup>+</sup> higher than 20 mmol/L ensures that Na<sup>+</sup> intake is adequate. Early introduction of even a small amount of enteral feeding by mouth or tube feeding is essential and enhances bowel adaptation.

**Table 385.6** Causes of Short Bowel Syndrome

#### CONGENITAL

Congenital short bowel syndrome  
Intestinal atresia  
Gastroschisis

#### BOWEL RESECTION

Necrotizing enterocolitis  
Volvulus with or without malrotation  
Long segment Hirschsprung disease  
Meconium peritonitis  
Crohn disease  
Trauma

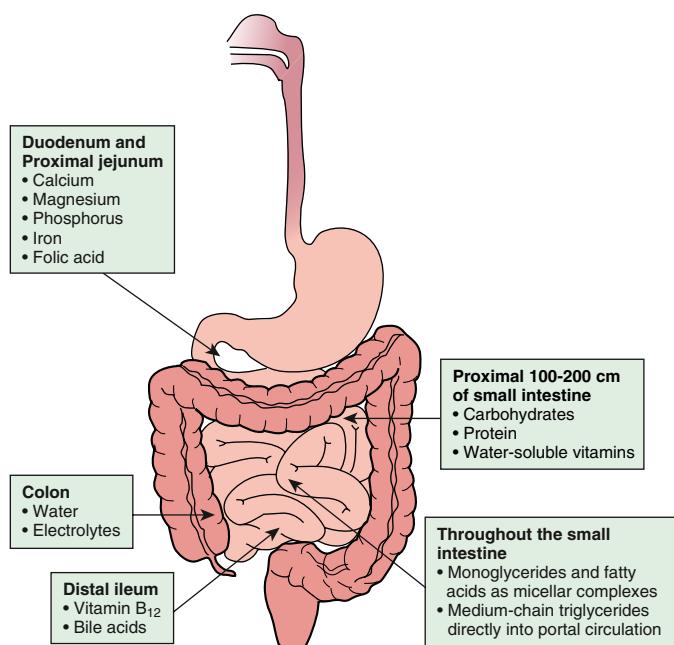
After the initial few weeks following resection, fluid and electrolyte losses begin to stabilize, and the focus of therapy shifts to bowel rehabilitation with a gradual increase in the volume of enteral feeds. Continuous or bolus small-volume enteral feeding should be promoted with an extensively or partially hydrolyzed protein with MCT-enriched formula if the colon is in continuity. Breast milk is preferable over formula, and its use should be encouraged as it stimulates gut hormones and promotes mucosal growth. Enteral feeding also increases pancreatic flow and reduces parenteral nutrition-induced hepatotoxicity. To maintain interest in oral feeds and minimize oral aversion, infants should be given a small amount of formula or mother's milk by mouth as early as possible. As intestinal adaptation occurs, enteral feeding increases, and parenteral supplementation decreases. The bowel mucosa surface area proliferates, and the bowel lengthens with growth.

Approximately 60% of patients with short bowel syndrome achieve **enteral autonomy** within 5 years of bowel resection, and the majority do so in the first 2–3 years after resection. In addition to bowel length, factors increasing the likelihood of achieving enteral autonomy include the presence of the ileocecal valve, a diagnosis of necrotizing enterocolitis, and care by an intestinal rehabilitation program.

Patients may require repeat surgeries for obstruction or bowel lengthening procedures (longitudinal lengthening, serial transverse enteroplasties or both) to optimize the bowel absorptive capacity. Bowel lengthening procedures are indicated in patients with dilated bowel who are unable to progress toward enteral autonomy or in those with refractory small intestinal bacterial overgrowth.

Vitamin and micronutrient deficiencies are common and increase over time. The management of specific micronutrient and vitamin deficiencies and the treatment of transient problems such as postinfectious mucosal malabsorption are required. GI infections or small bowel bacterial overgrowth can cause setbacks in the progression to full enteral feeding in patients with marginal absorptive function. Marked increase in stool output or evidence of carbohydrate malabsorption (stool pH <5.5 and positive test for reducing substances) is a contraindication for further increases in enteral feeds. Slow advancement of continuous or bolus enteral feeding rates continues until all nutrients are provided enterally.

In patients with large stool output, the addition of soluble fiber and antidiarrheal agents, such as loperamide and anticholinergics, can be beneficial, although these drugs can increase the risk of bacterial



**Fig. 385.7** Absorption of nutrients in the small bowel varies with the region.

overgrowth. Cholestyramine can be beneficial for patients with distal ileal resection, but its potential depletion of the BA pool can increase steatorrhea. Bacterial overgrowth is common in infants with a short bowel and can delay progression of enteral feedings. Empirical treatment with metronidazole or other antibiotics (nitazoxanide, rifaximin) is often useful. Diets high in fat and without simple sugars may be helpful in reducing bacterial overgrowth as well as in enhancing adaptation.

## COMPLICATIONS

Long-term complications of short bowel syndrome include those of parenteral nutrition: central catheter infection, thrombosis, intestinal failure associated liver disease (IFALD), and gallstones. Appropriate care of the central line to prevent infection and catheter-related thrombosis is extremely important. Sepsis is a leading cause of death and can occur any time after treatment is initiated (months to years later), and is most often bacterial (single organism more common than polymicrobial), although fungal infection may be noted in 20–25% of septic episodes. The use of an ethanol, sodium bicarbonate, or taurolidine lock can reduce the incidence of central catheter infections and prevent infections.

Some patients will continue to require long-term parenteral nutritional support, and lack of central line access is potentially life-threatening. Inappropriate removal or frequent changes of central lines in the neonatal period should be avoided. IFALD can lead to cholestasis, cirrhosis, and liver failure and is a common reason for death or need for transplantation. The incidence and severity of IFALD has significantly reduced over the past decade, probably due to the reduced use of soy-based lipid emulsions and the positive effect of omega-3-based lipid emulsions on cholestasis, as well as the collaboration of specialized intestinal failure teams to prevent recurrent septic episodes. Other complications of terminal ileal resection include vitamin B<sub>12</sub> deficiency, which might not appear until 1–2 years after parenteral nutrition is withdrawn. Long-term monitoring for deficiencies of vitamin B<sub>12</sub>, folate, iron, fat-soluble vitamins, and trace minerals, such as zinc and copper, is important. Renal stones can occur as a result of hyperoxaluria secondary to steatorrhea as calcium preferentially binds to the excess fat compared to oxalate, resulting in increased oxalate absorption and excretion in the urine. Venous thrombosis and vitamin deficiency have been associated with hyperhomocysteinemia in short bowel syndrome. Bloody diarrhea secondary to patchy, mild colitis can rarely develop during the progression of enteral feedings. The pathogenesis of this *feeding colitis* is unknown, but it is usually benign and can improve with a hypoallergenic diet or treatment with mesalamine.

In some children with life-threatening complications of parenteral nutrition, especially progressive liver failure and loss of vascular access, small intestine and liver transplantation becomes the preferred therapy (see Chapter 386).

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## 385.7 Chronic Malnutrition

Abdul-Aziz K. Elkadri

Malnutrition can be divided into primary malnutrition, which is more common in developing countries and due to the socioeconomic factors leading to inadequate access to an appropriate caloric intake, and secondary malnutrition, which is due to decreased food intake, disease processes that cause abnormal nutrient loss, or an increased expenditure of energy (see Chapter 64). The American Society for Parenteral and Enteral Nutrition (ASPEN) defined pediatric malnutrition in developed countries as an imbalance between nutrient requirements and intake that results in cumulative deficits of energy, protein, or micronutrients that may negatively affect growth, development, and other relevant outcomes. Malnutrition can also be classified into *illness related* (caused by disease/trauma) or *non-illness related* (caused by environmental/behavioral factors). Based upon duration, it can also be further classified into *acute* malnutrition (<3 months; short duration, weight loss without stunting) or *chronic* malnutrition (>3 months; weight loss and stunting) that may differ in their etiology,

growth patterns, and outcome. Chronic malnutrition is usually due to decreased food intake, malabsorption syndromes, or increased nutritional needs in children with chronic diseases. Malnutrition is diagnosed in 11–50% of hospitalized children and reports from Europe suggest a prevalence of close to 20% in chronically ill children. Child neglect and improper formula preparation can result in severe malnutrition. A detailed medical history should assess for symptoms that may lead to decreased oral intake, including decreased appetite, vomiting, dysphagia, abdominal pain, diarrhea, and tenesmus, as well as mood and behavioral changes. Obtaining a dietary history to determine caloric intake as well as obtaining anthropometric measurements will help determine nutritional status. Anthropometric measures to assess include reduced weight per age and weight per height, body mass index <5th percentile, and mid upper arm circumference <-1 z score. Physical exam findings suggestive of nutrient deficiencies include an atrophic tongue in iron deficiency, decreased subcutaneous fat, and alopecia in zinc deficiency. Laboratory testing can be used to assess vitamin and micronutrient deficiencies, including CBC and iron studies for anemia and serum albumin for protein losing enteropathy. Though screening tools for malnutrition are available in adults to provide a simple and fast way of diagnosing those patients at risk for malnutrition, few such screening tools for the pediatric population have been developed to assess children at risk, and their use in clinical practice is still questionable.

Malnourished children suffer from impaired immunity, chronic enteropathy, poor wound healing, muscle weakness, and diminished psychologic drive. Malnutrition has short-term consequences (increased disability, morbidity, and mortality) and long-term consequences (final adult size, developmental deficiencies, economic productivity). Undernutrition in hospitalized children is associated with increased infectious complications, delayed recovery, increased length of stay and costs, increased readmission rate, and increased mortality.

Nutritional rehabilitation in malnourished children is discussed in Chapter 64.

Chronic malnutrition complicated by diarrheal dehydration is a commonly observed phenomenon. Infectious diarrhea is common in tropical and subtropical countries, in the setting of poor hygiene practices and water quality, in immunocompromised hosts (e.g., HIV, congenital immunodeficiency), and when impairment of the immune response is due to chronic malnutrition itself. In children with chronic disorders, diarrhea may be related to the underlying disease, such as noncompliance with a gluten-free diet in celiac disease, noncompliance with pancreatic enzyme treatment in cystic fibrosis, and cholestatic liver disease with fat malabsorption. Malnutrition per se can lead to exocrine pancreatic insufficiency, which, in turn, aggravates malabsorption and diarrhea.

In infants and children with severe malnutrition, many of the signs normally used to assess the state of hydration or shock are unreliable. Severe malnutrition might be accompanied by sepsis; thus children with septic shock might not have diarrhea, thirst, or sunken eyes but may be hypothermic, hypoglycemic, or febrile. Cardiac reserve is lowered, and heart failure is a common complication.

Despite clinical signs of dehydration, urinary osmolality may be low in the chronically malnourished child. Renal acidifying ability is also limited in patients with malnutrition.

Management of diarrhea in chronically malnourished children is based on three principles: oral rehydration to correct dehydration, prompt resumption of feeds with avoidance of periods of nothing by mouth, and treating the underlying etiology behind the diarrhea.

When treating dehydration in malnutrition, the extracellular space appears to be overexpanded and intra- and extracellular spaces are hypo-osmolar. In this setting, reduced or hypotonic osmolarity oral rehydration solutions are indicated. When oral rehydration is not possible due to etiologies such as feeding aversion, the route of choice is nasogastric, and parenteral rehydration and nutrition should be avoided when possible.

Initial intravenous therapy in profound dehydration is designed to improve the circulation and expand extracellular volume. For patients with edema, the quality of fluid and the rate of administration might

require readjustment from recommended levels to avoid overhydration and pulmonary edema. Blood should be given if the patient is in shock and severely anemic. Potassium salts can be initiated early if urine output is good. Clinical improvement may be more rapid with magnesium therapy.

Children with chronic malnutrition are at risk for refeeding syndrome (see Chapter 63). Therefore initial calorie provision should not exceed the previous daily intake and is usually begun at 50–75% of estimated resting energy expenditure, with rapid increase to caloric goals once there are no severe abnormalities in sodium, potassium, phosphorus, calcium, or magnesium. Correction of malnutrition and catch-up growth are not part of the primary treatment of these children, but a nutrition rehabilitation plan is necessary.

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## 385.8 Enzyme Deficiencies

Abdul-Aziz K. Elkadri

### CARBOHYDRATE MALABSORPTION

Symptoms of carbohydrate malabsorption include loose watery diarrhea, flatulence, abdominal distention, and pain. Unless consumed in large amounts, children may remain asymptomatic. Disaccharidases are present on the brush border membrane of the small bowel. **Disaccharidase deficiency** can be caused by a genetic defect or secondary to damage to the small bowel epithelium, as occurs with infection or inflammatory disorders.

Nonabsorbed carbohydrates enter the large bowel and are fermented by intestinal bacteria, producing organic acids and gases such as methane and hydrogen. The gases can cause abdominal distension and discomfort, whereas the unabsorbed carbohydrates and the organic acids result in osmotic diarrhea characterized by an acidic pH and the presence of either reducing or nonreducing sugars in the stool. Hydrogen and methane gas can be detected in the breath as a sign of fermentation of unabsorbed carbohydrates (**hydrogen breath test**).

### LACTASE DEFICIENCY

**Congenital lactase deficiency** is rare and is associated with symptoms occurring on exposure to lactose in milk. Fewer than 50 cases have been reported worldwide. In patients with congenital lactase deficiency, five distinct disease causal variants in the coding region of the *LCT* gene were found. In most patients (84%), homozygosity for a nonsense variant, 4170T-A (Y1390X; OMIM 223000), designated Fin (major), was found.

**Primary adult-type hypolactasia** is caused by a physiologic decline in lactase activity that occurs following weaning in most mammals. The brush border lactase enzyme is expressed at low levels during fetal life; activity increases in late fetal life and peaks from term to 3 years, after which levels gradually decrease with age. This decline in lactase levels varies between ethnic groups. Lactase deficiency occurs in approximately 15% of White adults, 40% of Asian adults, and 85% of Black adults in the United States. Lactase is encoded by a single gene (*LCT*) of approximately 50 kb located on chromosome 2q21. C/T (-13910) polymorphisms of the *MCM6* gene were found to be related to adult-type hypolactasia in most European populations. In three African populations—Tanzanians, Kenyans, and Sudanese—three single-nucleotide polymorphisms, G/C(-14010), T/G(-13915), and C/G(-13907), were identified with lactase persistence and have derived alleles that significantly enhance transcription from the lactase gene promoter *in vitro*.

**Secondary lactose intolerance** follows small bowel mucosal damage (celiac disease, acute severe gastroenteritis) and is usually transient, improving with mucosal healing. Lactase deficiency can be diagnosed by the hydrogen breath test (2 g/kg up to 25 g) or by measurement of lactase activity in mucosal tissue retrieved by small bowel biopsy. Diagnostic testing is not mandatory, and often simple dietary changes that reduce or eliminate lactose from the diet relieve symptoms.

Treatment of lactase deficiency consists of a milk-free diet. A lactose-free formula (based on either soy or cow's milk) can be used in infants. In older children, low-lactose milk can be consumed. The addition of lactase to dairy products usually improves the symptoms.

Live-culture yogurt contains bacteria that produce lactase enzymes and is therefore tolerated in most patients with lactase deficiency. Hard cheeses and cottage cheeses have a small amount of lactose and are generally well tolerated.

### FRUCTOSE MALABSORPTION

Children consuming a large quantity of juice rich in fructose, corn syrup, or natural fructose in fruit juices can present with diarrhea, abdominal distention, and slow weight gain. Identification by history followed by the restriction of the amount of juice in the diet resolves the symptoms and helps avoid unnecessary investigations. A fructose hydrogen breath test can be helpful in the diagnosis of fructose malabsorption. The reason for fructose malabsorption is a reduced abundance of GLUT-5 transporter on the surface of the intestinal brush border membrane, which occurs in approximately 5% of the population.

### SUCRASE-ISOMALTASE DEFICIENCY

Sucrase-isomaltase (SI) deficiency is a rare autosomal recessive disorder with a complete absence of sucrase and reduced maltase digestive activity. The SI complex is composed of 1,927 amino acids encoded by a 3,385 bp messenger RNA. The gene locus on chromosome 3 has 30 exons spanning 106.6 kb. Most SI pathogenic variants result in a lack of enzyme protein synthesis (null variant). Posttranslational processing defects have also been identified.

Approximately 2% of Europeans and Americans are heterozygous for a causal variant. Sucrase deficiency is especially common in indigenous Greenlanders (estimated 5%) in whom it is often accompanied by lactase deficiency. Gene variants of the SI are found to have some implications in irritable bowel syndrome (IBS), as they were found more often in patients with IBS than in controls.

Symptoms of SI deficiency usually begin when the infant is exposed to sucrose or a glucose polymer diet. This can occur with ingestion of non-lactose-based infant formula or on the introduction of pureed food, especially fruits and sweets. Diarrhea, abdominal pain, and poor growth are observed. Occasionally, patients present with symptoms in late childhood or even adult life, but careful history often indicates that symptoms appeared earlier. Diagnosis of SI malabsorption requires acid hydrolysis of stool for reducing substances due to the fact that sucrase is a nonreducing sugar. Alternatively, hydrogen breath testing can be used, as well as direct enzyme assay of small bowel biopsy or genetic testing.

The mainstay of treatment is lifelong dietary restriction of sucrose-containing foods, although symptoms may diminish with age. Enzyme replacement with a purified yeast enzyme sacrosidase is a highly effective adjunct to dietary restriction.

### GLUCOSE-GALACTOSE MALABSORPTION

More than 30 different pathogenic variants of the sodium/glucose co-transporter gene (*SGLT1*) have been identified. These variants cause a rare autosomal recessive disorder of intestinal glucose and galactose/ $\text{Na}^+$  co-transport system that leads to osmotic diarrhea. Because most dietary sugars are polysaccharides or disaccharides with glucose or galactose moieties, diarrhea follows the ingestion of glucose, breast milk, or conventional lactose-containing formulas. Dehydration and acidosis can be severe, resulting in death.

Stools are noted to be acidic and contain sugar. Patients with the defect have normal absorption of fructose, and their small bowel function and structure are normal in all other aspects. Intermittent or permanent glycosuria after fasting, or after a glucose load, is a common finding due to the transport defect also being present in the kidney. The presence of reducing substances in watery stools and slight glycosuria despite low blood sugar levels is highly suggestive of glucose-galactose malabsorption. Malabsorption of glucose and galactose is easily identified using the breath hydrogen test. It is safe to perform the first test with a dose of

0.5 g/kg of glucose or galactose; if necessary, a second test can be performed using 2 g/kg. Breath hydrogen will rise more than 20 ppm. Biopsy of the small intestine is useful to document a normal villous architecture and normal disaccharidase activities and to rule out other etiologies. The identification of causal variants of *SLGT1* make it possible to perform prenatal screening in families at risk for the disease.

Treatment consists of rigorous restriction of glucose and galactose. Fructose, the only carbohydrate that can be given safely, should be added to a carbohydrate-free formula at a concentration of 6–8%. This formula results in almost immediate cessation of diarrhea. Although the defect is permanent and lifelong, limited amounts of glucose, starches, or sucrose may be tolerated later in life.

### EXOCRINE PANCREATIC INSUFFICIENCY

Chapter 397 discusses disorders of exocrine pancreatic insufficiency (see Table 385.5). **Cystic fibrosis** is the most common congenital disorder associated with exocrine pancreatic insufficiency. Although rare, the next most common cause of pancreatic insufficiency in children is **Shwachman-Diamond syndrome**. Other rare disorders with exocrine pancreatic insufficiency include **Johanson-Blizzard syndrome** (severe steatorrhea, aplasia of alae nasi, deafness, hypothyroidism, scalp defects), **Pearson bone marrow syndrome** (sideroblastic anemia, variable degree of neutropenia, thrombocytopenia), and isolated pancreatic enzyme deficiency (lipase, colipase, trypsinogen, amylase). Enterokinase deficiency, a key enzyme produced in the proximal small bowel and responsible for the activation of trypsinogen to trypsin, manifests clinically as exocrine pancreatic insufficiency.

**Autoimmune polyendocrinopathy syndrome type 1**, a rare autosomal recessive disorder, is caused by pathogenic variants in the autoimmune regulator gene (*AIRE*). Patients develop chronic mucocutaneous candidiasis along with failure of the parathyroid gland, adrenal cortex, pancreatic  $\beta$  cells, gonads, gastric parietal cells, and thyroid gland. Pancreatic insufficiency and steatorrhea are associated with this condition.

### ENTEROKINASE (ENTEROPEPTIDASE) DEFICIENCY

Enterokinase (enteropeptidase) is a brush border serine protease enzyme of the small intestine responsible for the cleavage of trypsinogen to trypsin. This in turn results in the cascade activation of a number of other pancreatic enzymes. Deficiency of this enzyme results in severe diarrhea, malabsorption, failure to thrive, and hypoproteinemic edema shortly after birth.

The diagnosis can be established by measuring the enzyme level in intestinal tissue or by genetic testing, as enterokinase deficiency is caused by pathogenic variants in the serine protease-7 gene (*PRSS7*) on chromosome 21q21. Treatment of this rare autosomal recessive disorder consists of replacement with pancreatic enzymes and administration of a protein hydrolyzed formula with added MCT oil in infancy.

### TREHALASE DEFICIENCY

The disaccharide trehalose is mainly present in mushrooms and has been approved to add to dried food. It is hydrolyzed by the intestinal trehalase into two molecules of glucose. Trehalase deficiency has been reported in 8% of Greenlanders; only three cases of this deficiency have been reported elsewhere. In untreated celiac disease, the intestinal trehalase activity is reduced as those of other disaccharidases and recovers after introduction of a gluten-free diet.

### TRYPSINOGEN DEFICIENCY

Trypsinogen deficiency is a rare syndrome with symptomatology similar to that of enterokinase deficiency. Enterokinase catalyzes the conversion of trypsinogen to trypsin, which, in turn, activates the various pancreatic proenzymes, such as chymotrypsin, procarboxypeptidase, and proelastase, for their active forms. Deficiency of trypsinogen results in severe diarrhea, malabsorption, failure to thrive, and hypoproteinemic edema soon after birth.

The trypsinogen gene is encoded on chromosome 7q35. Treatment is the same as for enterokinase deficiency, with pancreatic enzymes and protein hydrolysate formula with added MCT oil in infancy.

## 385.9 Liver and Biliary Disorders Causing Malabsorption

Abdul-Aziz K. Elkadri

Absorption of lipids and lipid-soluble vitamins depends to a great extent on an adequate bile flow delivering BA to the small intestine, which helps mixed micelle formation of lipid droplets. Most liver and biliary disorders lead to impairment of the bile flow, contributing to malabsorption of long-chain fatty acids and fat-soluble vitamins such as A, D, E, and K. Liver disorders associated with significant malabsorption and failure to thrive are mainly due to these categories:

In **PFIC syndromes and BA synthesis defects**, PFIC type 1 is associated with chronic diarrhea caused by a bile acid transport defect in the gut. It is not uncommon for these children to have symptomatic fat-soluble vitamin deficiencies and suffer from pathologic fractures and peripheral neuropathy.

Children with lipid storage disorders (e.g., **Wolman disease**) also manifest with severe failure to thrive and multiple vitamin deficiencies.

Children with biliary disorders such as biliary atresia after portoenterostomy surgery (Kasai portoenterostomy), cystic fibrosis, neonatal sclerosing cholangitis, Alagille syndrome, and sclerosing cholangitis constitute another major group of disorders with reduced bile flow where malabsorption could be a significant challenge.

Chronic liver disease of any etiology could also lead to lipid malabsorption mechanisms. In addition, severe portal hypertension can lead to portal hypertensive enteropathy, resulting in poor absorption of nutrients.

Decompensated liver disease leads to anorexia and increased energy expenditures, further widening the gap between calorie intake and net absorption and leading to severe malnutrition. Adequate management of nutrition is essential to improve the outcome with or without liver transplantation. This is usually achieved by using MCT-rich milk formula, supplemental vitamins, and continuous or bolus enteral feed where oral intake is poor.

**Vitamin D deficiency** is commonly observed on biochemical tests, and children can present with pathologic fractures. Simultaneous administration of vitamin D with the water-soluble vitamin E preparation (TPGS 1,000 succinate) enhances absorption of vitamin D as well. In young infants with cholestasis, oral vitamin D<sub>3</sub> is given at a dose of 1,000 IU/kg/24 hr. After 1 month, if the serum 25-hydroxyvitamin D level continues to be low, intramuscular administration of 10,000 units/kg or maximum of 60,000 is recommended. Monitoring of 25-hydroxy vitamin D serum levels every 1–2 months is recommended in children with severe cholestasis.

**Vitamin E deficiency** in patients with chronic cholestasis is not usually symptomatic but can manifest as a progressive neurologic syndrome, including peripheral neuropathy (manifesting as loss of deep tendon reflexes and ophthalmoplegia), cerebellar ataxia, and posterior column dysfunction. Early in the course, findings are partially reversible with treatment; late features may not be reversible. It may be difficult to identify vitamin E deficiency because the elevated blood lipid levels in cholestatic liver disease can falsely elevate the serum vitamin E level. Therefore it is important to also obtain serum lipid levels to measure the ratio of serum vitamin E to total serum lipids. A normal level for patients younger than 12 years of age is >0.6, and for patients older than 12 years is >0.8. Neurologic sequelae can be prevented with the use of an oral water-soluble vitamin E preparation (TPGS, Liqui-E) at a dose of 25–50 IU/day in neonates and 15–25 IU/kg/day in children.

**Vitamin K deficiency** can occur because of cholestasis and poor fat absorption. In children with liver disease, it is very important to differentiate between the coagulopathy related to vitamin K malabsorption and one secondary to the synthetic failure of coagulation factors from the liver. A single dose of vitamin K administered intravenously does not correct the prolonged prothrombin time in liver failure but will help correct the deficiency state within a few hours. Easy bruising may be the first sign. In neonatal cholestasis, coagulopathy because of vitamin K deficiency can manifest with intracranial bleeding with devastating consequences, and prothrombin time should be routinely measured to monitor for deficiency in children with cholestasis. All children with cholestasis should receive regular vitamin K supplementation.

**Vitamin A deficiency** is rare and is associated with night blindness, xerophthalmia, and increased mortality if patients contract measles. Serum vitamin A levels should be monitored, and adequate supplementation considered. Caution should be observed with supplementation, as high levels of vitamin A can cause liver damage.

### 385.10 Rare Inborn Defects Causing Malabsorption

Abdul-Aziz K. Elkadri

Congenital (primary) malabsorption disorders originate from a multitude of defects, which includes structural or functional defects of enterocytes or disorders involving other cellular lineages of the GI tract such as enteroendocrine or immune cells (see Chapters 385.3 and 388). Integral membrane proteins are another class of primary disorders of malabsorption as they fulfill the function of transporter of nutrients as a receptor or channel across the apical or basolateral membrane of enterocytes. Histologic examination of the mucosa of the small and large bowel is typically normal. Most of these disorders are rare and inherited in an autosomal recessive pattern as they are typically a loss of function of a protein. With increased access to genetic sequencing, patients are being discovered to carry pathologic variants in genes traditionally thought to carry a traditional phenotype. This broader phenotype is thought to be possibly due to modifier genes and variable penetrance and may provide us with a better understanding of the spectrum of these disorders.

## DISORDERS OF CARBOHYDRATE ABSORPTION

These are described in Chapter 385.9.

Patients with **Fanconi-Bickel syndrome** present with tubular nephropathy, hypophosphatemic rickets, hepatomegaly, and nephromegaly due to glycogen accumulation in liver and small bowel; failure to thrive; and fasting hypoglycemia and postprandial hyperglycemia. The disorder is caused by homozygous pathogenic variants of GLUT2 (SLC2A2), the facilitative monosaccharide transporter at the basolateral membrane of enterocytes, hepatocytes, renal tubules, pancreatic islet cells, and cerebral neurons. Patients exhibit postprandial hyperglycemia secondary to low insulin secretion (impaired glucose-sensing mechanisms in  $\beta$  cells) and fasting hypoglycemia due to altered glucose transport out of the liver. The increased intracellular glucose level inhibits glycogen degradation leading to intracellular glycogen accumulation. Similarly, altered monosaccharide transport out of enterocytes may be responsible for the putative glycogen accumulation and result in the diarrhea and malabsorption observed in some patients. Therapy includes the substitution of electrolyte losses and vitamin D and supplying uncooked cornstarch to prevent hypoglycemia. Patients who present in the neonatal period need frequent small meals and galactose-free milk.

## DISORDERS OF AMINO ACID AND PEPTIDE ABSORPTION

Protein digestion and absorption in the intestine is accomplished by a combination of proteases, peptidases, and transporters of peptides and amino acids. Amino acid transporters are essential for the absorption and transport of amino acids from luminal nutrients, through intracellular transfer and finally between cellular compartments. Due to their ontogenic origins, enterocytes and renal tubules share similar amino acid transporters. The highest intestinal transporter activity is found in the jejunum. The transporters causing Hartnup disease, cystinuria, iminoglycinuria, and dicarboxylic aminoaciduria are in the apical membrane, and those causing **lysinuric protein intolerance (LPI)** and blue diaper syndrome are anchored in the basolateral membrane of the intestinal epithelium.

Dibasic amino acids, including cystine, ornithine, lysine, and arginine, are taken up by the Na-independent heterodimeric transporter protein complex made up of SLC3A1 and SLC7A9. Cystinuria, a defect in this transporter, is the most common primary inherited aminoaciduria. This disorder is not associated with any GI or nutritional

consequences because of compensation by an alternative transporter. However, hypersecretion of cystine in the urine leads to recurrent cystine stones, which account for up to 6–8% of all urinary tract stones in children. Ample hydration, urine alkalinization, and cystine-binding thiol drugs can increase the solubility of cystine. Cystinuria type A (SLC3A1), or type 1 in the phenotypic classification, is inherited as an autosomal recessive trait, whereas cystinuria type B, classified phenotypically as type II and III, is due to pathogenic variants in SLC7A9. Parents of patients with type B cystinuria have increased cystine levels but do not form stones, which suggests that it is likely inherited in an autosomal dominant manner with incomplete penetrance. Cystinuria type I has been described in association with 2p21 deletion syndrome and hypotonia-cystinuria syndrome.

Lysinuric protein intolerance (LPI) is the second most common disorder of amino acid transport (see Chapter 105.14). It is caused by the  $\gamma^+$ LAT-1 (SLC7A7) subunit of the cationic amino acid transporter present at the basolateral membrane of the intestinal and renal epithelium and causes a failure to deliver cytosolic dibasic cationic amino acids into the paracellular space. This defect is not compensated by the SLC3A1/SLC7A9 transporter at the apical membrane. The symptoms of LPI, which appear after weaning, include diarrhea, failure to thrive, hepatosplenomegaly, nephritis, respiratory insufficiency, alveolar proteinosis, pulmonary fibrosis, and osteoporosis. Abnormalities of the bone marrow with anemia and thrombocytopenia have also been described in a subgroup of LPI patients. The disorder is characterized by low plasma concentrations of the dibasic amino acids lysine, arginine, and ornithine, high concentrations of glutamine, alanine, glycine, serine, and proline, and a massive urinary excretion of lysine, as well as orotic acid, ornithine, and arginine to a lesser extent. Hyperammmonemia episodes and coma along with emesis usually develop after fasting or with the ingestion of large amounts of protein, specifically alanine, likely due to a deficiency of intramitochondrial ornithine. Some patients show moderate intellectual disability. Cutaneous manifestations can include alopecia, perianal dermatitis, and sparse hair. Some patients learn to avoid protein-containing foods. Immune dysfunction is potentially attributable to nitric oxide overproduction secondary to arginine intracellular trapping and may be the underlying pathophysiological route explaining many LPI complications such as hemophagocytic lymphohistiocytosis, autoimmune disorders, and an incompletely characterized immune deficiency. Treatment includes dietary protein restriction (<1.5 g/kg/day) and orally administered citrulline (100 mg/kg/day), which is well absorbed from the intestine and carnitine supplementation.

**Hartnup disease** is characterized by the malabsorption of all neutral amino acids (except proline), including the essential amino acid tryptophan. It is characterized by aminoaciduria, photosensitive pellagra-like rash, headaches, cerebellar ataxia, delayed intellectual development, and diarrhea. The clinical spectrum ranges from asymptomatic to severely affected with progressive neurodegeneration leading to death by adolescence. SLC6A19, which is the major luminal sodium-dependent neutral amino acid transporter of small intestine and renal tubules, has been identified as the defective protein. A similar phenotype is observed in defects in collectrin (CLTRN), and the requirement of angiotensin-converting enzyme 2 may explain the phenotypic heterogeneity of Hartnup disorder. Tryptophan is a precursor of nicotinamide adenine dinucleotide phosphate biosynthesis; therefore the disorder can be treated by nicotinamide in addition to a diet of 4 g protein/kg. The use of lipid-soluble esters of amino acids and tryptophan ethyl ester has also been reported.

Defects in specific, basolateral tryptophan transporter (SLC16A10) are the cause of **blue diaper syndrome** (indicanuria, Drummond syndrome). Intestinal bacteria convert the unabsorbed tryptophan to indican, which is responsible for the bluish discoloration of the urine after its hydrolysis and oxidation. Symptoms can include digestive disturbances such as vomiting, constipation, poor appetite, failure to thrive, hypercalcemia, nephrocalcinosis, fever, irritability, and ocular abnormalities.

The underlying defect of **iminoglycinuria** is the malabsorption of proline, hydroxyproline, and glycine as a consequence of the proton amino acid transporter SLC36A2 defect, with a possible participation

of modifier genes, one of which (*SLC6A20*) is present in the intestinal epithelium. This disorder is usually benign, but sporadic cases with encephalopathy, intellectual disability, deafness, blindness, kidney stones, hypertension, and gyrate atrophy have been described.

The neuronal glutamate transporter EAAT3 (*SLC1A1*) is affected in **dicarboxylic aminoaciduria**. This carrier is present in the small intestine, kidney, and brain and transports the anionic acids L-glutamate, L- and D-aspartate, and L-cysteine. There are single-case reports indicating that this disorder could be associated with hyperprolinemia and neurologic symptoms such as POLIP (polyneuropathy, ophthalmoplegia, leukoencephalopathy, intestinal pseudoobstruction) syndrome.

## DISORDERS OF FAT TRANSPORT

These are described in Chapters 106.3 and 385.3.

## DISORDERS OF VITAMIN ABSORPTION

Transporters and receptors of the intestinal epithelium have been described for water-soluble but not fat-soluble vitamins with the latter absorbed primarily into enterocytes by passive diffusion after the emulsification of fats by bile salts. Transfer proteins (retinol-binding protein [RBP4] and α-tocopherol transfer protein [TTP1]) have been involved in deficiency states of vitamins E (spinocerebellar ataxia) and A (ophthalmologic signs), respectively.

**Vitamin B<sub>12</sub> (cobalamin)** is synthesized exclusively by microorganisms and is acquired mostly from meat and milk (see Chapter 503.2). Its absorption starts with the removal of cobalamin from dietary protein by gastric acidity and its binding to haptocorrin. In the duodenum, pancreatic proteases hydrolyze the cobalamin-haptocorrin complex, allowing the binding of cobalamin to intrinsic factor (IF), which originates from parietal cells from the stomach. The receptor of the cobalamin-IF complex (Cbl-IF) is located at the apical membrane of the ileal enterocytes and represents a heterodimer consisting of cubilin (CUBN) and amnionless (AMN). After endocytic uptake into endosomes, the Cbl-IF and its receptor binds to megalin and forms a cobalamin-transcobalamin (TC)-2 complex (after cleavage of IF) for further transcytosis. Vitamin B<sub>12</sub> exits the lysosome via LMBD1 and ABCD4 and is released to the bloodstream most likely through the basolateral transporter multifunctional multidrug resistance protein 1 (MRP1). Biologically available circulating vitamin B<sub>12</sub> is bound to TC, a nonglycosylated protein that carries 10–30% of the total vitamin B<sub>12</sub>. TC-vitamin B<sub>12</sub> complexes enter the cells via two members of the LDL receptor gene family, CD320 and renal Lrp2/megalin. As a cofactor for methionine synthase, cobalamin converts homocysteine to methionine. Cobalamin deficiency can be caused by inadequate intake of the vitamin (e.g., breastfeeding by mothers on a vegan diet) and primary or secondary achlorhydria including autoimmune gastritis, exocrine pancreatic insufficiency, bacterial overgrowth (see Chapter 385.4), ileal disease (Crohn disease, see Chapter 382.2), ileal (or gastric) resection, infections (fish tapeworm), and Whipple disease (see Chapter 388).

Clinical signs of congenital cobalamin malabsorption, which usually appear from a few months to more than 10 years, are pancytopenia including **megaloblastic anemia**, fatigue, failure to thrive, and neurologic symptoms, including developmental delay. Recurrent infections and bruising may be present. Laboratory evaluation indicates low serum cobalamin, hyperhomocysteinemia, methylmalonic aciduria, and mild proteinuria. The Schilling test is useful to differentiate between a lack of IF and the malabsorption of cobalamin. Several rare autosomal recessive disorders of congenital cobalamin deficiency affect absorption and transport of cobalamin (in addition to seven other inherited defects of cobalamin metabolism). These include pathogenic variants of the gastric IF (*GIF*) gene with absence of IF (but normal acid secretion and lack of autoantibodies against IF or parietal cells), variants of the *AMN* and *CUBN* gene subunits of the Cbl-IF receptor in ileum (**Imerslund-Grasbeck syndrome**), and variants in the TC 2 cDNA. Two inborn defects were identified recently in the genes encoding LMBD1 and ABCD4 transporters and are responsible for the rare inborn defect in Cbl-IF, which results in the trapping of free vitamin B<sub>12</sub> in lysosomes. These disorders require long-term parenteral cobalamin treatment: intramuscular injections of cobalamin. High-dose substitution with oral

cyanocobalamin (1 mg biweekly) does not seem to be sufficient for all patients with congenital cobalamin deficiency. Intramuscular cobalamin injections of 1000 mcg/day for 7 days, then three times a week for 3 weeks, then once a month for 3 months, followed by a change to 1000 mcg daily oral cobalamin has been successful in some cases.

**Folate** is an essential vitamin required to synthesize methionine from homocysteine. It is found mainly in green leafy vegetables, legumes, and oranges. After its uptake by enterocytes, folate is converted to 5-methyltetrahydrofolate. Secondary folate deficiency is caused by insufficient folate intake, villous atrophy (e.g., celiac disease, inflammatory bowel disease), treatment with phenytoin and trimethoprim, among others (see Chapter 503.1). Several inherited disorders of folate metabolism and transport have been described.

Three mammalian folate transporter systems have been described in a variety of tissues: (1) the bidirectional reduced folate carrier 1 (RFC1, *SLC19A1*), (2) the glycosyl-phosphatidylinositol-anchored folate receptors (FOLR1, FOLR2, and FOLR4) responsible for folate-receptor mediated endocytosis, and (3) the human proton-coupled folate transporter (PCFT). Hereditary **folate malabsorption** is characterized by a defect of the PCFT of the brush border, leading to impaired absorption of folate in the upper small intestine as well as impaired transport of folate into the central nervous system. Symptoms of congenital folate malabsorption are diarrhea, failure to thrive, megaloblastic anemia presenting in the first few months of life, glossitis, infections (*Pneumocystis jirovecii*) with episodes of hypogammaglobulinemia, and neurologic abnormalities (seizures, intellectual impairment, and basal ganglia calcifications). Macrocytosis, with or without neutropenia, multilobulated polymorphonuclear cells, increased lactate dehydrogenase and bilirubin, increased saturation of transferrin, and decreased cholesterol can also be found. Low levels of folate are present in serum and cerebrospinal fluid. Plasma homocysteine concentrations as well as urine excretion of formiminoglutamic acid and orotic acid are elevated. Long-standing deficiency of folate (around 3-4 months) is best documented using red cell folate. Therapy involves large doses of oral (up to 150-400 mg/day of folic acid) or systemic (intrathecal) folate. Folinic acid has been used in intramuscular and/or oral form, more readily correcting the systemic and CSF folate levels. 150-400 mg of oral folinic acid daily has been used (starting dose 10-15 mg/kg daily). CSF folate levels should be followed, monitoring for clinical response of the systemic signs of disease. Sulfasalazine and methotrexate are potent inhibitors of PCFT. Therefore folate deficiency may develop during treatment with these drugs. Although the RFC1 is ubiquitously expressed, including the brush border membrane in the small intestine, involvement of RFC1 in intestinal folate uptake has not been confirmed.

The molecular basis of intestinal transport of other water-soluble vitamins such as vitamin C (Na<sup>+</sup>-dependent vitamin C transporters 1 and 2), pyridoxine/vitamin B<sub>6</sub>, and biotin/vitamin B<sub>5</sub> (Na<sup>+</sup>-dependent multivitamin transporter) have been described; congenital defects of these transporter systems have not yet been found in humans. A **thiamine/vitamin B<sub>1</sub>-responsive megaloblastic anemia** syndrome, which is associated with early-onset type 1 diabetes mellitus and sensorineural deafness, is caused by pathogenic variants of the thiamine transporter protein gene, THTR-1 (*SLC19A2*), present in the brush border.

## DISORDERS OF ELECTROLYTE AND MINERAL ABSORPTION

**Congenital chloride diarrhea (CCD)** is a rare but relatively common group of congenital diarrheal disorders. It includes defects in *SLC26A3*, encoding a Na<sup>+</sup>-independent Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> exchanger within the apical membrane of ileal and colonic epithelium, and *GUCY2C*, encoding a guanylate cyclase receptor in the intestine for the bacterial heat-stable enterotoxin. Defects in *SLC26A3* have been found to have a prevalence in Finland of 1:20,000. Founder pathogenic variants have been described in Finnish, Polish, and Arab patients: V317del, I675-676ins, and G187X, respectively. The Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> exchanger absorbs chloride originating from gastric acid and the cystic fibrosis transmembrane conductance regulator and secretes bicarbonate into the lumen, neutralizing the acidity of gastric secretion.

Defects in *GUCY2C* have been identified, which leads to an autosomal dominant activation defect in guanylate cyclase C. This leads to

elevated levels of cyclic guanosine monophosphate (cGMP) and activation of the CFTR receptor. The mechanism is similar to the response to heat-stable enterotoxins from *Escherichia coli* and results in a chloride-losing diarrhea. Interestingly, a homozygous recessive inactivation defect has been described in a Bedouin cohort resulting in a meconium ileus phenotype due to the inactivation of CFTR.

Prenatally, CCD is characterized by maternal polyhydramnios, dilated fetal bowel loops, and preterm birth. Newborns with CCD present with severe life-threatening *secretory diarrhea* during the first few weeks of life. Volvulus has been reported in few patients with CCD. Laboratory findings are metabolic alkalosis, hypochloremia, hypokalemia, and hyponatremia (with high plasma renin and aldosterone activities). Fecal chloride concentrations are >90 mmol/L and exceed the sum of fecal sodium and potassium. Early diagnosis and aggressive lifelong enteral substitution of KCl in combination with NaCl (chloride doses of 6–8 mmol/kg/day for infants and 3–4 mmol/kg/day for older patients) prevent mortality and long-term complications (such as urinary infections, hyperuricemia with renal calcifications, renal insufficiency, and hypertension) and allow normal growth and development. Orally administered proton pump inhibitors, cholestyramine, and butyrate can reduce the severity of diarrhea. However, febrile diseases are likely to exacerbate symptoms as a consequence of severe dehydration and electrolyte imbalances. (See Chapter 71 for fluid and electrolyte management.) The diarrheal symptoms usually tend to regress with age, but the phenotype is highly variable. In familial cohorts carrying the same variant, individuals have demonstrated an increased incidence of inflammatory bowel disease as well as a phenotype of irritable bowel syndrome and motility issues.

The classic form of **congenital sodium diarrhea** (CSD) manifests with polyhydramnios, massive *secretory diarrhea*, severe metabolic acidosis, alkaline stools (fecal pH >7.5), and hyponatremia because of fecal losses of Na<sup>+</sup> (fecal Na<sup>+</sup> >70 mmol/L). Urinary secretion of sodium is low to normal. CSD is clinically and genetically heterogeneous. A syndromic form of CSD with superficial punctate keratitis, choanal or anal atresia, hypertelorism, and corneal erosions has been related to pathologic variants in *SPINT2*, which encodes a serine-protease inhibitor whose pathophysiological action on intestinal Na<sup>+</sup> absorption is unclear. This form of CSD is also referred to as **congenital tufting enteropathy** (intestinal epithelial dysplasia) as it often shows clustered enterocytes that form "tufts" with branching crypts on histology (described in Chapter 385.3). Pathogenic variants in *SLC9A3*, the gene encoding the Na<sup>+</sup>/H<sup>+</sup> antiporter 3 (NHE3), the major intestinal brush border Na<sup>+</sup>/H<sup>+</sup> exchanger, were identified in nine patients with nonsyndromic CSD. IBD developed in two of nine patients with recessive *SLC9A3* pathogenic variants, implicating NHE3 in the pathogenesis of IBD in a subset of patients.

The congenital form of **acrodermatitis enteropathica** manifests with severe deficiency of body zinc soon after birth in bottle-fed children or after weaning from breastfeeding (see Chapter 712). Clinical signs of this disorder are anorexia, diarrhea, failure to thrive, humoral and cell-mediated immunodeficiency (poor wound healing, recurrent infections), male hypogonadism, skin lesions (vesiculobullous dermatitis on the extremities and perirectal, perigenital, and perioral regions, and alopecia), and neurologic abnormalities (tremor, apathy, depression, irritability, nystagmus, photophobia, night blindness, and hypogeusia). The genetic defect of acrodermatitis enteropathica is caused by a pathogenic variant in the Zrt-Irt-like protein 4 (ZIP4, *SLC39A4*), normally expressed on the apical membrane, which enables the uptake of zinc into the cytosol of enterocytes. The zinc-dependent alkaline phosphatase and plasma zinc levels are low. Paneth cells in the crypt of the small intestinal mucosa show inclusion bodies. Acrodermatitis enteropathica requires long-term treatment with elemental zinc at 1–3 mg/kg/day. Maternal zinc deficiency impairs embryonic, fetal, and postnatal development. Chapter 72 described the *acquired* forms of zinc deficiency. Transient neonatal zinc deficiency is an autosomal dominant disorder with similar manifestations as acrodermatitis enteropathica. The disease is caused by pathogenic variants in ZnT2, the transporter responsible for supplying human milk with zinc.

**Menkes disease** and **occipital horn syndrome** are both caused by pathogenic variants in the gene encoding Cu<sup>2+</sup> transporting adenosine

triphosphatase (ATPase), α-polypeptide (ATP7A), which is also called Menkes or MNK protein. ATP7A is mainly expressed by enterocytes, placental cells, and the central nervous system, and is localized in the *trans*-Golgi network for copper transfer to enzymes in the secretory pathway or to endosomes to facilitate copper efflux. Copper values in liver and brain are low in contrast to an increase in mucosal cells, including enterocytes and fibroblasts. Plasma copper and ceruloplasmin levels decline postnatally. Clinical features of Menkes disease are progressive cerebral degeneration (convulsions), feeding difficulties, failure to thrive, hypothermia, apnea, infections (urinary tract), hypertelorism, hair abnormalities (kinky hair), hypopigmentation, bone changes, and cutis laxa. Patients with the classic form of Menkes disease usually die before the age of 3 years. A therapeutic trial with copper-histidinase should start before the age of 6 weeks. In contrast to Menkes disease, occipital horn syndrome usually manifests during adolescence with borderline intelligence, craniofacial abnormalities, skeletal dysplasia (short clavicles, pectus excavatum, genu valgum), connective tissue abnormalities, chronic diarrhea, orthostatic hypotension, obstructive uropathy, and osteoporosis. It should be differentiated from Ehlers-Danlos syndrome type V.

Active calcium absorption is mediated by the transient receptor potential channel 6 (TRPV6) at the brush border membrane, calbindin, and the Ca-ATPase, or the Na<sup>+</sup>-Ca<sup>2+</sup> exchanger for calcium efflux at the basolateral membrane within the proximal small bowel. A congenital defect of these transporters has not yet been described.

Intestinal absorption of dietary magnesium, which occurs via the transient receptor potential channel TRPM6 at the apical membrane, is impaired in familial **hypomagnesemia with secondary hypocalcemia**, which manifests with neonatal seizures and tetany.

**Intestinal iron absorption** consists of several complex regulated processes starting with the uptake of heme-containing iron by heme carrier protein 1 (HCP1) and Fe<sup>2+</sup> (after luminal reduction of oxidized Fe<sup>3+</sup>) by the divalent metal transporter 1 (DMT1) at the apical membrane, followed by the efflux of Fe<sup>2+</sup> by ferroportin 1 (also called the iron-regulated transporter) at the basolateral membrane of duodenal enterocytes. Hepatic hormone hepcidin has a key role in iron homeostasis by interacting with ferroportin. When it binds to ferroportin, hepcidin induces phosphorylation of the iron exporter, causing its internalization and degradation. A decrease in the ferroportin protein level on the cell surface inhibits iron export from intracellular pools. Thus hepcidin controls plasma iron levels by reducing iron absorption in the gut, lowering iron release from hepatocytes, and preventing iron recycling by macrophages. Hepcidin deficiency causes iron overload in hereditary hemochromatosis and iron-loading anemias, whereas hepcidin excess causes or contributes to the development of iron-restricted anemia in inflammatory diseases, infections, some cancers, and chronic kidney disease. Pathogenic variants of the ferroportin 1 gene have been found in the autosomal dominant form of **hemochromatosis** type 4. Variants within the hemochromatosis (*HFE*) gene (Cys282 Tyr, His63Asn, Ser65Cys) of classic hemochromatosis reduce the endocytic uptake of diferric transferrin by the transferrin receptor-1 at the basolateral membrane of the intestinal epithelium. Hepcidin is the defective gene of juvenile hemochromatosis (type 2, subtype B). Elevated hepcidin results in hypoferremia and insufficient supply of iron for erythropoiesis, leading to different types of anemia. The underlying causes of hepcidin elevation in iron-restricted anemias are varied. An example of a genetic cause of hepcidin increase is the familial **iron-refractory iron deficiency anemia** (IRIDA), an autosomal recessive disorder caused by a pathogenic variant in matriptase-2 (*TMPRSS6*), a negative regulator of hepcidin expression. This anemia is characterized by very low plasma iron levels, unresponsiveness to oral iron therapy, and partial correction by parenteral iron. Pathologic variants in the DMT1 transporter (*SLC11A2*) are another cause of IRIDA. The development of severe microcytic, hypochromic anemia typifies these patients; however, surprisingly, some of them load iron in the liver.

## Chapter 386

# Intestinal Transplantation in Children with Intestinal Failure

Jorge D. Reyes and Danielle R. Wendel

The introduction of tacrolimus and the development of the abdominal multiorgan procurement techniques allowed the tailoring of various types of intestine grafts that can contain other intraabdominal organs, such as the liver, pancreas, and stomach. The understanding that the liver protects the intestine against rejection demonstrates the interaction between recipient and donor immunocytes (host-versus-graft and graft-versus-host), which under the cover of immunosuppression allows varying degrees of graft acceptance and eventual minimization of drug therapy. *Over the past several years the number of patients placed on the list for and those undergoing intestinal transplantation has decreased, which is a result of improvements in the care of patients with intestinal failure (IF) under a multidisciplinary intestinal care team management.* Advances in care include prevention and treatment of intestinal failure-associated liver disease (IFALD), advances in central venous catheter care, improved prevention of life-threatening central line-associated bloodstream infections, and corrective surgery enhancing absorptive surface and motility, which have led to increased survival and decreased morbidity.

### INDICATIONS FOR INTESTINAL TRANSPLANT

IF describes a patient who has lost the ability to maintain nutritional support and adequate fluid requirements needed to sustain growth with their own intestine and is permanently dependent on parenteral nutrition (PN). The majority of these patients have short bowel syndrome as a result of a congenital deficiency or acquired condition (see Chapter 385.6). In others, the cause of IF is a functional disorder of motility or absorption (Table 386.1). Rarely do patients receive intestinal transplants for benign neoplasms, hepatic failure secondary to acute diffuse intestinal infarction, and failure of a first intestinal transplant. The complications of IF include loss of venous access, life-threatening infections, and IFALD.

**Table 386.1** Causes of Intestinal Failure in Children Requiring Transplantation

SHORT BOWEL
<ul style="list-style-type: none"> <li>• Volvulus</li> <li>• Gastrochisis</li> <li>• Necrotizing enterocolitis</li> <li>• Intestinal atresia</li> <li>• Trauma</li> </ul>
INTESTINAL DYSMOTILITY
<ul style="list-style-type: none"> <li>• Intestinal pseudoobstruction</li> <li>• MMIHS</li> <li>• Intestinal aganglionosis (Hirschsprung disease)</li> </ul>
ENTEROCYTE DYSFUNCTION
<ul style="list-style-type: none"> <li>• Microvillus inclusion disease</li> <li>• Tufting enteropathy</li> <li>• Other congenital enteropathies</li> </ul>
TUMORS
<ul style="list-style-type: none"> <li>• Invasive intraabdominal desmoid tumor</li> </ul>
VASCULAR
<ul style="list-style-type: none"> <li>• Acute diffuse intestinal infarction with hepatic failure</li> </ul>

MMIHS, megacystis microcolon intestinal hypoperistalsis syndrome.

### Paucity of Venous Access

Administration of PN requires the insertion of a centrally placed venous catheter, there being only six readily accessible sites (bilateral internal jugular, subclavian, iliac veins). The loss of venous access generally occurs in the setting of recurrent catheter sepsis and thrombosis. Children who have lost three of four upper body central veins (right or left subclavian or internal jugular) or have an occlusion of a brachiocephalic vein should be considered for intestinal transplant evaluation due to the risk of losing the ability to provide PN.

### Life-Threatening Infections

Life-threatening infections are usually catheter related, although their frequency is decreasing with improvements in central venous catheter care including antimicrobial locks. The absence of significant length of intestine is often associated with abnormal motility of the residual bowel (producing both delayed and/or rapid emptying), with varying degrees of bacterial overgrowth and translocation as a consequence of intestinal inflammation, loss of intestinal barrier function, and/or loss of gut immunity. This situation contributes to IFALD, multisystem organ failure, and metastatic infectious foci in lungs, kidneys, liver, bone, and the brain.

### Liver Disease

The development of IFALD is the most serious complication of IF and may be a consequence of the toxic effects of PN on hepatocytes, a disruption of bile flow as a result of lack of enteral intake, alterations in bile acid metabolism, the frequent occurrence of bacterial overgrowth/translocation, and sepsis with endotoxin release into the portal circulation, all often in the setting of a premature liver. Soy-based intravenous lipids may contribute to liver disease; the incidence of liver disease has decreased with the use of fish oil-based products. IFALD varies in frequency depending on the patient's age and the etiology of the IF; it is most common in neonates with extreme short gut. Initially characterized by cholestasis and inflammation, later phases involve steatosis and fibrosis. Cholestasis in IFALD is defined as direct/conjugated bilirubin >2 mg/dL and more than 20% of total bilirubin after other etiologies have been excluded. The histology includes cholestasis, bile ductular reaction, portal inflammation, steatosis, periportal fibrosis, and liver macrophages. Development of IFALD, as evidenced by cholestasis, is one of the greatest predictors of mortality in children with short bowel syndrome.

### TRANSPLANTATION OPERATION

#### Donor Selection

Intestinal grafts are usually procured from hemodynamically stable, ABO-identical brain-dead donors who have minimal clinical or laboratory evidence suggesting intraabdominal ischemia. Size matching varies according to age of the recipients, and present surgical techniques allow for significant reductions of the graft to achieve abdominal closure. Although the exact effect is still unknown, donor-specific antibodies (DSAs) have been linked to rejection and poor long-term outcomes in the recipient leading to increased use of pretransplant cross-matched results to improve organ allocation, especially in sensitized recipients. Exclusion criteria include a history of malignancy and intraabdominal evidence of infection; systemic viral or bacterial infections are not excluded. Donor preparation has been limited to the administration of systemic and enteral antibiotics. Prophylaxis for graft-versus-host disease with graft pretreatment using irradiation or a monoclonal antilymphocyte antibody has varied over time. Grafts have been preserved with the University of Wisconsin solution, as is the case with other types of abdominal organs.

### Types of Intestinal Grafts

Intestinal allografts are used in various forms, either alone (as an **isolated intestine graft**) or as a composite graft, which can include the liver, duodenum, and pancreas (**liver-intestine graft**). When this composite graft includes the stomach, and the recipient operation requires the removal of all of the patient's gastrointestinal tract (as with

intestinal pseudoobstruction) and liver, then this replacement graft is known as a **multivisceral graft**.

The procurement of these various types of grafts focuses on the preservation of the arterial vessels of celiac and/or superior mesenteric arteries, as well as appropriate venous outflow, which would include the superior mesenteric vein or the hepatic veins in the composite grafts. The larger composite grafts inherently retain the celiac and superior mesenteric arteries; this includes multivisceral grafts, liver plus small bowel grafts, and *modified multivisceral grafts* in which the liver is excluded, but the entire gastrointestinal tract is replaced, including the stomach. The isolated intestine graft retains the superior mesenteric artery and vein. This graft can be accomplished with preservation of the vessels going to the pancreas, when that organ has been allocated to another recipient. The graft that is to be used in a particular recipient is dissected out *in situ* and then removed after cardiac arrest of the donor, with core cooling of the organs, using an infusion of preservation solution (Fig. 386.1).

Various modifications in these grafts have included the preservation of visceral ganglia at the base of the arteries, the inclusion of donor duodenum and pancreas for the liver and intestine graft, the inclusion of colon, the reduction of the liver graft (into left or right side) and variable reduction of the intestine graft, and living donor intestine (4-foot segment of ileum) graft.

### The Recipient Operation

Because many children have had multiple previous abdominal operations, intestinal transplantation can be a formidable technical challenge; most children require replacement of the liver because of IFALD and often present with advanced liver failure. Transplantation of an isolated intestinal allograft involves exposure of the lower abdomen, infrarenal aorta, and inferior vena cava. Placement of vascular homografts using donor iliac artery and vein to these vessels allows arterialization and venous drainage of the intestinal graft. In patients who have retained their intestine and then undergo an enterectomy at the time of transplantation, use of the native superior mesenteric vessels is feasible.

Transplantation of a larger composite graft requires the removal and replacement of the native liver in the liver with intestine transplant, and complete abdominal exenteration in the multivisceral transplant. In a similar fashion, the infrarenal aorta is exposed for placement of an arterial conduit graft (donor thoracic aorta) for arterialization of the graft. The venous drainage is achieved to the retained hepatic veins, which are fashioned to a single conduit for anastomosis to the allograft liver.

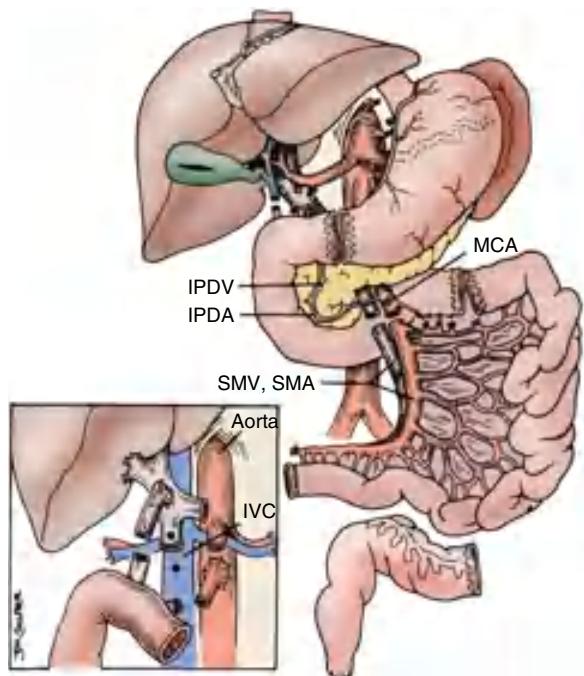
The intestinal anastomosis to native proximal and distal bowel is performed, leaving an enterostomy of distal allograft ileum; this will be used for routine posttransplantation surveillance endoscopy and

biopsy. This ostomy is closed 3–6 months after transplantation (Fig. 386.2).

### POSTOPERATIVE MANAGEMENT

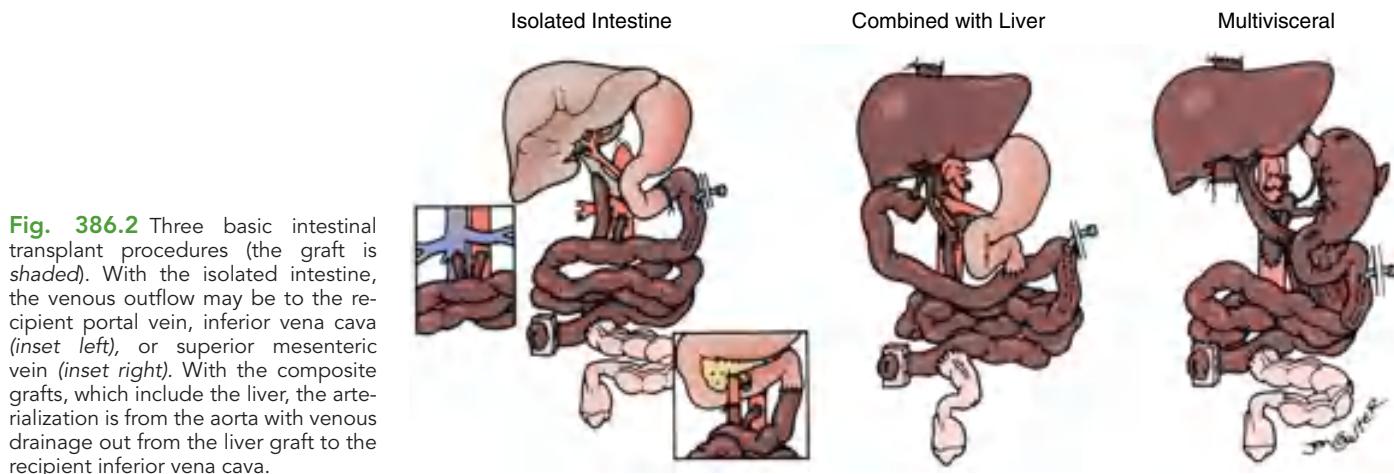
#### Immunosuppression

Successful immunosuppression for intestinal transplantation occurred with the introduction of tacrolimus in addition to corticosteroids. This required high levels of tacrolimus (in the nephrotoxic range), and although initial success rates were high, they were followed by rejection



**Fig. 386.1** Various abdominal organs can be dissected *in situ*, providing isolated or composite grafts to fit the individual patient's needs. Separation of intestine and pancreas is feasible, with preservation of the inferior pancreaticoduodenal artery (IPDA) and vein (IPDV). The use of vascular grafts from the donor allow connections to the superior mesenteric pedicle (artery [SMA] and vein [SMV]) to aorta and inferior vena cava (IVC) or portal vein (*inset*). MCA, Major coronary artery. (From Abu-Elmagd K, Fung J, Bueno J, et al. Logistics and technique for procurement of intestinal, pancreatic and hepatic grafts from the same donor. *Ann Surg*. 2000;232:680–697.)

### Small Bowel Transplantation Surgery



**Fig. 386.2** Three basic intestinal transplant procedures (the graft is shaded). With the isolated intestine, the venous outflow may be to the recipient portal vein, inferior vena cava (*inset left*), or superior mesenteric vein (*inset right*). With the composite grafts, which include the liver, the arterialization is from the aorta with venous drainage out from the liver graft to the recipient inferior vena cava.

rates of >80%, infection, and late drug toxicities, resulting in a gradual loss of grafts and patients. The next generation of protocols incorporated the addition of other agents, such as azathioprine, cyclophosphamide, induction with an interleukin (IL)-2 antibody antagonist, mycophenolate mofetil, and rapamycin. This modification resulted in a decreased incidence in the severity of initial rejection; the inability to decrease immunosuppression later did not allow for stabilization of long-term survival. The introduction of induction therapy has resulted in improved transplant survival as a result of a significant decrease in the incidence of rejection, permitting the gradual decrease of immunosuppressive drug therapy, resulting in a decline in drug toxicity events and infections. The most common induction regimen used is T-cell-depleting agents followed by IL-2 receptor antagonists. A mainstay of maintenance immunosuppression is tacrolimus and prednisone dual therapy, although many centers add mycophenolate mofetil or rapamycin for triple-drug regimens when patients have had episodes of rejection. By 1 year the majority of patients are on tacrolimus monotherapy.

### Allograft Assessment

There are no simple laboratory tools that allow assessment of the intestinal allograft. The gold standard for diagnosis of intestinal allograft rejection has been serial endoscopic surveillance and biopsies through the allograft ileostomy. Clinical signs and symptoms of rejection or infection of the allograft can overlap and mimic each other, producing either diarrhea or complete ileus with pseudoobstruction syndromes, abdominal pain, or gastrointestinal bleeding. Any changes in clinical status should warrant thorough evaluation for rejection with endoscopic biopsies and an evaluation for opportunistic infection, malabsorption, and other enteral infections.

The diagnosis of *acute rejection* is based on seeing destruction of crypt epithelial cells from apoptosis, in association with a mixed lymphocytic infiltrate. These histologic findings may or may not correlate with endoscopic evidence of injury, which varies from diffuse erythema and friability to ulcers and, in cases of severe rejection, exfoliation of the intestinal mucosa. *Chronic rejection* of the allograft can be diagnosed only through full-thickness sampling of the intestine, which shows the typical vasculopathy that can result in progressive ischemia of the allograft.

### Rejection and Graft-Versus-Host Disease

Acute rejection rates for the intestinal allograft are significantly higher than with any other organ, in the range of 60–70%, and severe rejection requiring the use of antilymphocyte antibody preparations may be as high as 30%. Triple-drug regimens and the use of IL-2 antibody inhibitors have resulted in significant decreases in rejection rates; nonetheless, the amount of immunosuppression was incompatible with improvements in long-term patient and graft survival. Rejection rates of 40% are achievable with the use of antilymphocyte globulin. These protocols induce varying degrees of *prope tolerance* (*or almost tolerant*), which can eventually allow for minimization of immunosuppression, thus reducing the risk of drug toxicity and infection. Vascular rejection has been an uncommon occurrence, and chronic rejection has been seen in approximately 10–15% of cases.

Many intestine transplant recipients are immunologically sensitized, increasing the risk of DSA formation. DSA can be pre-formed before transplant or develop de novo afterward. While the negative effects of DSA have been recognized in other types of solid organ transplant for years, the effects in intestinal transplants are less clear. Studies show increased episodes of both acute and chronic rejection as well as graft loss in recipients with positive DSA antibody mediated rejection.

Graft-versus-host disease is infrequent but potentially life-threatening; the mortality rate exceeds 80%, and most recipients die from infectious complications from bone marrow failure. The incidence seen in intestinal transplantation is 5–10% with increased risk

associated with liver inclusive grafts. Although no standard treatment is available, early diagnosis, prevention of infection, and initiation of treatment with corticosteroids as soon as possible may improve outcomes.

### Infections

Infectious complications are the most significant cause of morbidity and mortality after intestinal transplantation. The most common is infectious enteritis although there are also bacterial, fungal, and polymicrobial infections that occur as a result of a need for venous catheter placement in the immediate posttransplant period or during episodes of intestinal graft dysfunction. Infections as a consequence of immunosuppressive drug management are from cytomegalovirus (CMV; 22% incidence), Epstein-Barr virus (EBV; 21% incidence), and adenovirus enteritis (40% incidence). Despite improvements in monitoring and preventative measures, CMV remains the most common viral infection postintestinal transplantation. CMV may be acquired from blood transfusions, reactivation of endogenous viruses, or the donated allograft. The highest-risk recipients for CMV infection are those who are immunologically naïve and receive an allograft from a donor who is seropositive. The two CMV prevention strategies commonly employed are universal prophylaxis and preemptive therapy. Consensus guidelines recommend prophylaxis treatment for high-risk patients (donor+/recipient−). The preferred drugs for CMV prophylaxis are ganciclovir and oral valganciclovir.

Patients at the highest risk for EBV infection are those who are seronegative at the time of transplantation and those requiring a high-burden immunosuppressive therapy to maintain their graft. EBV disease varies from asymptomatic viremia to **posttransplant lymphoproliferative disorder (PTLD)**. The incidence of EBV-related PTLD is highest in patients receiving intestinal allografts compared to liver, heart, or kidney. Children have a higher incidence of PTLD compared to adults and are most likely to have EBV + PTLD. Early diagnosis and prevention of PTLD is essential, and the mainstay of therapy is to reduce immunosuppression, although some patients have required chemotherapy. The use of anti-B-cell monoclonal antibodies, such as the anti-CD20 antibody rituximab, in PTLD has been successful as noted in anecdotal reports. Successful management of these viral infections is achieved through early detection and preemptive therapy, for both CMV and EBV, before the development of a serious life-threatening infection. This approach has improved outcomes for CMV (see Chapters 223, 301, and 302).

### Outcomes

Intestinal transplantation is the standard of care for children with IF who have significant complications of PN and can no longer tolerate such therapy. Graft survival at 1 and 5 years are ~68% and 50%, respectively. One-year graft survival was associated with first-time transplantation and liver-inclusive grafts, whereas poor overall graft survival was associated with retransplantation. Patient survival was associated with elective status of the procedure versus hospitalized status with sepsis continuing to be the most significant factor leading to patient death. Colon inclusion was associated with improved rates of enteral autonomy, which increased in general over the recent decades. Rejection remained the main factor associated with long-term graft loss with decreasing contributions from PTLD and technical complications. Combined adult and pediatric registry data show stable long-term graft survival of approximately 40%, although single centers have reported rates as high as 60–70%. Rehabilitation and quality-of-life studies have shown that more than 80% of survivors reach total independence from PN and have meaningful life activities. Consequently, there has been a shift in efforts to improve long-term outcomes and quality of life.

## Chapter 387

# Acute Gastroenteritis in Children

E. Adrienne Hammershaimb and Karen L. Kotloff

The term *gastroenteritis* denotes inflammation of the gastrointestinal tract, most commonly the result of infections with bacterial, viral, or parasitic pathogens (Tables 387.1–387.3). Many of these infections are food-borne illnesses (Table 387.4). Several clinical syndromes are often described because they have different (albeit overlapping) etiologies, outcomes, and treatments. **Acute gastroenteritis** (AGE) captures the bulk of infectious cases of diarrhea. The most common manifestations are diarrhea and vomiting, which can also be associated with systemic features such as abdominal pain and fever. **Dysentery** refers to a syndrome characterized by frequent small stools containing visible blood, often accompanied by fever, tenesmus, and abdominal pain. This should be distinguished from bloody diarrhea (larger volume bloody stools with less systemic illness) because the etiologies may differ. **Prolonged** (lasting 7–13 days) and **persistent diarrhea** (lasting 14 days or longer) are important because of their impact on growth and nutrition.

### BURDEN OF CHILDHOOD DIARRHEA

Although global mortality due to diarrheal diseases has declined substantially (39%) during the past 2 decades, it remains unacceptably high. In 2019 diarrheal disease caused an estimated 500,000, or 10% of all deaths in children under 5 years, making it the third leading cause of under-5 child mortality worldwide. Approximately 88% of those deaths occurred in sub-Saharan Africa and South Asia (71% and 17%, respectively). Over the same period, a smaller decline (10%) was observed in the incidence of diarrheal disease among children younger than 5 years. Almost 1 billion episodes occurred in 2019 worldwide, resulting in an estimated 45.5 million childhood disability-adjusted life years. The decline in diarrheal mortality, despite the lack of significant changes in incidence, is the result of preventive rotavirus vaccination and improved case management of diarrhea, as well as improved nutrition of infants and children. These interventions have included widespread home- and hospital-based oral rehydration solution (ORS) therapy and improved nutritional management of children with diarrhea.

In addition to the risk of mortality, high rates of diarrhea can be associated with long-term adverse outcomes. Diarrheal illnesses, especially episodes among young children that are recurrent, prolonged, or persistent, can be associated with malnutrition, stunting, micronutrient deficiencies, and significant deficits in psychomotor and cognitive development.

### PATHOGENS

Rotavirus is the most common cause of AGE among children throughout the world. Several other viruses occur less frequently. Norovirus and sapovirus are the two genera of *caliciviruses* that cause AGE. Norovirus genogroup II, genotype 4 (GII.4) has predominated globally since the mid-1990s. Among the more than 50 serotypes of adenovirus, 40 and 41 are most often associated with diarrhea. Astroviruses are identified less often (see Table 387.1). SARS-CoV-2 is also recognized as a cause of AGE in adults and in children, both as a manifestation of COVID-19 and as a symptom of multisystem inflammatory syndrome in children (MIS-C).

The major bacterial pathogens that cause AGE are nontyphoidal *Salmonella* (NTS), *Shigella*, *Campylobacter*, and *Yersinia* (see Table 387.2). Five pathotypes of *Escherichia coli* infect humans: Shiga toxin-producing (STEC), also known as enterohemorrhagic (EHEC),

enterotoxigenic (ETEC), enteropathogenic (EPEC), enteroaggregative (EAEC), and enteroinvasive (EIEC). Two serogroups of *Vibrio cholerae* (O1 and O139) produce epidemic cholera and cause nearly all sporadic cases. *Clostridioides difficile* (formerly *Clostridium difficile*) disease can be both nosocomial and community acquired in children. Bacterial pathogens that cause food-borne illness due to their ability to produce emetic and/or enterotoxins include *Bacillus cereus*, *Clostridium perfringens*, and *Staphylococcus aureus*. The significance of isolating *Aeromonas* and *Plesiomonas* in a diarrheal stool remains uncertain.

*Giardia duodenalis*, *Cryptosporidium* spp., *Cyclospora cayetanensis*, and *Entamoeba histolytica* are the most common parasites that cause diarrhea in the United States (see Table 387.3). At least 13 species of *Cryptosporidium* are associated with human disease, but *C. hominis* and, to a lesser extent, *C. parvum* are most common. The genus *Entamoeba* comprises six species that colonize humans, but only *E. histolytica* is considered a human pathogen. *G. duodenalis* (formerly *G. lamblia* and *G. intestinalis*) is a flagellate protozoa that infects the small intestine and biliary tract. Other protozoa that uncommonly cause AGE are *Cystoisospora belli* (formerly *Isospora belli*) and *Blastocystis hominis*.

### EPIDEMIOLOGY IN THE UNITED STATES AND OTHER MIDDLE- AND HIGH-INCOME COUNTRIES

#### Risk Factors Related to Economic Development

Insufficient access to adequate hygiene, sanitation, and clean drinking water are the main factors leading to the heavy burden of AGE in developing countries. Although the severe consequences have become uncommon, infectious AGE remains ubiquitous in middle- and high-income countries. Economic development poses its own risks for transmission of enteric pathogens. The ability to mass produce and widely distribute food has led to large multistate outbreaks of AGE due to NTS, STEC, and other agents (see Table 387.4). Globalization has cultivated a taste for tropical fruits and vegetables, creating a mechanism for importation of novel pathogens. The increasing frequency of antimicrobial resistance among bacteria that cause AGE has been linked to the use of antibiotics as growth promoters for animals bred for food. Recreational swimming facilities and water treatment systems have provided a vehicle for massive outbreaks of *Cryptosporidium*, a chlorine-resistant organism. Venues serving catered food to large groups of people, such as hotels and cruise ships, are conducive to outbreaks, as are institutions where hygiene is compromised, such as daycare centers, prisons, and nursing homes. Hospitalization and modern medical therapy have created a niche for nosocomial *C. difficile* toxin infection. Childcare and school-based outbreaks are often due to norovirus and *Shigella* spp.

#### Endemic Diarrhea

In the United States, rotavirus was the most common cause of medically attended AGE among children younger than 5 years until the introduction of rotavirus vaccine for routine immunization of infants in 2006. Before 2006, annual epidemics swept across the country beginning in the southwest in November and reaching the northeast by May, affecting nearly every child by the age of 2 years. Since vaccine introduction, healthcare utilization for AGE has decreased markedly at a considerable cost savings. Norovirus is now the leading cause of AGE among children in the United States seeking healthcare, followed by sapovirus, adenoviruses 40 and 41, and astrovirus (see Table 387.1).

#### Laboratory-Based Surveillance for Food-Borne Pathogens

The most comprehensive resource for describing the burden of bacterial and protozoal diarrhea in the United States is the Foodborne Diseases Active Surveillance Network (FoodNet) maintained by the Centers for Disease Control and Prevention (CDC) (see Table 387.4). FoodNet performs active laboratory-based surveillance of nine bacterial and protozoal enteric pathogens commonly transmitted by food. Among children 0–19 years of age in 2019, NTS was most common, followed by *Campylobacter*, STEC, and *Shigella*. *Vibrio* and *Yersinia* were the least common. As of January 1, 2018, FoodNet has stopped conducting active surveillance for *Cryptosporidium*;

**Table 387.1** Etiologies of Viral Gastroenteritis

Etiology	Incubation Period	Signs and Symptoms	Duration of Illness	Principal Vehicle and Transmission	Risk Factors	Commercially Available Diagnostic Test
Caliciviruses (including noroviruses and sapoviruses)	12-48 hr	Nausea, vomiting, abdominal cramping, diarrhea, fever, myalgia, and some headache	1-3 days	Person-to-person (fecal-oral and aerosolized vomit), and food, water, and fomites contaminated with human feces	Very contagious (chlorine and heat resistant); produces large outbreaks in closed settings such as cruise ships, daycares, schools, and restaurants Shellfish	Multiplex PCR RT-qPCR of stool and vomit is the preferred method for outbreak investigation, available in public health laboratories Immunoassays for norovirus have poor sensitivity Norovirus genotyping (GI and GII) is performed by CDC
Rotavirus (groups A-C), astrovirus, and enteric adenovirus (serotypes 40 and 41)	2-4 days	Often begins with vomiting, followed by watery diarrhea, low-grade fever	3-8 days	Person-to-person (fecal-oral), fomites Aerosol transmission of rotavirus may be possible	Nearly all infants and children worldwide were infected by 2 yr of age before vaccine introduction	Multiplex PCR Immunoassays for rotavirus and enteric adenovirus
SARS-CoV-2	2-14 days	Acute COVID-19: Fever, chills, cough, shortness of breath, difficulty breathing, fatigue, myalgia, headache, anosmia, dysgeusia, sore throat, congestion, runny nose, nausea, vomiting, diarrhea is usually nonbloody but may be blood tinged  MIS-C: fever, abdominal pain, vomiting, diarrhea, rash, conjunctivitis, dizziness or light-headedness	Acute COVID-19: May be self-limited, less than 2 wk Prolonged symptoms may last months (e.g., fatigue, anosmia, dysgeusia) MIS-C: unclear; often fatal if untreated	Respiratory aerosols and droplets; airborne precautions recommended	Unvaccinated immune status Local epidemiology and lack of transmission mitigating precautions	RT-PCR (may be included in a multiplex PCR) Antigen immunoassay Serology (may be useful for the diagnosis of MIS-C but not for acute COVID-19)

Note: Commercially available denotes that the diagnostic tests have been cleared by the U.S. Food and Drug Administration.  
 RT, Real-time reverse transcriptase; PCR, polymerase chain reaction; CDC, Centers for Disease Control and Prevention; MIS-C, multisystem inflammatory syndrome in children.  
 Adapted from Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses. MMWR. 2004;53(RR-4):1-33.

in 2015, *Cryptosporidium* was the fourth most commonly identified food-borne pathogen in U.S. children less than 19 years of age. Children younger than 5 years have the highest incidence of food-borne diarrheal disease, whereas the elderly have the highest frequency of hospitalization and death. Only 5% of these infections are associated with recognized outbreaks.

Toxin-mediated food-borne gastroenteritis may be infectious or noninfectious. Pathogens that cause toxin-mediated food-borne gastroenteritis include *S. aureus*, *B. cereus*, and *C. perfringens*. Ingestion of food contaminated with the preformed *S. aureus* heat-stable enterotoxin types A to E causes staphylococcal food poisoning. *B. cereus* produces two forms of gastrointestinal illness, one resembling staphylococcal food poisoning and caused by a preformed emetic toxin, and the other caused by a group of three enterotoxins formed in vivo. Ingested *C. perfringens* sporulates in the small intestine, releasing a heat-labile, single-polypeptide enterotoxin. Noninfectious agents may also cause food-borne gastrointestinal symptoms due to a direct toxic effect of the food (mushrooms), contamination (heavy metals), or fish or shellfish toxins (Table 387.5).

### Diarrhea Outbreaks

The U.S. Foodborne Disease Outbreak Surveillance System quantifies enteric infections associated with food-borne outbreaks. In 2017, among all age-groups, norovirus was the most common agent (49%), followed by NTS (19%). Less common were *C. perfringens* (6%), *Campylobacter* (4%), STEC (3%), *S. aureus* (2%), and *B. cereus* (2%), followed much less often (each 1%) by *Clostridium botulinum*, *Shigella*, *Cryptosporidium*, *Yersinia*, *Listeria*, *Vibrio parahaemolyticus*, and *Shigella*. Outbreaks of enteric pathogens propagated by direct person-to-person contact are most often caused by norovirus and *Shigella* species; other pathogens include NTS, rotavirus, *Giardia*, *Cryptosporidium*, *C. difficile*, and *Campylobacter jejuni*.

### Nosocomial Diarrhea

*C. difficile* is the most common cause of healthcare-associated infection in the United States. Severe disease occurs most often in those with predisposing conditions (e.g., recent antibiotics, gastric acid suppression, immunosuppression, gastrointestinal comorbidities). In contrast to adults, rates of colostomy and in-hospital mortality have not increased in children despite increasing rates of community and

**Table 387.2** Etiologies of Bacterial Gastroenteritis

Etiology	Incubation Period	Signs and Symptoms	Duration of Illness	Principal Vehicle and Transmission	Risk Factors	Commercially Available Diagnostic Test
<i>Bacillus cereus</i> (preformed emetic toxin)	1-6 hr	Sudden onset of severe nausea and vomiting; diarrhea may be present	24 hr	Soil and water	Improperly refrigerated cooked or fried rice, meats	Routine stool culture to look for overabundance of pathogen, does not detect toxins Reference laboratory used for outbreaks
<i>B. cereus</i> (enterotoxins formed in vivo)	8-16 hr	Abdominal cramps, watery diarrhea; nausea and vomiting may be present	1-2 days	Soil and water	Meats, stews, gravies, vanilla sauce	Routine stool culture to look for overabundance of pathogen, does not detect toxins Reference laboratory used for outbreaks
<i>Campylobacter jejuni</i>	1-5 days	Diarrhea, (10–20% of episodes are prolonged), cramps, fever, and vomiting; bloody diarrhea, bacteremia, extraintestinal infections, severe disease in immunocompromised	5-7 days (sometimes >10 days) usually self-limiting	Wild and domestic animals and animal products	Raw and undercooked poultry, unpasteurized milk, untreated surface water	Stool culture on selective agar, microaerobic conditions, and incubation at 42°C Antigen detection by EIA Multiplex PCR
<i>Clostridioides difficile</i> toxin	Unknown Can appear weeks after antibiotic cessation	Mild to moderate watery diarrhea that can progress to severe, pseudomembranous colitis with systemic toxicity	Variable	Person-to-person (fecal-oral), mostly within healthcare facilities	Immunosuppression, intestinal disease or surgery, prolonged hospitalization, antibiotics	PCR, <sup>t</sup> immunoassay Multistep approach using EIA for GDH and toxins A and B ± NAAT
<i>Clostridium perfringens</i> toxin	8-16 hr	Watery diarrhea, nausea, abdominal cramps; fever is rare	1-2 days	Environment, human and animal intestines	Meats, poultry, gravy, dried or precooked foods with poor temperature control	None Reference laboratory used for outbreaks
<i>Escherichia coli</i> O157:H7 and other Shiga toxin-producing <i>E. coli</i> (STEC)	1-9 days (usually 3-4 days)	Watery diarrhea that becomes bloody in 1-4 days in ~40% of infections; in contrast to dysentery, bloody stools are large volume and fever/toxicity is minimal More common in children <4 yr old	4-7 days	Food and water contaminated with feces from ruminants; infected people and animals (fecal-oral); predominantly high-resource countries	Undercooked beef especially hamburger, unpasteurized milk and juice, raw fruits, and petting zoos, recreational swimming, daycare Antimotility agents and antibiotics increase risk of hemolytic uremic syndrome	Multiplex PCR to detect <i>E. coli</i> O157:H7 and non-O157:H7 Shiga toxin genes simultaneously with stool culture on sorbitol-MacConkey agar Immunoassay for O157:H7; presumptive <i>E. coli</i> O157:H7 isolates and all <i>Shiga</i> toxin-positive stool specimens that did not yield a presumptive <i>E. coli</i> O157:H7 isolate should be sent to a public health laboratory to identify non-O157:H7 STEC and for serotyping and whole genome sequencing
Enterotoxigenic <i>E. coli</i> (ETEC)	1-5 days	Watery diarrhea, abdominal cramps, some vomiting	3-7 days	Water or food contaminated with human feces	Infants and young children in LMIC and travelers	Multiplex PCR, <sup>t</sup> or reference laboratory
Salmonella, nontyphoidal	1-5 days	Diarrhea, (10–20% prolonged), cramps, fever, and vomiting; bloody diarrhea, bacteremia, extraintestinal infections, severe disease in immunocompromised	5-7 days (sometimes >10 days) usually self-limiting	Domestic poultry, cattle, reptiles, amphibians, birds	Ingestion of raw or undercooked food, improper food handling, travelers, immunosuppression, hemolytic anemia, achlorhydria, contact with infected animal	Multiplex PCR Routine stool culture

Continued

**Table 387.2** Etiologies of Bacterial Gastroenteritis—cont'd

Etiology	Incubation Period	Signs and Symptoms	Duration of Illness	Principal Vehicle and Transmission	Risk Factors	Commercially Available Diagnostic Test
<i>Shigella</i> spp.	1-5 days (up to 10 days for <i>S. dysenteriae</i> type 1)	Abdominal cramps, fever, diarrhea Begins with watery stools that can be the only manifestation or proceed to dysentery	5-7 days	Infected people or fecally contaminated surfaces (fecal-oral)	Poor hygiene and sanitation, crowding, travelers, daycare, MSM, prisoners	Multiplex PCR Routine stool culture
<i>Staphylococcus aureus</i> (preformed enterotoxin)	1-6 hours	Sudden onset of severe nausea and vomiting Abdominal cramps Diarrhea and fever may be present	1-3 days	Birds, mammals, dairy, and environment	Unrefrigerated or improperly refrigerated meats, potato and egg salads, cream pastries	Routine stool culture to look for overabundance of pathogen, does not detect toxins Reference laboratory used for outbreaks
<i>Vibrio cholerae</i> O1 and O139	1-5 days	Watery diarrhea and vomiting, which can be profuse and lead to severe dehydration and death within hours	3-7 days	Food and water contaminated with human feces	Contaminated water, fish, shellfish, street-vended food from endemic or epidemic settings; blood group O, vitamin A deficiency	Stool culture (requires special TCBS media so laboratory must be notified) Rapid test is useful in epidemics but does not provide susceptibility or subtype so should not be used for routine diagnosis. FDA-approved multiplex PCR
<i>Vibrio parahaemolyticus</i>	2-48 hr	Watery diarrhea, abdominal cramps, nausea, vomiting Bacteremia and wound infections occur uncommonly, especially in high-risk patients, e.g., with liver disease and diabetes	2-5 days	Estuaries and marine environments; currently undergoing pandemic spread	Undercooked or raw seafood, such as fish, shellfish	Culture of stool, wound, or blood depending on suspected source Requires special TCBS media so laboratory must be notified Multiplex PCR
<i>Vibrio vulnificus</i>	1-7 days	Vomiting, diarrhea, abdominal pain Bacteremia and wound infections, particularly in patients with chronic liver disease (presents with septic shock and hemorrhagic bullous skin lesions)	2-8 days	Estuaries and marine environments	Undercooked or raw shellfish, especially oysters, other contaminated seafood, and open wounds exposed to seawater	Culture of stool, wound, or blood depending on suspected source Requires special TCBS media so laboratory must be notified Multiplex PCR
<i>Yersinia enterocolitica</i> and <i>Y. pseudo-tuberculosis</i>	1-5 days	Diarrhea, (10–20% prolonged), cramps, fever, and vomiting; bloody diarrhea, bacteremia, extraintestinal infections, severe disease in immunocompromised; pseudoappendicitis occurs primarily in older children	5-7 days (sometimes >10 days) usually self-limiting	Swine products, occasionally person-to-person and animal-to-humans, water-borne, blood-borne (can multiply during refrigeration)	Undercooked pork, improper food handling, unpasteurized milk, tofu, contaminated water, transfusion from a bacteremic person, cirrhosis, chelation therapy	Stool culture or multiplex PCR Culture requires special media and incubation at 25°C. Not performed in many laboratories unless requested When clinically relevant, can isolate from vomit, blood, throat, lymph nodes, joint fluid, urine, and bile

<sup>†</sup>FDA-cleared multiplex PCR assays are available but cannot determine antimicrobial susceptibility to guide treatment or speciate the organism for outbreak investigation.

EIA, Enzyme immunoassays; PCR, polymerase chain reaction; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification test; LMIC, low- and middle-income countries; MSM, men who have sex with men; TCBS, thiosulfate-citrate-bile salts-sucrose agar; FDA, U.S. Food and Drug Administration.

Adapted from Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses. MMWR. 2004;53(RR-4):1-33.

**Table 387.3** Etiologies of Parasitic Gastroenteritis

Etiology	Incubation Period	Signs and Symptoms	Duration of Illness	Principal Vehicle and Transmission	Risk Factors	Commercially Available Diagnostic Test
Cryptosporidium	1-11 days	Diarrhea (usually watery), bloating, flatulence, cramps, malabsorption, weight loss, and fatigue may wax and wane Persons with AIDS or malnutrition have more severe disease	1-2 wk; may be remitting and relapsing over weeks to months	Person-to-person (fecal-oral), contaminated food and water (including municipal and recreational water contaminated with human feces)	Infants 6-18 mo of age living in endemic settings in LMIC, patients with AIDS, childcare settings, drinking unfiltered surface water, MSM, Ig deficiency	Immunoassays, PCR, and multiplex PCR are most sensitive Microscopy (direct fluorescent antibody staining is preferable to modified acid fast)
Cyclospora cayetanensis	1-11 days	Same as Cryptosporidium	Same as Cryptosporidium	Fresh produce (imported berries, lettuce)	Travelers, consumption of fresh produce imported from the tropics	Fecal microscopy, multiplex PCR May need to examine water or food
Entamoeba histolytica	2-4 wk	Gradual onset of cramps, watery diarrhea and often dysentery with cramps but rarely fever Can wax and wane with weight loss Dissemination to liver and other organs can occur	Variable; may be protracted (several weeks to several months)	Fecal-oral transmission Any uncooked food or food contaminated by an ill food handler after cooking; drinking water	Persons living in or traveling to LMIC, institutionalized persons, MSM	Immunoassay or multiplex PCR are preferred Fecal microscopy of fresh stool for cysts and parasites on at least three samples can also be performed Serology for extraintestinal infections
Giardia duodenalis	1-4 wk	Diarrhea, stomach cramps, gas, weight loss; symptoms may wax and wane	2-4 wk	Any uncooked food or food contaminated by an ill food handler after cooking; drinking water	Hikers drinking unfiltered surface water, persons living in or traveling to LMIC, MSM, IgA deficiency	Immunoassay or multiplex PCR preferred Fecal microscopy for ova and parasites can be performed; at least three samples recommended

LMIC, Low- and middle-income countries; PCR, polymerase chain reaction; MSM, men having sex with men.

hospital-acquired *C. difficile* infection, suggesting that *C. difficile* may be less pathogenic in children. Moreover, high rates of asymptomatic carriage among children younger than 2 years create diagnostic uncertainty, so children <1 year should never be routinely tested; testing and treatment in children 1-2 years of age should be reserved for those in whom noninfectious or other infectious causes have been ruled out, and children ≥2 years may be tested if they have prolonged or worsening diarrhea and relevant risk factors or exposures (see Table 387.2).

### Zoonotic Transmission

Many diarrheal pathogens are acquired from animal reservoirs (see Tables 387.1-387.3). The ability of NTS to undergo transovarian passage in hens allows infection of intact grade A pasteurized eggs, a source of multiple large outbreaks. Although *Campylobacter* is prevalent in poultry, its lower outbreak potential has been attributed to its lack of transovarian spread in hens and stringent growth requirements, which limit its ability to replicate in foods. On the other hand, *Campylobacter* has an extensive reservoir in domestic and wild animals and remains a major cause of sporadic bacterial food-borne disease in industrialized countries, usually from consumption of contaminated chicken meat, beef, and milk. Its ubiquitous animal reservoir also has resulted in widespread contamination of surface waters, resulting in diarrhea among hikers and campers who drink from streams, ponds, and lakes in wilderness areas. The predilection

for STEC to asymptotically colonize the intestines of ruminant animals explains why unpasteurized dairy products, fruits harvested from fields where cattle graze, and undercooked hamburger are common vehicles. The major animal reservoir for *Yersinia* is pigs, so ingestion of raw or undercooked pork products is an important risk factor. Pets can be the source of NTS (asymptomatic young birds, amphibians, and reptiles), *Campylobacter*, and *Yersinia* (puppies and kittens that are usually ill with diarrhea).

### Seasonality

Seasonality provides a clue to implicate specific pathogens, although patterns may differ in tropical and temperate climates. Rotavirus and norovirus peak in cool seasons, while enteric adenovirus infections occur throughout the year, with some increase in summer. *Salmonella*, *Shigella*, and *Campylobacter* favor warm weather, whereas the tendency for *Yersinia* to tolerate cold manifests as a winter seasonality, with higher prevalence in northern countries, and the ability to survive in contaminated food products during refrigeration.

### EPIDEMIOLOGY IN LOW- AND MIDDLE-INCOME COUNTRIES

Large epidemiologic studies conducted during the previous decade have advanced our understanding of the etiology of diarrheal disease among children in low-resource countries. The Global Enteric Multicenter

**Table 387.4** Number of Laboratory-Diagnosed Bacterial and Parasitic Infections, Hospitalizations, Deaths, Outbreak-Associated Infections, and Crude Incidence by Pathogen — Foodborne Diseases Active Surveillance Network, 10 U.S. sites,\* 2021†

PATHOGEN	NUMBER OF INFECTIONS§	HOSPITALIZATIONS¶	2021		CRUDE INCIDENCE§§
			DEATHS**	OUTBREAK-ASSOCIATED INFECTIONS††	
Total	22,019	5,359 (24)	153 (0.7)	861 (4)	—
Campylobacter	8,974	1,822 (20)	33 (0.4)	51 (0.6)	17.8
Salmonella	7,148	1,974 (28)	52 (0.7)	597 (8)	14.2
STEC	2,542	600 (24)	10 (0.4)	79 (3)	5.0
Shigella	1,699	532 (31)	8 (0.5)	67 (4)	3.4
Yersinia	683	146 (21)	3 (0.4)	2 (0.3)	1.4
Vibrio	461	117 (25)	9 (2)	8 (2)	0.9
Listeria	148	140 (95)	37 (25)	9 (6)	0.3
Cyclospora	364	28 (8)	1 (0.3)	48 (13)	0.7

\*Data were obtained from laboratories in Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, Tennessee, and selected counties in California, Colorado, and New York. † 2021 data are preliminary. § Bacterial infections diagnosed by culture or CIDI. Cyclospora infections diagnosed by microscopy or polymerase chain reaction. ¶ Admission to an inpatient unit or an observation stay of >24 hours within 7 days before or after specimen collection or determined to be related to the infection if beyond this time frame. Absolute change in percentage of infections resulting in hospitalization during 2021 compared with annual average for 2016–2018: Campylobacter (0.3), Salmonella (0.3), STEC (1), Shigella (8), Yersinia (−4), Vibrio (−5), Listeria (−2), Cyclospora (2), and overall (0.6). Unknown hospitalization status (10% of infections during 2021 and 4% during 2016–2018) was classified as not hospitalized.

\*\*Attributed to infection when deaths occurred during hospitalization or within 7 days after specimen collection for nonhospitalized patients. Absolute change in percentage of infections resulting in death during 2021 compared with annual average for 2016–2018: Campylobacter (<0.1), Salmonella (0.3), STEC (<0.1), Shigella (0.4), Yersinia (−0.7), Vibrio (−0.2), Listeria (6), Cyclospora (0.1), and overall (0.2). Unknown death status (8% of infections during 2021 and 3% during 2016–2018) was not classified as a death. †† Generally defined as two or more cases of similar illness associated with a common exposure; some sites also stipulate that illnesses be from more than one household. Absolute change in percentage of outbreak-associated infections during 2021 compared with annual average for 2016–2018: Campylobacter (0.2), Salmonella (1), STEC (−1), Shigella (−1), Yersinia (0.2), Vibrio (−2), Listeria (1), Cyclospora (−10), and overall (<0.1). Unknown outbreak-association status (0.02% of infections during 2021 and 0% during 2016–2018) was classified as not outbreak-associated. §§ Cases per 100,000 population. Domestic incidences (cases with no or unknown travel) by pathogen during 2021: Campylobacter (17.0), Salmonella (13.1), STEC (4.6), Shigella (3.0), Yersinia (1.3), Vibrio (0.8), Listeria (0.3), and Cyclospora (0.6).

CIDI, Culture-independent diagnostic test; STEC, Shiga toxin-producing *E. coli*.

Modified from Collins JP, Shah HJ, Weller DL, et al. Preliminary incidence and trends of infections caused by pathogens transmitted commonly through food – foodborne diseases active surveillance network, 10 U.S. sites, 2016–2021. MMWR. 2022;71(4):1260–1263.

Study (GEMS) evaluated children younger than 5 years living in seven low-income countries in sub-Saharan Africa and South Asia and seeking healthcare for moderate to severe diarrhea (Fig. 387.1). Although a broad array of pathogens was identified, most episodes of moderate to severe diarrhea were attributed to four pathogens: rotavirus, *Cryptosporidium*, *Shigella*, and ETEC producing heat-stable toxin (ST) either alone or in combination with heat-labile toxin (LT), herein termed ST-ETEC and LT-ETEC, and, to a lesser extent, adenoviruses 40 and 41. On the other hand, several etiologic agents that are common causes of AGE in high-resource settings are notable for their low frequency in resource-limited settings: NTS, STEC, norovirus, and *C. difficile* toxin. The three agents associated with most deaths among children <5 years are rotavirus (29%), *Cryptosporidium* (12%), and *Shigella* (11%). The Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development Project (MAL-ED) was a study of less severe, community-based diarrhea. Viral causes predominated (36.4% of the overall incidence), but *Shigella* had the single highest attributable incidence (26.1 attributable episodes per 100 child-years).

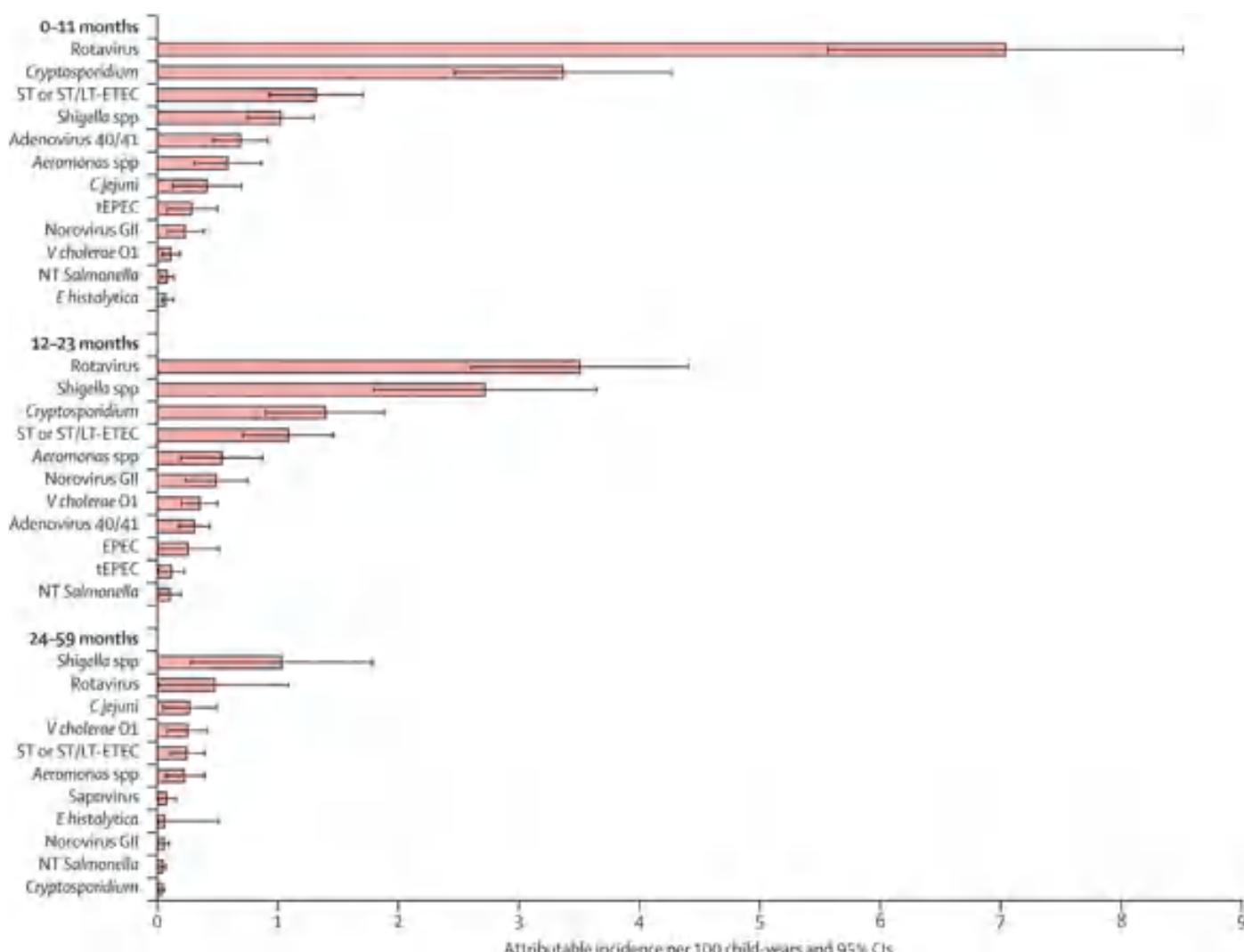
### Host Risk Factors

Most pathogens show an age predilection. The incidence of rotavirus and NTS are highest in infancy. Endemic shigellosis peaks in 1- to 4-year olds, whereas *Campylobacter* and *Cryptosporidium* show a bimodal distribution with the greatest number of reported cases in infants and young children with a secondary peak in young adults. Pandemic *V. cholerae* and *Shigella dysenteriae* type 1 produce high attack rates and mortality in all age-groups and often afflict displaced persons in emergency settings. Some agents (e.g., NTS, *Shigella*, *Campylobacter*, *Yersinia*, and *Cryptosporidium*) are more frequent and more severe when the host is immunocompromised or malnourished.

Additional risks factors for AGE include immunodeficiency, measles, malnutrition, and lack of exclusive or predominant breastfeeding. Malnutrition increases the risk of diarrhea and associated mortality, and moderate to severe stunting increases the odds of diarrhea-associated mortality. The fraction of such infectious diarrhea deaths that are attributable to nutritional deficiencies varies with the prevalence of deficiencies; the highest attributable fractions are in sub-Saharan Africa, South Asia, and Andean Latin America. The risks are especially high with malnutrition, particularly when associated with micronutrient deficiency. Vitamin A deficiency accounts for 157,000 deaths from diarrhea, measles, and malaria. Zinc deficiency is estimated to cause 116,000 deaths from diarrhea and pneumonia.

### PATHOGENESIS OF INFECTIOUS GASTROENTERITIS

Intrinsic properties of the organism help to define the mode of transmission and incubation period (Table 387.6). Enteropathogens that are infectious in small inocula (*Shigella*, STEC, norovirus, rotavirus, *G. duodenalis*, *Cryptosporidium* spp., *C. difficile*, *E. histolytica*) are readily transmitted by person-to-person contact via the fecal-oral route. Pathogens with larger infectious doses, such as cholera, NTS, ETEC, and *Campylobacter*, generally require food or water vehicles (see Tables 387.1–387.3). Pathogens that produce preformed toxins (*S. aureus*, *B. cereus* emetic toxin) have shorter incubation periods (1–6 hours) compared with 8–16 hours for those that must elaborate enterotoxins *in situ* (e.g., *C. perfringens* and *B. cereus* enterotoxin). Incubation periods of 1–5 days are seen with pathogens that attach to the epithelium and elaborate enterotoxins (e.g., *V. cholerae*, ETEC) or cytotoxins (e.g., *S. dysenteriae* type 1 and STEC) or those that invade and disrupt the intestinal epithelium (*Shigella*, NTS, *Campylobacter*, and *Yersinia*). The requirement for protozoa to progress through a life cycle to trigger pathogenic processes results in a more extended incubation period. Other



**Fig. 387.1** Attributable incidence of pathogen-specific moderate to severe diarrhea per 100 child-years by age stratum, all sites combined. The bars show the incidence rates and the error bars show the 95% confidence intervals. ST/LT-ETEC, heat-stable toxin (ST) / heat labile toxin (LT)-enterotoxigenic *Escherichia coli*; tEPEC, traditional (t) enteropathogenic *Escherichia coli*. (From Kotloff KL, Nataro JP, Blackwelder WC, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries [the Global Enteric Multicenter Study, GEMS]: a prospective, case-control study. Lancet. 2013;382:209–222. Fig. 4.)

properties affecting transmissibility are bioavailability as conferred by a copious and/or prolonged fecal shedding, extended infectivity in the environment, and resistance to disinfection (all exhibited by norovirus and *Cryptosporidium*), or a large environmental or animal reservoir (e.g., *Campylobacter*). The ability to circumvent immune surveillance by frequent antigenic changes resulting from recombinational events (e.g., norovirus) or a large serotype diversity (e.g., *Shigella*) maintains a susceptible host population.

Viral AGE causes a cytopathic infection of the small intestinal villus tips resulting in decreased absorption of water, disaccharide malabsorption, inflammation, and cytokine activation. The rotavirus protein NSP4 acts as a viral enterotoxin that causes secretory diarrhea. In addition, rotavirus activates the enteric nervous system, causing decreased gastric emptying and increased intestinal motility. There is a genetic susceptibility to both rotavirus and norovirus infection that is mediated by histo-blood group antigens on the epithelial cell surface and in mucus secretions (Fig. 387.2).

Pathogens primarily manifesting as secretory diarrhea attach to the surface of the epithelium and stimulate secretion of water and electrolytes by activating adenylate cyclase and raising intracellular cAMP (*V. cholerae* and LT-ETEC) and/or cGMP (ST-ETEC) (Figs. 387.3 and 387.4). The diarrheagenic phenotype of *C. difficile* is attributed to production of toxins A (an enterotoxin) and B (an enterotoxin and cytotoxin). The

epidemic hypervirulent NAP1 *C. difficile* also makes binary toxin, which may enhance colonization and augment toxin production.

*Shigella*, NTS, *Campylobacter*, and *Yersinia* all possess an invasive phenotype and elicit diarrhea by a variety of mechanisms that generally involves elicitation of inflammatory cytokines with or without associated toxin production (Fig. 387.5). The pathogenesis of *Shigella*, the most common cause of bacillary dysentery, has been characterized in greatest detail. Following invasion, *Shigella* induces extensive destruction and inflammation of the intestinal epithelium, producing ulcers and microabscesses that manifest with diarrheal stools containing blood and pus. Production of enterotoxins contributes to secretory diarrhea, which can be seen early in shigellosis or as the sole manifestation. A single serotype of *Shigella*, *S. dysenteriae* type 1, elaborates the Shiga toxin, which increases the severity of illness and is responsible for the development of hemolytic uremic syndrome (HUS).

*Cryptosporidium* sporozoites released from ingested cysts penetrate intestinal epithelial cells and develop into trophozoites within the intracellular but extracytoplasmic environment. After undergoing asexual multiplication and sexual development, they are released in the colon as infectious oocysts capable of causing autoinfection. Host factors, in particular T-cell function, play a critical role in disease severity. *Cyclospora* cysts are not infectious in freshly passed stools but must sporulate in the environment for 1–2 weeks to become

Table 387.5   Food-Borne Noninfectious Illnesses						
Etiology	Incubation Period	Signs and Symptoms	Duration of Illness	Associated Foods	Laboratory Testing	Treatment
Antimony	5 min-8 hr usually <1 hr	Vomiting, metallic taste	Usually self-limited	Metallic container	Identification of metal in beverage or food	Supportive care
Arsenic	Few hours	Vomiting, colic, diarrhea	Several days	Contaminated food	Urine Can cause eosinophilia	Gastric lavage, BAL (dimercaprol)
Cadmium	5 min-8 hr usually <1 hr	Nausea, vomiting, myalgia, increase in salivation, stomach pain	Usually self-limited	Seafood, oysters, clams, lobster, grains, peanuts	Identification of metal in food	Supportive care
Ciguatera fish poisoning (ciguatera toxin)	2-6 hr	GI: abdominal pain, nausea, vomiting, diarrhea	Days to weeks to months	A variety of large reef fish: grouper, red snapper, amberjack, and barracuda (most common)	Radioassay for toxin in fish or a consistent history	Supportive care, IV mannitol Children more vulnerable
	3 hr	Neurologic: paresthesias, reversal of hot or cold, pain, weakness				
	2-5 days	Cardiovascular: bradycardia, hypotension, increase in T-wave abnormalities				
Copper	5 min-8 hr usually <1 hr	Nausea, vomiting, blue or green vomitus	Usually self-limited	Metallic container	Identification of metal in beverage or food	Supportive care
Mercury	1 wk or longer	Numbness, weakness of legs, spastic paralysis, impaired vision, blindness, coma  Pregnant women and the developing fetus are especially vulnerable	May be protracted	Fish exposed to organic mercury, grains treated with mercury fungicides	Analysis of blood, hair	Supportive care
Mushroom toxins, short-acting (muscimol, muscarine, psilocybin, <i>Coprinus atramentaria</i> , ibotenic acid)	<2 hr	Vomiting, diarrhea, confusion, visual disturbance, salivation, diaphoresis, hallucinations, disulfiram-like reaction, confusion, visual disturbance	Self-limited	Wild mushrooms (cooking might not destroy these toxins)	Typical syndrome and mushroom identified or demonstration of the toxin	Supportive care
Mushroom toxins, long-acting (amanitin)	4-8 hr diarrhea; 24-48 hr liver failure	Diarrhea, abdominal cramps, leading to hepatic and renal failure	Often fatal	Mushrooms	Typical syndrome and mushroom identified and/or demonstration of the toxin	Supportive care, life-threatening, may need life support
Nitrite poisoning	1-2 hr	Nausea, vomiting, cyanosis, headache, dizziness, weakness, loss of consciousness, chocolate-brown blood	Usually self-limited	Cured meats, any contaminated foods, spinach exposed to excessive nitrification	Analysis of the food, blood	Supportive care, methylene blue

**Table 387.5** Food-Borne Noninfectious Illnesses—cont'd

Etiology	Incubation Period	Signs and Symptoms	Duration of Illness	Associated Foods	Laboratory Testing	Treatment
Pesticides (organophosphates or carbamates)	Few minutes to few hours	Nausea, vomiting, abdominal cramps, diarrhea, headache, nervousness, blurred vision, twitching, convulsions, salivation, meiosis	Usually self-limited	Any contaminated food	Analysis of the food, blood	Atropine; 2-PAM (pralidoxime) is used when atropine is not able to control symptoms; rarely necessary in carbamate poisoning
Puffer fish (tetrodotoxin)	<30 min	Paresthesias, vomiting, diarrhea, abdominal pain, ascending paralysis, respiratory failure	Death usually in 4-6 hr	Puffer fish	Detection of tetrodotoxin in fish	Life-threatening, may need respiratory support
Scombroid (histamine)	1 min-3 hr	Flushing, rash, burning sensation of skin, mouth and throat, dizziness, urticaria, paresthesias	3-6 hr	Fish: bluefin, tuna, skipjack, mackerel, marlin, escolar, and mahi	Demonstration of histamine in food or clinical diagnosis	Supportive care, antihistamines
Shellfish toxins (diarrheic, neurotoxic, amnesic)	Diarrheic shellfish poisoning: 30 min-2 hr	Nausea, vomiting, diarrhea, and abdominal pain accompanied by chills, headache, and fever	Hours to 2-3 days	A variety of shellfish, primarily mussels, oysters, scallops, and shellfish from the Florida coast and the Gulf of Mexico	Detection of the toxin in shellfish; high-pressure liquid chromatography	Supportive care, generally self-limiting
	Neurotoxic shellfish poisoning: few minutes to hours	Tingling and numbness of lips, tongue, and throat, muscular aches, dizziness, reversal of the sensations of hot and cold, diarrhea, and vomiting				
	Amnesic shellfish poisoning: 24-48 hr	Vomiting, diarrhea, abdominal pain and neurologic problems such as confusion, memory loss, disorientation, seizure, coma				Elderly are especially sensitive to amnesic shellfish poisoning
Shellfish toxins (paralytic shellfish poisoning)	30 min-3 hr	Diarrhea, nausea, vomiting leading to paresthesias of mouth and lips, weakness, dysphasia, dysphonia, respiratory paralysis	Days	Scallops, mussels, clams, cockles	Detection of toxin in food or water where fish are located; high-pressure liquid chromatography	Life-threatening, may need respiratory support
Sodium fluoride	Few minutes to 2 hr	Salty or soapy taste, numbness of mouth, vomiting, diarrhea, dilated pupils, spasms, pallor, shock, collapse	Usually self-limited	Dry foods (e.g., dry milk, flour, baking powder, cake mixes) contaminated with NaF-containing insecticides and rodenticides	Testing of vomitus or gastric washings Analysis of the food	Supportive care
Thallium	Few hours	Nausea, vomiting, diarrhea, painful paresthesias, motor polyneuropathy, hair loss	Several days	Contaminated food	Urine, hair	Supportive care
Tin	5 min-8 hr usually <1 hr	Nausea, vomiting, diarrhea	Usually self-limited	Metallic container	Analysis of the food	Supportive care

Continued

**Table 387.5** Food-Borne Noninfectious Illnesses—cont'd

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Vomitoxin	Few minutes to 3 hr	Nausea, headache, abdominal pain, vomiting	Usually self-limited	Grains such as wheat, corn, barley	Analysis of the food	Supportive care
Zinc	Few hours	Stomach cramps, nausea, vomiting, diarrhea, myalgias	Usually self-limited	Metallic container	Analysis of the food, blood and feces, saliva or urine	Supportive care

BAL, Bronchoalveolar lavage; GI, gastrointestinal.

From Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, MMWR. 53(RR-4):1–33, 2004.

**Table 387.6** Comparison of Three General Pathogenic Mechanisms of Enteric Infection

PARAMETER	TYPE OF INFECTION		
Mechanism	Noninflammatory (enterotoxin or adherence/superficial invasion)	Inflammatory, epithelial destruction (invasion, cytotoxin)	Penetrating
Location	Proximal small bowel	Colon	Distal small bowel
Illness	Watery diarrhea	Dysentery	Enteric fever
Stool examination	No fecal leukocytes Mild or no ↑ lactoferrin	Fecal polymorphonuclear leukocytes ↑ Lactoferrin	Fecal mononuclear leukocytes
Examples	<i>Vibrio cholerae</i> ETEC <i>Clostridium perfringens</i> <i>Bacillus cereus</i> <i>Staphylococcus aureus</i> Also*: <i>Giardia duodenalis</i> <i>Rotavirus</i> <i>Noroviruses</i> <i>Cryptosporidium</i> spp. EPEC, EAEC <i>Cyclospora cayetanensis</i>	<i>Shigella</i> EIEC STEC <i>Vibrio parahaemolyticus</i> <i>Clostridioides difficile</i> <i>Campylobacter jejuni</i> <i>Entamoeba histolytica</i> †	NTS <i>Yersinia enterocolitica</i> <i>Campylobacter fetus</i>

\*Although not typically enterotoxic, these pathogens alter bowel physiology via adherence, superficial cell entry, cytokine induction, or toxins that inhibit cell function.

†Although amebic dysentery involves tissue inflammation, the leukocytes are characteristically pyknotic or absent, having been destroyed by the virulent amebae.

EAEC, Enteropathogenic *E. coli*; EIEC, enteroinvasive *E. coli*; EPEC, enteropathogenic *E. coli*; ETEC, enterotoxigenic *E. coli*; STEC, Shiga toxin-producing *E. coli*; NTS: nontyphoidal *Salmonella*.

infectious; they are usually transmitted in contaminated produce and water (see Table 387.3).

## CLINICAL MANIFESTATION OF ACUTE GASTROENTERITIS

### General Findings

Diarrhea is usually defined as the passage of three or more abnormally loose or liquid stools per day. Frequent passage of formed stools is not diarrhea, nor is the passing of loose, pasty stools by breastfed babies. Clinical clues as to the possible etiology of AGE are noted in Tables 387.1–387.3 and Table 387.7.

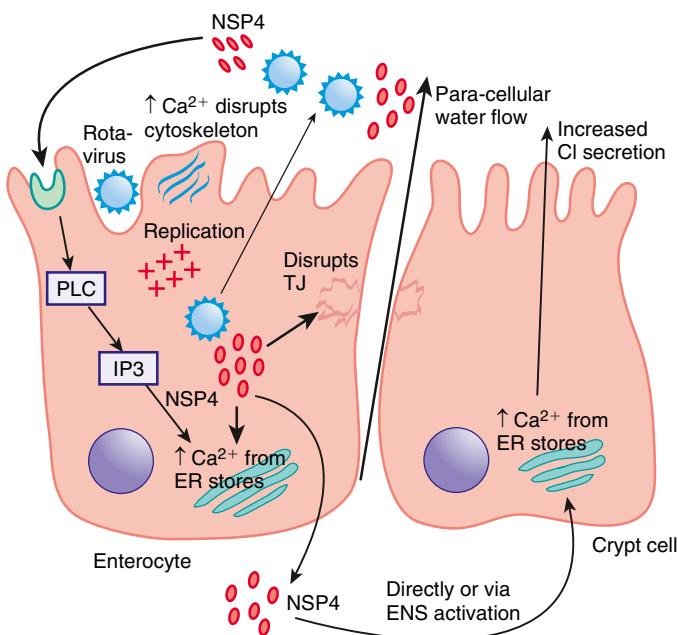
In the past, many guidelines divided patients into subgroups for mild (3–5%), moderate (6–9%), and severe ( $\geq 10\%$ ) dehydration; however, it is difficult to distinguish between mild and moderate dehydration based on clinical signs alone. Therefore current guidelines combine mild and moderate dehydration and simply use none, some, and severe dehydration. Commonly used guidelines include the World Health Organization (WHO) Integrated Management of Childhood Illness scale, the Clinical Dehydration Scale, the Modified Vesikari Score, and the Gorelick scale, but the accuracy and applicability of these scales varies by clinical setting and by the individual assigning the patients' scores. The signs that best predict dehydration are prolonged capillary

refill time >2 seconds, abnormal skin turgor, hyperpnea (deep, rapid breathing suggesting acidosis), dry mucous membranes, absent tears, and general appearance (including activity level and thirst). As the number of signs increases, so does the likelihood of dehydration. Tachycardia, altered level of consciousness, and cold extremities with or without hypotension suggest severe dehydration.

### Viral Diarrhea

Symptoms of rotavirus AGE usually begin with vomiting followed by frequent passage of watery, nonbloody stools associated with fever in about half the cases (see Table 387.1). The diarrhea lacks fecal leukocytes, but stools from 20% of cases contain mucus. Recovery with complete resolution of symptoms generally occurs within 7 days. Although disaccharide malabsorption is found in 10–20% of episodes, it is rarely clinically significant.

Other viral agents elicit similar symptoms and cannot be distinguished from rotavirus based on clinical findings. In an outbreak setting, the pattern of a brief incubation period (12–48 hours), short duration of illness, and clustering of cases is shared by caliciviruses and preformed bacterial toxin. However, unlike preformed toxins, caliciviruses cause secondary infections, which confirm the contagious nature of the outbreak. Diarrheal illnesses caused by enteric adenovirus infections tend to be more prolonged than rotavirus (7–10 days),



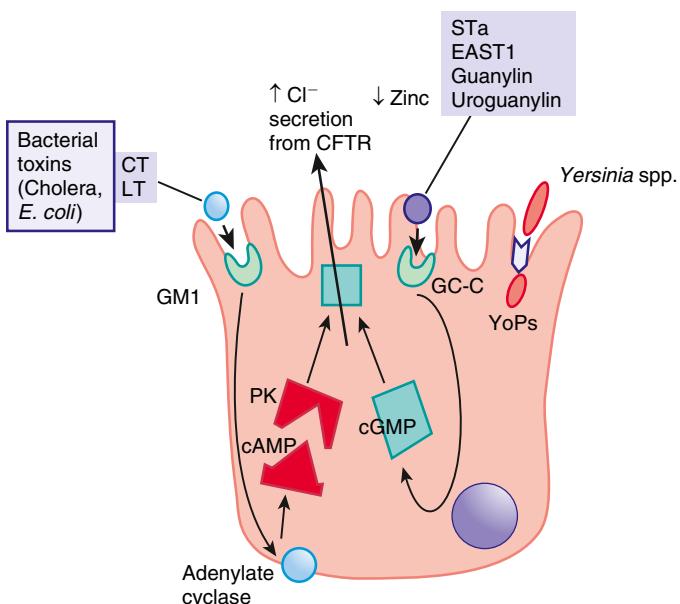
**Fig. 387.2** Pathogenesis of rotavirus infection and diarrhea. ENS, Enteric nervous system; ER, endoplasmic reticulum; IP3, inositol trisphosphate; PLC, phospholipase C; TJ, tight junction. (Adapted from Ramig RF. Pathogenesis of intestinal and systemic rotavirus infection. *J Virol*. 2004;78:10213–10220.)

whereas astroviruses cause a shorter course (~5 days), usually without significant vomiting. The incubation period of SARS-CoV-2 varies depending on circulating variant and the host's vaccination status and immunocompetence with symptoms of acute COVID-19 developing 2–14 days after exposure and symptoms of MIS-C developing approximately ~4 weeks after exposure, with or without preceding known symptomatic COVID-19. Acute COVID-19 encompasses a spectrum of disease ranging from mild congestion and headache to acute respiratory failure, hypercoagulability, and multisystem organ failure, but it may be limited to AGE in some patients. Other gastrointestinal manifestations of acute COVID-19 include colitis, mesenteric adenitis, and pseudoappendicitis as a manifestation of mesenteric adenitis. Whereas fever is present in fewer than half of acute COVID-19 cases in children, it is a diagnostic criterion of MIS-C, in which abdominal pain and other gastrointestinal symptoms are a prominent feature, often accompanied by rash, conjunctivitis, and lymphadenopathy, and which may rapidly progress to cardiogenic shock if not identified and treated promptly.

### Bacterial Diarrhea

Although there is considerable overlap, high fever >40°C, overt fecal blood, abdominal pain, no vomiting before diarrhea onset, and high stool frequency (>10 per day) are more common with bacterial pathogens (see Table 387.2). Although high fever and overt fecal blood are often absent in bacterial enteritis, when present, there is a high probability of a bacterial etiology. The classical bacterial agents, NTS, *Shigella*, *Campylobacter*, and *Yersinia*, present with one of five syndromes.

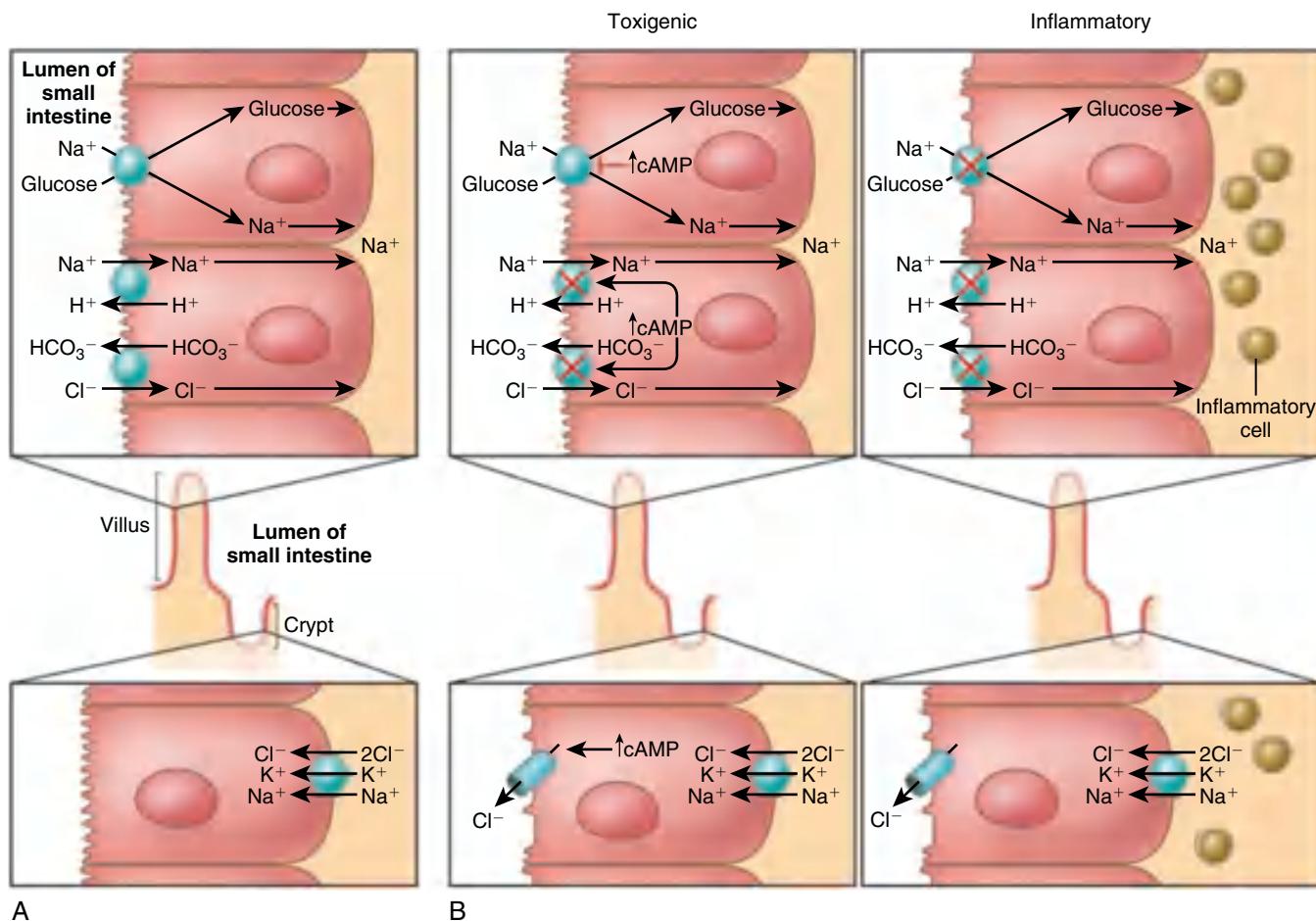
1. Acute diarrhea, the most common presentation, may be accompanied by fever and vomiting. Clinically silent bacteremia associated with uncomplicated NTS AGE can be seen among otherwise healthy children younger than 2 years living in industrialized countries.
2. Bloody diarrhea or frank dysentery is classically caused by *Shigella*. Watery diarrhea typically precedes dysentery and is often the sole clinical manifestation of mild infection. Progression to dysentery indicates colitis and may occur within hours to days. Patients with severe infection may pass more than 20 dysenteric stools in one day. Dysenteric illnesses due to *Campylobacter* have been confused with inflammatory bowel disease.
3. Invasive, nonfocal disease (enteric fever) is a febrile illness associated with bacteremia without localized infection. Diarrhea may be mini-



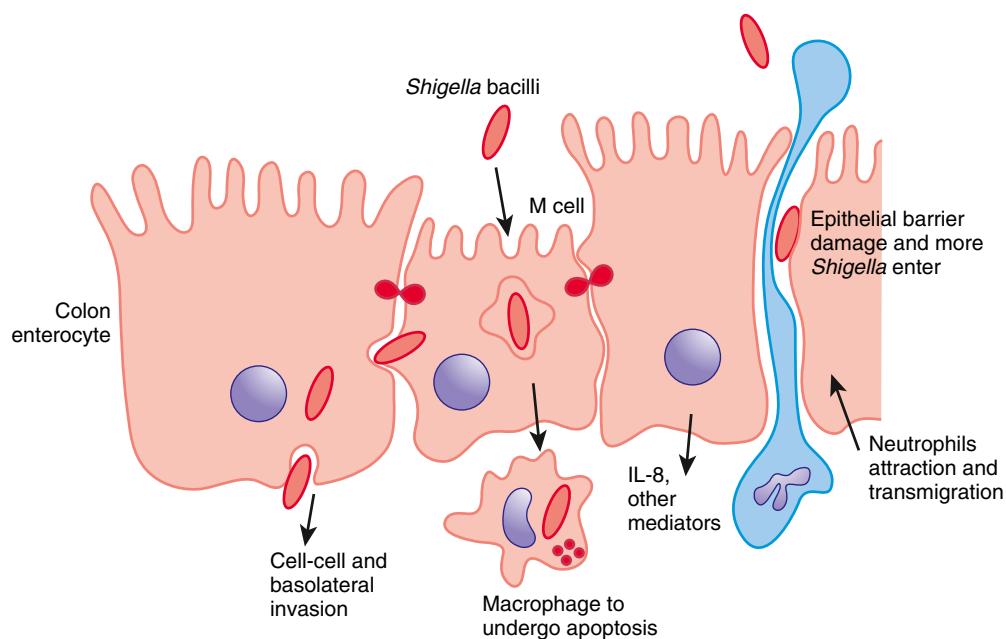
**Fig. 387.3** Mechanism of secretory and penetrating diarrhea. cAMP, Cyclic adenosine monophosphate; CFTR, cystic fibrosis transmembrane conductance regulator through which chloride is secreted; cGMP, cyclic guanosine monophosphate; YoPs, *Yersinia* outer proteins that alter host cell functions to promote disease; CT, cholera toxin; EAST1, entero-aggregative *E. coli* ST; GC-C, guanylate cyclase, the transmembrane receptor for STa and other toxins; GM1, a ganglioside containing one sialic acid residue that serves as the receptor for CT and LT; LT, heat labile toxin; PK, protein kinase; STa, heat stable toxin A. (Modified from Thapar M, Sanderson IR. Diarrhoea in children: an interface between developing and developed countries. *Lancet*. 2004;363:641–653; and Montes M, DuPont HL. Enteritis, enterocolitis and infectious diarrhea syndromes. In Cohen J, Powderly WG, Opal SM, et al., eds. *Infectious Diseases*, 2nd ed. London: Mosby; 2004. pp. 31–52.)

mal or absent. Although classically the result of *S. Typhi* or *Paratyphi* A and B, enteric fever can result from systemic spread of the classical bacterial enteropathogens. Whereas enteric fever caused by *S. Typhi* or *Paratyphi* A and B primarily affect preschool and school-age children in endemic countries, other bacterial enteropathogens most often cause disease in infants (particularly <3 months), the immunocompromised, and children with malnutrition. Additional risk factors include hemolytic anemia and intravascular lesions for NTS, and iron overload, cirrhosis, and chelation therapy for *Yersinia* sepsis. The distinct clones of NTS that have arisen in sub-Saharan Africa described earlier often cause enteric-fever type illnesses in the absence of AGE. *Shigella* sepsis is rare and is seen most often in malnourished and immunocompromised hosts.

4. Localized extraintestinal invasive infections can result from either local invasion or bacteremic spread (see Table 387.7). Examples of local invasion include mesenteric adenitis, appendicitis, and rarely cholecystitis, mesenteric venous thrombosis, pancreatitis, and hepatic or splenic abscess. Bacteremic spread may result in pneumonia, osteomyelitis, meningitis (three conditions seen most commonly with NTS), abscesses, cellulitis, septic arthritis, and endocarditis. *Shigella* can cause noninvasive contiguous infections such as vaginitis and urinary tract infections.
  5. Vertical transmission of *Shigella*, NTS, and *Campylobacter* can produce perinatal infection resulting in a spectrum of illness from isolated diarrhea or hematochezia to fulminant neonatal sepsis. One species of *Campylobacter*, *C. fetus*, is particularly virulent in pregnant women and can result in chorioamnionitis, abortion, and neonatal sepsis and meningitis.
- Crampy abdominal pain and nonbloody diarrhea are the first symptoms of STEC infection, sometimes with vomiting. Within several days, diarrhea becomes bloody, and abdominal pain worsens. Bloody diarrhea lasts between 1 and 22 days (median 4 days). In contrast to



**Fig. 387.4** Movement of  $\text{Na}^+$  and  $\text{Cl}^-$  in the small intestine. A, Movement in normal subjects.  $\text{Na}^+$  is absorbed by two different mechanisms in absorptive cells from villi: glucose-stimulated absorption and electroneutral absorption (which represents the coupling of  $\text{Na}^+/\text{H}^+$  and  $\text{Cl}^-/\text{HCO}_3^-$  exchanges). B, Movement during diarrhea caused by a toxin and inflammation. (From Petri WA, Miller M, Binder HJ, et al. Enteric infections, diarrhea and their impact on function and development. *J Clin Invest*. 2008;118:1277–1290.)



**Fig. 387.5** Pathogenesis of *Shigella* infection and diarrhea. IL, Interleukin. (Adapted from Opal SM, Keusch GT. Host responses to infection. In: Cohen J, Powderly WG, Opal SM, et al., eds. Infectious Diseases, 2nd ed. London: Mosby; 2004. pp. 31–52.)

dysentery, the stools associated with STEC hemorrhagic colitis are large volume and rarely accompanied by high fever. ETEC causes a secretory watery diarrhea that affects infants and young children in developing countries and is the major causative agents of traveler's diarrhea, accounting for about half of all episodes in some studies. EPEC remains a leading cause of persistent diarrhea associated with malnutrition among infants from developing countries. EIEC, which is genetically, biochemically, and clinically nearly identical to *Shigella*, causes rare food-borne outbreaks in industrialized countries. EAEC has been associated with persistent diarrhea in immunocompromised persons and sporadic diarrhea in infants in countries with varying levels of economic development; however, some other studies have not found an association with disease.

*C. difficile* toxin is associated with several clinical syndromes. The most common is mild to moderate watery diarrhea, low-grade fever, and mild abdominal pain. Occasionally, the illness will progress to full-blown pseudomembranous colitis characterized by diarrhea, abdominal cramps, and fever. The colonic mucosa contains 2-5 mm raised, yellowish plaques. Fatal cases are associated with toxic megacolon, systemic toxicity, and multisystem organ failure, possibly related to systemic absorption of toxin. The illness associated with *S. aureus* and *B. cereus* emetic toxin is dominated by vomiting, whereas diarrhea is the major manifestation of *C. perfringens* and *B. cereus* enterotoxins.

### Protozoal Diarrhea

Illnesses due to intestinal protozoa tend to be more prolonged, sometimes for 2 weeks or more, but are usually self-limited in the otherwise healthy host (see Table 387.3). In general, the duration and severity of *Cryptosporidium* diarrhea is strongly influenced by the immune and nutritional status of the host. A protozoal etiology should be suspected when there is a prolonged diarrheal illness characterized by episodes of sometimes explosive diarrhea with nausea, abdominal cramps, and abdominal bloating. The stools are usually watery but can be greasy and foul smelling due to concomitant malabsorption of fats, which is more likely to occur if the parasite load is high. Occasionally, diarrhea may alternate with constipation.

In addition to diarrhea, *E. histolytica* causes a range of other syndromes. Amebic dysentery is characterized by bloody or mucoid diarrhea, which may be profuse and lead to dehydration or electrolyte imbalances. Amebic granulomas (amebomas) may form in the colon, and extraintestinal disease most commonly manifests as liver abscesses but may also spread to the lungs, pericardium, genitourinary tract, skin, and, hematogenously, to the brain or other sites. Extraintestinal *Entamoeba* disease may occur with or without intestinal disease.

### INTESTINAL AND EXTRAINTESTINAL COMPLICATIONS

The major complications of diarrhea from any cause are dehydration and electrolyte or acid-base derangements, which can be life-threatening (see Table 387.7). Avoiding delays in diagnosis and treatment and providing appropriate supportive care using either oral, enteral, or intravenous hydration can prevent or treat most of these conditions. Children who experience frequent episodes of acute diarrhea or prolonged or persistent episodes (seen especially in low-resource settings) are at risk for poor growth and nutrition and complications such as secondary infections and micronutrient deficiencies (iron, zinc, vitamin A). Ensuring continued nutritional support during diarrheal episodes is important because prolonged limitation of the diet may extend diarrheal symptoms. Reestablishing a normal diet generally restores villous anatomy and function with resolution of loose stools.

Viral AGE illnesses are usually self-limited and resolve after several days. Rarely, **intussusception** is triggered by lymphoid hyperplasia associated with viral AGE. Complications of bacterial AGE may be the result of local or systemic spread of the organism; in malnourished children and HIV-infected populations, associated **bacteremia** is well recognized. Toxic megacolon, intestinal perforation, and rectal prolapse can occur, particularly in association with *Shigella* in developing countries and *C. difficile*. The most dreaded complication of pediatric diarrhea in the United States is HUS, the leading cause of acquired

renal failure in children, which develops in 5–10% of patients infected with STEC. It is usually diagnosed 2–14 days after the onset of diarrhea. HUS is unlikely to occur once diarrhea has remained resolved for 2 or 3 days with no evidence of hemolysis. Risk factors include age 6 months to 4 years, bloody diarrhea, fever, elevated leukocyte count, and treatment with antibiotics and antimotility agents. Patients may no longer excrete the organism at the time they develop HUS (see Chapter 560.5).

**Pseudoappendicitis** secondary to mesenteric adenitis is a notable complication of *Yersinia*, sometimes *Campylobacter* and COVID-19. Older children and adolescents are most often affected. It typically presents with fever and abdominal pain with tenderness localized to the right lower quadrant, with or without diarrhea, and can be confused with appendicitis. When available, ultrasound is the preferred method for diagnosing true appendicitis; abdominal CT or MRI may be helpful when ultrasound is not available.

Immune-mediated complications that are thought to result from immunologic cross reactivity between bacterial antigens and host tissues are more often seen in adults than children. These include reactive arthritis following infection with the classical bacterial enteropathogens and Guillain-Barré syndrome following *Campylobacter* infection.

Protozoan illnesses, when persistent, can lead to poor weight gain in the young and in immunocompromised individuals, weight loss, malnutrition, or vitamin deficiencies. Infection with *Entamoeba* can cause severe ulcerating colitis, colonic dilation, and perforation. The parasite may spread systemically, most commonly causing liver abscesses. In high-risk settings, it is critical to exclude *Entamoeba* infection and tuberculosis before initiating corticosteroids for presumed ulcerative colitis.

### DIFFERENTIAL DIAGNOSIS

The physician should also consider noninfectious diseases that can present with bright red blood per rectum or hematochezia (Table 387.8). In an infant or young child without systemic symptoms, these may include anal fissures, intermittent intussusception, juvenile polyps, and Meckel diverticulum. Necrotizing enterocolitis can cause lower gastrointestinal bleeding in infants, especially premature neonates. Inflammatory bowel disease should be considered in older children. Examples of noninfectious causes of nonbloody diarrhea include congenital secretory diarrheas, endocrine disorders (hyperthyroidism), neoplasms, food intolerance, and medications (particularly antibiotics). Noninfectious causes of chronic or relapsing diarrhea include cystic fibrosis, celiac disease, milk protein, lactose, fructose, or sucrose intolerance and other food allergies, congenital or acquired disaccharidase deficiency, and functional gastrointestinal disorders. Significant abdominal pain should raise suspicion of other infectious processes in the abdomen such as appendicitis and pelvic inflammatory disease. Prominent vomiting with or without abdominal pain can be a manifestation of pyloric stenosis, intestinal obstruction, pancreatitis, appendicitis, and cholecystitis.

### Clinical Evaluation of Diarrhea

In the initial evaluation of all patients with AGE, the physician should focus on the patient's hydration status and electrolyte balance, as well as evidence of sepsis or invasive bacterial infection, which could complicate bacterial AGE (Fig. 387.6). Once the patient is stabilized, the history and physical examination can focus on detecting risk factors and exposures, as well as the clinical features that may suggest specific etiologic agents.

Important elements of the medical history include the duration of diarrhea and a description of stools (frequency, amount, presence of blood or mucus), fever (duration, magnitude, pattern), vomiting (onset, amount, and frequency), and the amount and type of solid and liquid oral intake. Clinical signs of dehydration should be evaluated (Table 387.9): urine output (number of wet diapers per day and time since the last urination), whether eyes appear sunken, whether the child is active, whether the child drinks vigorously, and the date and value of the most recent weight measurement. A documented weight loss can be used to calculate the fluid deficit. The past medical history should identify comorbidities that might increase the risk or severity of AGE.

**Table 387.7** Intestinal and Extraintestinal Complications of Enteric Infections

COMPLICATION	ASSOCIATED ENTERIC PATHOGEN(S)
<b>INTESTINAL COMPLICATIONS</b>	
Persistent diarrhea	All causes
Recurrent diarrhea (usually immunocompromised persons)	<i>Shigella</i> spp., NTS, <i>Campylobacter</i> spp., <i>Clostridioides difficile</i> , <i>Yersinia</i> spp., <i>Entamoeba histolytica</i> , <i>Cryptosporidium</i> spp.
Postinfectious irritable bowel syndrome	<i>Shigella</i> spp., NTS, <i>Campylobacter</i> spp., <i>C. difficile</i>
Protein-losing enteropathy	<i>Shigella</i> and <i>Salmonella</i> spp., rotavirus, CMV, Giardiasis, <i>Strongyloides stercoralis</i> , tuberculosis, HIV
Toxic megacolon	<i>Shigella</i> spp., NTS, <i>Campylobacter</i> spp., <i>C. difficile</i> , <i>Yersinia</i> spp., <i>E. histolytica</i> , STEC
Intestinal perforation	<i>Shigella</i> spp., NTS, <i>C. difficile</i> , <i>Yersinia</i> spp., <i>E. histolytica</i> , STEC
Rectal prolapse	<i>Shigella</i> spp., NTS, <i>Campylobacter</i> spp., <i>C. difficile</i> , <i>E. histolytica</i> , STEC
Pseudomembranous colitis	<i>Shigella</i> spp., NTS, <i>C. difficile</i> , <i>Yersinia</i> spp., STEC
Appendicitis	<i>Shigella</i> spp., NTS, <i>Yersinia</i> spp., <i>Schistosoma</i> spp., <i>Strongyloides stercoralis</i> , SARS-CoV-2
Intussusception	<i>Shigella</i> spp., NTS, <i>Campylobacter</i> spp., <i>Yersinia</i> spp., STEC
Chronic carriage	NTS
<b>EXTRAINTESTINAL COMPLICATIONS</b>	
Dehydration, metabolic abnormalities, malnutrition, micronutrient deficiency	All causes
Systemic invasion with bacteremia/parasitemia ± distant foci	<i>Shigella</i> spp., NTS, <i>Campylobacter</i> spp., <i>Yersinia</i> spp., <i>E. histolytica</i>
Local invasion Mesenteric adenitis Cholecystitis	<i>Campylobacter</i> spp. (rarely), <i>Yersinia</i> spp., COVID-19 NTS, SARS-CoV-2
Local noninvasive spread Vulvovaginitis Urinary tract infection	<i>Shigella</i> spp. <i>Shigella</i> spp., <i>Yersinia</i> spp.
Seizures, encephalopathy	<i>Shigella</i> spp., STEC
Leukemoid reaction, bandemia	<i>Shigella</i> spp., <i>Yersinia</i> spp.
Pharyngitis, adenopathy, rash	<i>Yersinia</i> spp., SARS-CoV-2*
Fetal/placental infection	<i>Campylobacter fetus</i> , <i>Shigella</i> spp.
<b>POSTINFECTIOUS COMPLICATIONS</b>	
Reactive arthritis	<i>Shigella</i> spp., NTS, <i>Campylobacter</i> spp., <i>C. difficile</i> , <i>Yersinia</i> spp.
Guillain-Barré syndrome	<i>Campylobacter</i> spp.
Hemolytic uremic syndrome	<i>Shigella dysenteriae</i> type 1, STEC
Glomerulonephritis, myocarditis, pericarditis	<i>Campylobacter</i> spp., <i>Yersinia</i> spp., SARS-CoV-2
Immunoglobulin A (IgA) nephropathy	<i>Campylobacter</i> spp.
Erythema nodosum	NTS, <i>Campylobacter</i> spp., <i>Yersinia</i> spp.
Hemolytic anemia	<i>Campylobacter</i> spp., <i>Yersinia</i> spp.

\**Yersinia* spp. is associated with a scarlatiniform rash, cervical adenopathy, and exudative pharyngitis whereas SARS-CoV-2 is typically associated with a nonexudative pharyngitis and diffuse lymphadenopathy, and the rash of SARS-CoV-2 can be polymorphous.

NTS, Nontyphoidal *Salmonella* spp.; CMV, cytomegalovirus; STEC, Shiga toxin-producing *E. coli*.

Certain physical signs are best assessed before approaching the child directly, so the child remains calm, including general appearance (activity, response to stimulation) and respiratory patterns. Skin turgor is assessed by pinching a small skinfold on the lateral abdominal wall at the level of the umbilicus. If the fold does not promptly return to normal after release, the recoil time is quantified as delayed slightly or  $\geq 2$  seconds. Excess subcutaneous tissue and hypernatremia may produce a false-negative test, and malnutrition can prolong the recoil time. To measure capillary refill time, the palmar surface of the child's distal fingertip is pressed until blanching occurs, with the child's arm at heart level. The time elapsed until restoration of normal color after release usually exceeds 2

seconds in the presence of dehydration. Mucous membrane moisture level, presence of tears, and extremity temperature should also be assessed.

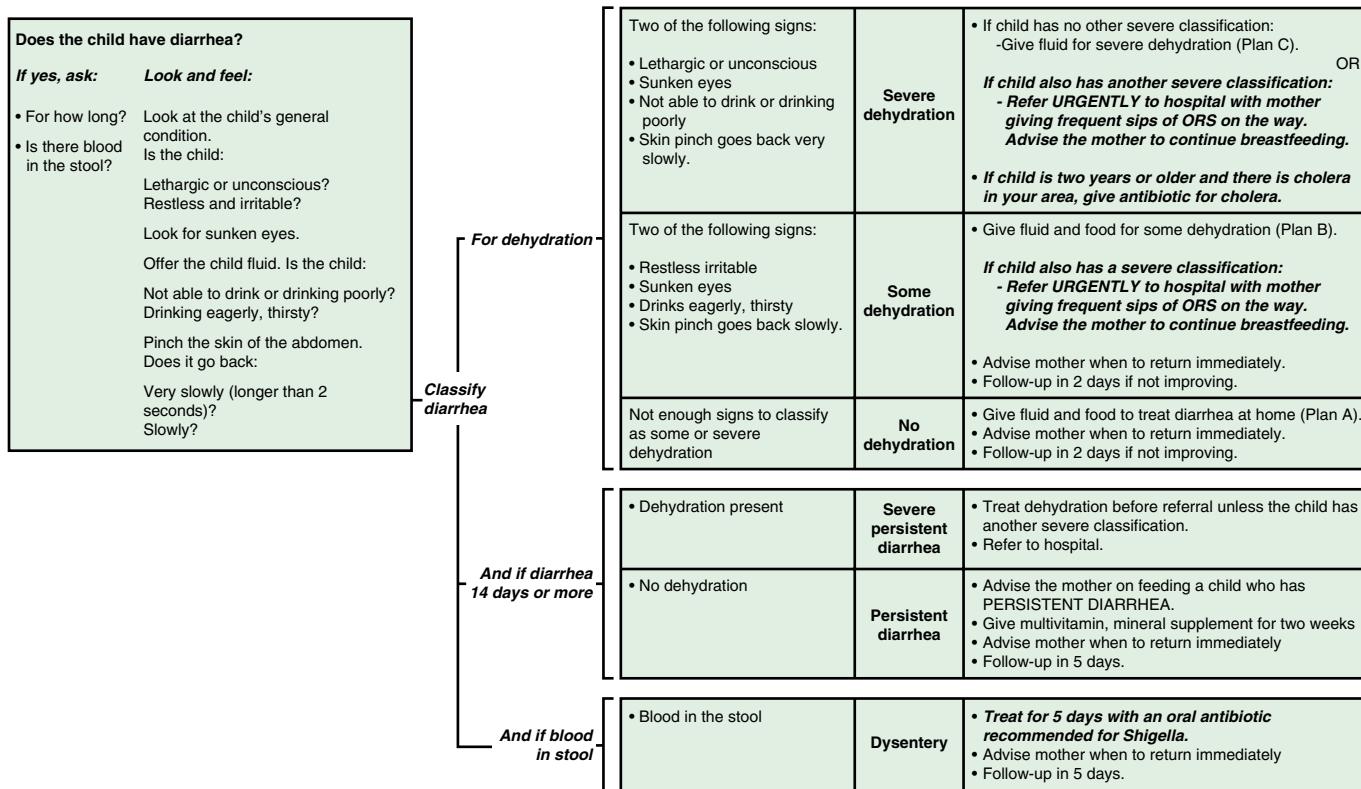
### Laboratory Diagnosis

Most cases of AGE do not require diagnostic laboratory testing. Stool specimens may be examined for mucus, blood, neutrophils, or fecal lactoferrin, a neutrophil product. The finding of more than five leukocytes per high-power field or a positive lactoferrin assay in an infant not breastfeeding suggests an infection with a classical bacterial enteropathogen; patients infected with STEC and *E. histolytica* usually have negative tests.

<b>Table 387.8</b>	Differential Diagnosis of Acute Dysentery and Inflammatory Enterocolitis
<b>SPECIFIC INFECTIOUS PROCESSES</b>	
Bacillary dysentery ( <i>Shigella</i> spp.; invasive <i>Escherichia coli</i> )	
Campylobacteriosis ( <i>Campylobacter jejuni</i> )	
Amebic dysentery ( <i>Entamoeba histolytica</i> )	
Bilharzial dysentery ( <i>Schistosoma japonicum</i> , <i>S. mansoni</i> )	
Vibriosis ( <i>Vibrio cholera</i> )	
Salmonellosis (nontyphoidal <i>Salmonella</i> )	
Enteric fever ( <i>Salmonella Typhi</i> , <i>Salmonella Paratyphi A, B, and C</i> )	
Yersiniosis ( <i>Yersinia enterocolitica</i> )	
<b>PROCTITIS</b>	
Gonococcal ( <i>Neisseria gonorrhoeae</i> )	
Herpetic (herpes simplex virus)	
Chlamydial ( <i>Chlamydia trachomatis</i> )	
Syphilitic ( <i>Treponema pallidum</i> )	
<b>OTHER SYNDROMES</b>	
Necrotizing enterocolitis of the newborn	
Enteritis necroticans	
Pseudomembranous enterocolitis ( <i>Clostridioides difficile</i> )	
Typhlitis	
<b>CHRONIC INFLAMMATORY PROCESSES</b>	
Enteropathogenic and enteroaggregative <i>Escherichia coli</i>	
Gastrointestinal tuberculosis	
Gastrointestinal mycosis	
Parasitic enteritis	
<b>SYNDROMES WITHOUT KNOWN INFECTIOUS CAUSE</b>	
Idiopathic ulcerative colitis	
Crohn disease	
Radiation enteritis	
Ischemic colitis	
Allergic enteritis	

Laboratory diagnosis of viral AGE may be helpful when an outbreak is suspected, cases are linked to a suspected outbreak, or when cohorting of patients is considered to limit the spread of infection. The preferred method of testing norovirus is real-time reverse-transcription quantitative polymerase chain reaction (RT-qPCR), available at most public health and virology laboratories. Commercial multiplex PCR tests are available in the United States for the diagnosis of bacterial, parasitic, and viral enteric pathogens, including rotavirus, enteric adenoviruses, astrovirus, norovirus, and sapovirus (see Table 387.1). Although SARS-CoV-2 has been identified in enteric specimens in research settings, the mainstay of clinical diagnosis remains upper respiratory sampling for either PCR or immunoassay.

Stool cultures for detection of bacterial agents are costly, so requests should be restricted to patients with clinical features predictive of bacterial AGE, have moderate or severe disease, are immunocompromised, in outbreaks with suspected HUS, or have a highly suggestive epidemiologic history. To optimize recovery of pathogens, stool specimens for culture need to be transported and plated quickly; if the latter is not quickly available, specimens might need to be transported in special transport media. If antibiotics will be administered and the child has not produced a stool sample, a rectal swab should be collected promptly so as not to delay initiation of antibiotics. After dipping the cotton tip into the medium that will be used for transport, it is gently inserted into the child's rectum and rotated 360 degrees. A properly collected rectal swab is stained or covered with fecal material. Standard stool culture methods performed in clinical microbiology laboratories recover *Shigella* and *Salmonella* species. If *Campylobacter*, *Yersinia*, or *Vibrio* species are suspected, the laboratory should be notified unless media are routinely used for their detection. All bloody stools should also be inoculated into media specific for detection of *E. coli* 0157:H7 or directly tested for the presence of Shiga-like toxin (or both). Except for *C. difficile*, nosocomial acquisition of a bacterial enteric pathogen is very unlikely. Nucleic acid amplification tests (NAAT) have replaced stool culture in some settings; reflex culture is necessary to identify



**Fig. 387.6** Algorithm showing the Integrated Management of Childhood Illnesses (IMCI) protocol for the recognition and management of diarrhea in developing countries. ORS, Oral rehydration solution.

**Table 387.9** Signs and Symptoms Associated with Dehydration

SYMPOTM	MINIMAL OR NO DEHYDRATION	SOME DEHYDRATION	SEVERE DEHYDRATION
Mental status <sup>C,G4,W</sup>	Well; alert	Normal, fatigued or restless, irritable	Apathetic, lethargic, limp, unconscious/comatose
Thirst <sup>W</sup>	Drinks normally; might refuse liquids	Thirsty; eager to drink	Drinks poorly; unable to drink
Heart rate <sup>G10</sup>	Normal	Normal to increased	Tachycardia, with bradycardia in most severe cases
Quality of pulses <sup>G10</sup>	Normal	Normal to decreased	Weak, thready, or impalpable
Breathing <sup>G10</sup>	Normal	Normal; fast	Deep, fast
Eyes <sup>C,G10,W</sup>	Normal	Slightly sunken	Deeply sunken
Tears <sup>C,G4</sup>	Present	Decreased	Absent
Mouth and tongue/mucous membranes <sup>C,G4</sup>	Moist	Dry, "sticky" or "tacky"	Parched
Skinfold <sup>G10,W</sup>	Instant recoil	Recoil in <2 sec (slow)	Recoil in >2 sec (very slow)
Capillary refill <sup>G4</sup>	Normal	Prolonged	Prolonged; minimal
Extremities	Warm	Cool	Cold; mottled; cyanotic
Urine output <sup>G10</sup>	Normal to decreased	Decreased	Minimal

<sup>C</sup>Denotes inclusion in Clinical Dehydration Scale (CDS); CDS scores each category from 0 to 2 with an overall score of 0 = no dehydration (<3%), 1-4 = some dehydration (<6%).

<sup>G4</sup>Denotes inclusion in 4-point and 10-point Gorelick scales: ≥2 Clinical Signs ≥5% ΔBW; ≥3 Clinical Signs ≥10% ΔBW.

<sup>G10</sup>Denotes items included in 10-point Gorelick scale but not in the 4-point Gorelick scale: ≥3 Clinical Signs ≥5% ΔBW; ≥7 Clinical Signs ≥10% ΔBW. Gorelick Scale uses "no or minimal dehydration" and "moderate to severe dehydration."

<sup>W</sup>Denotes inclusion in the World Health Organization (WHO) scale.

BW, Body weight.

antimicrobial sensitivities. Hence, stool microbiologic assays are generally not indicated for patients in whom diarrhea develops more than 3 days after admission unless the patient is immunocompromised or to investigate a hospital outbreak (see Table 387.2).

For children older than 2 years who have recently received antibiotics or have other risk factors, evaluation for *C. difficile* infection may be appropriate. The cytotoxin assay detects toxin B, but testing for toxin A is also available in some laboratories; however, this test is laborious. Several tests are commercially available to detect toxin-producing *C. difficile* in stool, including enzyme immunoassays (EIA) for toxins A and B, cell culture cytotoxicity assay, PCR, and glutamate dehydrogenase (GDH) immunoassay. The sensitivities of cell culture, PCR, and GDH EIA are superior to that of toxin EIA. A multistep diagnostic approach combining toxin testing with NAAT and/or GDH EIA may improve the sensitivity, specificity, and positive predictive value of *C. difficile* testing. Testing for *C. difficile* toxin in children younger than 2 years is discouraged because the organism and its toxins are commonly detected in asymptomatic infants (see Table 387.2).

Evaluation for intestinal protozoa that cause diarrhea is usually indicated in patients who recently traveled to an endemic area, had contact with untreated water, and manifest suggestive symptoms. Previously, the most commonly used method was direct microscopy of stool for cysts and trophozoites. However, this approach is time-consuming and lacks sensitivity, in part because shedding can be intermittent. Analyzing three specimens from separate days is optimal, and fecal concentration techniques provide some benefit. The sensitivity and specificity of microscopy is substantially improved using immunofluorescence antibodies that are commercially available for visualization of *Cryptosporidium* and *Giardia* cysts. In addition, EIAs are available for *Cryptosporidium*, *Giardia*, and *Entamoeba* that are more sensitive and specific than direct microscopy and provide a useful diagnostic tool. (Not all commercial kits distinguish between pathogenic *E. histolytica* and non-pathogenic *E. dispar*.) Molecular methods (NAATs and multiplex PCR assays) have largely replaced microscopy and EIAs (see Table 387.3).

Several culture-independent rapid multiplex molecular panels for detection of viral, bacterial, and protozoal gastrointestinal pathogens

directly from stool samples are approved by the U.S. Food and Drug Administration (FDA), including xTag GPP (14 pathogens), Verigene EP (9 pathogens), and the FilmArray GI Panel (22 pathogens). These methods offer several advantages over conventional diagnostics, including reduced sample volume requirements, broad coverage without the need to select specific tests, enhanced ability to detect co-infections, increased sensitivity, and rapid turnaround. However, the available tests do not provide strain specificity or susceptibility testing, so culture is still necessary to guide outbreak detection and treatment decisions.

Most episodes of diarrheal dehydration are isonatremic and do not warrant serum electrolyte measurements. Electrolyte measurements are most useful in children with severe dehydration, when intravenous fluids are administered, when there is a history of frequent watery stools, yet the skin pinch feels doughy without delayed recoil, which suggests hypernatremia, when the child is unable to drink due to anorexia or emesis, and when inappropriate or inadequate rehydration fluids have been administered at home. A suspicion for HUS prompts a complete blood count with review of the peripheral smear, serum electrolytes, and renal function tests. Patients with shigellosis can demonstrate bandemia or even a leukemoid reaction. Blood culture should be obtained if there is concern for systemic bacterial infection. This includes infants and children with fever and/or blood in the stool who are younger than 3 months, are immunocompromised, or have hemolytic anemia or other risk factors. If diarrhea persists with no cause identified, endoscopic evaluation may be indicated. Biopsy specimens help in diagnosing inflammatory bowel disease or identifying infecting agents that may mimic it. A sweat test is warranted if cystic fibrosis is suspected.

## TREATMENT

The broad principles of management of AGE in children include rehydration and maintenance ORS plus replacement of continued losses in diarrheal stools and vomitus after rehydration, continued breastfeeding, and refeeding with an age-appropriate, unrestricted diet as soon as dehydration is corrected. Zinc supplementation is recommended for children in developing countries.

## Hydration

Children, especially infants, are more susceptible than adults to dehydration because of the greater basal fluid and electrolyte requirements per kilogram and because they are dependent on others to meet these demands (Table 387.10). Dehydration must be evaluated rapidly and corrected in 4–6 hours according to the degree of dehydration and estimated daily requirements. When there is emesis, small volumes of ORS can be given initially by a dropper, teaspoon, or syringe, beginning with as little as 5 mL at a time. The volume is increased as tolerated. The low-osmolality WHO ORS containing 75 mEq of sodium, 64 mEq of chloride, 20 mEq of potassium, and 75 mmol of glucose/L, with total osmolarity of 245 mOsm/L, is now the global standard of care and more effective than home fluids. Soda beverages, fruit juices, and tea and other home fluids are not suitable for rehydration or maintenance therapy because they have inappropriately high glucose concentration and osmolalities and low sodium concentrations. Tables 387.9 and 387.10 outline a clinical evaluation plan and management strategy for children with moderate to severe diarrhea. Replacement for emesis or stool losses is noted in Table 387.10. Oral rehydration can also be given by a nasogastric tube if needed.

A small minority of children, including those with severe dehydration or unable to tolerate oral fluids, require initial intravenous rehydration, but oral rehydration is the preferred mode of rehydration and replacement of ongoing losses. Signs of severe dehydration that might necessitate intravenous resuscitation include those shown in Table 387.9. Limitations to ORS include shock, decreased level of consciousness, ileus, intussusception, carbohydrate intolerance (rare), severe emesis, and high stool output (>10 mL/kg/hr).

## Enteral Feeding and Diet Selection

Continued breastfeeding and refeeding with an age-appropriate, unrestricted diet as soon as dehydration is corrected aids in recovery from the episode. Foods with complex carbohydrates (rice, wheat, potatoes, bread, and cereals), fresh fruits, lean meats, yogurt, and vegetables should be reintroduced while ORS is given to replace ongoing losses from emesis or stools and for maintenance. Fatty foods or foods high in

simple sugars (juices, carbonated sodas) should be avoided. The usual energy density of any diet used for the therapy of diarrhea should be around 1 kcal/g, aiming to provide an energy intake of a minimum of 100 kcal/kg/day and a protein intake of 2–3 g/kg/day. In selected circumstances when adequate intake of energy-dense food is problematic, the addition of amylase to the diet through germination techniques can also be helpful.

If the normal diet includes infant formula, it should not be diluted, or changed to a lactose-free preparation unless lactose malabsorption is evident. With the exception of acute lactose intolerance in a small subgroup, most children with diarrhea are able to tolerate milk and lactose-containing diets. Withdrawal of milk and replacement with specialized lactose-free formulations are unnecessary. Although children with persistent diarrhea are not lactose intolerant, administration of a lactose load exceeding 5 g/kg/day may be associated with higher purging rates and treatment failure. Alternative strategies for reducing the lactose load while feeding malnourished children who have prolonged diarrhea include addition of milk to cereals and replacement of milk with fermented milk products such as yogurt.

Rarely, when dietary intolerance precludes the administration of cow's milk-based formulations or whole milk, it may be necessary to administer specialized milk-free diets such as a comminuted or blended chicken-based diet or an elemental formulation. Although effective in some settings, the latter are unaffordable in most developing countries. In addition to rice-lentil formulations, the addition of green banana or pectin to the diet has also been shown to be effective in the treatment of persistent diarrhea. Figure 387.7 provides an algorithm for managing children with prolonged diarrhea in developing countries.

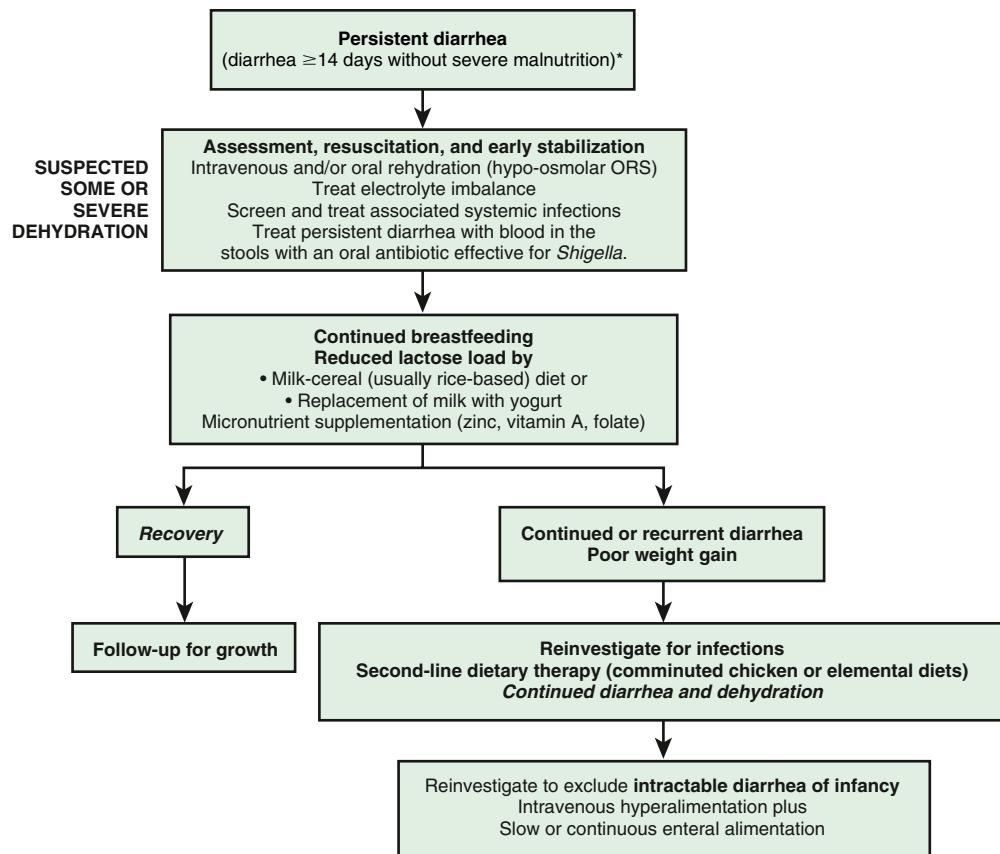
Among children in low- and middle-income countries, where the dual burden of diarrhea and malnutrition is greatest and where access to proprietary formulas and specialized ingredients is limited, the use of locally available age-appropriate foods should be promoted for the majority of acute diarrhea cases. Even among those children for whom lactose avoidance may be necessary, nutritionally complete diets comprised of locally available ingredients can be used at least as effectively

**Table 387.10** | Summary of Treatment Based on Degree of Dehydration

DEGREE OF DEHYDRATION	REHYDRATION THERAPY	REPLACEMENT OF LOSSES
Some dehydration	Infants and children: ORS, 75 mL/kg over 3–4 hr. Continue breastfeeding. After 4 hr, give food every 3–4 hr for children who normally receive solid foods.	Infants and children: <2 yr old: 50–100 mL ORS for each diarrheal stool or vomiting episode, up to ~500 mL/day ≥2 yr old: 100–200 mL ORS for each diarrheal stool or vomiting episode, up to ~1 L/day Replace losses as above as long as diarrhea or vomiting continues
Severe dehydration	Malnourished infants may benefit from smaller-volume, frequent boluses of 5–10 mL/kg body weight due to reduced capacity to increase cardiac output with larger volume resuscitation. Infants (<12 mo) and children (12 mo to 5 yr) without malnutrition: Give 20–30 mL/kg boluses of IV isotonic crystalloid solution (e.g., Ringer lactate or normal saline solution) over 30–60 min. Repeat boluses as necessary to restore adequate perfusion. Then give 70 mL/kg over 2.5–5 hr. (Note the slower infusion times are for infants.) If IV hydration is not possible, administer ORS 20 mL/kg/hr × 6 hours via nasogastric tube. Reassess the infant or child frequently and adjust infusion rate if needed. Give ORS as soon as the child can drink. Allow to feed (breast milk or solid food) as described for some dehydration. Adjust electrolytes and administer dextrose based on chemistry values.	Infants and children: <10 kg body weight (children <2 yr): 50–100 mL ORS for each diarrheal stool or vomiting episode >10 kg body weight (children ≥2 yr): 100–200 mL ORS for each diarrheal stool or vomiting episode Adolescents and adults: Ad libitum Replace losses as above as long as diarrhea or vomiting continue If unable to drink, either administer ORS through a nasogastric tube or give dextrose-containing IV fluids as appropriate based on chemistry values

Note: Low-osmolality ORS can be given to all age-groups, with any cause of diarrhea. It is safe in the presence of hypernatremia, as well as hyponatremia (except when edema is present). Some commercially available formulations that can be used as ORS include Pedialyte Liters (Abbott Nutrition), CeraLyte (Cera Products), and Enfalac Lytren (Mead Johnson). Popular beverages that should not be used for rehydration include apple juice, Gatorade, and commercial soft drinks.

ORS, Oral rehydration solution; IV, intravenous.



**Fig. 387.7** Management algorithm for persistent diarrhea. ORS, Oral rehydration solution.

as commercial preparations or specialized ingredients. These same conclusions may also apply to the dietary management of children with persistent diarrhea, but the evidence remains limited.

### Zinc Supplementation

Zinc supplementation in children with diarrhea in developing countries leads to reduced duration and severity of diarrhea and could potentially prevent a large proportion of cases from recurring. Zinc administration for diarrhea management can significantly reduce all-cause mortality by 46% and hospital admission by 23%. In addition to improving diarrhea recovery rates, administration of zinc in community settings leads to increased use of ORS and reduction in the inappropriate use of antimicrobials. All children older than 6 months of age with acute diarrhea in at-risk areas should receive oral zinc (20 mg/day is recommended by most guidelines, but 5 mg/day and 10 mg/day may be better tolerated and equally effective) in some form for 10–14 days during and continued after diarrhea. The role of zinc in well-nourished, zinc replete populations in developed countries is less certain.

### Additional Therapies

The use of probiotic nonpathogenic bacteria for prevention and therapy of diarrhea has been successful in some settings, although the evidence does not support a recommendation for their use in all settings. A variety of organisms (*Lactobacillus*, *Bifidobacterium*) have a good safety record; therapy has not been standardized, and the most effective (and safe) organism has not been identified. *Saccharomyces boulardii* is effective in antibiotic-associated and in *C. difficile* diarrhea, and there is some evidence that it might prevent diarrhea in daycare centers. Two large randomized placebo-controlled trials evaluating the efficacy of two *Lactobacillus*-based probiotic formulations failed to reduce a clinical severity score in Canadian infants and preschool children with AGE. *Lactobacillus rhamnosus* GG or a combination probiotic product containing *L. rhamnosus* R0011 and *L. helveticus* R0052 has shown variable efficacy; reduction is more evident in cases of childhood rotavirus diarrhea.

Ondansetron (oral mucosal absorption preparation) reduces the incidence of emesis, thus permitting more effective oral rehydration, and is well established in emergency management of AGE in high-resource settings, reducing intravenous fluid requirements and hospitalization. Because persistent vomiting can limit oral rehydration therapy, a single sublingual dose of an oral dissolvable tablet of ondansetron (2 mg for children 8–15 kg, 4 mg for children 16–30 kg, and 8 mg for children >31 kg) may be given off-label. However, most children do not require specific antiemetic therapy; careful ORS is usually sufficient. Antimotility agents (loperamide) are contraindicated in children with dysentery and probably have no role in the management of acute watery diarrhea in otherwise healthy children. Similarly, antiemetic agents, such as the phenothiazines, are of little value and are associated with potentially serious side effects (lethargy, dystonia, malignant hyperpyrexia).

### Antibiotic Therapy

Judicious antibiotic therapy for suspected or proven bacterial infections can reduce the duration and severity of illness and prevent complications (Table 387.11). Several factors justify limited use. First, most episodes of AGE are self-limited among otherwise healthy children. Second, the increasing prevalence of antibiotic resistance has prompted restricted use of these drugs. Third, antibiotics may worsen outcomes, as some studies have shown that antibiotic therapy with STEC infection increases the risk of HUS and prolongs excretion of NTS without improving clinical outcomes. Therefore antibiotics are used primarily to treat severe infections, prevent complications in high-risk hosts, or to limit the spread of infection. Microbiologic (culture) confirmation of the etiology and susceptibility testing should be sought before treatment if possible.

Treatment of *C. difficile* infection warrants special consideration (see Table 387.11). Removal of the offending antibiotic, if possible, is the first step. Antibiotic therapy directed against *C. difficile* should be instituted if the symptoms are severe or persistent. In children, oral vancomycin and metronidazole for 7–14 days (first-line agents)

displayed equivalent efficacy in a prospective randomized trial; however, metronidazole may be preferred because of lower cost and concerns about inducing vancomycin-resistant enterococci. Twenty percent of patients treated for *C. difficile* diarrhea have a relapse. The first relapse should be treated with another course of antibiotics based on severity of illness. For multiply recurrent disease, tapering and/or pulsed regimen of oral vancomycin over a 4- to 6-week period has been proposed. Rifaximin is an alternative option in children  $\geq 12$  years to treat persistent or recurrent *C. difficile* colitis, and fecal microbiota transplant is being explored. Fidaxomicin is an alternate agent approved for patients  $>6$  months of age. The phase 3, multicenter, randomized, single-blind SUNSHINE trial demonstrated equivalent clinical cure rates in pediatric patients receiving either oral vancomycin or fidaxomicin and increased rates of global cure in the fidaxomicin arm, but the study excluded patients with life-threatening and fulminant infection. In patients  $\geq 18$  years old, it is now preferred over vancomycin as the first-line therapy for the initial episode (whether severe or nonsevere) and recurrences. Bezlotoxumab, a monoclonal antibody against *C. difficile* toxins A and B,

has been shown to reduce the recurrence rate and is recommended in addition to standard antibiotic therapy for adults experiencing a recurrence, but it has not been approved for use in children. Studies are underway to determine the safety, tolerability, pharmacokinetics, and efficacy of bezlotoxumab in children. In the absence of ongoing symptoms, a test of cure is not necessary. The role of probiotics in the prevention of *C. difficile*-associated diarrhea in children has not been established.

Antimicrobial therapy for parasitic infections is shown in Table 387.11. Antivirals such as remdesivir have not been studied for efficacy in the treatment of AGE related to SARS-CoV-2 infection.

## PREVENTION

### Promotion of Exclusive Breastfeeding and Vitamin A

Exclusive breastfeeding (administration of no other fluids or foods for the first 6 months of life) protects young infants from diarrheal disease through the promotion of passive immunity and through reduction in the intake of potentially contaminated food and water. In developing countries, exclusive breastfeeding for the first 6 months of life is widely

**Table 387.11** | Antimicrobial Therapy for Infectious Diarrhea

ORGANISM	INDICATION FOR THERAPY	DOSAGE AND DURATION OF TREATMENT
<i>Shigella</i> spp.	In high-income countries, judicious treatment is recommended to curtail growing antibiotic resistance because most shigellosis is self-limited. Treatment should be reserved for severe disease (require hospitalization, have systemic disease or complications), immunocompromised, or to prevent or mitigate outbreaks in certain settings (e.g., childcare or food handling). Also consider treating patients with significant discomfort, intestinal comorbidities, institutional settings, or household exposure to high-risk individuals. WHO recommends empiric antibiotics for all children in developing countries with dysentery assuming that most cases are caused by <i>Shigella</i> .	<p><b>First line:</b></p> <ul style="list-style-type: none"> <li>• Ciprofloxacin* 20 mg/kg/day PO bid <math>\times</math> 3 days (max. 1.5 g/day); OR</li> <li>• Azithromycin† 12 mg/kg once on first day, then 6 mg/kg once daily on days 2 through 4 (total course: 4 days); OR</li> <li>• Ceftriaxone 50-100 mg/kg/day IV or IM, qd <math>\times</math> 3 days for severe illness requiring parenteral therapy.</li> </ul> <p><b>Second line:</b></p> <ul style="list-style-type: none"> <li>• Cefixime 8 mg/kg once daily for 3 days if susceptibility is known or likely based on local data; OR</li> <li>• Trimethoprim (TMP)-sulfamethoxazole (SMX): 4 mg/kg/day of TMP and 20 mg/kg/day SMX twice a day for 5 days (if susceptibility known or likely based on local data); OR</li> <li>• Ampicillin 100 mg PO, divided qid, max 2 g/day for 5 days if susceptibility known or likely based on local data (amoxicillin is not effective presumably due to rapid gut absorption)</li> </ul>
ETEC	Watery diarrhea in a traveler returning from an endemic area that interferes with planned activities or is persistent ( $>14$ days).	<p><b>First line:</b></p> <ul style="list-style-type: none"> <li>• Azithromycin* 12 mg/kg once on first day, then 6 mg/kg once daily on days 2 and 3 (total course: 3 days)</li> </ul> <p><b>Second line:</b></p> <ul style="list-style-type: none"> <li>• Ciprofloxacin† 15 mg/kg/day PO bid <math>\times</math> 3 days; OR</li> <li>• Children <math>\geq 12</math> yr: Rifaximin 600 mg/day (not per kilogram), divided tid <math>\times</math> 3 days</li> </ul>
STEC	Avoid antimicrobials and antimotility drugs.	
<i>Salmonella</i> , nontyphoidal	Antibiotics for uncomplicated gastroenteritis in normal hosts are ineffective, may prolong excretion, and are not recommended. Infection in infants younger than 3 mo and patients with immunocompromise, malignancy, chronic GI disease, severe colitis hemolytic anemia, or HIV infection Most strains are resistant to multiple antibiotics.	See treatment of <i>Shigella</i> . Patients without bacteremia can be treated orally for 5-7 days. Patients with bacteremia (proven or until blood culture results are available in a high-risk host) should be treated parenterally until blood cultures clear and then transitioned to PO to complete a total 7- to 10-day course. Focal or disseminated invasive infections (e.g., osteomyelitis, meningitis) and bacteremic patients with HIV/AIDS should be treated parenterally for 4-6 wk. Depending on susceptibilities, ampicillin, TMP-SMX, or fluoroquinolones may be used.
<i>Yersinia</i> spp.	Antibiotics are not usually required for diarrhea, which is usually self-limited and clinical benefits of antibiotics are not established. Neonates and immunocompromised patients and patients with bacteremia and/or focal invasive infections should be treated. Deferoxamine therapy should be withheld for severe infections or associated bacteremia.	For bacteremia or focal invasive infections, use parenteral third-generation cephalosporins. Can also consider TMP-SMX, aminoglycosides, fluoroquinolones, tetracycline or doxycycline, or chloramphenicol. Begin IV then switch to oral when clinically stable, for a total course of 2-6 wk.

*Continued*

**Table 387.11** Antimicrobial Therapy for Infectious Diarrhea—cont'd

ORGANISM	INDICATION FOR THERAPY	DOSAGE AND DURATION OF TREATMENT
<i>Campylobacter</i> spp.	Dysentery, moderate and severe gastroenteritis or at risk for severe disease (e.g., elderly, pregnant, or immunocompromised), and bacteremia or focal invasive infection. Treatment of gastroenteritis appears effective if given within 3 days of onset of illness.	<b>For gastroenteritis or dysentery:</b> <ul style="list-style-type: none"> <li>Erythromycin PO 40 mg/kg/day divided qid × 5 days</li> <li>Azithromycin PO 10 mg/kg/day × 3 days</li> </ul> <b>For bacteremia or focal invasive infection:</b> <ul style="list-style-type: none"> <li>Consider parenteral macrolides or carbapenems pending susceptibility results. Fluoroquinolone resistance is &gt;50% in some areas of the world.</li> </ul>
<i>Clostridioides difficile</i>	Colitis <ul style="list-style-type: none"> <li>Discontinue inciting antibiotics if possible.</li> <li>Infectious disease consult suggested if disease is persistent or recurrent.</li> </ul>	<b>First occurrence</b> <p><i>Mild-moderate:</i></p> <ul style="list-style-type: none"> <li>Metronidazole PO (or IV) 7.5 mg/kg/dose tid or qid × 10 days; max 500 mg per dose</li> <li>If failure to respond in 5-7 days, consider switch to vancomycin PO 40 mg/kg/day divided qid × 10 days; max 125 mg/dose</li> <li>For metronidazole-intolerant patients, start with vancomycin PO as above</li> <li>For patients in whom oral therapy cannot reach the colon, add vancomycin PR 500 mg/100 mL normal saline q8h prn until improvement</li> </ul> <p><i>Severe:</i></p> <ul style="list-style-type: none"> <li>Vancomycin PO as above</li> </ul> <p><i>Severe and complicated:</i></p> <ul style="list-style-type: none"> <li>Vancomycin PO as above PLUS metronidazole IV 30 mg/kg/day divided qid, max 500 mg/dose</li> <li>If complicated with ileus or toxic colitis and/or significant abdominal distension, give vancomycin PO PLUS metronidazole IV PLUS vancomycin PR as above × 10 days</li> </ul> <b>First recurrence</b> <p><i>Mild-moderate:</i></p> <ul style="list-style-type: none"> <li>Same regimen as for first occurrence</li> </ul> <p><i>Severe:</i></p> <ul style="list-style-type: none"> <li>Vancomycin PO as above</li> </ul> <p><b>Subsequent recurrences:</b></p> <ul style="list-style-type: none"> <li>DO NOT use metronidazole due to risk of neurotoxicity with repeated or prolonged use</li> <li>Vancomycin PO pulsed or prolonged taper (recommend consulting ID or GI for choice of regimen), OR</li> <li>Vancomycin × 10 days followed by rifaximin 400 mg/dose tid × 14-20 days (N.B. that rifaximin is not approved in the United States for children &lt;12 yr old), OR</li> <li>Fidaxomicin × 10 days Children 6 mo to 5 yr: 16 mg/kg/dose (max 200 mg/dose) bid Children 6 yr and older: 200 mg/dose bid</li> </ul>
<i>Entamoeba histolytica</i>	<ul style="list-style-type: none"> <li>Asymptomatic cyst excretors</li> <li>Mild to moderate intestinal disease</li> <li>Severe intestinal or extraintestinal disease (including liver abscess)</li> </ul>	<p><b>Asymptomatic cyst excretors:</b></p> <ul style="list-style-type: none"> <li>Iodoquinol PO 30-40 mg/kg/day, (max 650 mg/dose) divided tid × 20 days; OR</li> <li>Paromomycin PO 25-35 mg/kg/day divided tid × 7 days; OR</li> <li>Diloxanide furoate 20 mg/kg/day (max 500 mg/dose), orally, divided tid × 10 days</li> </ul> <p><b>Mild to moderate intestinal disease and severe intestinal or extraintestinal disease:</b></p> <ul style="list-style-type: none"> <li>Metronidazole PO 30-50 mg/kg/day divided tid × 7-10 days; OR</li> <li>Children ≥3 yr: Tinidazole PO 50 mg/kg, single dose, max 2 g × 3 days, OR 5 days for severe disease FOLLOWED BY EITHER (to prevent relapse) Iodoquinol PO 30-40 mg/kg/day (max. 650 mg/dose) divided tid × 20 days; OR Paromomycin PO 25-35 mg/kg/day divided tid × 7 days</li> </ul>
<i>Giardia duodenalis</i>	Persistent symptoms	<ul style="list-style-type: none"> <li>Tinidazole PO 50 mg/kg, single dose, max 2 g (for children ≥3 yr)</li> <li>Nitazoxanide PO Age 1-3 yr: 100 mg bid × 3 days Age 4-11 yr: 200 mg bid × 3 days Age over 11 yr: 500 mg bid × 3 days</li> <li>Metronidazole PO 15 mg/kg/day (max 250 mg/dose), divided tid × 5-7 days</li> </ul>
<i>Cryptosporidium</i> spp.	Treat immunocompromised and HIV-infected hosts, although efficacy is equivocal. Treatment may not be needed in normal hosts.	<p><b>Immunocompetent children:</b></p> <ul style="list-style-type: none"> <li>Nitazoxanide, as for <i>Giardia</i></li> </ul> <p><b>Solid organ transplants:</b></p> <ul style="list-style-type: none"> <li>Nitazoxanide, as for <i>Giardia</i>, × 14 days or longer</li> </ul> <p><b>HIV-infected children:</b></p> <ul style="list-style-type: none"> <li>Combined antiretroviral therapy is the primary treatment</li> <li>Nitazoxanide, as for <i>Giardia</i></li> <li>Paromomycin</li> </ul>

**Table 387.11** Antimicrobial Therapy for Infectious Diarrhea—cont'd

ORGANISM	INDICATION FOR THERAPY	DOSAGE AND DURATION OF TREATMENT
Cyclospora spp.	All symptomatic children	Age >2 mo: 8-10 mg/kg/day TMP and 40-50 mg/kg/day SMX PO divided bid × 7-10 days (HIV-infected children may need longer courses)
Cystoisospora spp.	Immunocompromised patients, symptoms that do not resolve after 5-7 days; treat prophylactically in HIV-infected patients with CD4+ count <200 cells/mm <sup>3</sup>	<ul style="list-style-type: none"> <li>Age &gt;2 mo: 8-10 mg/kg/day TMP and 40-50 mg/kg/day SMX PO divided bid × 7-10 days;</li> <li>Adults: 50-75 mg/day pyrimethamine PO, either qd or divided bid PLUS 10-25 mg/day leucovorin PO; OR</li> <li>Ciprofloxacin 500 mg PO bid × 7 days</li> </ul>
<i>Blastocystis hominis</i>	The significance of <i>B. hominis</i> as a cause of disease is controversial, so treatment should be reserved for those with suggestive symptoms and no other pathogen that could be the cause.	<ul style="list-style-type: none"> <li>Metronidazole PO 35-50 mg/kg/day divided tid × 10 days (max 500-750 mg/dose); OR</li> <li>Age &gt;2 mo: 8 mg/kg/day TMP and 40 mg/kg/day SMX PO divided BID × 7 days; OR</li> <li>Nitazoxanide, as for <i>Giardia</i>, × 3 days; OR</li> <li>Age ≥3 yr: 50 mg/kg (max 2 g) tinidazole PO once</li> </ul>

\*Azithromycin and fluoroquinolones should be avoided in patients taking the antimalarial artemether. These drugs can prolong the QT interval on electrocardiogram and trigger arrhythmias.

WHO, World Health Organization; PO, by mouth; prn, as needed; bid, two times a day; IV, intravenous; IM, intramuscular; qd, every day; ETEC, enterotoxigenic *E. coli*; qid, four times a day; STEC, Shiga toxin-producing *E. coli*; SGI, gastrointestinal; tid, three times a day; ID, infectious diseases; GI, gastrointestinal; N.B., nota bene.

regarded as one of the most effective interventions to reduce the risk of premature childhood mortality and has the potential to prevent 12% of all deaths of children younger than 5 years of age. Vitamin A supplementation reduces all-cause childhood mortality by 25% and diarrhea-specific mortality by 30%.

### Rotavirus Immunization

Five live-attenuated oral **rotavirus** vaccines are available internationally and WHO prequalified: the three-dose pentavalent G1, G2, G3, G4, P[8] human-bovine vaccine (RotaTeq), the two-dose monovalent human G1P[8] vaccine (Rotarix), the three-dose monovalent human-bovine 116E G6P[11] vaccine (Rotavac), and two formulations of the three-dose pentavalent G1, G2, G3, G4, G9 human-bovine vaccine (Rotasail and Rotasail Thermo). The result has been substantial reductions in rotavirus-associated and all-cause hospitalizations for diarrheal disease in both vaccinated infants (direct protection) and unvaccinated individuals (indirect, or herd protection), as well as reductions in office visits for less severe rotavirus diarrhea. Reductions in all-cause diarrhea deaths have been demonstrated in some countries since the introduction of these vaccines.

Programmatic uptake is lagging in low-resource settings where most severe disease and death occurs; however, Gavi, the Vaccine Alliance, has supported introduction of rotavirus vaccine into approximately 45 countries. Even though vaccine efficacy against severe rotavirus AGE is lower (50–64%) in low-resource compared with high-resource countries; the number of severe rotavirus AGE prevented per vaccinated child is higher because of the substantially greater baseline rate of severe rotavirus gastroenteritis in developing countries. Vaccine (live virus)-associated rotavirus infection has been reported in children with severe combined immunodeficiency disease, but the vaccine has been shown to be safe in HIV-infected populations. Because of sub-optimal efficacy, alternative vaccine formulations are being explored, including parenteral and neonatal vaccines.

Two licensed, efficacious two-dose oral inactivated cholera vaccines (Dukoral for children 2 years and older and Shanchol for children 1 year or older) are available in many countries but currently have no specific indication in endemic and epidemic settings where they could potentially reduce the burden of severe diarrhea and mortality in young children. For travelers, a single-dose live oral cholera vaccine (Vaxchora) is licensed for adults in the United States.

### Improved Water and Sanitary Facilities and Promotion of Personal and Domestic Hygiene

Much of the reduction in diarrhea prevalence in the developed world is the result of improvement in standards of hygiene, sanitation, and water supply. Strikingly, an estimated 88% of all diarrheal deaths

worldwide can be attributed to unsafe water, inadequate sanitation, and poor hygiene. Handwashing with soap and safe excreta disposal can reduce the risk of diarrhea by 48% and 36%, respectively, whereas a 17% reduction is estimated as a result of improvements in water quality.

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## 387.1 Traveler's Diarrhea

E. Adrienne Hammerschamb and Karen L. Kotloff

Traveler's diarrhea is a common complication of visitors to developing countries and is caused by a variety of pathogens, in part depending on the season and the region visited. It is the most common (28%) travel-associated health problem in children. Traveler's diarrhea can manifest with watery diarrhea or as dysentery. Without treatment, 90% will have resolved within a week and 98% within a month of onset. Some individuals develop more severe or persistent diarrhea and become dehydrated or unwell and may experience complications such as bacteremia and intestinal perforation. Children younger than 2 years are at higher risk for traveler's diarrhea, as well as more severe disease. According to FoodNet, the pathogens identified most commonly in travelers in the United States were ETEC, *C. jejuni*, *Shigella* spp., and NTS. EAEC and *G. duodenalis* are also important.

### TREATMENT

For infants and children, rehydration, as discussed in Chapter 387, is appropriate, followed by a standard diet. Adolescents and adults should increase their intake of electrolyte-rich fluids. Kaolin-pectin, anticholinergic agents, *Lactobacillus*, and bismuth salicylate are not effective therapies. Loperamide, an antimotility and antisecretory agent, reduces the number of stools in older children with watery diarrhea and improves outcomes when used in combination with antibiotics in traveler's diarrhea. However, loperamide should not be used in febrile or toxic patients with dysentery, in those with bloody diarrhea, and in children younger than 6 years.

The effectiveness of antibiotics depends on the pathogen and its susceptibility profile. In forming a treatment plan, the potential side effects should be weighed against the treatment need for a short-lasting and self-limiting disease such as traveler's diarrhea. Antibiotics are not recommended for mild diarrhea that is tolerable, is not distressing, and does not interfere with planned activities but may be considered for moderate diarrhea that is distressing and interferes with planned activities. Antibiotics are recommended for treatment of severe diarrhea that is incapacitating or completely prevents planned activities and

for treatment of dysentery. When empiric therapy is required abroad, azithromycin is suggested for young children, and fluoroquinolones are recommended for older children and adults and as second-line therapy for younger children, depending on local pathogens and susceptibility patterns. Short-duration (3 days) therapy is effective. Rifaximin is approved for use in children 12 years and older but should not be used to treat bloody diarrhea. Rifamycin is an alternative to rifaximin that may be used in patients 18 years and older. Fluoroquinolones, rifaximin, and rifamycin should be avoided in patients of all ages with dysenteric diarrhea. Travelers should be reminded that diarrhea can be a symptom of other severe diseases, such as malaria and MIS-C. Therefore if diarrhea persists or additional symptoms such as fever occur, travelers should seek medical advice. For up-to-date information on local pathogens and resistance patterns, see [www.cdc.gov/travel](http://www.cdc.gov/travel).

If the patient has returned home with diarrhea, a microbiologic evaluation can be obtained before initiating antibiotic therapy. Prolonged diarrhea should prompt further investigation into possible parasitic infections or NTS. Prophylactic antibiotics for travelers are not recommended.

## PREVENTION

In the pretravel visit, caregivers should be advised about diarrhea prevention, the signs, symptoms, and management of dehydration, and the use of ORS. ORS and age-appropriate antibiotics should be included in a routine health packet. Travelers should drink bottled or canned beverages or boiled water. They should avoid ice, salads, and fruit they did not peel themselves. Food should be eaten hot, if possible. Raw or poorly cooked seafood is a risk, as is eating in a restaurant rather than a private home. Swimming pools and other recreational water sites can also be contaminated.

Chemoprophylaxis is not routinely recommended for previously healthy children or adults. Nonetheless, travelers should bring azithromycin (younger than 16 years of age) or ciprofloxacin (older than 16 years of age) and begin antimicrobial therapy if diarrhea develops.

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## Chapter 388

# Chronic Diarrhea

Anat Guz-Mark and Raanan Shamir

See also Chapters 382.3 and 385.

**Chronic diarrhea** is defined as stool volume of more than 10 g/kg/day in toddlers/infants and greater than 200 g/day in older children that lasts for 4 weeks or more. **Persistent diarrhea** begins acutely but lasts longer than 14 days. In practice this usually means having loose or watery stools more than 3 times a day, with a deviation from the previous regular stool pattern. *Awakening at night to pass stool, beyond the period of infancy, is often a sign of an organic cause of diarrhea.* The epidemiology has two distinct patterns. In developing countries, chronic diarrhea is, in many cases, the result of an intestinal infection that persists longer than expected. This syndrome is often defined as **protracted (persistent) diarrhea**, but there is no clear distinction between protracted (persistent) and chronic diarrhea. In countries with higher socioeconomic conditions, chronic diarrhea is less frequent, and the etiology often varies with age. The outcome of diarrhea depends on the cause and ranges from benign, self-limited conditions, such as toddler's diarrhea, to severe congenital diseases, such as microvillus inclusion disease, which may lead to progressive intestinal failure.

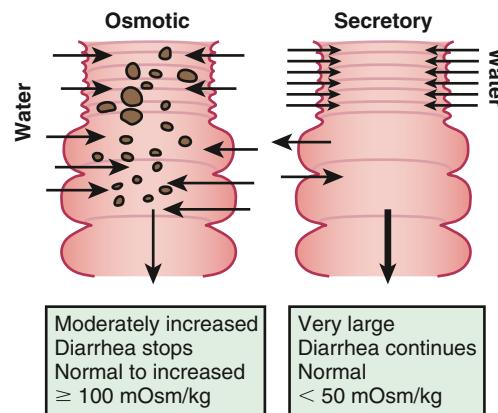
## PATOPHYSIOLOGY

The mechanisms of diarrhea are generally divided into **secretory** and **osmotic**, but often diarrhea is a *combination of both mechanisms*. In addition, *inflammation* and *motility disorders* may contribute to diarrhea. Secretory diarrhea is usually associated with large volume of watery stools and persists when oral feeding is withdrawn. Osmotic diarrhea is dependent on oral feeding, and stool volumes are usually not as massive as in secretory diarrhea (Fig. 388.1). The cessation of diarrhea after a 24-hour fasting trial may define “*diet-induced diarrhea*,” which is mainly osmotic in nature, whereas no or minimal change in stool volume and consistency despite fasting will suggest a secretory mechanism, also defined as “*electrolyte-transport-related diarrhea*.”

**Secretory diarrhea** is characterized by active electrolyte and water fluxes toward the intestinal lumen, resulting from either the inhibition of neutral NaCl absorption in villous enterocytes or an increase in electrogenic chloride secretion in secretory crypt cells as a result of the opening of the cystic fibrosis transmembrane regulator (CFTR) chloride channel, or both. The result is more secretion from the crypts than absorption in the villi that persists during fasting. The other components of the enterocyte ion secretory machinery are (1) the Na-K 2Cl co-transporter for the electroneutral chloride entrance into the enterocyte; (2) the Na-K pump, which decreases the intracellular Na<sup>+</sup> concentration, determining the driving gradient for further Na<sup>+</sup> influx; and (3) the K<sup>+</sup> selective channel, that enables K<sup>+</sup>, once it has entered the cell together with Na<sup>+</sup>, to return to the extracellular fluid.

Electrogenic secretion is induced by an increase of intracellular concentration of cyclic adenosine monophosphate, cyclic guanosine monophosphate, or calcium in response to microbial enterotoxins, or to endogenous endocrine or nonendocrine molecules, including inflammatory cytokines. Another mechanism of secretory diarrhea is the inhibition of the electroneutral NaCl-coupled pathway that involves the Na<sup>+</sup>/H<sup>+</sup> and the Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> exchangers. Defects in the genes of the Na<sup>+</sup>/H<sup>+</sup> and the Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> exchangers are responsible for congenital sodium and congenital chloride diarrhea, respectively.

**Osmotic diarrhea** is caused by nonabsorbed nutrients in the intestinal lumen as a result of one or more of the following mechanisms: (1) intestinal damage (e.g., enteric infection); (2) reduced absorptive surface area (e.g., active celiac disease); (3) defective digestive enzyme or nutrient carrier (e.g., lactase deficiency); (4) decreased intestinal transit time (e.g., functional diarrhea); and (5) nutrient overload, exceeding the digestive capacity (e.g., overfeeding, sorbitol in fruit juice). Whatever the mechanism, the osmotic force generated by nonabsorbed solutes drives water into the intestinal lumen. A very common example of



**Fig. 388.1** Pathways of osmotic and secretory diarrhea. Osmotic diarrhea is caused by functional or structural damage of intestinal epithelium. Nonabsorbed osmotically active solutes drive water into the lumen. Stool osmolality and ion gap are generally increased. Diarrhea stops or improves dramatically in children when not eating. In secretory diarrhea, ions are actively pumped into the intestine by the action of exogenous and endogenous secretagogues. Usually there is no intestinal damage. Osmolality and ion gap are within normal levels. Large volumes of stools are lost independent of food ingestion.

osmotic diarrhea is lactose intolerance. Lactose, if not absorbed in the small intestine, reaches the colon, where it is fermented to short-chain organic acids, releasing hydrogen that is detected in the lactose breath test, and generating an osmotic overload.

In many children chronic diarrhea may be caused by the combination of multiple mechanisms.

## Etiology

Table 388.1 summarizes the main etiologies of chronic diarrhea in infants and children.

### Infectious

Enteric infections are by far the most frequent cause of persistent or chronic diarrhea, both in developing and industrialized countries; however, outcomes are often very different. In the former, comorbid conditions, such as HIV/AIDS, malaria, or tuberculosis, may result in malnutrition that impairs the child's immune response, thereby potentiating the likelihood of prolonging diarrhea or acquiring another enteric infection. Prolonged diarrhea in poor-resource countries may lead to undernutrition, which predisposes the child to additional episodes of diarrhea. Sequential infections with the same or different pathogens may also be responsible for chronic diarrhea. In *developing* countries, enteroadherent *Escherichia coli* and *Giardia lamblia* have been implicated in chronic diarrhea, whereas, in *developed* countries, chronic infectious diarrhea usually runs a more benign course and the etiology is often viral, with rotavirus and norovirus playing major roles (Table 388.2).

Chronic diarrhea in travelers to or expatriates from developing countries may depend on the country of origin. Nonetheless, common pathogens include *Giardia*, *E. coli*, *Shigella*, *Campylobacter*, *Salmonella*, and enteric viruses. Less common pathogens include amebiasis, *Strongyloides*, and tropical sprue.

**Table 388.1** Main Etiologies of Chronic Diarrhea in Children Older and Younger than 2 Years of Age

ETIOLOGY	AGE <2 YR	AGE >2 YR
Infections	+++	+++
Postenteritis syndrome	+++	+++
Immune deficiency	++	Rare
Celiac disease	+++ (after gluten introduction)	+++
Food allergy	+++	+
Inflammatory bowel disease	+ (rare)	+++
Pancreatic insufficiency	++	++
Cholestasis and insufficient bile acids	++	++
Cystic fibrosis	++	+
Lactose intolerance	++ (mostly postinfectious)	+++
Intestinal lymphangiectasia	+	+
Motility disorders	++	Rare
Short bowel syndrome	+++	+
Toddler's and functional diarrhea	++	++
Excessive intake of fruit juices and fluids	++	++
Congenital diarrheal disorders, including structural enterocyte defects and enzymatic or transport malabsorption syndromes	++	Unlikely

Opportunistic microorganisms induce diarrhea exclusively, more severely, or for more prolonged periods, in specific populations, such as immunocompromised children. Specific agents cause chronic diarrhea or exacerbate diarrhea in many chronic diseases. *Clostridium difficile* or cytomegalovirus act as opportunistic agents in patients with malignant diseases as well as in patients with **inflammatory bowel disease (IBD)**. *Cryptosporidium* may induce severe and protracted diarrhea in AIDS patients.

**Small intestinal bacterial overgrowth (SIBO)** results in chronic diarrhea by either a direct interaction between the microorganism and the enterocytes, or the consequence of deconjugation and dihydroxylation of bile salts and hydroxylation of fatty acids due to an increased proliferation of bacteria in the proximal intestine. *Risk factors for SIBO* in children include acid-suppressive therapies, alterations in gastrointestinal (GI) motility and anatomy, as well as poor sanitation conditions.

**Postenteritis diarrhea syndrome** (see Chapter 387) is a clinicopathologic condition in which small intestinal mucosal damage persists after acute gastroenteritis. Sensitization to food antigens, secondary disaccharidase deficiency, persistent infections, or reinfection with another enteric pathogen may be responsible for causing postenteritis diarrhea syndrome, which is thought to be related to dysregulation of the intestinal microbiota. Functional diarrhea, which may be related to the pathogenesis of irritable bowel syndrome, may be caused by complications of an acute gastroenteritis.

### Inflammatory/Immunologic

**Celiac disease** (see Chapter 384) is a genetically determined immune-mediated intestinal disorder that affects about 1 in 100 individuals, depending on geographic origin. In the genetically susceptible host, gliadin, the major protein of gluten, reacts with the immune system to cause inflammation and villous atrophy. A reduction of intestinal absorptive surface is responsible for the diarrhea in celiac disease, which is reversible upon elimination of gluten from the diet.

**Food allergy (mainly cow's milk protein allergy, see Chapter 192)** may present during infancy with chronic diarrhea. An abnormal immune response to food proteins can cause a proctitis/colitis or an enteropathy, which may result in inflammatory or malabsorptive diarrhea. **Eosinophilic gastroenteropathy** is characterized by an eosinophilic infiltration of the intestinal wall and is strongly associated with atopy (see Chapter 383). However, although diarrhea in food allergy responds to withdrawal of the responsible food, this does not always occur in eosinophilic gastroenteropathy, in which immune-suppressive therapy may be needed.

**IBDs, including Crohn disease, ulcerative colitis, and IBD-undetermined**, cause chronic diarrhea that is often associated with abdominal pain, elevated inflammatory markers, and increased concentrations of fecal calprotectin or lactoferrin (see Chapter 382). The age of onset of IBD is broad, with rare cases described in the first few months

**Table 388.2** Comparative List of Prevalent Agents and Conditions in Children with Persistent Infectious Diarrhea in Industrialized and Developing Countries

AGENT/DISEASE	
INDUSTRIALIZED COUNTRIES	DEVELOPING COUNTRIES
<i>Clostridium difficile</i>	Enteroinvasive <i>E. coli</i>
Enteroinvasive <i>Escherichia coli</i>	Atypical <i>E. coli</i>
Atypical <i>E. coli</i>	<i>Shigella</i> spp.
Astrovirus	Heat-stable/heat-labile enterotoxin-producing <i>E. coli</i>
Norovirus	Rotavirus*
Sapovirus	Cryptosporidium
Rotavirus*	<i>Giardia lamblia</i>
Small intestinal bacterial overgrowth (SIBO)	Tropical sprue
Postenteritis diarrhea syndrome	

\*More frequent in industrialized than in developing countries as agent of chronic diarrhea.

of life, and the peak incidence in childhood occurs in adolescence. The severity of the symptoms is highly variable with a pattern characterized by long periods of well-being followed by exacerbations.

**Autoimmune processes** may target the intestinal epithelium, alone or in association with extraintestinal symptoms. **Autoimmune enteropathy** is associated with the production of anti-enterocyte and antigoblet cell antibodies, primarily immunoglobulin A, but also immunoglobulin G, directed against components of the enterocyte brush border or cytoplasm and by a cell-mediated autoimmune response with mucosal T-cell activation. An X-linked immune-dysregulation, polyendocrinopathy, and enteropathy (**IPEX syndrome**) is associated with variable gene mutations and phenotypes of chronic diarrhea (more on autoimmune enteropathy and IPEX syndrome is available in Chapter 382.3).

**Immune deficiency** can present as chronic diarrhea in children. In these cases (for example, severe combined immunodeficiency or AIDS) the child can be infected by an opportunistic pathogen, can exhibit a persistent diarrhea due to a pathogen usually causing an acute gastroenteritis, or be infected by multiple and recurrent different pathogens causing mucosal damage to the intestines. Other immunoregulatory defects, found in patients with agammaglobulinemia, isolated immunoglobulin A deficiency, and common variable immunodeficiency disorder, may result in mild persistent diarrhea.

### Pancreatic Deficiency

Chronic diarrhea may be the manifestation of maldigestion caused by exocrine pancreatic disorders (see Chapters 397 and 399.2). In most patients with **cystic fibrosis**, exocrine pancreatic insufficiency results in steatorrhea and protein malabsorption. In **Shwachman-Diamond syndrome**, exocrine pancreatic hypoplasia may be associated with neutropenia, bone changes, and intestinal protein-losing enteropathy. Specific isolated pancreatic enzyme defects, such as lipase deficiency, result in fat and/or protein malabsorption. Familial pancreatitis, associated with a pathogenic variant in the trypsinogen gene, may be associated with exocrine pancreatic insufficiency and chronic diarrhea. Pathogenic variants in *CFTR*, *CTRC*, *PRSS1*, *PRSS2*, *SPINK 1*, and *SPINK 5* are associated with hereditary pancreatitis.

### Liver and Bile Acids Disorders

Liver disorders and **cholestasis** may lead to a reduction in the bile salts pool resulting in fat malabsorption causing chronic diarrhea in the form of steatorrhea. Bile acid loss may be associated with diseases affecting the terminal ileum, such as Crohn disease, or following ileal resection. In **primary bile acid malabsorption**, neonates and young infants present with chronic diarrhea and fat malabsorption caused by pathogenic variants of the ileal bile transporter gene. In addition to the fat malabsorption, the bile acid loss from the intestinal lumen is a form of secretory diarrhea by itself (called **cholerheic diarrhea** or **choleretic diarrhea**, which is usually associated with significant diaper dermatitis).

### Carbohydrate Malabsorption

Rare genetic pathogenic variants (see Chapters 385.8 and 385.10) can cause carbohydrate malabsorption. More commonly, **lactose intolerance** is *secondary* to lactase deficiency caused by intestinal mucosal damage (usually as part of postenteritis syndrome, which is a self-limited process). Depending on ethnicity, a progressive, age-related, loss of lactase activity may begin around 7 years of age and affects approximately 80% of the non-White population, and acquired hypolactasia may be responsible for chronic diarrhea in older children receiving cow's milk (adult-type lactase deficiency).

Similarly, **fructose malabsorption** is common in Western countries with estimates as high as 40% of the population. These individuals cannot absorb fructose and often develop bloating, abdominal pain, diarrhea, and flatulence. Typically, they do not have liver disease. This is in contrast to **hereditary fructose intolerance**, a rare genetic disorder with incidence estimated to be 1 in 20,000–30,000. This disease is associated with pathogenic variants in the *ASDOB* gene that encodes for the aldolase B enzyme that is found primarily in the liver and is involved in the metabolism of fructose. Individuals with hereditary fructose intolerance may have nausea, abdominal pain/bloating, vomiting, diarrhea, and hypoglycemia. Continued ingestion of fructose results in **hepatomegaly** and eventually cirrhosis.

### Protein-Losing Enteropathy

Chronic diarrhea can be the manifestation of obstructed intestinal lymphatic drainage, causing protein-losing enteropathy with steatorrhea, diarrhea, and lymphopenia. Early-onset protein-losing enteropathy and lymphangiectasia, together with complement activation, could be associated with congenital **CD55 deficiency**. Infantile-onset severe protein-losing enteropathy and altered lipid metabolism could be attributed to pathogenic variants in **DGAT1**.

Along with **intestinal lymphangiectasia**, many diseases that cause intestinal mucosal injury can also result in a secondary protein-losing enteropathy, characterized by low serum protein levels and elevated fecal  $\alpha_1$ -antitrypsin (see Chapter 385.2).

### Motility Disorders

Disorders of intestinal motility include abnormal development and function of the enteric nervous system, such as in **Hirschsprung disease** and **pediatric intestinal pseudoobstruction (PIPO)**, previously termed **chronic intestinal pseudoobstruction**. PIPO encompasses both the neurogenic and the myogenic forms, and is sometimes associated with genitourinary manifestations. Other motility disorders may be secondary to extraintestinal disorders, such as in **hyperthyroidism** and **scleroderma**. Motility disorders are associated with either constipation or diarrhea, or both, with the former usually dominating the clinical picture.

### Short Bowel Syndrome

Short bowel syndrome is the single most frequent etiology of intestinal failure in children (see Chapter 385.6). Many intestinal abnormalities such as stenosis, segmental atresia, gastroschisis, and malrotation may require surgical resection, but the most frequent primary cause of short bowel is **necrotizing enterocolitis**. Rarely, a child can be born with congenital short bowel. In these conditions, the residual intestine may be insufficient to carry on its digestive-absorptive functions, resulting in severe chronic diarrhea, malnutrition, and failure to thrive, requiring long-term treatment with parenteral nutrition.

### Nonspecific Diarrhea, Including Toddler's Diarrhea

The most benign and common etiology of chronic diarrhea is nonspecific diarrhea that encompasses **functional diarrhea** (or **toddler's diarrhea**) in children younger than 4 years of age and **irritable bowel syndrome** in those, usually, 5 years of age and older. Toddler's diarrhea is defined by the daily painless recurrent passage of four or more large unformed stools, for 4 or more weeks, with onset in infancy or preschool years. Nighttime defecation is usually absent. The child appears unperturbed by the diarrhea, there is no evidence of failure to thrive, and the symptoms resolve spontaneously by school age.

Diarrhea may also be the result of an **excessive intake of fluids and nonabsorbable carbohydrates**. If the child's fluid intake was  $>150 \text{ mL/kg}/24 \text{ hr}$ , *fluid intake should be reduced not to exceed 90 mL/kg/24 hr* to decrease the stool frequency and volume. If the dietary history suggests that the child is ingesting significant amounts of fruit juice, especially apple juice, then *the consumption of juice should be decreased*. Sorbitol, which is a nonabsorbable sugar, is found in apple, pear, and prune juices and often causes diarrhea in toddlers. Moreover, apple and pear juices contain higher amounts of fructose than glucose, a feature postulated to cause diarrhea in toddlers. In older children, irritable bowel syndrome is often associated with abdominal pain and may be related to anxiety, depression, and other psychological disturbances (see Chapter 389). When the cause of the diarrhea remains undetermined and the clinical course is inconsistent with organic disorders, **factitious** disorder by proxy should be considered.

### Congenital Diarrheal Disorders

The most severe etiology of chronic diarrhea includes a number of heterogeneous congenital conditions leading to syndromes often referred to as **intractable or protracted diarrhea**. The genetic and molecular basis of many causes of protracted diarrhea has been identified recently, and the classification of **congenital diarrheal disorders (CDDs)** has been proposed (Table 388.3), also referred to as congenital diarrheas and enteropathies (CODEs). These terms represent a group of rare but severe enteropathies, with a similar clinical presentation despite different pathogenesis and outcome. The diarrhea can be either secretory,

**Table 388.3** Classification of Congenital Diarrheal Disorders Based on Their Molecular Defect and Their Inheritance

DEFECTS OF DIGESTION, ABSORPTION, AND TRANSPORT OF NUTRIENTS AND ELECTROLYTES				
DISEASE	GENE NAME	GENE LOCATION	TRANSMISSION AND INCIDENCE	MECHANISM
<b>GENES ENCODING BRUSH-BORDER ENZYMES</b>				
Congenital lactase deficiency (LD)	LCT	2q21.3	AR, 1 in 60,000 in Finland; lower in other ethnic groups	Osmotic
Congenital sucrase-isomaltase deficiency (SID)	SI	3q26.1	AR, 1 in 5,000; higher incidence in Greenland, Alaska, and Canada	Osmotic
Congenital maltase-glucoamylase deficiency (MGD)	Not defined	—	Few cases described	Osmotic
<b>GENES ENCODING MEMBRANE CARRIERS</b>				
Glucose-galactose malabsorption (GGM)	SLC5A1	22q13.1	AR, few hundred cases described	Osmotic
Fructose malabsorption (FM)	Not defined	—	Up to 40%	Osmotic
Fanconi-Bickel syndrome (FBS)	SLC2A2	3q26.2	AR, rare, higher frequency in consanguineous	Osmotic
Acrodermatitis enteropathica (ADE)	SLC39A4	8q24.3	AR, 1 in 500,000	Osmotic
Congenital chloride diarrhea (CCD)	SLC26A3	7q31.1	AR, sporadic; frequent in some ethnicities	Osmotic
Lysinuric protein intolerance (LPI)	SLC7A7	14q11.2	AR, about 1 in 60,000 in Finland and Japan; rare in other ethnic groups	Osmotic
Primary bile acid malabsorption (PBAM)	SLC10A2 SLC51B	13q33.1 15q22.31	AR	Secretory
Cystic fibrosis (CF)	CFTR	7q31.2	AR, 1 in 2,500	Osmotic
<b>GENES ENCODING PANCREATIC ENZYMES</b>				
Enterokinase deficiency (EKD)	PRSS7	21q21	AR	Osmotic
Hereditary pancreatitis (HP)	PRSS1 PRSS2 SPINK1 CTRC CFTR	7q34 7q34 5q32 1p36.21 7q31.2	AD, cases with compound pathogenic variants in different genes; SPINK1 pathogenic variants may also cause tropical pancreatitis	Osmotic, malabsorption
Congenital absence of pancreatic lipase (APL)	PNLIP	10q25.3	AR	Osmotic, malabsorption
<b>GENES ENCODING PROTEINS OF LIPOPROTEIN METABOLISM</b>				
Abetalipoproteinemia (ALP)	MTP	4q27	AR, about 100 cases described; higher frequency among Ashkenazi Jews	Osmotic
Hypobetalipoproteinemia (HLP)	APOB ANGPTL3	2p24.1 1p31.3	Autosomal codominant/AR	Osmotic
Chylomicron retention disease (CRD)	SAR1B	5q31.1	AR, about 40 cases described	Osmotic
<b>GENES ENCODING OTHER TYPES OF PROTEINS</b>				
Congenital sodium diarrhea (CSD)	SPINT2 (only syndromic CSD) SLC9A3	19q13.2 5p15.33	AR	Osmotic
Shwachman-Diamond syndrome (SDS)	SBDS	7q11	AR	Osmotic
Activating guanylate cyclase-C pathogenic variant	GUCY2C	12p12.3	AD	Secretory
<b>GENES ENCODING FOR OTHER ENZYMES</b>				
Defect in triglyceride synthesis	DGAT1	8q24.3	AR	Protein-losing enteropathy
<b>DEFECTS OF ENTEROCYTE DIFFERENTIATION AND POLARIZATION</b>				
Microvillus inclusion disease (MVID)	MYO5B STX3	18q21.1 11q12.1	AR; rare	Secretory
Congenital tufting enteropathy (CTE)	EPCAM	2p21	AR; 1 in 50,000-100,000; higher among Arabs	Secretory
Trichohepatoenteric syndrome (THE)	TTC37 SKIV2L	5q15 6p21.33	AR; 1 in 400,000	Secretory
Neonatal-onset chronic diarrhea-9 (DIAR9)	WNT2B	1p13.2	AR; few cases described	Osmotic

*Continued*

**Table 388.3** Classification of Congenital Diarrheal Disorders Based on Their Molecular Defect and Their Inheritance—cont'd

DEFECTS OF DIGESTION, ABSORPTION, AND TRANSPORT OF NUTRIENTS AND ELECTROLYTES				
DISEASE	GENE NAME	GENE LOCATION	TRANSMISSION AND INCIDENCE	MECHANISM
<b>DEFECTS OF ENTEROENDOCRINE CELL DIFFERENTIATION</b>				
Congenital malabsorptive diarrhea (CMD), Enteric anendocrinosis	NEUROG3	10q22.1	AR; few cases described	Osmotic
Proprotein convertase 1/3 deficiency (PCD)	PCSK1	5q15	AR	Osmotic
Intractable malabsorptive diarrhea of infancy (DIAR11)	PERCC1	16p13.3	AR; few cases described in Jewish Iraqi families	Presumed impaired function of enteroendocrine cells (EECs)
<b>DEFECTS OF MODULATION OF INTESTINAL IMMUNE RESPONSE</b>				
Autoimmune polyglandular syndrome type 1 (APS1)	AIRE	21q22.3	AR; AD (1 family)	Inflammatory
Immune dysfunction, polyendocrinopathy, X-linked (IPEX)	FOXP3	Xp11.23	X-linked (autosomal cases described), very rare	Inflammatory
IPEX-like syndrome	CD25 STAT5b STAT3 STAT1(GOF) LRBA CTLA4	Multiple	Not X-linked	Inflammatory
CD55 deficiency	CD55	1q32.2	AR, rare	Protein-losing enteropathy

AD, Autosomal dominant; AR, autosomal recessive; GOF, gain of function.

osmotic, or combined, depending on the specific defect. Often severe diarrhea presents at birth or shortly thereafter, but in milder forms diarrhea may go unrecognized for years. *CDDs can be classified in four groups:* defects of digestion, absorption, and transport of nutrients and electrolytes; defects of enterocyte differentiation and polarization; defects of enteroendocrine cell (EEC) differentiation; and defects of modulation of intestinal immune response.

Although CDDs are rare diseases, in most specific disorders the genetic defect and transmission are known. The incidence of genetic disorders associated with CDD can range from 1 in 2,500 for cystic fibrosis, 1 in 5,000 for sucrose-isomaltose deficiency, 1 in 60,000 for congenital lactase deficiency, to 1 in 400,000 for trichohepatoenteric syndrome. For most CDDs, such as IPEX syndrome or autoimmune polyglandular syndrome type 1, the clinical application of exome sequencing is likely to increase identification of more patients with these rare causes of chronic diarrhea. Selected CDDs are more frequent in ethnic groups where consanguineous marriages are common, or in some geographic areas because of founder effects. Congenital lactase deficiency is more common in Finland; lysinuric protein intolerance has a higher incidence either in Finland and in Japan because of founder effect, and a specific pathogenic variant is typically found in each of the two ethnic groups. A defect in the *DGAT1* gene was first identified using whole exome sequencing in an Ashkenazi Jewish family and associated with the early onset of vomiting and nonbloody diarrhea with protein-losing enteropathy. In few families of Jewish Iraqi origin with intractable diarrhea of infancy, a noncoding deletion was recently identified on chromosome 16p13, presumably leading to impairment in EEC function. For specific CDDs see Chapters 385.2 and 385.10.

Most cases of protracted diarrhea syndrome are not easily treated. The natural history of protracted diarrhea is related to the primary intestinal disease or the specific defect in nutrient absorption. Although some specific conditions may improve with nutritional therapy and dietary eliminations (for example, glucose-galactose malabsorption or congenital protein-losing enteropathy), most cases of CDDs result in chronic intestinal failure requiring long-term parenteral nutrition, with poorer prognosis, and are more likely to be candidates for intestinal transplantation (see Chapter 386). Some late-onset CDDs may be relatively mild and are recognized only later in life. Infantile-onset or neonatal IBDs are a distinct

group of diseases, also occurring during infancy, characterized by more inflammatory and often bloody component in stools (see Chapter 382.3).

### EVALUATION OF PATIENTS

Because of the wide spectrum of etiologies, the medical approach should be based on diagnostic algorithms that begin with assessment for infectious causes, and then consider the age of the child, growth, and clinical and epidemiologic factors. Early onset in the neonatal period is rare and may suggest a congenital or severe condition (see Chapter 382.3); however, infections and food allergy are more frequent in this age group, and together with GI malformations should be high on the differential diagnosis. In later infancy and up to 2 years of age, infections and allergies are the most common causes, while inflammatory diseases are more frequent in older children and adolescents. Celiac disease as well as functional nonspecific diarrhea should always be considered independently of age because of their relatively high frequency at all ages beyond early infancy.

Specific clues in the family and personal history may provide useful indications, suggesting a congenital, allergic, or inflammatory etiology. A history of *polyhydramnios* is consistent with congenital chloride/sodium diarrhea (where a typical sonographic finding of dilated fetal bowel loops is present), microvillus inclusion disease, cystic fibrosis, and other CDDs, as well as a family history of a chronic or intractable diarrhea in a relative presenting in the first month of life, and particularly *consanguinity*. An acute onset of diarrhea that runs a protracted course suggests postenteritis diarrhea, secondary lactase deficiency, SIBO, or the onset of nonspecific functional diarrhea. The association of diarrhea with specific foods may indicate a nutrient basis, such as intolerance to selected nutrients (fructose). Anthropometric evaluation is essential to understand if diarrhea has affected weight gain and growth, providing estimation of the severity of diarrhea. Normal weight and growth strongly support functional diarrhea that may respond to simple dietary management. It should be noted that a child with functional diarrhea may be inappropriately “treated” with a diluted hypocaloric diet in an effort to reduce the diarrhea, resulting in impaired growth.

Initial clinical examination should include the evaluation of general and nutritional status. Dehydration, marasmus, or kwashiorkor require prompt supportive interventions to stabilize the patient. Nutritional

evaluation should start with the evaluation of the weight and height curves, and anthropometric indices to determine the impact of diarrhea on growth. Weight is generally impaired before height, but with time, linear growth also becomes affected, and both parameters may be equally abnormal in the long term. **Assessment of nutritional status** includes a dietary history, physical examination, and biochemical testing including nutritional investigations. *Caloric intake* should be quantitatively determined, energy requirements determined, and the relationship between weight modifications and energy intake should be carefully considered. Assessment of body composition may be performed by measuring mid-arm circumference and triceps skinfold thickness or by bioelectrical impedance analysis, dual-emission x-ray absorptiometry scans, or air plethysmography. Biochemical markers including albumin, prealbumin, retinol binding protein, serum iron, and transferrin may assist in grading malnutrition, as the half-life of serum proteins may distinguish between short- and long-term malnutrition. Evaluation of micronutrient concentrations should always be considered. Zinc, magnesium, vitamin A, and folate deficiency are associated with chronic diarrhea and should be provided if needed.

In infants with chronic diarrhea, feeding history must be carefully obtained, providing clues for allergy or specific food intolerance, such as cow's milk protein allergy or sucrose-isomaltase deficiency. Associated symptoms and selected investigations provide important diagnostic clues. Signs of general inflammation such as fever, mucoid or bloody stools, and abdominal pain may suggest IBD. The presence of eczema or asthma is associated with an allergic disorder, whereas specific extraintestinal manifestations (arthritis, diabetes, thrombocytopenia, etc.) may suggest an autoimmune disease. Specific skin lesions may be suggestive of **acrodermatitis enteropathica**, which might respond to zinc supplementation. Typical facial abnormalities and woolly hair are associated with phenotypic diarrhea (**trichohepatoenteric syndrome**).

## INVESTIGATIONS

Microbiologic investigation should include a thorough list of intestinal bacterial, viral, and protozoan pathogens. Proximal intestinal bacterial overgrowth may be determined using the lactulose hydrogen breath test, but false-positive tests are common (see Chapter 385.8).

Initial investigations of a child with chronic diarrhea beyond the period of infancy should always include an assessment of intestinal inflammation using fecal markers as calprotectin or lactoferrin, and serology for celiac disease (see Chapter 384). The role of intestinal

mucosal biopsy is determined by the noninvasive diagnostic evaluation in consultation with a pediatric gastroenterologist.

Noninvasive assessment of digestive-absorptive function and of intestinal inflammation plays a key role in the diagnostic workup (Table 388.4). Abnormalities in the digestive-absorptive function tests suggest small bowel involvement, whereas intestinal inflammation, as demonstrated by increased fecal calprotectin, supports colitis.

Determining the osmotic versus secretory nature of the diarrhea in neonates and infants with protracted diarrhea is especially important. The **stool osmolar gap**, sometimes called stool ion gap, is calculated as  $290 \text{ mOsm/kg}$  (or measured stool osmolality) minus  $[2 \times (\text{stool Na} + \text{stool K})]$ . If the osmolar gap is above  $100 \text{ mOsm/kg}$ , fecal osmolality is derived from ingested or nonabsorbed osmotically active solutes or nonmeasured ions. In contrast, a low gap ( $<50 \text{ mOsm/kg}$ ) is typically observed in secretory diarrhea. It is also important to measure  $\text{Cl}^-$  concentration in the stool to rule out **congenital chloride diarrhea**, which is characterized by low osmolar gap combined with high fecal  $\text{Cl}^-$  loss ( $>90 \text{ mmol/L}$ ).

Whereas most etiologies of chronic diarrhea can be exaggerated by feeding and have osmotic or mixed nature to the stool, secretory diarrhea necessitates investigation for congenital defects in enterocytes, defects in the intestinal immune response (IPEX and autoimmune enteropathy), and disorders of bile acid malabsorption. Because of the overlap between secretory and osmotic features of the diarrhea in many diseases, a classification based on the response to bowel rest was also introduced. Severe diarrhea that persists at bowel rest is characteristic of **congenital enteropathies (microvillus inclusion disease, tufting enteropathy)**. Diarrhea that disappears at bowel rest can imply carbohydrate or fat malabsorptive syndromes, as well as defects in EECs. In most other etiologies the diarrhea can decrease significantly, but not disappear, in response to bowel rest, including some congenital diseases as well as acquired inflammatory and other enteropathies.

**Histology** is important in establishing mucosal involvement, noting changes in the epithelial cells and villus/crypt ration, presence of mucosal inflammation or in identifying specific intracellular inclusion bodies caused by pathogens, such as cytomegalovirus, or the presence of parasites. Electron microscopy is essential to detect subcellular structural abnormalities such as microvillus inclusion disease, though the latter can be diagnosed with specific staining of the basal membrane on regular biopsies. Immunohistochemistry allows the study of

**Table 388.4** Noninvasive Tests for Intestinal Digestive–Absorptive Function and Inflammation

TEST	NORMAL VALUES	IMPLICATION
$\alpha_1$ -Antitrypsin concentration	<0.9 mg/g	Increased intestinal permeability/protein loss
Steatocrit	<2.5%-fold (older than 2 yr) increase over age-related values (younger than 2 yr)	Fat malabsorption
Fecal-reducing substances	Absent	Carbohydrate malabsorption
Elastase concentration	>200 $\mu\text{g/g}$	Pancreatic function
Chymotrypsin concentration	>7.5 units/g >375 units/24 hr	Pancreatic function
Fecal occult blood	Absent	Blood loss in the stools/inflammation
Fecal calprotectin concentration	<100 $\mu\text{g/g}$ (in children up to 4 yr of age) <50 $\mu\text{g/g}$ (older than 4 yr)	Intestinal inflammation
Fecal leukocytes	<5 per microscopic field	Colonic inflammation
Fecal lactoferrin	Absent	Inflammation
Nitric oxide in rectal dialysate	<5 $\mu\text{M}$ of $\text{NO}_2^-/\text{NO}_3^-$	Rectal inflammation
Dual sugar (cellobiose/mannitol) absorption test	Urine excretion ratio: $0.010 \pm 0.018$	Increased intestinal permeability
Xylose oral load	25 mg/dL	Reduced intestinal surface

mucosal immunity as well as of other cell types (smooth muscle cells and enteric neuronal cells).

Imaging may also have a role in the diagnostic approach. Abdominal ultrasound may help in detecting liver and pancreatic abnormalities or an increase in bowel wall thickness that suggests IBD. A preliminary plain abdominal x-ray is useful for detection of abdominal distention, suggestive of intestinal obstruction, or increased retention of colonic feces. Intramural or portal gas may be seen in necrotizing enterocolitis or intussusception. Structural abnormalities such as diverticula, malrotation, stenosis, blind loop, and congenital short bowel, as well as motility disorders, may be investigated through a barium meal and a small bowel follow-through. In older children, capsule endoscopy may be considered to further assess intestinal inflammation or bleeding, and capsule technology can be used to measure pressure, pH, and temperature through the GI tract, assessing motility. Bile malabsorption may be explored by the retention of the bile acid analog  $^{75}\text{Se}$ -homocholic acid-taurine ( $^{75}\text{SeHCAT}$ ) in the enterohepatic circulation.

Specific investigations should be carried out for specific diagnostic indications. Prick and patch test may support a diagnosis of food allergy. However, an elimination diet with withdrawal of the suspected harmful food from the diet and subsequent challenge is the most reliable strategy by which to establish a diagnosis.

Once infectious agents have been excluded and nutritional assessment performed, a stepwise approach to the child with chronic diarrhea may be applied. The main causes of chronic diarrhea should be investigated, based on the features of the diarrhea (watery, fatty, mucous, or bloody) and the specific nutrient(s) that is (are) affected. The use of whole exome sequencing or specific molecular analysis may be especially essential in children suspected of having CDD, and early genomic testing is recommended in these circumstances. A step-by-step diagnostic approach is important to minimize the unnecessary use of invasive procedures as well as the cost, while optimizing the yield of the diagnostic evaluation (Table 388.5).

## TREATMENT

Chronic diarrhea associated with impaired nutritional status should always be considered a serious disease, and therapy should be started promptly. Treatment includes general supportive measures, nutritional rehabilitation, elimination diet, and medications. The latter include therapies for specific etiologies as well as interventions aimed at counteracting fluid secretion and/or promoting restoration of disrupted intestinal epithelium. Because death may be caused by dehydration or electrolyte abnormalities, replacement of fluid and electrolyte losses is the most important early intervention.

Nutritional rehabilitation is often essential and is based on clinical and biochemical assessment. In moderate to severe malnutrition, caloric intake should be carefully advanced to avoid the development of *refeeding syndrome* and may be progressively increased to 50% or more above the recommended dietary allowances to also allow catch-up growth. In children with steatorrhea, medium-chain triglycerides may be a major source of lipids. A lactose-free diet should be considered in children with chronic diarrhea. In these cases, lactose is generally replaced by maltodextrin or a combination of complex carbohydrates. A sucrose-free formula is indicated in sucrase-isomaltase deficiency. Semi-elemental or elemental diets have the dual purpose of overcoming food intolerance, which may be the primary cause of chronic diarrhea, particularly in infancy and early childhood, and facilitating nutrient absorption. The sequence of elimination should usually begin from less to more restricted diets, that is, cow's milk protein hydrolysate to amino-acid-based formulas, depending on the child's condition. In severely compromised infants, it may be prudent to start with amino-acid-based feeding.

When oral nutrition is not feasible or fails, enteral or parenteral supplementation should be considered. **Enteral nutrition** may be provided via nasogastric or gastrostomy tube and is indicated in a child who is not able to be adequately fed orally. In extreme wasting and in cases of significant intestinal mucosal damage or dysfunction, enteral nutrition may not be tolerated, and **parenteral nutrition** is required.

Micronutrient and vitamin supplementation are part of nutritional rehabilitation, especially in malnourished children in developing countries. Zinc supplementation is important in both prevention and therapy of chronic diarrhea, since it promotes ion absorption, restores epithelial proliferation, and stimulates immune response. Nutritional rehabilitation has a general beneficial effect on the patient's general condition, intestinal function, and immune response.

Functional diarrhea in children may benefit from a diet based on the "4 F" principles (reduce fructose and fluids, increase fat and fiber). The use of probiotics (mostly *Lactobacillus GG* or *Saccharomyces boulardii*) in infectious and postinfectious diarrhea in children may be tried as adjunctive therapy with reduction in symptom duration, but there is insufficient evidence to recommend their routine use for chronic diarrhea.

Pharmacologic therapy includes, based on the etiology, antiinfectious drugs, immune suppression, and drugs that may inhibit fluid loss and promote cell growth. If a bacterial agent is detected, specific antibiotics should be prescribed. Empiric antibiotic therapy may be used in children with either small bowel bacterial overgrowth or with suspected infectious diarrhea. Table 388.6 summarizes the antimicrobial treatment of infectious persistent diarrhea. Immune suppression

**Table 388.5** Stepwise Diagnostic Approach to Children and Infants with Chronic Diarrhea

INITIAL EVALUATION	
<b>Personal and family history:</b> Prenatal sonography; feeding history; family history of protracted diarrhea; consanguinity	<b>Infectious workup:</b> Stool cultures; parasites; viruses <b>Allergic workup:</b> Elimination diet trial
<b>Physical examination:</b> Signs of malnutrition; dysmorphism; skeletal abnormalities; organomegaly; dermatitis	
<b>↓</b>	
LABORATORY TESTS	
<b>Stool analysis:</b> Stool volume following fasting; stool electrolytes and ion gap; pH and reducing substances; steatocrit; fecal leukocytes and calprotectin; fecal elastase; $\alpha_1$ -antitrypsin	<b>Blood and serum analysis:</b> Serum electrolytes; lipid profile; albumin and prealbumin; amylase and lipase; inflammatory markers; ammonia; celiac serology
<b>↓</b>	
IMAGING	
<b>Abdominal ultrasound:</b> Bowel wall thickening; liver and bile disorders	<b>X-ray, contrast studies, computed tomography, magnetic resonance imaging:</b> Congenital malformation; signs of motility disorders
<b>↓</b>	
ENDOSCOPIES AND INTESTINAL HISTOLOGY	
Endoscopy and standard jejunal/colonic histology*; morphometry; PAS staining; intestinal immunohistochemistry; electron microscopy	
<b>↓</b>	
GENETIC INVESTIGATION	
Specific molecular analysis	Whole exome sequencing
<b>↓</b>	
OTHER SPECIAL INVESTIGATIONS	
Sweat test; specific carbohydrates breath tests; $^{75}\text{SeHCAT}$ measurement; anti-enterocyte antibodies; metabolic diseases workup; motility studies; neuroendocrine tumor markers	

\*The decision to perform an upper or a lower endoscopy may be supported by noninvasive tests.

PAS, Periodic acid-Schiff;  $^{75}\text{SeHCAT}$ ,  $^{75}\text{Se}$ -homocholic acid-taurine.

**Table 388.6** Antimicrobial Treatment for Persistent Diarrhea

	<b>DRUG</b>	<b>INDICATIONS</b>	<b>DOSAGE</b>	<b>DURATION</b>
Antibiotics	Trimethoprim-sulfamethoxazole	<i>Salmonella</i> spp., <i>Shigella</i> spp.	6-12 mg/kg/day (of trimethoprim) in 2 divided doses daily per os	5-7 days
	Azithromycin	<i>Shigella</i> spp., <i>Campylobacter</i>	1 day: 12 mg/kg/day once daily per os 2-5 days: 6 mg/kg/day once daily per os * Alternative: 10 mg/kg/day once daily per os, for 3 days	5 days
	Ciprofloxacin	<i>Shigella</i> spp.	20-30 mg/kg/day in 2 divided doses, per os or IV	3 days
	Ceftriaxone	<i>Shigella</i> spp.	50-100 mg/kg/day once daily per IM or IV	2-5 days
	Metronidazole	<i>Giardia</i> , <i>Amebiasis</i> , <i>Blastocystis</i> , <i>Clostridium difficile</i>	15-35 mg/kg/day in 2-3 divided doses per os	7-10 days
	Paromomycin	<i>Amebiasis</i>	25-35 mg/kg/day in 3 divided doses per os	7 days
Antiparasitic	Vancomycin	<i>C. difficile</i>	40 mg/kg/day in 4 divided doses per os	10 days
	Nitazoxanide	<i>Amebiasis</i> , <i>Giardiasis</i> , <i>Blastocystis</i> , <i>Cryptosporidiosis</i>	100 mg every 12 hr for children ages 12-47 mo 200 mg every 12 hr for children ages 4-11 yr 500 mg every 12 hr for children older than 11 yr	3 days
	Albendazole	<i>Ascaris</i> , hookworm, and pinworm infection	400 mg	Once

\*Depends on local susceptibility profile.

IM, Intramuscular; IV, intravenous; os, by mouth.

should be considered in selected conditions such as autoimmune enteropathy and IBD.

Treatment may be also directed at modifying specific pathophysiological processes. Secretion of ions may be reduced by antisecretory agents, such as the enkephalinase inhibitor racecadotril. Some benefit from absorbents, such as diosmectite, has been described, with reduction of diarrhea duration in infectious diarrhea. In diarrhea caused by neuroendocrine tumors (NETs), microvillus inclusion disease and enterotoxin-induced severe diarrhea, a trial of somatostatin analog octreotide may be considered. Zinc promotes both enterocyte growth and ion absorption and may be effective when intestinal atrophy and ion secretion are associated.

When therapeutic attempts and other nutritional supportive measures have failed, the only option to treat children with intestinal failure, while maintaining adequate growth and development, may be long-term parenteral nutrition or eventually intestinal transplantation.

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## 388.1 Diarrhea from Neuroendocrine Tumors

Shimon Reif and Raanan Shamir

The incidence of NETs originating in the GI tract is increasing globally. Physicians' awareness, endoscopic screening, and increased sensitivity of diagnostic tools may at least in part explain this trend. Most of these tumors involve the gastro-entero-pancreatic tract. Neuroendocrine neoplasm cells possess features of both neural and epithelial cells. The commonly perceived notion of NETs is of slow-growing malignancies with a benign course. Although well-differentiated GI-NETs may exhibit indolent clinical behavior, studies indicate that they are frequently already metastatic at diagnosis, and in which case they are neuroendocrine carcinomas.

The majority of NETs (75–90%) are not associated with elevated hormone levels and do not cause a clinical syndrome such as diarrhea. Functional tumors are tumors that make excess hormone, leading to clinical syndromes. These include insulinoma, gastrinoma, vasoactive intestinal polypeptide (VIP) secreting tumors, glucagonoma, and somatostatinoma. A child with persisted watery secretory diarrhea should be evaluated for a functional NET.

The most common NET in children is **carcinoid**, which is generally a low-grade tumor, especially when it is small (<1 cm). It is equally distributed between the small and large intestine and can commonly be found in the appendix. Most carcinoids are found incidentally and are asymptomatic, especially those that are located in the appendix. Some NET patients (around 10%) will develop secretory diarrhea requiring symptom control to optimize quality of life and clinical outcomes. Such patients are defined as having carcinoid syndrome, characterized by excessive production of one or more peptides, which, when released into the circulation, exert their endocrine effects and can be measured by radioimmunoassay methods (in the plasma or as their urinary metabolites). These peptides, therefore, also act as tumor markers. Compared to carcinoid, VIPomas are much less frequent. Because VIP is a more potent vasoactive peptide, it induces more profuse diarrhea, with up to 70% of patients having volumes greater than 3 L/day. Though rare as a cause of watery diarrhea, a NET should be considered in the differential diagnosis when diarrhea is unusually severe or takes a chronic course (resulting in electrolyte and fluid depletion). GI-NETs may be associated with flushing, palpitations, or bronchospasm. Family history may reveal multiple endocrine neoplasia (MEN) 1 or 2 syndromes (Table 388.7).

Baseline tests should include plasma chromogranin A and urinary 5-hydroxyindoleacetic acid (a metabolite of serotonin) and other specific biochemistry being guided by the suspected syndrome (see Table 388.7). Localization of any NET is best achieved using a multimodality approach. Whole body CT or MRI with somatostatin receptor PET screening may be required with gallium-68 DOTATOC (synthetic octreotide) PET.

**Table 388.7** Diarrhea Caused by Neuroendocrine Tumors

TUMOR AND CELL TYPE	SITE	MARKERS	SIGNS OF HORMONE HYPERSECRETION	THERAPY
Carcinoid	Intestinal argentaffin cells, typically midgut, also foregut and hindgut, ectopic bronchial tree	<b>Serotonin (5-HT), urine 5-HIAA*</b> (diagnostic) Also produce substance P, neuropeptide K, somatostatin, VIP chromogranin A	Secretory diarrhea, crampy abdominal pain, flushing, wheezing (and cardiac valve damage if foregut site)	Resection Somatostatin analog, (palliative) Genetic MEN-1
Gastrinoma, Zollinger-Ellison syndrome	Pancreas, small bowel, liver, and spleen	<b>Gastrin</b>	Multiple peptic ulcers, secretory diarrhea	H <sub>2</sub> -blockers, PPI, tumor resection, (gastrectomy) Genetic MEN-1
Mastocytoma	Cutaneous, intestine, liver, spleen	<b>Histamine, VIP</b>	Pruritus, flushing, apnea If VIP, diarrhea	H <sub>1</sub> - and H <sub>2</sub> -blockers, steroids, resection if solitary
Medullary carcinoma	Thyroid C-cells	<b>Calcitonin, VIP, prostaglandins</b>	Secretory diarrhea	Radical thyroidectomy ± lymphadenectomy (genetic MEN-2A/B, familial MTC)
Ganglioneuroma, pheochromocytoma, ganglioneuroblastoma, neuroblastoma	Chromaffin cells; abdominal > other sites; extraadrenal or adrenal	<b>Metanephries and catecholamines, VIP</b> VMA, HMA in neuroblastoma	Hypertension, tachycardia, paroxysmal palpitations, sweating, anxiety, watery diarrhea <sup>†</sup>	Perioperative α-adrenergic (BP) and β-adrenergic blockade with volume support tumor resection Genetic MEN-2 (RET gene), VHL, NF-1, SDH
Somatostatinoma	Pancreas	<b>Somatostatin</b>	Secretory diarrhea, steatorrhea, cholelithiasis, diabetes	Resection Genetic MEN-1
VIPoma	Pancreas	<b>VIP, prostaglandins</b>	Secretory diarrhea, achlorhydria, hypokalemia	Somatostatin analogs, resection Genetic MEN-1

\*Bold indicates major markers.

<sup>†</sup>Diarrhea has been reported only in adult patients with pheochromocytoma.

BP, Blood pressure; H<sub>1</sub>, histamine receptor type 1; H<sub>2</sub>, histamine receptor type 2; HMA, homovanillic acid; MEN-1, multiple endocrine neoplasia type 1; MTC, medullary thyroid carcinoma; NF-1, neurofibromatosis type 1; PPI, proton pump inhibitor; SDH, succinate dehydrogenase; VHL, von Hippel-Lindau disease; VIP, vasoactive intestinal polypeptide; VMA, vanillylmandelic acid.

Therapeutic interventions to be considered include surgical, pharmacologic, and radioisotope therapy; choice of therapy is based on disease extent and location, tumor grade, pace of disease progression, symptoms, and comorbidities.

Tumor resection is the treatment of choice when the tumor is small and localized. The goals of resection are twofold: (1) management of the endocrine syndrome to control symptoms and (2) tumor control to improve survival. However, resection can precipitate life-threatening adrenergic crises. When arising in the appendix, carcinoid tumors less than 2 cm in size can be managed by simple appendectomy. When greater than 2 cm in size or arising from the base of the appendix, a right hemicolectomy is indicated. Fortunately, in pediatric patients, metastases are rare; when they occur, it is usually in the liver. Tumor histochemistry will confirm the NET type and classification. Pharmacologic treatment may include the use of long-acting somatostatin analogues as first-line therapy. This usually results in a pronounced improvement of symptoms including diarrhea. However, many patients become resistant to somatostatin. Diarrhea caused by

pancreatic insufficiency, secondary to somatostatin analog use, is often oily and malodorous and should be treated with pancreatic enzyme replacement. Everolimus is an oral medication and a more specific target of rapamycin (mTOR) inhibitor, and has been reported as add-on treatment to octreotide, primarily in adult patients. The tyrosine kinase inhibitor sunitinib is another option. Data suggest a positive effect of ondansetron, a serotonin-3-receptor antagonist, on diarrhea. Peptide receptor radioisotope therapy also has been reported as a therapeutic modality.

Diarrhea and flushing associated with the carcinoid syndrome can be debilitating. Telotristat ethyl is an inhibitor of tryptophan hydroxylase that acts to reduce serotonin levels and has emerged as a promising agent for control of refractory carcinoid syndrome diarrhea.

The diagnosis of NET in children should prompt a genetic referral to exclude a familial syndrome.

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## Chapter 389

# Disorders of Brain-Gut Interaction (Functional Gastrointestinal Disorders)

Asim Maqbool, Chris A. Liacouras,  
Jefferson N. Brownell, and Paul J. Ufberg

Disorders of brain-gut interaction (DBGI), formerly classified as functional gastrointestinal disorders (FGIDs), comprise a group of conditions that relate to the gastrointestinal (GI) tract and cannot be completely explained by other underlying etiologies such as GI, anatomic, physiologic, or biochemical abnormalities. Conversely, DBGI are defined as a group of disorders classified by GI symptoms related to any combination of motility disturbances, visceral hypersensitivity, altered mucosal and immune function, gut microbiota, and/or central nervous system processing. DBGI are common worldwide in children of all ages and often pose diagnostic challenges, as there is no anatomic or laboratory-based testing that can be used to define them. The symptom-based criteria employed to classify DBGI have been developed and reevaluated through multiple iterations by expert consensus under the auspices of the Rome Foundation and are thus referred to, in their most recent form, as the Rome IV criteria. In this newest iteration, published in May 2016, the term *functional gastrointestinal disorders* has been retired due to its nonspecificity and potential for stigma in favor of the more specific DBGI. The criteria defining DBGI strive not to be entirely based on diagnoses of exclusion, but rather aim to be based on objective, unambiguous, and accurate criteria derived from the presentation as elicited during a medical history and clinical examination. They aim to provide a uniform, reliable, and reproducible framework to minimize unnecessary evaluations that are likely to have low diagnostic yield or relevance. It is important to recognize that DBGI may coexist or interact with other organic GI disorders, such as inflammatory bowel disease, celiac disease, or chronic pancreatitis; at the same time, DBGI themselves exist as related entities on a spectrum with considerable overlap. Ongoing research has implicated a complex interaction between gut microbiota and host immune responses, altered motility, visceral hypersensitivity, genetic factors, and the enteric nervous system in the pathophysiology of DBGI (Fig. 389.1). Furthermore, DBGI may be influenced by psychosocial stressors or a result of an otherwise benign episode of abdominal pain (Fig. 389.2). Early life physical or psychologic stressors may manifest later via DBGI. Maladaptive responses or lack of adequate coping skills may complicate the treatment of DBGI but may also allow for a valuable approach to management using behavioral therapies.

DBGI in children encompass two age-groups: infants/toddlers and children/adolescents. Rumination syndrome, functional constipation, and cyclical vomiting span both age-groups (Fig. 389.3).

## DISORDERS OF BRAIN-GUT INTERACTION IN INFANTS AND TODDLERS

**Infant regurgitation** is the most common DBGI in the first year of life and describes effortless retrograde and involuntary passage of gastric contents from the stomach cephalad and is more commonly referred to as gastroesophageal reflux (Table 389.1). When refluxate reaches the oropharynx and is visible, it is labeled as regurgitation. This phenomenon is normal for healthy infants unless there are complications

associated with the process, such as esophageal inflammation, dysphagia, feeding difficulties, inadequate oral intake to meet needs leading to failure to thrive, or the inability to protect the airway with risk for aspiration; in this setting gastroesophageal reflux *disease* is the correct designation (see Chapter 369). Unlike vomiting, regurgitation does not include the forceful expulsion of gastric contents. The peak incidence of infant regurgitation is 4 months of age, followed by a decline in frequency through 12 months of age.

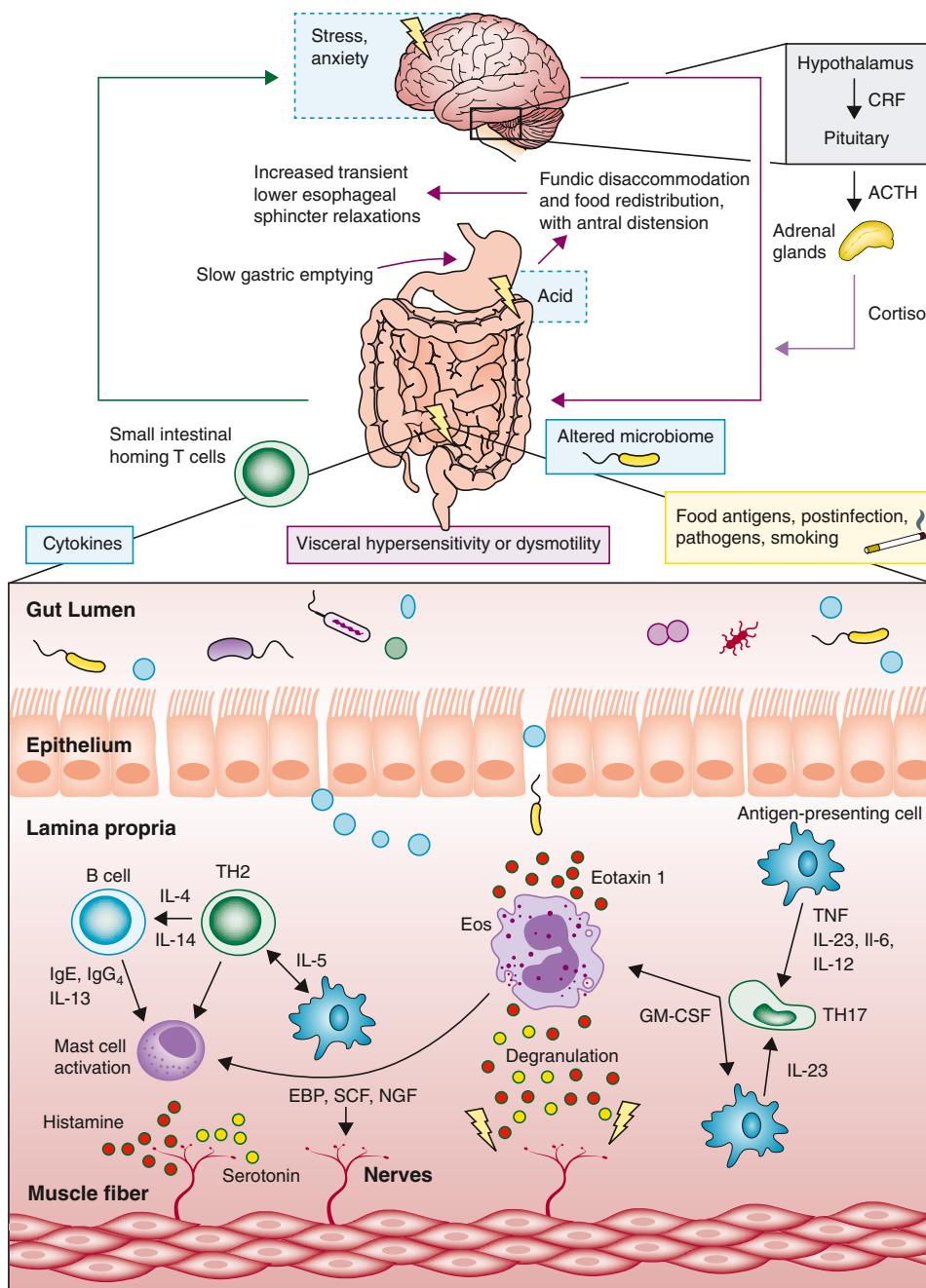
**Infant rumination** is defined as a habitual regurgitation of gastric contents into the oropharynx to allow for mastication and swallowing (Table 389.2). It is thought to be a form of self-stimulation and may occur in the setting of emotional or sensory deprivation. The regurgitation of gastric contents is effortless, and the refluxate can be chewed and reswallowed instead of expelled from the oropharynx. Infant rumination occurs between 3 and 8 months of age and does not respond to measures used to manage regurgitation. This phenomenon does not occur during socialization/interaction with individuals, does not occur during sleep, and is not associated with distress. Empathy and nurturing lay the foundation for management.

**Cyclic vomiting syndrome (CVS)** is characterized by repeated episodes of stereotypical vomiting punctuated by periods of normal health in between. It has been reported in infants and children younger than 3 years of age and is most common between ages 2 and 7. The median age of presentation is 4 years (see Chapter 390).

**Infant colic** (see Chapter 23.1) is a normal developmental process associated with fussiness, irritability, and difficulty consoling the infant (Table 389.3). A trigger is not identifiable; the unexplained episodes of apparent discomfort are often quite stressful to the caregivers and identifying a cause may be their main concern. Infant colic typically occurs between 1 and 4 months of age, with episodes of crying occurring more often in the afternoon or evening. The behavior tends to peak after 4-6 weeks, followed by a gradual decline to resolution about 12 weeks after initial onset. The typical behavior usually leads to consultation with a pediatrician or a pediatric gastroenterologist out of suspicion for abdominal pain despite the absence of any correlating evidence. Associated behaviors, including facial grimace, abdominal distension, increasing gas, skin flushing, and drawing legs up to the abdomen are nondiagnostic but may be worrisome to the caregiver. Patients are often treated for gastroesophageal reflux, gas, or suspected allergy, leading to unnecessary dietary changes and medication use. Treatment includes multiple approaches based on caregiver vulnerabilities. Approaches may include reassuring the caregiver through demonstration that a held, rocked infant may be soothed, prospectively logging crying and other behaviors, and ensuring that caregiver exhaustion is addressed via support system. Probiotics have been investigated as a possible treatment; however, systematic reviews have not demonstrated any beneficial effect. Regardless of the primary approach, providing reassurance, education, and ensuring adequate coping skills and support for caregivers is key. Infant colic ultimately resolves on its own.

**Functional diarrhea** is often also referred to as *toddler's diarrhea* or *chronic nonspecific diarrhea of toddlerhood* and describes the daily painless passage of three or more large unformed stools for four or more weeks in a well-nourished child. The stools often contain visibly undigested food and mucus, which may be distressing to the caregiver. The onset is typically in infancy or preschool years and excludes steatorrhea and other malabsorptive etiologies (Table 389.4). Nutritional factors such as excessive total calorie intake, as well as excessive dietary intake of the sugar alcohol sorbitol and the carbohydrate fructose, coupled with a low-fat diet, have been implicated in this osmotic process. An evaluation of the diet for other possible etiologies as well as assessment for infections, inflammation, and medication use including antibiotics and laxatives is important. In addition, assessments of growth as well as ruling out fecal impaction and encopresis via digital rectal examination are important. Dietary changes such as reducing fruit juice and processed fructose intake are helpful in resolving symptoms. Care should be taken to not overly restrict the child's diet in an effort to avoid simple sugars. Fiber supplementation may be of some benefit, but evidence is lacking.

**Fig. 389.1** Intestinal immune activation model of functional gastrointestinal disorders. It is hypothesized that, in a genetically primed host, environmental factors induce immune activation. Antigen presentation of luminal antigens, such as pathogens or food peptides, to T cells drives maturation of naïve T cells to T-helper (TH) 2 cells. The release of associated cytokines (interleukin [IL]-4, IL-5, and IL-14) promotes the activation and recruitment of eosinophils (Eos), B cells, and mast cells. In addition to the traditional TH2 pathway, secretion of IL-23 from antigen-presenting cells, such as dendritic cells, B cells, and macrophages, promotes TH17 differentiation. The production of granulocyte-macrophage colony-stimulating factor (GM-CSF) from Th17 further drives Eos recruitment. Degranulation of mast cells and eosinophils results in the release of inflammatory mediators, which can damage the intestinal barrier and stimulate and damage enteric nerve fibers, which induces visceral hypersensitivity and motility disturbances resulting in gastrointestinal symptoms.  $\alpha$ 4 $\beta$ 7 gut homing T cells are a marker of intestinal inflammation in both functional dyspepsia and irritable bowel syndrome, and correlate with delayed gastric emptying. Duodenal motor dysfunction might also impair duodenal acid clearance, inducing intestinogastric reflex responses that impair accommodation of the gastric fundus, and increase transient lower esophageal sphincter relaxations leading to gastroesophageal reflux. Signaling cascades, leading to further cytokine release, might result in extraintestinal symptoms, such as anxiety and fatigue. The site and extent of intestinal immune activation can define the phenotype (i.e., proximal intestinal involvement might give rise to functional heartburn, or functional dyspepsia, more distal involvement to irritable bowel syndrome, functional constipation, or functional diarrhea). CRF, Corticotropin-releasing factor; ACTH, adrenocorticotrophic hormone; Ig, immunoglobulin; TNF, tumor necrosis factor; EBP, enhancer binding protein; SCF, stem cell factor; NGF, nerve growth factor. (From Black CJ, Drossman DA, Talley NJ, et al. Functional gastrointestinal disorders: advances in understanding and management. *Lancet*. 2020;396:16644–16674. Fig. 2.)

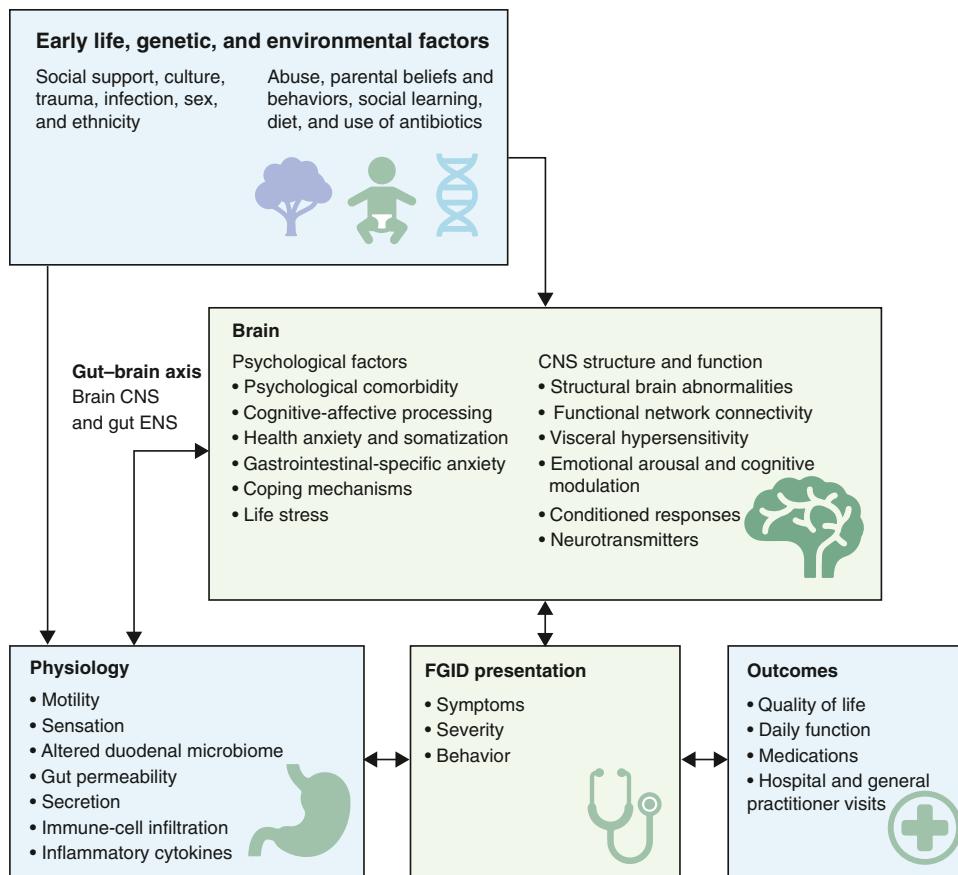


**Infant dyschezia** describes apparent discomfort before defecation in an infant less than 9 months of age. Infants with dyschezia will strain before defecation for 10–20 minutes with associated screaming, crying, and possible red/purple facial discoloration. Typically, stools are passed several times daily and are not associated with other health problems or anatomic abnormalities. Dyschezia is the result of disorganized abdominal and pelvic floor musculature contraction, raising the intraabdominal pressure. A good medical history and examination to rule out anatomic or neuromuscular abnormalities are key. Normal growth is to be expected. Reassurance provides the basis of management, and most caregivers will accept the explanation that the infant needs to learn the proper mechanics to stool, relaxing the pelvic floor while bearing down. Laxative, suppository, or digital manipulation is not required and may be counterproductive. Infant dyschezia typically resolves after 3–4 weeks of symptoms.

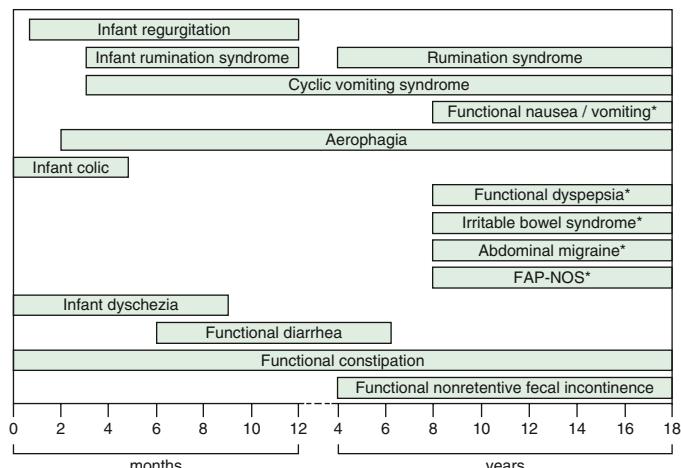
**Functional constipation** (see Chapter 378.3) is associated with chronic stool retention, often the result of deliberate withholding as the child voluntarily tries to avoid defecation due to fear or pain. To

meet criteria for functional constipation, infants and children must have symptoms for 1 month, including at least two of five criteria listed in Table 389.5. There is often an episode of acute constipation that prompts further avoidance, creating a cycle of pain and withholding. In infancy, the onset is often at the time of diet changes with either the introduction of solid foods or the transition to cow's milk at 12 months of age. In toddlerhood, the initiation of toilet training often correlates with onset of constipation.

In addition to the clinical criteria, symptoms may include hematochezia due to an anal fissure. Though the blood coating the stool is often distressing to caregivers, the blood loss associated with constipation is typically not clinically significant. Physical examination may reveal a palpable abdominal mass, small amounts of fecal matter or a midline fissure on perianal exam, or a hard mass of stool in the rectal vault on digital rectal exam. It should be noted that if the history is typical for functional constipation, a digital rectal examination may not be necessary until treatment failure, if there is diagnostic uncertainty, or an anatomic malformation is suspected. Digital manipulation of the



**Fig. 389.2** Biopsychosocial model of functional gastrointestinal disorders (FGID). CNS, Central nervous system; ENS, enteric nervous system. (From Black CJ, Drossman DA, Talley NJ, et al. Functional gastrointestinal disorders: advances in understanding and management. Lancet. 2020;396:16644–1674. Fig. 1, p 1667.)



**Fig. 389.3** Age distribution of functional gastrointestinal disorders in infants, toddlers, children, and adolescents. \*History may not be reliable below this age. FAP-NOS, Functional abdominal pain-not otherwise specified. (Modified from Benninga MA, Nurko S, Faure C, et al. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology. 2016;150:1443–1455.e2.)

anal canal and rectum may further traumatize the child in whom painful defecation has prompted withholding behaviors.

The differential diagnosis for constipation is extensive. In infancy, care must be taken to exclude, via history or physical exam, etiologies including anatomic obstructions, Hirschsprung disease, spinal and neuromuscular abnormalities, and metabolic disorders. A defecation history extending to the first 24 hours of life is particularly important, as 90% of healthy infants and fewer than 10% of infants with Hirschsprung disease will pass their first bowel movement within

**Table 389.1** Diagnostic Criteria for Infant Regurgitation

Must include both of the following in otherwise healthy infants 3wk to 12 mo of age:

1. Regurgitation 2 or more times per day for 3 or more weeks
2. No retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties, or abnormal posturing

From Benninga MA, Nurko S, Faure C, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology*. 2016;150(6):1443–1455.e2.

**Table 389.2** Diagnostic Criteria for Infant Rumination Syndrome

Must include all of the following for at least 2mo:

1. Repetitive contractions of the abdominal muscles, diaphragm, and tongue
2. Effortless regurgitation of gastric contents, which are either expelled from the mouth or rechewed and reswallowed
3. Three or more of the following:
  - a. Onset between 3 and 8 mo
  - b. Does not respond to management for gastroesophageal reflux disease and regurgitation
  - c. Unaccompanied by signs of distress
  - d. Does not occur during sleep and when the infant is interacting with individuals in the environment

From Benninga MA, Nurko S, Faure C, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology*. 2016;150(6):1443–1455.e2.

the first 24 hours of life. Assessment for associated signs and symptoms and growth trends are important, as growth is often affected in the previously mentioned disorders. Red flags are noted in Table 389.6. Management involves naming and explaining the diagnosis, dietary and lifestyle changes, and early use of medications to soften stool with

**Table 389.3** Diagnostic Criteria for Infant Colic

For clinical purposes, must include all of the following:

1. An infant who is <5 mo of age when the symptoms start and stop
2. Recurrent and prolonged periods of infant crying, fussing, or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers
3. No evidence of infant failure to thrive, fever, or illness

"Fussing" refers to intermittent distressed vocalization and has been defined as "behavior that is not quite crying but not awake and content either." Infants often fluctuate between crying and fussing, so that the two symptoms are difficult to distinguish in practice

For clinical research purposes, a diagnosis of infant colic must meet the preceding diagnostic criteria and also include both of the following:

1. Caregiver reports infant has cried or fussed for 3 or more hours per day during 3 or more days in 7 days in a telephone or face-to-face screening interview with a researcher or clinician
2. Total 24-hr crying plus fussing in the selected group of infants is confirmed to be 3 hours or more when measured by at least one prospectively kept, 24-hr behavior diary

From Benninga MA, Nurko S, Faure C, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology*. 2016;150(6):1443–1455.e2.

**Table 389.4** Diagnostic Criteria for Functional Diarrhea

Must include all of the following:

1. Daily painless, recurrent passage of four or more large, unformed stools
2. Symptoms last more than 4 wk
3. Onset between 6 and 60 mo of age
4. No failure to thrive if caloric intake is adequate

From Benninga MA, Nurko S, Faure C, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology*. 2016;150(6):1443–1455.e2.

**Table 389.5** Diagnostic Criteria for Functional Constipation

Must include 1 mo of at least two of the following in infants up to 4 yr of age:

1. Two or fewer defecations per week
2. History of excessive stool retention
3. History of painful or hard bowel movements
4. History of large-diameter stools
5. Presence of a large fecal mass in the rectum

In toilet-trained children, the following additional criteria may be used:

6. At least one episode per week of incontinence after the acquisition of toileting skills
7. History of large-diameter stools that may obstruct the toilet

From Benninga MA, Nurko S, Faure C, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology*. 2016;150(6):1443–1455.e2.

daily osmotic laxatives preferred over stimulant laxatives. The primary goal is to achieve painless defecation to facilitate resolution of the fear and withholding around defecation. Avoidance of toilet training until symptoms resolve and the child shows interest or willingness to proceed are generally advocated. Behavior modification including reassurance and positive incentive reward systems are useful.

### DISORDERS OF BRAIN-GUT INTERACTION IN OLDER CHILDREN AND ADOLESCENTS

DBGI in children and adolescents are divided by symptoms into nausea and vomiting disorders, abdominal pain disorders, and defecation

**Table 389.6** Potential Alarm Features in Constipation

- Passage of meconium >48 hours in a term newborn
- Constipation starting in the first month of life
- Family history of Hirschsprung disease
- Ribbon stools
- Blood in the stools in the absence of anal fissures
- Failure to thrive
- Bilious vomiting
- Severe abdominal distension
- Abnormal thyroid gland or newborn screen
- Abnormal position of the anus
- Absent anal or cremasteric reflex
- Decreased lower extremity strength/tone/reflex
- Sacral dimple
- Tuft of hair on lower spine
- Gluteal cleft deviation
- Anal scars

From Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2016;150(6):1456–1468.e2. Table 3.

disorders. For individual diagnoses, the term *functional* is still used in some cases.

### Nausea and Vomiting Disorders

Cyclic vomiting syndrome describes stereotypical, episodic attacks of vomiting with intervening periods of normal health and no vomiting symptoms (see Chapter 390). Per the Rome IV criteria, at least two episodes must occur in a 6-month period and not be attributable to another condition (Table 389.7). CVS can occur from infancy to adulthood, with 46% of patients having symptom onset at or before 3 years of age. In younger patients, extra care must be taken to rule out metabolic and anatomic disorders, as there is a higher likelihood of these disorders at younger ages. Chronic cannabis use in adolescents can be associated with repeated episodes of nausea and vomiting, termed the cannabinoid hyperemesis syndrome (see Chapter 157.3), and should be excluded in this age-group.

**Functional nausea and functional vomiting** may coexist or may occur independently of one another and describe isolated nausea or isolated vomiting (Table 389.8). Importantly, these conditions occur without coincident abdominal pain. The presentation may be accompanied by autonomic symptoms such as diaphoresis, pallor, tachycardia, and dizziness. The differential diagnosis includes anatomic, inflammatory, infectious, and motility etiologies. Anxiety and other behavioral conditions can be present with these DBGI and should be evaluated for and managed accordingly; children with functional nausea or functional vomiting should undergo psychologic evaluation. In children with psychologic comorbidities, cognitive-behavioral therapy or other psychologic interventions are appropriate. Cyproheptadine and transcutaneous gastric stimulation may be effective in the management of nausea.

**Rumination syndrome** in children and adolescents is defined similarly to the condition in infants, with the added notation that the effortless regurgitation of stomach contents may be associated with an unpleasant sensation or discomfort such as abdominal pressure or burning (Table 389.9). Repeated regurgitation and remastication or oral repulsion of the regurgitated gastric contents occurs soon after ingesting foodstuffs and does not occur during sleep. It is not preceded by active expulsion of gastric contents/retching and cannot be explained by any other medical condition. The diagnosis does not require prior failure of treatment for gastroesophageal reflux. A triggering event can often be identified before symptoms, which may occur following resolution of an infectious illness or with psychosocial stress. In adolescents, eating disorders may present similarly and must be ruled out. Other GI issues to be considered include anatomic, infectious, inflammatory, and motility disorders. An important distinction between rumination and other GI etiologies of vomiting includes effortless versus forceful regurgitation, and the time course, which is usually immediately following ingestion of foodstuffs. As with most

**Table 389.7** Diagnostic Criteria for Cyclic Vomiting Syndrome

Must include all of the following:

1. The occurrence of two or more periods of intense, unremitting nausea and paroxysmal vomiting, lasting hours to days within a 6-mo period
2. Episodes are stereotypical in each patient
3. Episodes are separated by weeks to months with return to baseline health between episodes
4. After appropriate medical evaluation, the symptoms cannot be attributed to another condition

**Table 389.8** Diagnostic Criteria\* for Functional Nausea and Functional Vomiting

#### FUNCTIONAL NAUSEA

Must include all of the following fulfilled for the last 2 mo:

1. Bothersome nausea as the predominant symptom, occurring at least twice per week, and generally not related to meals
2. Not consistently associated with vomiting
3. After appropriate evaluation, the nausea cannot be fully explained by another medical condition

#### FUNCTIONAL VOMITING

Must include all of the following:

1. On average, one or more episodes of vomiting per week
2. Absence of self-induced vomiting or criteria for an eating disorder or rumination
3. After appropriate evaluation, the vomiting cannot be fully explained by another medical condition

\*Criteria fulfilled for at least 2 mo before diagnosis.

From Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2016;150(6):1456–1468.

**Table 389.9** Diagnostic Criteria\* for Rumination Syndrome in Children

Must include all of the following:

1. Repeated regurgitation and rechewing or expulsion of food that:
  - a. Begins soon after ingestion of a meal
  - b. Does not occur during sleep
2. Not preceded by retching
3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition. An eating disorder must be ruled out

\*Criteria fulfilled for at least 2 mo before diagnosis.

From Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2016;150(6):1456–1468.

**DBGI**, a thorough understanding of the disorder and motivation to overcome it are key to treatment. Because rumination syndrome is essentially a learned habit, therapy focusing on managing the habit has proven effective. Deep breathing exercises to counteract the noxious stimulus are often employed to change the pressure differential and prevent regurgitation of gastric contents.

**Aerophagia** is often seen in neurocognitively impaired patients. It involves excessive air swallowing occurring throughout the day with progressive abdominal distention and with repetitive passage of gas via belching and/or flatus. Abdominal distension and flatus symptoms may be more severe in those children who cannot belch. Symptoms cannot be attributed to any other causes such as partial obstructions, small bowel bacterial overgrowth, GI dysmotility (pseudoobstruction), or to malabsorptive disorders. In children with age-appropriate cognition and neurologic status, chewing gum and gulping down liquids may be risk factors for aerophagia. Abdominal pain, nausea, and early satiety are possible associated GI symptoms; sleeping difficulty, headaches, and dizziness are also reported. Anxiety is a frequent comorbidity and

**Table 389.10** Diagnostic Criteria\* for Functional Dyspepsia

Must include one or more of the following bothersome symptoms at least 4 days/mo:

1. Postprandial fullness.
2. Early satiation.
3. Epigastric pain or burning not associated with defecation.
4. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

Within functional dyspepsia, the following subtypes are now adopted:

1. Postprandial distress syndrome includes bothersome postprandial fullness or early satiation that prevents finishing a regular meal. Supportive features include upper abdominal bloating, postprandial nausea, or excessive belching.
2. Epigastric pain syndrome, which includes all of the following: bothersome (severe enough to interfere with normal activities) pain or burning localized to the epigastrium. The pain is not generalized or localized to other abdominal or chest regions and is not relieved by defecation or passage of flatus. Supportive criteria can include (1) burning quality of the pain but without a retrosternal component and (2) the pain is commonly induced or relieved by ingestion of a meal but may occur while fasting.

\*Criteria fulfilled for at least 2 mo before diagnosis.

From Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2016;150(6):1456–1468.

may contribute to the behavior. Treatment is multidisciplinary and may include behavioral therapy, deep breathing, and potentially medications to relieve anxiety.

#### Abdominal Pain Disorders

**Functional dyspepsia** (FD) describes postprandial fullness, early satiety, or epigastric pain or burning that is exclusive of defecation and not fully explainable by another or an underlying medical condition (Table 389.10). Subtypes of FD include *postprandial distress syndrome* (symptoms may preclude finishing a meal or be manifest by bloating, nausea, and excessive belching following a meal) as well as *epigastric pain syndrome* (epigastric pain/burning sufficient to preclude or disrupt normal activities, with pain not generalizable or localizable to other abdominal or chest regions, and not relieved by defecation or passage of flatus). Multiple pathophysiologic mechanisms have been proposed for FD; it is likely that each or multiple etiology contributes. An impaired gastric accommodation, visceral hypersensitivity, food allergy, delayed gastric emptying, and post-viral gastroparesis have all been implicated. The differential diagnosis includes GI etiologies of epigastric pain, including gastritis, esophagitis, and pancreatitis, among others. These etiologies can be guided by family, personal, and medical histories, exam, and by the nature of symptoms including abdominal pain and other alarm features (Tables 389.11 and 389.12). Initial treatment measures include a trial of dietary and lifestyle changes including avoiding spicy foods, caffeine, fatty foods, and nonsteroidal antiinflammatory drugs (NSAIDs). Gastric acid reduction therapy may be initiated. Assessment by a pediatric gastroenterologist and upper endoscopy are often performed. Treatment with cyproheptadine to improve gastric accommodation in patients with early satiety or attempts to treat visceral hypersensitivity in children with FD are reasonable, safe, and supported by available evidence. Low-dose tricyclic antidepressant therapy with amitriptyline may have efficacy in refractory cases. Early satiety may also respond to prokinetic medications such as erythromycin or metoclopramide. Percutaneous electrical stimulation of the stomach is a potential option for patients with FD refractory to standard therapy.

**Irritable Bowel Syndrome** (IBS) can be classified into the same four subtypes as adult IBS, depending on stool pattern: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS with constipation and diarrhea, and unspecified IBS. Diagnosis of IBS requires abdominal pain on four or more days per month associated with defecation and/or a change in frequency of stool from baseline and/or a change in form/

**Table 389.11** Alarm Symptoms Usually Needing Further Investigations in Children with Chronic Abdominal Pain

- Pain that wakes up the child from sleep
- Persistent right upper or right lower quadrant pain
- Significant vomiting (bilious vomiting, protracted vomiting, cyclical vomiting, or worrisome pattern to the physician)
- Unexplained fever
- Genitourinary tract symptoms
- Dysphagia
- Odynophagia
- Chronic severe diarrhea or nocturnal diarrhea
- Gastrointestinal blood loss
- Involuntary weight loss
- Deceleration of linear growth
- Delayed puberty
- Family history of inflammatory bowel disease, celiac disease, and peptic ulcer disease

**Table 389.12** Alarm Signs Usually Needing Further Investigations in Children with Chronic Abdominal Pain

- Localized tenderness in the right upper quadrant
- Localized tenderness in the right lower quadrant
- Localized fullness or mass
- Hepatomegaly
- Splenomegaly
- Jaundice
- Costovertebral angle tenderness
- Arthritis
- Spinal tenderness
- Perianal disease
- Abnormal or unexplained physical findings
- Hematochezia
- Anemia

appearance of stool (Table 389.13). Symptoms, including the predominant stool pattern, severity of pain, and functional impairment, reflect the degree of disordered brain-gut interaction. Visceral sensitivity may be attenuated or amplified by psychosocial stressors as well as mucosal proinflammatory cytokines related to infections or alterations in the gut microbiota.

As with other DBGI, the GI differential diagnosis includes anatomic, infectious, inflammatory, and motility disorders as well as conditions associated with malabsorption. Differentiation between those GI disorders and IBS is guided by the history, physical, and often biochemical markers of inflammation, particularly fecal calprotectin (see Tables 389.11 and 389.12). Management of symptoms may include dietary modification (under the guidance of a registered dietitian to prevent inadequate intake) to reduce or restrict foods that may provoke symptoms or cause gas (see section on fiber and the FODMAPS [fermentable oligo-di-monosaccharides and polyols] discussion Chapter 60). The use of probiotics has been effective in reducing symptoms in children with IBS, likely through production of short-chain fatty acids; drug therapy for IBS is noted in Table 389.14. In small trials, peppermint was effective in reducing pain in children with IBS. Cognitive-behavioral therapy is important to identify possible psychosocial stressors and to help identify coping mechanisms to maximize daily function and quality of life. Small studies have suggested that transcutaneous neurostimulation may also be efficacious.

**Abdominal migraine** shares some features with CVS. Stereotypical patterns and symptoms afflict the patient, are typically of acute onset, intense, lasting for at least an hour, either perumbilical or generalized in location, and usually are debilitating (Table 389.15). Episodes may also include associated anorexia, nausea, emesis, headaches, photophobia, and pallor. Episodes are separated by weeks to months, with at least two attacks occurring over a 6-month period. Between bouts, children return to baseline functioning and are symptom free.

**Table 389.13** Diagnostic Criteria\* for Irritable Bowel Syndrome

- Must include all of the following:
1. Abdominal pain at least 4 days/mo associated with one or more of the following:
    - a. Related to defecation
    - b. A change in frequency of stool
    - c. A change in form (appearance) of stool
  2. In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not irritable bowel syndrome)
  3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

\*Criteria fulfilled for at least 2 mo before diagnosis.

From Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2016;150(6):1456–1468.

**Table 389.14** Recommendations for Treatment of Irritable Bowel Syndrome

#### RECOMMENDATIONS FOR TREATMENT OF IRRITABLE BOWEL SYNDROME (IBS)

- Mild symptoms often respond to dietary changes.
- Antispasmodics can be used as needed for abdominal pain or postprandial symptoms.
- Antidepressants can improve abdominal pain and global symptoms. They may be considered for patients with moderate to severe symptoms.

#### IBS WITH CONSTIPATION (IBS-C)

- Fiber may relieve constipation in patients with mild symptoms.
- Polyethylene glycol can increase the frequency of bowel movements but may not improve overall symptoms or abdominal pain.
- Lubiprostone or linaclotide can be tried in patients whose symptoms have not responded to polyethylene glycol.

#### IBS WITH DIARRHEA (IBS-D)

- Taken as needed, loperamide can reduce postprandial urgency and stool frequency, but it does not improve global symptoms.
- Rifaximin and eluxadoline have been modestly more effective than placebo in relieving symptoms.

From Drugs for irritable bowel syndrome. *The Medical Letter*. 2016;58(1504):121–126.

**Table 389.15** Diagnostic Criteria\* for Abdominal Migraine

- Must include all of the following occurring at least twice:
1. Paroxysmal episodes of intense, acute perumbilical, midline, or diffuse abdominal pain lasting 1 hour or more (should be the most severe and distressing symptom)
  2. Episodes are separated by weeks to months
  3. The pain is incapacitating and interferes with normal activities
  4. Stereotypical pattern and symptoms in the individual patient
  5. The pain is associated with two or more of the following:
    - a. Anorexia
    - b. Nausea
    - c. Vomiting
    - d. Headache
    - e. Photophobia
    - f. Pallor
  6. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

\*Criteria fulfilled for at least 6 mo before diagnosis.

From Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2016;150(6):1456–1468.

Triggers may vary, but common triggers include sleep hygiene disruption, fatigue, and travel, and are usually alleviated by sleep. The differential diagnosis includes anatomic obstructions or abnormalities predisposing to intermittent obstruction of the GI or urologic tract,

infectious or inflammatory conditions, hepatobiliary and pancreatic disorders, neurologic and metabolic conditions, and psychiatric disorders. Frequently, a family history of migraine headaches or abdominal migraines is present. Preventing exposure to known triggers once identified is important; further treatment depends on the frequency and severity of episodes as well as their impact on quality of life. Acute episodes may be treated similarly to migraine headaches with abortive medications such as triptans. Similar to CVS prophylaxis, cyproheptadine, amitriptyline, and propranolol may be effective. Oral pizotifen (antiserotonin, antihistamine) has been shown in small studies to be an effective prophylactic agent as well. Antimigraine therapies such as triptans may be effective in aborting bouts. A large number of children may have their symptom pattern evolve into migraine headaches as they progress toward adulthood.

**Functional abdominal pain not otherwise specified** (FAP-NOS) describes pain that occurs at least 4 times per month with either intermittent or continuous abdominal pain not associated with a particular activity or coincident to another physiologic event such as menses or eating and cannot be explained by any other underlying medical condition. These episodes occur in less than a 2-month span. In many ways, it is a DBGI of exclusion, as it does not meet criteria for either IBS, FD, or abdominal migraine. Psychosocial stressors may play a role, and behavioral approaches may be helpful to identify and manage stressors and other exacerbating factors. Pharmacologic data is limited, but small trials have suggested efficacy of amitriptyline and citalopram, though it should be noted that the latter is associated with suicidal ideation in adolescent patients.

## DEFECATION DISORDERS

**Functional constipation** in children and adolescents describes decreased defecation frequency associated with volitional stool retention, similar to the classification in infants and toddlers. Large, hard, painful bowel movements are again a hallmark of the disorder, though patients in this age-group may also demonstrate fecal incontinence related to overflow of liquid stool beyond a large rectal stool ball as well as large-diameter stools that obstruct the toilet (Table 389.16). Onset in children peaks at the time of toilet training; in older children and adolescent, withholding may be triggered by a social stressor such as a major change in the school or home environment. Repeated distension of the rectum with large, hard stool over time may reduce the sensation to defecate and may lead to encopresis, the unintentional passage of liquid stool. Children experiencing encopresis often do not smell the stool that has passed, leading to embarrassment in social situations. Anorexia, abdominal distention, and pain are often coincident, though notably children do not meet criteria for IBS-C.

The diagnosis is based on medical history and physical examination. In addition to the clinical criteria, symptoms may include hematochezia due to an anal fissure. Though the blood coating the stool is often distressing to caregivers, the blood loss associated with constipation is typically not clinically significant. Physical examination may reveal a palpable abdominal mass, small amounts of fecal matter or a midline fissure on perianal exam, or a hard mass of stool in the rectal vault on digital rectal exam. It should be noted that if the history is typical for functional constipation, a digital rectal examination may not be necessary until treatment failure, diagnostic uncertainty, or an anatomic malformation is suspected. Digital manipulation of the anal canal and rectum may further traumatize the child or adolescent in whom painful defecation has prompted withholding behaviors. An abdominal x-ray is not required to make the diagnosis, and the stool burden observed rarely correlates with historical defecation pattern. The diameter of the

Table 389.16

Diagnostic Criteria for Functional Constipation in Children with Chronic Abdominal Pain

Must include two or more of the following occurring at least once per week for a minimum of 1 month with insufficient criteria for a diagnosis of irritable bowel syndrome:

1. Two or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years
2. At least one episode of fecal incontinence per week
3. History of retentive posturing or excessive volitional stool retention
4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum
6. History of large-diameter stools that can obstruct the toilet

After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

From Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2016;150(6):1456–1468.

rectum and any rectal stool on x-ray may be helpful to illustrate the degree of stool accumulation in the rectum.

The differential diagnosis for constipation in children and adolescents is similar to infants and toddlers, though metabolic and anatomic abnormalities are much less likely to present in older children and adolescents. As in younger children, alarm symptoms should be assessed; in the absence of these symptoms, further testing is not indicated (see Table 389.6). Management includes disimpaction of the rectal stool ball followed by maintenance therapy with osmotic laxatives to soften stools for ease of passage, dietary changes to optimize fiber intake (a general rule is that daily fiber intake in grams can be approximated by adding age in years plus 5 to 10), and behavioral approaches similar to those employed for younger children (see Chapter 378.3).

**Nonretentive fecal incontinence** (NFI) describes the passage of stool in the absence of fecal retention that occurs in inappropriate settings for a specific society and culture, and that occurs without evidence of another or underlying medical condition in a child 4 years of age or older over at least a 1-month period. These patients otherwise have normal defecatory patterns and function, as well as normal colonic transit time, differentiating and distinguishing them from functional constipation. Another key difference is that children with NFI will have passage of their entire rectal contents as opposed to the smears or small amounts of stool in patients with functional constipation and encopresis. Psychologic comorbidities are frequent in children with NFI. A thorough medical history and physical examination including a comprehensive neurologic and digital rectal exam are required to fully appreciate what factors are involved in this condition. The diagnosis should be based on an otherwise normal defecation frequency, absence of an abdominal or rectal mass, a normal neurologic exam, and a normal transit marker study. Given the significant comorbidity of behavior and emotional axis issues, involvement of behavioral health professionals is essential to the evaluation and management of this condition. Therapy focuses on proactive regular toilet use. Unfortunately, biofeedback therapy, helpful in other disorders of defecation dynamics, has not proven beneficial in children with NFI.

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## Chapter 390

**Cyclic Vomiting Syndrome**

Asim Maqbool, Prasanna K. Kapavarapu,  
and Chris A. Liacouras

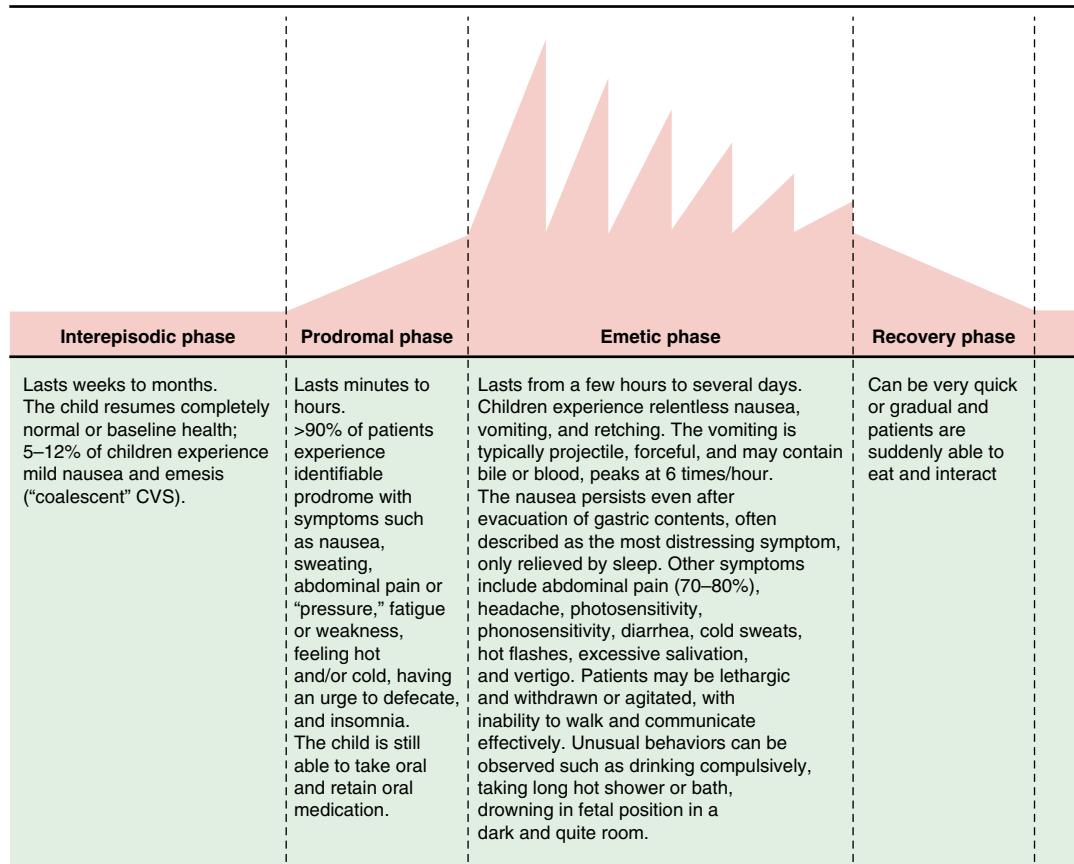
Cyclic vomiting syndrome (CVS) is an idiopathic disorder manifested as episodic vomiting, usually of sudden onset and high intensity/frequency (4/hr:12-15 episodes per day) of vomiting, with eventual resolution and return to a normal baseline between attacks (Fig. 390.1). Typical bouts last for 24-48 hours and usually respond promptly to hydration. To meet the criteria for CVS, identifiable organic disorders are excluded following an appropriate workup (Fig. 390.2). The guidelines for the frequency of episodes to fulfill the CVS criteria differ between societies. The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) consensus statement in 2008 on CVS requires at least five vomiting episodes in any interval period or a minimum of three episodes in a 6-month period, whereas the 2016 Rome IV criteria on childhood functional gastrointestinal (GI) disorders requires at least two or more episodes in a 6-month period (Table 390.1).

The prevalence of CVS in children is estimated at ~2% in predominantly White populations, although it does occur in those of African or Asian descent, and Hispanic ethnicity. There is a slight female predominance. The median age of onset is 5 years, but it can begin in infancy

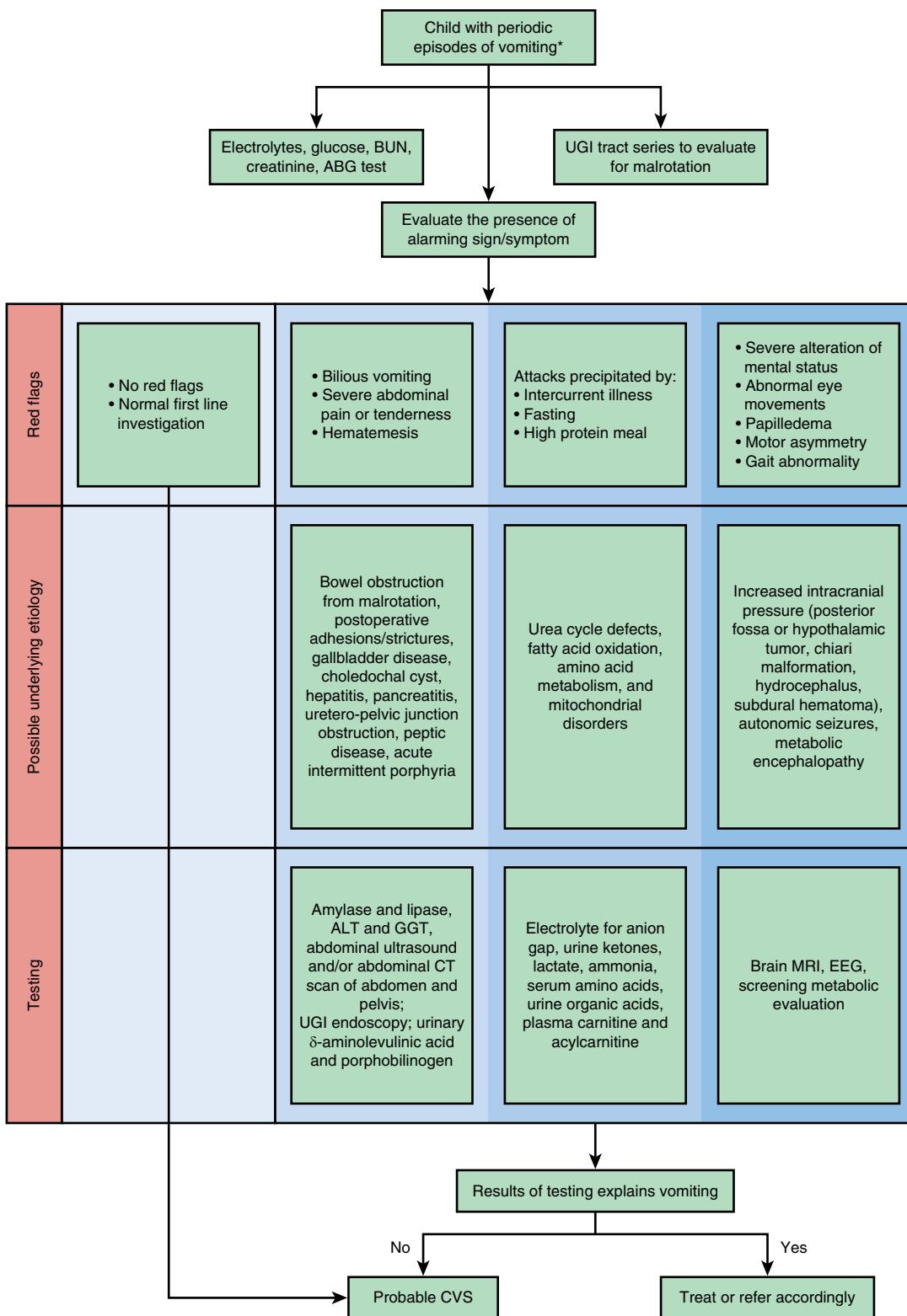
and adolescence. Typically, there is a delay of 2.5 years in making the diagnosis despite multiple episodes and emergency room visits. The natural history of CVS is that most children outgrow it during preadolescence or adolescence, and of those, many will develop migraines. There are also later pediatric-onset (mean age 13 years) and adult-onset (mean age 32 years) subgroups indicating that in a minority it can begin or persist in adulthood.

One key clinical feature of CVS is its consistent and stereotypical pattern of vomiting within individuals. Typically, symptoms start at the same time, often during early morning hours, last the same duration, and demonstrate identical autonomic symptoms of pallor and listlessness, unrelenting nausea, abdominal pain, and in less than half, headaches and photophobia. About half of cases occur on a cycle as often as monthly; some cycle as infrequently as every 3-4 months. Other patients have unpredictable sporadic vomiting that may be associated with a specific trigger. Potential triggers include infectious illnesses, stress and especially excitement (holidays), sleep deprivation (sleepovers), dietary triggers (chocolate, monosodium glutamate), food allergy, onset of menses, and weather changes. Typically, the vomiting is intense, with greater than four bouts of emesis per hour at the peak, and can include gastric contents or frequent dry heaves. Although most attacks last 2 days, an episode can last anywhere from hours and rarely up to 10 days. CVS attacks are debilitating, often necessitating IV rehydration, and resulting in hospitalization. Seasonal variation apparently occurs in approximately a third of patients, with more attacks in winter and fewer during summer.

Subgroups of CVS include *migraine-related*, with either personal history of migraines or family history of migraines; *Sato variant*, driven by hyperresponsive hypothalamic-pituitary-adrenal axis



**Fig. 390.1** Temporal pattern of cyclic vomiting syndrome. Schematic representation of the four phases. (From Raucci U, Borrelli O, Di Nardo G, et al. Cyclic vomiting syndrome in children. *Frontiers Neurol.* 2020;11:Article 583425. Fig. 1.)



**Fig. 390.2** Algorithm for the evaluation of children with cyclic vomiting pattern. \*Fulfilling clinical criteria for CVS (see Table 390.1). ABG, Arterial-blood gas; ALT, alanine aminotransferase; CVS, cyclic vomiting syndrome; GGT,  $\gamma$ -glutamyl-transferase; UGI, upper gastrointestinal. (From Raucci U, Borrelli O, Di Nardo G, et al. Cyclic vomiting syndrome in children. *Frontiers Neurol*. 2020;11:Article 583425. Fig. 2.)

(elevated cortisol levels), hypertension, extreme lethargy, and presenting with more severe and prolonged CVS episodes; *catamenial* CVS, occurring in adolescent girls who are hormonally sensitive and presenting with CVS episodes either within a day, prior or post menstrual period; underlying *mitochondrial dysfunction*, associated

with single nucleotide polymorphisms and evidence of improvement with mitochondrial supplements like coenzyme Q10; and the *coalescent form*, presenting with daily nausea between episodes of emesis (which becomes less frequent). CVS may also be more common in children with autism.

**Table 390.1** North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, International Classification of Headache Disorders 3, and Rome IV Diagnostic Criteria

**NASPGHAN**

- At least five attacks in any interval or a minimum of three attacks during a 6-mo period
- Episodic attacks of intense nausea and vomiting lasting 1 hour to 10 days, occurring at least 1 wk apart
- Stereotypical pattern and symptoms in the individual patient
- Vomiting during attacks at least 4 times per hour for at least 1 hour
- Return to baseline health between episodes
- Not attributed to another disorder

**ICHD-3**

- At least five attacks of intense nausea and vomiting fulfilling criteria B and C
- Stereotypical in the individual patient and recurring with predictable periodicity
- All of the following:
  - Nausea and vomiting occur ≥4 times per hour
  - Attacks last ≥1 hour and up to 10 days
  - Attacks occur ≥1 wk apart
- Complete freedom from symptoms between attacks
- Not attributable to another disorder

Note: History and physical exam do not show sign of gastrointestinal disease

**PEDIATRIC ROME IV**

- Two or more periods of intense unremitting nausea and paroxysmal vomiting, lasting hours to days within a 6-mo period
- Episodes are stereotypical in each patient
- Episodes separated by weeks to months with return to baseline health between episodes
- Symptoms not attributed to another medical condition

**ADULT ROME IV**

Stereotypical episodes of vomiting regarding onset (acute) and duration (<1 wk)

- ≥3 discrete episodes in the prior year and two episodes in past 6 mo, occurring ≥1 wk apart
- Absence of vomiting between episodes, but other milder symptoms can be present between cycles

**Supportive remarks**

- Personal or family history of migraine headaches

Criteria must be fulfilled for the last 6 mo with symptom onset at least 3 mo before diagnosis.

Note: All respective criteria must be met to meet consensus definitions for both NASPGHAN, ICHD-3, and Rome IV.

NASPGHAN, North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; ICHD-3, International Classification of Headache Disorders 3.

From Kovacic K, Li BUK. Cyclic vomiting syndrome: a narrative review and guide to management. *Headache*. 2021;61:231–243. Table 1.

Multiple comorbid disorders can further comprise quality of life between episodes; these include anxiety, constipation-predominant irritable bowel syndrome, chronic fatigue or limited stamina, sleep disorders, postural orthostatic tachycardia syndrome, daily nausea, and complex regional pain syndrome. There is often a positive family history of migraines in children with CVS; attacks of both conditions share many clinical features. Although the pathophysiology is not fully known, there is suggestive evidence that an overresponsive hypothalamic-pituitary-adrenal axis (including corticotropin-releasing factor), autonomic nervous system dysregulation (sympathetic predominance), mitochondrial

**Table 390.2** Diagnostic Tests for Ruling Out Conditions in the Differential Diagnosis with Cyclic Vomiting Syndrome

CONDITION	DIAGNOSTIC TESTING
<b>GASTROINTESTINAL DISORDERS</b>	
Peptic ulcer disease	Upper GI endoscopy
Gastroparesis	Scintigraphic gastric emptying study
Hepatitis	Abdominal ultrasound
Pancreatitis	Abdominal ultrasound
Cholecystitis	Abdominal ultrasound
Biliary tract anomalies	Hepatobiliary scintigraphy, endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography
Malrotation with volvulus, postoperative adhesions/strictures	Upper GI series with small bowel follow-through, abdominal CT scans, upper GI endoscopy
Chronic intestinal pseudoobstruction	Plain abdominal x-ray, upper GI series with small bowel follow-through, antroduodenal manometry
<b>EXTRAINTESTINAL DISORDERS</b>	
<i>Central Nervous System</i>	
Mass	Brain MRI, Brain CT
Hydrocephalus	Brain MRI, Brain CT
Subdural hematoma	Brain CT
Autonomic seizures	EEG
<i>Renal Disorders</i>	
Ureteropelvic junction obstruction	Abdominal ultrasound
Nephrolithiasis	Abdominal ultrasound, abdominal CT
<i>Metabolic Disorders</i>	
	Ammonia, organic acids, lactate, amino gap

From Raucci U, Borrelli O, Di Nardo G, et al. Cyclic vomiting syndrome in children. *Frontiers Neurol*. 2020;11:Article 583425. Table 3.

dysfunction (16519T and 3010A), and nuclear pathogenic variants (RYR2) may play contributory roles.

Patients with chronic vomiting should always be evaluated for potential etiologies other than CVS. The differential diagnosis includes GI anomalies (malrotation, duplication cysts, choledochal cysts, recurrent intussusceptions), CNS disorders (neoplasm, epilepsy, vestibular pathology), nephrolithiasis, cholelithiasis, hydronephrosis, metabolic-endocrine disorders (urea cycle, mitochondrial disorders, fatty acid metabolism, Addison disease, porphyria, hereditary angioedema, familial Mediterranean fever), chronic appendicitis, and inflammatory bowel disease (see Fig. 390.2; Tables 390.2 and 390.3). Laboratory evaluation is based on a careful history and physical examination and may include, if indicated, endoscopy, contrast upper GI radiography, brain MRI, and metabolic studies (lactate, organic acids, ammonia). Bilious emesis usually suggests a small bowel obstruction and is considered a red flag; however, children with CVS may have bile-stained emesis. A tender abdomen is also unusual for CVS and warrants further workup. Acute and chronic appendicitis can mimic CVS. Prior

<b>Table 390.3</b>	Relevant Causes of Vomiting in Metabolic Disorders
<b>ASSOCIATED OR NOT WITH ENCEPHALOPATHY</b>	
Organic acidurias	
Urea cycle disorders	
Fatty acid oxidation disorders	
MCT1 defect	
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)	
Glutaric aciduria type I	
<b>ASSOCIATED WITH ACIDOSIS/KETOACIDOSIS</b>	
Organic acidurias	
Mitochondrial diseases	
<b>ASSOCIATED WITH KETOSIS ONLY</b>	
Ketosis defects	
<b>ASSOCIATED WITH SEVERE ABDOMINAL PAIN</b>	
Porphyrias (acute intermittent porphyria, coproporphyria)	
<b>ASSOCIATED WITH HEPATOPATHY</b>	
Organic acidurias	
Urea cycle disorders	
Galactosemia	
Hereditary fructose intolerance	
Tyrosinemia type I	
Fatty acid oxidation disorders	

From Raucci U, Borrelli O, Di Nardo G, et al. Cyclic vomiting syndrome in children. *Frontiers Neurol.* 2020;11:Article 583425, Table 5.

abdominal surgery may increase risk for adhesion-related partial bowel obstructions.

Non-GI causes of frequent vomiting include renal, metabolic, endocrine, and neurologic disorders. Renal abnormalities to consider include acute or chronic ureteropelvic junction (UPJ) obstruction presenting with hydronephrosis (Dietl's crisis) and nephrolithiasis. The clinician must also consider metabolic disorders, especially in the infant or toddler less than 2 years of age. Fasting or high-protein meals that provoke emesis raise a red flag for metabolic disorders, such as disorders of fatty acid oxidation, organic acidemias, or partial ornithine transcarbamylase deficiency. Acute intermittent porphyria can present in the adolescent triggered by alcohol or medications. Endocrine disorders, including diabetic ketoacidosis, Addison disease, and pheochromocytoma, can mimic CVS episodes. Although an atypical presentation, CNS tumors can have episodic vomiting and papilledema; altered mental status and focal neurologic findings are red flags requiring neuroimaging. Pregnancy can present with CVS-like symptoms.

The management of acute CVS episodes includes early and aggressive hydration (especially with dextrose in normal saline), which may shorten episodes in addition to correcting fluid losses. Reducing extraneous sensory stimulation, similar to the management approach for migraines, may also be beneficial (Table 390.4). Regardless of intervention, episodes will eventually spontaneously resolve with return to a normal baseline. Triptans can be used as an *abortive medication* in patients with the *migraine-related* subgroup of CVS, a family history of migraines, at the onset of symptoms. Ondansetron may reduce nausea and emesis. Sedation may reduce severity or stop a CVS episode; drugs include antihistamines such as diphenhydramine and promethazine. Lorazepam or rectal diazepam can also be used. These measures are empiric; a lack of evidence base limits our understanding of efficacy. For rare but severe refractory cases, general anesthetics have been used. A dramatic change in presentation of attacks suggests a red flag such as acute hydronephrosis or small bowel obstruction from volvulus.

<b>Table 390.4</b>	Abortive and Rescue Pharmacotherapy
<b>ANTI-MIGRAINE</b>	Sumatriptan 20 mg intranasal at episode onset and may repeat once vs 25 mg PO once vs 3-6 mg SC once SE: Chest and neck burning, coronary vasospasm, headache Alternatives: Rizatriptan, zolmitriptan, frovatriptan ( <i>longer half-life</i> )
<b>ANTIEMETIC</b>	Ondansetron 0.2-0.3 mg/kg per dose ( $\leq$ 12 mg) q4-6h IV/PO/rectal/ topical SE: Headache, drowsiness, dry mouth Alternatives: Granisetron Aprepitant 3-day regimen: Weight <15 kg: 80 mg at start of episode on day 1, followed by 40 mg on days 2 and 3 Weight 15-20 kg: 80 mg on days 1, 2, and 3 Weight >20 kg: 125 mg on day 1 and 80 mg on days 2 and 3 Fosaprepitant 3-4 mg/kg (max. 150 mg) IV day one (aprepitant days 2-3)
<b>SEDATIVE</b>	Lorazepam 0.05-0.1 mg/kg per dose q6h IV/PO: useful adjunct to ondansetron SE: Sedation, respiratory depression Chlorpromazine 0.5-1 mg/kg per dose q6h IV/PO SE: Drowsiness, hypotension, seizures, dystonic reaction Diphenhydramine 1.25 mg/kg per dose q6h IV/PO: useful adjunct to chlorpromazine SE: Hypotension, sedation, dizziness
<b>ANALGESIC</b>	Ketorolac 0.5-1 mg/kg per dose q6h IV/PO SE: Gastrointestinal bleeding, dyspepsia

IV, Intravenous; PO, orally; SC, subcutaneously; SE, side effects.  
Modified from Kovacic K, Li BUK. Cyclic vomiting syndrome: a narrative review and guide to management. *Headache*. 2021;61:231-243. Table 3.

*Prophylactic* management begins with lifestyle measures (maintenance fluid intake, adequate calories, sleep hygiene, and exercise), including avoidance of known triggering foods (allergens, chocolate, aged cheese, monosodium glutamate; Table 390.5). Recommendations for prophylactic regimens include cyproheptadine in patients <5 years of age and amitriptyline in patients  $\geq$ 5 years; propranolol serves as a secondary agent in both age-groups. When standard care fails, the addition of anticonvulsants such as topiramate has been implemented. For those with *catamenial* CVS, low-dose estrogen oral contraceptives or medroxyprogesterone acetate may prevent episodes. For those with *Sato variant*, CVS treatment with angiotensin-converting enzyme (ACE)-inhibitors or  $\beta$  blockers for acute hypertension may be helpful. Supplements such as coenzyme Q10, L-carnitine, and riboflavin have been reported to be useful adjuncts for those with underlying mitochondrial dysfunction. Treatment of *comorbid disorders*, especially anxiety (cognitive behavioral therapy, antianxiety agents) and postural orthostatic tachycardia syndrome (fluids, salt, fludrocortisone), may be needed for effective management of CVS. Newer drugs that are being explored in the management of CVS include mirtazapine and aprepitant. Mirtazapine is an antidepressant medication and is a potent antagonist of 5HT<sub>2</sub> and 5HT<sub>3</sub> receptors, with anti-migraine properties. It is of potential benefit in *migraine-related* CVS, starting at 7.5 mg at bed time, with a maximum dose of 15 mg; common side effects include drowsiness and increased appetite. Aprepitant is a neurokinin-1 receptor (NK<sub>1</sub>R) antagonist used in postoperative and chemotherapy-related nausea and vomiting. In CVS, aprepitant is used for both prophylaxis and abortive purposes. In children, aprepitant has been shown to decrease the number of vomiting episodes per hour/frequency of episodes per year/number of hospitalizations per year and increase the interval period in between the episodes. Common reported side effects of aprepitant include headache, hiccups, neutropenia, and fatigue.

**Table 390.5** Prophylactic Lifestyle Changes and Pharmacologic Options for Cyclic Vomiting Syndrome

LIFESTYLE MEASURES		
Reassurance and anticipatory guidance	<ul style="list-style-type: none"> <li>Episodes are not intentional</li> <li>The natural history of CVS is that it will resolve with time</li> </ul>	
Avoidance of triggers	<ul style="list-style-type: none"> <li>Identify dietary triggers ("vomit diary") and avoid precipitating factors</li> <li>Triggering foods may include chocolate, cheese, monosodium glutamate</li> <li>Fasting a common trigger</li> <li>Excitement a potential trigger</li> <li>Excessive activity/exhaustion</li> <li>Avoid sleep deprivation and practice good sleep hygiene</li> </ul>	
Managing triggers	<ul style="list-style-type: none"> <li>Provide supplemental energy as carbohydrates for fasting-induced episodes</li> <li>Provision of snacks between meals, before sleep, and before exertion</li> </ul>	
Migraine headache-type lifestyle interventions	<ul style="list-style-type: none"> <li>Aerobic exercise and avoidance of overexertion</li> <li>Regular mealtime schedule—avoid skipping meals</li> <li>Avoid/moderate caffeine intake</li> </ul>	
PROPHYLACTIC PHARMACOLOGIC APPROACHES		
	<b>AGE &lt;5 YR</b>	<b>AGE ≥5 YR</b>
	<p>Antihistamines:</p> <ul style="list-style-type: none"> <li>Cyproheptadine           <ul style="list-style-type: none"> <li>0.25-0.5 mg/kg/day in two daily divided doses or as a single dose qhs</li> <li>Side effects of increased appetite, weight gain, and sedation</li> </ul> </li> <li>Pizotifen</li> <li>β blockers: (second choice)</li> <li>Propranolol           <ul style="list-style-type: none"> <li>0.25-1 mg/kg/day, most often 10 mg 2-3×/day.</li> <li>Side effects include lethargy and reduced exercise tolerance</li> <li>Contraindicated in asthma, diabetes, heart disease, depression</li> <li>Taper over 1-2 wk to discontinue</li> </ul> </li> </ul>	<p>Tricyclic antidepressants:</p> <ul style="list-style-type: none"> <li>Amitriptyline           <ul style="list-style-type: none"> <li>Begin at 0.25-0.5 mg/kg qhs and increase weekly by 5-10 mg until achieve 1-1.5 mg/kg</li> <li>Monitor ECG for prolonged QTc interval at baseline before initiation and 10 days after peak dose achieved</li> <li>Side effects: constipation, sedation, arrhythmias, behavioral changes</li> </ul> </li> </ul> <p>Alternatives: nortriptyline</p> <p>β blockers: (second choice):</p> <ul style="list-style-type: none"> <li>Propranolol</li> </ul> <p>Other agents:</p> <p>Anticonvulsants:</p> <ul style="list-style-type: none"> <li>Phenobarbital 2 mg/kg qhs</li> <li>Side effects: sedation, cognitive impairment</li> </ul> <p>Alternatives:</p> <ul style="list-style-type: none"> <li>Topiramate, valproic acid, gabapentin, levetiracetam</li> </ul>
DIETARY SUPPLEMENTS	<ul style="list-style-type: none"> <li>L-Carnitine 50-100 mg/kg/day divided 2-3×/day, maximum dose of 2 g 2×/day</li> <li>Coenzyme Q10 10 mg/kg/day divided 2-3×/day, maximum dose 100 mg 3×/day</li> </ul>	

Medications listed in table are for off-label use.

CVS, Cyclic vomiting syndrome; qhs, every night at bedtime.

Modified from Li BU, Lefevre F, Chelimsky GG, et al. North American Society for Pediatric Gastroenterology, Hepatology and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome. *J Pediatr Gastroenterol Nutr.* 2008;47(3):379-393.

*Cannabinoid hyperemesis syndrome* (CHS) involves the endocannabinoid system (ECS), which plays a major role in nausea and vomiting. Cannabinoid receptors (CBRs) consist of cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CB2R); the current hypothesis is that CBR agonists inhibit vomiting and CB1R antagonists initiate or potentiate vomiting. The current theory is that with chronic cannabis use, there is a paradoxical effect with downregulation of CB1R, which in turn potentiates vomiting in CHS. *CHS shares many features with*

CVS, including patterns of onset, frequency, and duration. CHS, however, differs from CVS in that it is associated with prolonged cannabis use (>2 years), and relief of episodes occurs following sustained cessation (>6 months) of cannabis use. Another common feature across CHS is the observed association with pathologic bathing behavior, specifically, prolonged hot showers (see Chapter 157.3).

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## Chapter 391

# Acute Appendicitis

José H. Salazar and John J. Aiken

Acute appendicitis remains the most common acute surgical condition in children and a major cause of childhood morbidity and healthcare costs, mostly associated with complicated/perforated appendicitis (PA). The peak incidence of acute appendicitis occurs in children in the second decade, and approximately 100,000 children are treated in children's hospitals for appendicitis each year. The broad spectrum of clinical presentation in acute appendicitis has been associated with significant practice variation in evaluation, diagnostic measures, and treatment of abdominal pain and suspected appendicitis. The traditional strategy of the liberal use of computed tomography (CT) to avoid misdiagnosis and early surgery to avoid progression to perforation has lacked validation in large reviews and resulted in high negative appendectomy rates and excessive radiation exposure. Perforation rates have remained ~40% and negative appendectomy rates as high as 10% in the past 2 decades. In current practice, most centers have adopted clinical practice guidelines (CPGs) combining history, physical examination findings, laboratory data, and appendicitis risk scoring systems to standardize care, improve diagnostic accuracy and outcomes, and direct cost-conscious resource use. Appendiceal ultrasound has emerged as a highly sensitive and specific imaging modality for diagnosis and led to a significant decrease in the use of CT and radiation exposure in the initial evaluation of children presenting with abdominal pain and possible suspected appendicitis. Although prompt appendectomy remains the standard treatment in acute appendicitis, advances in imaging techniques, improved antibiotic regimens, increased use of percutaneous drainage procedures by interventional radiologists, and emerging data on high success rates with initial antibiotic treatment alone have led to an increase in the initial nonoperative management of both simple and complicated (abscess, phlegmon) appendicitis. Laparoscopic appendectomy (LA, a minimally invasive technique) has emerged as the preferred surgical approach for both simple and PA, with an open surgical approach reserved as an alternative for selected cases or when attempted LA is technically difficult and/or deemed unsafe.

## EPIDEMIOLOGY

The incidence of acute appendicitis increases with age, from a rate of 1-2 per 10,000 children from birth to 4 years of age, to a rate of 19-28 per 10,000 children younger than age 14 years annually. Children have a lifetime risk of 7-9%, and appendicitis is diagnosed in 1-8% of children presenting to the emergency department (ED) for evaluation of abdominal pain. Appendicitis is most common in older children, with peak incidence between the ages of 10 and 18 years; it is rare in children younger than 5 years of age (<5% of cases) and extremely rare (<1% of cases) in children younger than 3 years of age.

Infants with appendicitis are often misdiagnosed with sepsis, and because of the diagnostic delay, they present in advanced stages of the disease. Most infant cases are primary, but some may be associated with Hirschsprung disease, cystic fibrosis, inguinal hernia, prematurity, meconium plug syndrome, or complex multiorgan syndromes.

Mortality is low (<0.01%), but morbidity remains high, mostly in association with PA. Up to 40% of children have PA at presentation, and perforation rates approach 90% in young children (<3 years). Children with simple (nonperforated) appendicitis typically recover easily, with a low complication rate and rapid return to premorbid state and full activities. In contrast, PA is associated with substantial postoperative morbidity, including readmission rates estimated at 12.8%, postoperative intraabdominal abscess rates ~20%, surgical site infection (SSI) rate ~20%, prolonged length of stay (LOS), need for prolonged antibiotic exposure, increased postoperative use of CT, and significant delay in return to wellness and normal activities.

## PATHOPHYSIOLOGY

The clinical entity of acute appendiceal inflammation followed by perforation, abscess formation, and peritonitis is most likely a disease of multiple etiologies, the final common pathway of which involves invasion of the appendiceal wall by bacteria. Genetic, environmental, and infectious etiologies (bacterial, viral, fungal, and parasitic) have all been implicated in acute appendicitis. One pathway to acute appendicitis begins with luminal obstruction; inspissated fecal material, lymphoid hyperplasia, ingested foreign body, parasites, and tumors have been described. Obstruction of the appendiceal lumen initiates a progressive cascade involving increasing intraluminal pressure, lymphatic and venous congestion and edema, impaired arterial perfusion, ischemia of the appendiceal wall, bacterial proliferation and invasion of the wall, and necrosis. This sequence correlates with the clinical disease progression from simple appendicitis to gangrenous appendicitis and, thereafter, appendiceal perforation.

Because the appendix has the highest concentration of gut-associated lymphoid tissue (GALT) in the intestine, some have hypothesized that the appendix may have an immune function similar to that of the thymus or bursa of Fabricius. Submucosal lymphoid follicles, which can obstruct the appendiceal lumen, are few at birth but multiply steadily during childhood, reaching a peak in number during the teen years, when acute appendicitis is most common.

Enteric infection likely plays a role in many cases of acute appendicitis in association with mucosal ulceration and invasion of the appendiceal wall by bacteria. Bacteria such as *Yersinia*, *Salmonella*, and *Shigella* spp. and viruses such as infectious mononucleosis, mumps, coxsackievirus B, and adenovirus are implicated. In addition, case reports demonstrate the occurrence of appendicitis from ingested foreign bodies, in association with carcinoid tumors of the appendix, *Ascaris* infestation, and rarely, after blunt abdominal trauma. Children with cystic fibrosis have an increased incidence of appendicitis; the cause is believed to be the abnormal thickened mucus. Appendicitis in neonates is rare and warrants diagnostic evaluation for cystic fibrosis and Hirschsprung disease.

Appendectomy decreases the risk of ulcerative colitis and increases the risk of recurrent *Clostridium difficile*-associated colitis. Appendicoliths and appendicitis are more common in developed countries with refined, low-fiber diets than in developing countries with a high-fiber diet; no causal relationship has been established between lack of dietary fiber and appendicitis. A family history is associated with a nearly threefold increased appendicitis risk, and genetic factors may account for 30% of appendicitis risk.

## Clinical Features

Appendicitis in children has an immensely broad spectrum of clinical presentation; <50% of cases have the classic presentation. The signs and symptoms in acute appendicitis can vary depending on the timing of presentation, patient age, the abdominal/pelvic location of the appendix, and most importantly, individual variability in the evolution of the disease process. Children early in the disease process can appear well and demonstrate mild symptoms, minimal findings on physical examination, and normal laboratory studies, whereas those with perforation and advanced peritonitis can demonstrate severe illness with bowel obstruction, renal failure, and septic shock. Most patients with appendicitis demonstrate an insidious onset of illness characterized by generalized nonspecific malaise or anorexia in the first 12 hours, and a steady, escalating progression in severity of signs and symptoms over 2-3 days with increasing abdominal pain, vomiting, fever, and tachycardia; perforation is common beyond 48 hours of illness. Thus the opportunity for diagnosis before perforation in acute appendicitis in children is most often brief (48-72 hours), and a high percentage of patients are perforated at presentation.

Abdominal pain is consistently the primary symptom in acute appendicitis; beginning shortly (hours) after the onset of illness. There are no somatic pain fibers within the appendix; therefore early appendiceal inflammation results in pain that is vague, poorly localized, unrelated to activity or position, often colicky, and perumbilical in location as a result of visceral inflammation from a distended appendix. Progression

of the inflammatory process in the next 24 hours leads to involvement of the adjacent parietal peritoneal surfaces, resulting in somatic pain localized to the right lower quadrant (RLQ)—*thus the classic description of periumbilical mid-abdominal pain migrating to the RLQ. The position of the appendix is a critical factor affecting interpretation of presenting signs and symptoms and accurate diagnosis.* When the appendix is in a retrocecal or pelvic position, a slower progression of illness is typical and clinical presentation is likely to be delayed. Localized pain in the RLQ leads to spasm in the overlying abdominal wall muscles, and now the pain is predictably exacerbated by movement. The child often describes marked discomfort with the bumpy car ride to the hospital, moves cautiously, and has difficulty getting onto the examining room stretcher. Nausea and vomiting occur in more than half of the patients and typically follow the onset of abdominal pain by several hours. Anorexia is a classic and consistent finding in acute appendicitis, but occasionally affected patients are hungry. Diarrhea and urinary symptoms are also common, particularly in cases of PA when there is likely inflammation near the rectum and possible abscess in the pelvis. Painful voiding may not be from dysuria, but pressure transmitted to an inflamed peritoneum. As it progresses, appendicitis is often associated with adynamic ileus, leading to the complaint of constipation and possible misdiagnosis.

Because enteric infections can cause appendicitis, diarrhea may be a manifestation and gastroenteritis may be the assumed diagnosis. In contrast to gastroenteritis, the abdominal pain in early appendicitis is *constant* (not cramping or relieved by defecation), the emesis may become bile stained and persistent, and the clinical course worsens steadily rather than demonstrating a waxing and waning pattern often seen in viral gastroenteritis. Fever is common in appendicitis and typically low-grade unless perforation has occurred. Most patients demonstrate at least mild tachycardia, likely secondary to pain and dehydration. The temporal progression of symptoms from vague, mild pain, malaise, and anorexia to severe localized pain, fever, and vomiting typically occurs rapidly (24–48 hours) in the majority of cases. If the diagnosis is delayed beyond 48 hours, perforation is likely (>65%). When several days have elapsed in the progression of appendicitis, patients typically develop signs and symptoms evidencing advanced disease, including worsening and diffuse pain, abdominal distention, and bilious emesis suggestive of developing small bowel obstruction. The retrocecal appendix can demonstrate symptoms suggestive of septic arthritis of the hip or a psoas muscle abscess.

A primary focus in the management of appendicitis is the avoidance of sepsis and the infectious complications leading to increased morbidity, mostly seen with PA.

Bacteria can be cultured from the serosal surface of the appendix before microscopic or gross perforation and bacterial invasion of the mesenteric veins (pylephlebitis) can result (rarely) in thrombosis and possible liver abscess or portal hypertension. A period after perforation of lessened abdominal pain and acute symptoms has been described, presumably with the elimination of pressure within the appendix. If, after perforation, the omentum or adjacent intestine is able to wall off the fecal contamination, the evolution of illness is less predictable and delay in presentation is likely. If perforation leads to diffuse peritonitis, the child generally has escalating diffuse abdominal pain and rapid development of toxicity evidenced by dehydration and signs of sepsis, including hypotension, oliguria, acidosis, and high-grade fever. Young children have a poorly developed omentum and are often unable to control the spread of infection. Perforation and abscess formation with appendicitis can lead to intestinal fistula formation, scrotal cellulitis and abscess through a patent processus vaginalis (indirect inguinal hernia), or small bowel obstruction. The most likely diagnosis in children who present with signs and symptoms of mechanical small bowel obstruction who have not had prior abdominal surgery is complicated appendicitis.

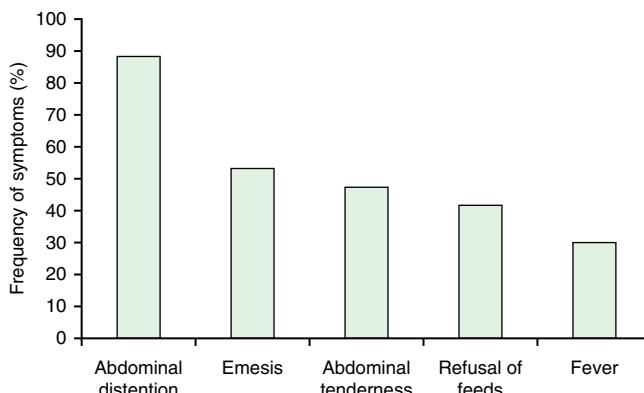
### Physical Examination

Although the hallmark of diagnosing acute appendicitis remains a careful and thorough history and physical examination, all clinicians know the arcane nature of acute appendicitis, the consistent or

typical clinical features are not present in all patients, and the diagnosis can be a humbling experience even for the most experienced clinicians. A primary focus of the initial assessment is attention to the *temporal evolution* of the illness in relation to specific presenting signs and symptoms. In some patients, the diagnosis can be made on history and physical examination alone; in current practice the selective use of advanced imaging has improved diagnostic accuracy and resulted in significant progress in the lowering of negative appendectomy rates.

Physical examination begins with inspection of the child's demeanor and the appearance of the abdomen. Because appendicitis most often has an insidious onset, children rarely present <12 hours from the onset of illness. Children with early appendicitis (18–36 hours) typically appear mildly ill and move tentatively, hunched forward, and often with a slight limp favoring the right side. Supine, they often lie quietly on their right side with their knees pulled up to relax the abdominal muscles, and when asked to lie flat or sit up, they move cautiously and might use a hand to protect the RLQ. Early in appendicitis, the abdomen is typically flat; abdominal distention suggests more advanced disease characteristic of perforation or developing small bowel obstruction. Auscultation can reveal normal or hyperactive bowel sounds in early appendicitis, which are replaced by hypoactive bowel sounds as the disease progresses to perforation. *The judicious use of morphine analgesia to relieve abdominal pain does not change diagnostic accuracy or interfere with surgical decision-making, and patients should receive adequate pain control.* Localized abdominal tenderness is the single most reliable finding in the diagnosis of acute appendicitis. McBurney described the classic point of localized tenderness in acute appendicitis, which is the junction of the lateral and middle thirds of the line joining the right anterior-superior iliac spine and the umbilicus, but the tenderness can also localize to any of the aberrant locations of the appendix. Localized tenderness is a later and less consistent finding when the appendix is retrocecal in position (>50% of cases). In cases of an appendix localized entirely in the pelvis, tenderness on abdominal examination may be minimal. A gentle touch on the child's arm at the beginning of the examination with the reassurance that the abdominal examination will be similarly gentle can help to establish trust and increase the chance for a reliable and reproducible examination. The examination is best initiated in the left lower abdomen, so that the immediate part of the exam is not uncomfortable, and conducted in a counterclockwise direction, moving gently to the left upper abdomen, right upper abdomen, and, lastly, the right lower abdomen. This should alleviate anxiety, allow relaxation of the abdominal musculature, and enhance trust. The examiner makes several circles of the abdomen with sequentially more pressure. A soft, compressible, non-tender abdominal wall is reassuring. In appendicitis, any abdominal wall movement, including coughing (Dunphy sign), may elicit pain. A consistent finding in acute appendicitis is guarding—rigidity of the overlying abdominal wall muscles in the RLQ. This rigidity may be voluntary, to protect the area of tenderness from the examiner's hand, or involuntary, if the inflammation has progressed to peritonitis causing spasm of the overlying muscle.

Abdominal tenderness may be vague or even absent early in the course of appendicitis and is often diffuse after rupture. Rebound tenderness and referred tenderness (Rovsing sign) are also consistent findings in acute appendicitis but are not always present. Rebound tenderness is elicited by deep palpation of the abdomen followed by the sudden release of the examining hand. This is often very painful to the child and has demonstrated poor correlation with peritonitis, so it should be avoided. Gentle finger percussion is a better test for peritoneal irritation. Similarly, digital rectal examination is uncomfortable and unlikely to contribute to the evaluation of appendicitis in most cases in children. Psoas and obturator internus signs are pain with passive stretch of these muscles. The psoas sign is elicited with active right thigh flexion or passive extension of the hip and is typically positive in cases of a retrocecal appendix. The obturator sign is demonstrated by adductor pain after internal rotation of the flexed thigh and typically positive in cases of a pelvic appendix. Physical examination may demonstrate a mass in the RLQ representing an inflammatory



**Fig. 391.1** Frequency of presenting symptoms in neonatal appendicitis. (Data from Raveenthiran V. Neonatal appendicitis (Part 1): a review of 52 cases with abdominal manifestation. *J Neonatal Surg.* 2015;4:4.)

**Table 391.1** Pediatric Appendicitis Scores

FEATURE	SCORE
Fever >38°C (100.4°F)	1
Anorexia	1
Nausea/vomiting	1
Cough/percussion/hopping tenderness	2
Right lower quadrant tenderness	2
Migration of pain	1
Leukocytosis >10,000 ( $10^9/L$ )	1
Polymorphonuclear neutrophilia >7,500 ( $10^9/L$ )	1
Total	10

From Acheson J, Banerjee J. Management of suspected appendicitis in children. *Arch Dis Child Educ Pract Ed.* 2010;95:9–13.

mass (phlegmon) around the appendix or a localized intraabdominal abscess (fluid collection).

Appendicitis in infants and toddlers does not follow the characteristic features observed in older children. Perforation is observed in most infants at presentation. The diagnosis is often delayed, and the initial impression is often sepsis (Fig. 391.1)

### APPENDICITIS RISK SCORING SYSTEMS

Several risk scoring systems have become commonly used tools to promote standardization of the approach to the child with abdominal pain and suspected appendicitis. The clear aim is to maximize diagnostic accuracy in acute appendicitis and guide imaging evaluation and resource use. They all combine the predictive value of consistent symptoms, physical examination findings, and laboratory data yielding a numerical score. The systems most widely used are the Alvarado score and the Pediatric Appendicitis Score (PAS). The PAS combines elements of history (migration of pain, anorexia, nausea, vomiting) with physical examination findings (RLQ tenderness, rebound tenderness, fever) and laboratory data (white blood cell [WBC] >10,000, polymorphonuclear neutrophils >75%) to assign a risk score in the low, intermediate, or high-risk range for acute appendicitis (Table 391.1). Scores of ≤4 suggest a very low likelihood of appendicitis, whereas scores ≥8 are highly sensitive and specific for appendicitis. Intermediate scores, between 4 and 7 on the PAS, are considered inconclusive and typically trigger advanced imaging studies. Targeted (appendiceal) ultrasound has demonstrated high sensitivity and specificity (~90%) in the diagnosis of acute appendicitis in centers experienced with the technique and has become the initial imaging study of choice for

suspected appendicitis. The notable benefits of ultrasound compared to CT scan include that it is well-tolerated, is noninvasive, and lacks ionizing radiation exposure. CT is reserved for cases of nonvisualization of the appendix on ultrasound or when the ultrasound findings are inconclusive.

The use of appendicitis risk scoring systems in conjunction with clinical judgment has demonstrated high sensitivity and specificity for acute appendicitis (80–90%), and their application has reduced practice variability, improved diagnostic accuracy, decreased preoperative radiation exposure, and enabled efficient resource use—all important elements of current quality improvement and safety initiatives. Their greatest value to date appears to be in predicting patients who have a low likelihood of the diagnosis of appendicitis (negative predictive value) and can avoid imaging studies, and particularly ionizing radiation exposure.

### LABORATORY FINDINGS

A variety of laboratory tests have been used in the evaluation of children with suspected appendicitis. Individually, none are very sensitive or specific for appendicitis, but collectively they can affect the clinician's level of suspicion and decision-making to proceed with pediatric surgery consultation, discharge, or imaging studies.

A complete blood count with differential and urinalysis are obtained. The leukocyte count in early appendicitis may be normal and typically is only mildly elevated (11,000–16,000/mm<sup>3</sup>) with a left shift as the illness progresses in the initial 24–48 hours. Whereas a normal WBC count never completely eliminates appendicitis, a count <8,000/mm<sup>3</sup> in a patient with a history of illness longer than 48 hours should be viewed as highly suspicious for an alternative diagnosis. The leukocyte count may be markedly elevated (>20,000/mm<sup>3</sup>) in PA and rarely in nonperforated cases; a markedly elevated WBC count, other than in cases of advanced PA, should raise suspicion of an alternative diagnosis. Urinalysis often demonstrates a few white or red blood cells as a result of the proximity of the inflamed appendix to the ureter or bladder, but it should be free of bacteria. The urine is often concentrated and contains ketones from diminished oral intake and vomiting. Gross hematuria is uncommon, and in association with purpuric skin lesions and arthritis may indicate IgA vasculitis (Henoch-Schönlein purpura).

Electrolytes and liver chemistries are generally normal unless there has been a delay in diagnosis, leading to severe dehydration and/or sepsis. Amylase and liver enzymes are only helpful to exclude alternative diagnoses such as pancreatitis and cholecystitis and are not commonly obtained if appendicitis is the strongly suspected diagnosis. C-reactive protein (CRP) increases in proportion to the degree of appendiceal inflammation. It has not demonstrated high sensitivity or specificity in the diagnosis of appendicitis; some studies have demonstrated an association between disease severity (PA and abscess formation) and elevated CRP levels. In this context, CRP may have a role in identifying patients with complicated appendicitis, which may be managed initially nonoperatively with antibiotics and drainage of fluid collections.

### IMAGING STUDIES

After a thorough initial evaluation, including history, physical examination, review of vital signs, and laboratory studies, if the diagnosis is uncertain, radiographic studies can substantially improve diagnostic accuracy.

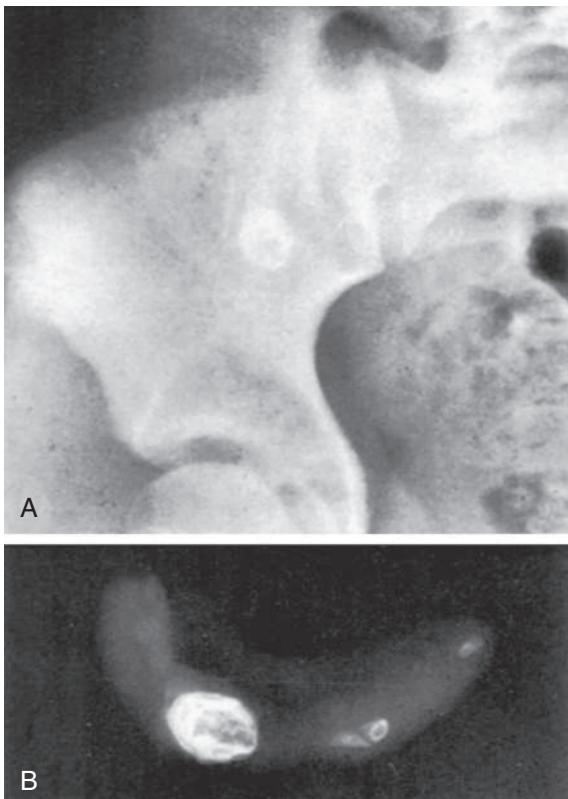
#### Plain Radiographs

In the majority of cases, appendiceal ultrasound and CT scan have become the predominant studies in inconclusive cases of acute appendicitis. Plain abdominal radiographs may be helpful in rare select cases of abdominal pain/suspected appendicitis. Plain abdominal x-rays may demonstrate several findings suggestive of acute appendicitis, including sentinel loops of bowel and localized ileus, scoliosis from psoas muscle spasm, a colonic air-fluid level above the right iliac fossa (colon cutoff sign), a RLQ soft tissue mass, or a calcified appendicolith (5–10% of cases); they are normal in 50% of patients, have a low sensitivity, and are not generally recommended (Fig. 391.2). Plain films are most

helpful in evaluating complicated cases in which small bowel obstruction or free air is suspected.

### Ultrasound

Ultrasound has emerged as the first-choice tool for children requiring an imaging study in the evaluation of suspected acute appendicitis. Ultrasound has demonstrated sensitivity and specificity approaching 90% in pediatric centers experienced with the technique and has

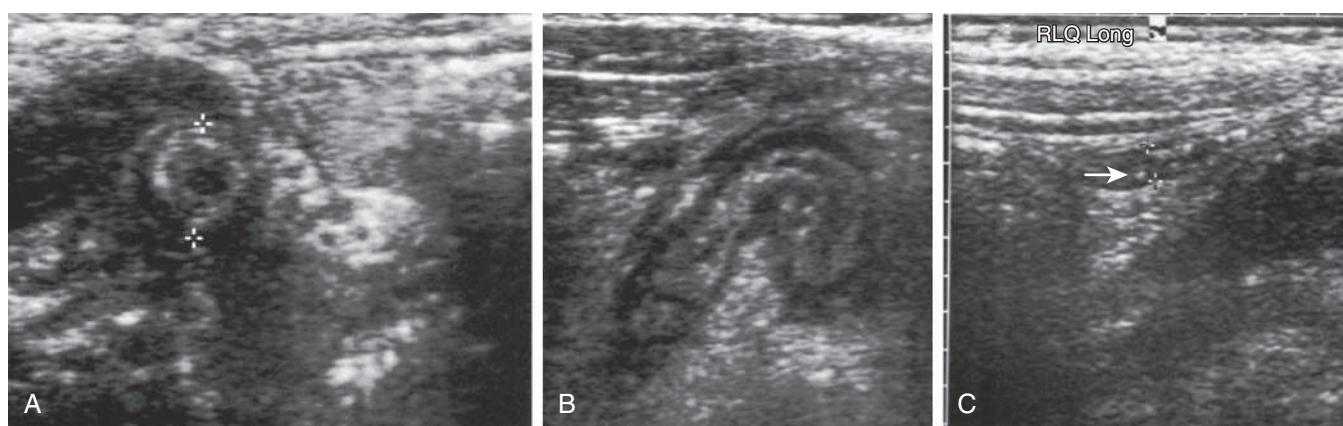


**Fig. 391.2** Calcified appendicoliths are seen in a coned-down anteroposterior view of the right lower quadrant (A) and in the resected appendix of a 10-yr-old female with acute appendicitis (B). (From Kuhn JP, Slovis TL, Haller JO. Caffrey's Pediatric Diagnostic Imaging, 10th ed. Philadelphia: Mosby; 2004:1682.)

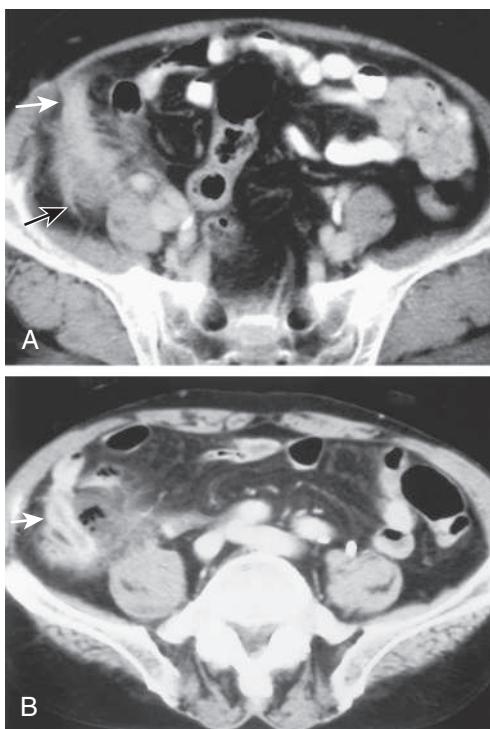
substantial advantages, including low cost, ready availability, rapidity, and avoidance of sedation, contrast agents, and radiation exposure. Ultrasound can be particularly helpful in adolescent females, a group with a high negative appendectomy rate (normal appendix found at surgery), because of its ability to evaluate for ovarian pathology without ionizing radiation. Graded abdominal compression is used to displace the cecum and ascending colon and identify the appendix, which has a typical target appearance (Fig. 391.3). The ultrasound criteria for appendicitis include wall thickness >6 mm, luminal distention, lack of compressibility, a complex mass in the RLQ, or an appendicolith. The visualized appendix usually coincides with the site of localized pain and tenderness. In addition, ultrasound may identify PA on *initial evaluation*; initial management of PA has increasingly moved toward percutaneous drainage procedures, broad-spectrum antibiotics, and nonoperative treatment. An enlarged appendix (>6 mm), hyperemia, noncompressibility of the appendiceal wall, localized tenderness, and associated mesenteric fat stranding or fluid are all consistent with acute appendicitis. Findings that suggest advanced appendicitis on ultrasound include asymmetric wall thickening, abscess formation, associated free intraabdominal/pelvic fluid, surrounding tissue edema, and decreased local tenderness to compression. *The main limitation of ultrasound is an inability to visualize the appendix, which is reported in 25–60% of cases.* It has been postulated that a normal appendix must be visualized to exclude the diagnosis of appendicitis by ultrasound; however, one report concluded that in patients with a nonvisualized appendix on ultrasound imaging, no evidence of secondary inflammatory changes, and an absolute neutrophil count <8,000/mm<sup>3</sup>, the likelihood of appendicitis was <3%. Certain conditions predictably decrease the sensitivity and reliability of ultrasound for appendicitis, including obesity, bowel distention, and uncontrolled pain.

### Computed Tomography

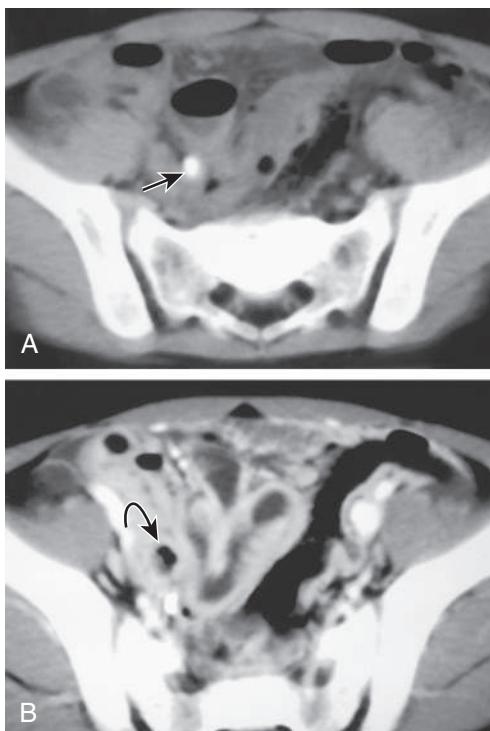
CT scan has been the gold-standard imaging study for evaluating children with suspected appendicitis and has a sensitivity of 97%, specificity 99%, positive predictive value 98%, and negative predictive value 98% (Figs. 391.4 and 391.5). The advantages of CT imaging include ready availability, rapid acquisition time, and lack of operator dependency. CT carries the significant negative effects of exposure of children to ionizing radiation and increased costs. The exam can be performed using intravenous and enteral (oral or rectal) contrast; however, the administration of enteral contrast has several drawbacks, including delay in diagnostic evaluation, increasing abdominal distension, risk of emesis and aspiration, and increasing radiation exposure without demonstrable improvement in accuracy of diagnosis. The use of oral contrast should be reserved for patients in whom alternative



**Fig. 391.3** Ultrasound examination of patients with appendicitis. A, Transverse ultrasound scan of the appendix demonstrates the characteristic "target sign." In this case, the innermost portion is sonolucent, compatible with fluid or pus. B, Longitudinal view of another patient demonstrates the alternating hyperechoic and hypoechoic layers with an outermost hypoechoic layer, suggesting periappendiceal fluid. C, Longitudinal ultrasound scan of the right lower quadrant demonstrates a dilated, noncompressible appendix. The bright echo within the appendix represents an appendicolith with acoustic shadowing (arrow). (From Kuhn JP, Slovis TL, Haller JO. Caffrey's Pediatric Diagnostic Imaging, 10th ed. Philadelphia: Mosby; 2004:1684.)



**Fig. 391.4** A, Phlegmon (black arrow) is noted around the enlarged appendix (white arrow) in perforated appendicitis. B, Extraluminal air is shown adjacent to the wall-enhanced appendix (arrow) in perforated appendicitis. (From Yeung KW, Chang MS, Hsiao CP. Evaluation of perforated and non-perforated appendicitis with CT. Clin Imaging. 2004;28:422-427, Figs. 1 and 3)



**Fig. 391.5** A, Precontrast-enhanced CT reveals an appendicolith (arrow) in perforated appendicitis. B, Postcontrast-enhanced CT (1 cm below the level in A) reveals intraluminal air in the appendix (curved arrow) associated with ileal wall enhancement in perforated appendicitis. (From Yeung KW, Chang MS, Hsiao CP. Evaluation of perforated and non-perforated appendicitis with CT. Clin Imaging. 2004;28:422-427, Fig. 5.)

diagnoses are suspected, particularly Crohn disease. Because the finding of fat stranding in surrounding tissues is a key component of CT evaluation for appendicitis, CT is less reliable in thin children with minimal body fat.

The avoidance of enteral contrast, targeted CT imaging, and the use of pediatric-specific protocols can significantly lower radiation dosages without sacrificing diagnostic accuracy. The use of appendicitis risk scoring systems in conjunction with CPGs and increasing experience with appendiceal ultrasound have led to a decreased use of CT scans (<6.6% in most reports), without negatively affecting time to appendectomy or negative appendectomy rates.

### Magnetic Resonance Imaging

MRI is at least equivalent to CT in diagnostic accuracy for appendicitis and does not involve ionizing radiation; however, its use in the evaluation of appendicitis is limited because it is less available, is associated with higher costs, and does not offer equivalent access for drainage of fluid collections. MRI may prove most useful in adolescent females when ultrasound imaging is equivocal. The use of MRI is becoming more common in institutions with high resources, and it has become a good alternative to CT in cases with equivocal ultrasound.

### DIAGNOSIS AND TREATMENT

Acute appendicitis is believed to be a time-sensitive condition; thus any delay in diagnosis or treatment may lead to an increased risk of perforation and its attendant morbidity. The misdiagnosis of appendicitis is second only to meningitis as a cause of medical malpractice suits in pediatric emergency care. A careful history and physical examination remain primary in the initial assessment of a child presenting with abdominal symptoms. The classic history in acute appendicitis, although possibly not most common, is a 24-hour history of diffuse mid-abdominal pain that migrates and becomes localized to the RLQ. Patients should have a WBC count with differential analysis, as this is a component of most appendicitis risk scoring systems. A urinalysis is also typically obtained and a pregnancy test in appropriately selected patients. CPGs have become common practice in many centers for evaluation of patients with abdominal pain and suspected appendicitis to reduce practice variability and improve diagnostic accuracy and resource use. CPGs have been shown to have high positive and negative predictive values (~95%) and to decrease both LOS and costs without increasing morbidity or complications. These guidelines combine initial history, physical examination, and laboratory data with predictive risk scoring systems to cohort patients into low, intermediate, and high risk for the diagnosis of acute appendicitis. In general, low-risk patients can be discharged without imaging studies, high-risk patients would have pediatric surgical consultation, and the inconclusive or intermediate-risk group would most predictably benefit from a period of observation or proceeding with advanced imaging studies. If the initial assessment leads to a high level of suspicion for appendicitis, pediatric surgical consultation should be the next step, with the likelihood of an appendectomy without further studies. In patients with a low concern for appendicitis, the child may be discharged with family education regarding the natural history and progression of acute appendicitis and advice to return for repeat evaluation if the child is not improving on liquids and a bland diet in the next 24 hours. The group of patients with an intermediate-risk score would proceed with targeted ultrasound of the appendix if the center has experience with the technique. If the ultrasound study is unable to visualize the appendix, or the appendix is visualized but the findings are inconclusive, the next options would include admission for a period of observation and planned reassessment, CT imaging or MRI, or diagnostic laparoscopy.

The use of observation units, where the child may be observed with intravenous fluids, serial vital signs, and planned reexaminations, is another strategy. At the end of a period of observation, typically 12–24 hours, the clinician decides on discharge based on reassuring clinical status, proceeds to diagnostic laparoscopy and appendectomy, or proceeds with advanced imaging evaluation. The period of observation can occur at home provided the patient is physiologically well; a hospital-based observational unit has the advantage of being able to

provide intravenous fluids. An observation strategy seems most useful in patients who present with a brief history of illness (<12 hours) when advanced imaging studies predictably have lower sensitivity and specificity. If observed patients remain equivocal, advanced imaging should be more reliable further into the disease process.

## DIFFERENTIAL DIAGNOSIS

The list of illnesses that can mimic acute appendicitis is extensive because many gastrointestinal, gynecologic, and inflammatory disorders can manifest with similar illness history, signs, and symptoms. Differential diagnosis, even limited to common conditions, includes gastroenteritis, mesenteric adenitis, Meckel diverticulitis, intussusception, inflammatory bowel disease, diabetes mellitus, sickle cell disease, streptococcal pharyngitis, lower lobe pneumonia, cholecystitis, pancreatitis, urinary tract infection (UTI), infectious enteritis, and, in females, ovarian torsion, ectopic pregnancy, ruptured/hemorrhagic ovarian cysts, and pelvic inflammatory disease (including tubo-ovarian abscess). *Epiploic appendagitis*, an inflammation of the fat-filled structures on the antimesenteric surface of the colon, may present with acute lower quadrant abdominal pain after torsion, thrombosis, and ischemic injury to the structure. Viral infections, bacterial infections, and parasitic infections can all closely mimic acute appendicitis. Intestinal tract lymphoma, tumors of the appendix (carcinoid in children), and ovarian tumors are rare but can also masquerade as acute appendicitis. Henoch-Schönlein purpura can initially present as severe abdominal pain. Urinary tract causes of abdominal pain include UTI, nephrolithiasis, and pyelonephritis. In patients with pyelonephritis, the fever and WBC count are likely much higher, symptoms of dysuria will be present, and the tenderness is located more in the flank or costovertebral angle. Rarely, appendicitis may recur in the stump of a previous appendectomy. *Children younger than 3 years of age and adolescent females have historically proven to be at particularly high risk for an incorrect diagnosis.*

Viral illnesses are common in children, often are associated with abdominal pain and vomiting, and thus mimic acute appendicitis. The classic patient with acute appendicitis describes abdominal pain as the preeminent symptom, and in general, symptoms of systemic illness such as headache, chills, and myalgias are infrequent in appendicitis and common when viral illness is the correct diagnosis.

Infection with SARS-CoV-2 (COVID-19) or associated with the development of multisystem inflammatory syndrome in children (MIS-C) has produced a pseudo-appendicitis picture with RLQ pain, mesenteric adenopathy, fat stranding, and phlegmon formation. Additional features of COVID-19 are usually, but not always, present (Fig. 391.6).

The diagnosis of appendicitis in adolescent females is especially challenging, and some series report negative appendectomy rates as

high as 30–40%. Ovarian cysts are often acutely painful as a result of rupture, rapid enlargement, or hemorrhage. Rupture of an ovarian follicle associated with ovulation often causes midcycle lateralizing pain (mittelschmerz), but there is no progression of symptoms and systemic illness is absent. Ovarian tumors and torsion can also mimic acute appendicitis, although ovarian torsion is typically characterized by the acute onset of severe pain and is associated with more frequent and forceful nausea and vomiting than is typically seen in early appendicitis. In pelvic inflammatory disease, the pain is typically suprapubic, bilateral, and of longer duration. The need for accurate urgent diagnosis in females is influenced by concern that PA can predispose the patient to future ectopic pregnancy or tubal infertility, although data have not consistently demonstrated increased incidence of infertility after PA. For these reasons, adjunct diagnostic studies (ultrasound, CT, MRI, or diagnostic laparoscopy) should be used more liberally in females to keep negative appendectomy rates low.

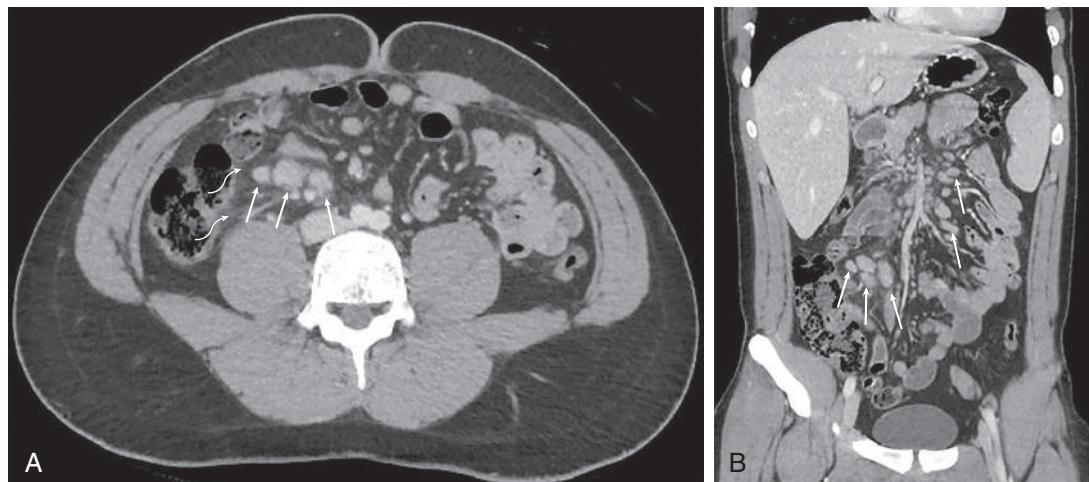
Torsion of an undescended testis and epididymitis are common but should be discovered on physical exam. Meckel diverticulitis is an infrequent condition, but the clinical presentation closely mimics appendicitis. The diagnosis is rarely made before surgery. Primary spontaneous peritonitis (PSP) is classically seen in prepubertal females or patients with either nephrotic syndrome or cirrhosis and is frequently mistaken for appendicitis.

Atypical presentations of appendicitis are expected in association with other conditions such as pregnancy, Crohn disease, steroid treatment, and immunosuppressive therapy. Appendicitis in association with Crohn disease often has a protracted presentation with an atypical pattern of recurring but localized abdominal pain. It should be recognized that *missed appendicitis* is the most common cause of small bowel obstruction in children without a history of prior abdominal surgery.

## ANTIBIOTICS

*Antibiotics should be initiated promptly once the diagnosis of appendicitis is made or highly suspected.* Antibiotics substantially lower the incidence of postoperative wound infections (SSIs) and intraabdominal abscesses—the source of the majority of the substantial morbidity and costs in PA. Many believe the time from onset of illness to the initiation of antibiotics has more impact on postoperative complication rates, LOS, and overall costs than time from diagnosis to surgery.

The antibiotic regimen should be directed against the typical bacterial flora found in the appendix, including anaerobic organisms (*Bacteroides*, *Clostridia*, and *Peptostreptococcus* spp.) and gram-negative aerobic bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Enterobacter*, and *Klebsiella* spp.). Many antibiotic combinations have demonstrated equivalent efficacy in controlled trials in terms of wound



**Fig. 391.6** Initial CT scan of a patient with COVID-19 presenting as mesenteric adenopathy. Axial image (A) and coronal reformat (B) of abdominopelvic CT with intravenous contrast agent in a 17-yr-old male demonstrate enlarged lymph nodes (straight arrows) and adjacent fat stranding (curved arrows). (From Noda S, Ma J, Romberg EK, et al. Severe COVID-19 initially presenting as mesenteric adenopathy. *Pediatr Radiol*. 2021;51:140–143, Fig. 1.)

infection rate, resolution of fever, LOS, and incidence of complications. Historically, a triple-antibiotic regimen consisting of ampicillin, gentamicin, and clindamycin was standard. Exhaustive studies of different antibiotic regimens have been performed, mostly aimed at lowering costs and frequency of dosing while maintaining efficacy. Both piperacillin/tazobactam and cefoxitin have demonstrated equivalent effectiveness and may decrease LOS and pharmaceutical costs compared to the triple-antibiotic regimen.

For simple (nonperforated) appendicitis, one preoperative dose of a single broad-spectrum agent (piperacillin/tazobactam) or equivalent is sufficient. In PA, the antibiotic is continued intravenously for 2–3 days postoperatively until the child is afebrile ( $\geq 24$  hours), tolerating a general diet, and ready for discharge. Some centers prefer to add metronidazole in PA to augment coverage of anaerobes. The decision to discharge patients with PA managed with up-front appendectomy on a course of oral antibiotics (typically 3–5 days) remains controversial. The literature does not support improved outcomes with PA if antibiotics are extended beyond a 4- to 5-day course.

## SURGICAL INTERVENTION

Once the diagnosis of appendicitis is confirmed or highly suspected, the standard treatment for acute appendicitis, both simple and complicated, in current practice is most often prompt appendectomy. LA (a minimally invasive technique) is the preferred surgical approach (65–70%) in both simple and PA, with open appendectomy markedly declining in the past decade. The laparoscopic approach has demonstrated slight improvement in clinical outcome measures (wound infection rate, intraabdominal abscess, analgesic requirements, wound cosmesis, and return to full activity); however, costs can be higher. The laparoscopic approach (diagnostic laparoscopy/LA) has particular advantages for obese patients, when alternative diagnoses are suspected, and in adolescent females to evaluate for ovarian pathology and alternative diagnoses while avoiding the ionizing radiation associated with CT imaging. The operation should proceed semi-electively within 12–24 hours of diagnosis. Children with appendicitis are typically at least mildly dehydrated and should receive supportive care before surgery, including fluid resuscitation to correct hypovolemia and electrolyte abnormalities, antipyretics to lower fever, and broad-spectrum antibiotics. These important fundamentals of care ensure safe anesthesia and optimize outcomes. In most cases, preoperative management can be accomplished during the period of diagnostic evaluation and prompt appendectomy can be performed. Pain management begins even before a definitive diagnosis is made, and consultation of a pain service, if available, is appropriate. Emergency surgery (middle of the night) is rarely indicated in acute appendicitis and should only be performed in the rare circumstance when physiologic resuscitation requires urgent control of advanced intraabdominal sepsis not amenable to percutaneous drainage by interventional radiology or when this is not available. No correlation has been demonstrated between timing of surgery and perforation rates or postoperative morbidity when the operation proceeds within 24 hours of diagnosis. When comparing emergent appendectomy (within 5 hours of admission) with urgent appendectomy (within 17 hours of admission), no differences in PA, operative time, readmission rate, postoperative complications, LOS, or hospital charges have been noted. In addition, occasionally unexpected pathology (appendiceal tumors, intestinal lymphoma, congenital renal anomalies, Crohn disease) is discovered at operation, and intraoperative consultation with other specialists and/or frozen section evaluation may be required. The laparoscopic approach, in conjunction with standardized, expedited postoperative recovery protocols, and improved (single drug) and shorter-duration antibiotic regimens have led to decreased LOS in both simple and complicated (perforated) appendicitis. The average LOS in most centers is approximately 24 hours for simple appendicitis and 4–5 days for perforated cases that recover without postoperative complications. In simple appendicitis, some centers have initiated same-day discharge.

## PERFORATED APPENDICITIS

A major area of focus and challenge in the management of acute appendicitis is the group of patients with delayed presentation ( $>48$  hours) of symptoms. Because acute appendicitis often has an insidious onset

of generalized malaise, as many as 40–50% of patients have delayed presentation. This cohort of patients has a high incidence of PA at presentation (40–59%) and a 56% greater LOS stay than those presenting within  $\leq 24$  hours of the onset of symptoms. The risk for development of postoperative complications (SSI, intraabdominal abscess, small bowel obstruction) approaches 20–30% for children with PA versus an approximately 3% risk of complications in patients with simple appendicitis.

Management options for children presenting with PA include up-front appendectomy after a brief period of stabilization with intravenous fluids and antibiotics, antibiotics alone, and antibiotics in conjunction with percutaneous drainage of intraabdominal fluid collections/abscesses. The past decade has witnessed a substantial trend toward nonoperative management in children with delayed presentation and suspected PA to avoid the high complication rate in these patients and the potential technical challenges of operative treatment in the setting of marked intraabdominal inflammation/peritonitis. Based on patient status, findings on imaging studies, and availability of experienced interventional radiologists, initial nonoperative management of PA with percutaneous drainage of fluid collections, intravenous fluids, and broad-spectrum antibiotics has demonstrated success in >80% of patients. Antibiotics are initiated and typically continued intravenously for 1–2 days along with pain control. If the child demonstrates clinical recovery by resolution of fever and pain and can tolerate a general diet, the child is converted to oral antibiotics and discharged to complete an outpatient antibiotic course (typically 7–10 days of ciprofloxacin/metronidazole or amoxicillin/clavulanate). A patient who fails to demonstrate clinical recovery proceeds to prompt appendectomy. This nonoperative management, and particularly the transition to oral antibiotics, has contributed to a decreased LOS and costs in the management of PA. Patients who do not have up-front appendectomy will require a decision regarding interval appendectomy (IA) in 4–6 weeks, provided the child does not fail nonoperative management after discharge by recurrence of pain, fever, or vomiting.

## NONOPERATIVE MANAGEMENT OF UNCOMPLICATED APPENDICITIS

Multiple studies in adults have demonstrated highly effective treatment of appendicitis with antibiotics alone. In addition, other conditions similar to appendicitis, such as diverticulitis, intraabdominal abscess in Crohn disease, and tubo-ovarian abscess, are primarily treated with antibiotics alone, with surgery reserved for failures of medical management. These outcomes have led many centers to evaluate initial nonoperative management of acute (simple) appendicitis in children, and currently several randomized controlled studies are ongoing. Advantages of the antibiotic-alone/nonoperative approach in acute appendicitis include avoidance of surgical complications and the risk of general anesthesia and an operative procedure that may not be necessary. Selection criteria for nonoperative management are designed to exclude signs and symptoms suggestive of PA and typically include duration of symptoms  $<48$  hours, age  $>7$  years, imaging confirmation of acute non-PA, appendiceal diameter  $<1.2$  cm, absence of appendicolith, abscess, or phlegmon, and WBC  $>5,000$  and  $<18,000$  cells/ $\mu$ L. The clinical pathway for children enrolled consists of an initial 1–2 days of intravenous broad-spectrum antibiotics and pain control. If the child demonstrates clinical recovery by resolution of pain and fever and is tolerating a general diet, he or she is discharged to complete 7–10 days of oral antibiotics. If the child does not demonstrate clinical recovery, prompt appendectomy is performed. Early nonoperative trials found that predictors of failure of nonoperative management included pain  $>48$  hours in duration, presence of an appendicolith, inflammatory mass or abscess on imaging, and elevated laboratory values (WBC  $>18,000$ , CRP  $>4$  mg/dL). The largest prospective trial (nonrandomized, treatment assigned by parent selection) comparing surgery and medical management of appendicitis in the United States followed patients for 1 year. Out of the children who were initially treated medically, 37% underwent an appendectomy within 1 year. Multiple reports indicate a more rapid return to full activities; however, patients with nonoperative management had more subsequent ED visits, advanced

imaging studies, and hospitalizations compared with those managed operatively at the first visit. Controversies remain in the initial nonoperative management of PA.

### RECURRENT APPENDICITIS

Prospective studies of the incidence of early recurrent appendicitis (within 1 year) describe a range between 10% and 30% in patients initially managed nonoperatively. The lifetime risk of recurrent appendicitis in children treated nonoperatively is unknown, but the few data that have been published beyond the 1-year follow-up suggest that the risk for recurrent appendicitis continues to increase past the first year. Currently under review is the need for delayed appendectomy (IA) in patients with complicated appendicitis initially managed nonoperatively. Although the trend in cases of PA at presentation is toward initial nonoperative management, the data remain uncertain, and there are no convincing data to recommend one approach in all patients.

### INTERVAL APPENDECTOMY

In patients with PA initially treated nonoperatively, the decision to proceed with IA, typically in 4–6 weeks, is another area of management lacking consensus. Traditionally, most surgeons recommended IA to avoid recurrent appendicitis and to confirm the original diagnosis, citing reports that demonstrated an incidence of unexpected pathology in 30% of IA specimens. This has been questioned, with nonoperative management of simple appendicitis gaining acceptance and many debating the risk of recurrent appendicitis (5–20%), believing it to be lower. The lifetime risk of recurrent appendicitis is unknown. Decision-making for IA must be individualized to balance the risks of recurrent appendicitis with the risks of anesthesia and comorbid conditions such as obesity, congenital heart disease, chronic respiratory conditions, and others.

### INCIDENTAL APPENDICOLITHS

The question of the incidental appendicolith is an intriguing one for pediatric practitioners. These are patients who do not have appendicitis but are found to have an appendicolith on imaging studies. An appendicolith is defined as a calcification within the appendiceal lumen. In adults, incidental appendicoliths identified by CT scans vary in incidence from <1% to as high as 10%. They have a characteristic dense and laminated appearance when compared to other lower abdominal calcifications, including phleboliths (venous calcifications) and, in females, ovarian calcifications, most commonly seen in ovarian tumors. They can be appreciated on plain film, ultrasound, and CT scan. When an appendicolith is noted in the evaluation of a child with abdominal pain and suspected appendicitis, the finding of the appendicolith confirms the diagnosis; surgical consultation and prompt appendectomy are indicated. Appendicoliths may be noted in the evaluation of patients who have no signs of appendicitis, such as imaging obtained after trauma or for nonspecific abdominal complaints in patients with a low likelihood of appendicitis. The concern in this setting is that the appendicolith may increase the eventual development of acute appendicitis. In addition, there is the concern that should appendicitis develop in association with an appendicolith, there may be a rapidly escalating course and early perforation. Some physicians believe that a persistent appendicolith may be associated with recurrent RLQ/iliac fossa pain.

Incidental appendicoliths may be transient and in most short-term follow-up studies have a low risk of subsequent acute appendicitis. In addition, the lifetime risk for the development of appendicitis in patients with an incidental appendicolith is approximately 5%, which is not different from the normal population. The risk of subsequent appendicitis may be higher in those presenting with abdominal pain or those younger than 19 years of age. Radiographically detected incidental appendicoliths are usually managed with observation, planned follow-up, and patient education for signs of acute appendicitis. After discussing the risks and benefits with the family and persistence of the appendicolith, an individualized approach is best between the physician and the family relative to elective appendectomy.

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## Chapter 392

# Surgical Conditions of the Anus and Rectum

### 392.1 Anorectal Malformations

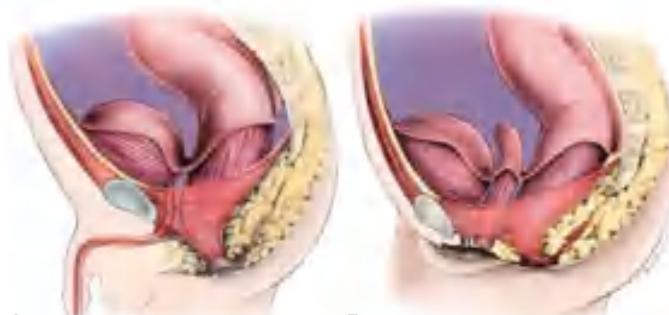
Christina M. Shanti

To fully understand the spectrum of anorectal anomalies, it is necessary to consider the importance of the sphincter complex, a mass of muscle fibers surrounding the anorectum (Fig. 392.1). This complex is the combination of the puborectalis, levator ani, external and internal sphincters, and the superficial external sphincter muscles, all meeting at the rectum. Anorectal malformations are defined by the relationship of the rectum to this complex and include varying degrees of stenosis to complete atresia. The incidence is 1/3,000 live births. Significant long-term concerns focus on bowel control and urinary and sexual functions.

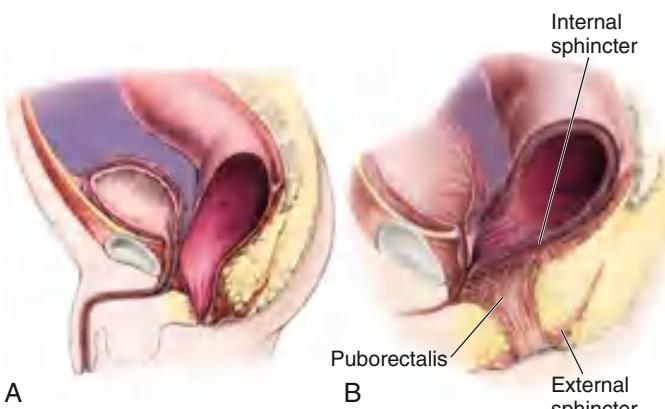
### EMBRYOLOGY

The hindgut forms early as the part of the primitive gut tube that extends into the tail fold in the second week of gestation. At about day 13, it develops a ventral diverticulum, the allantois, or primitive bladder. The junction of the allantois and hindgut becomes the cloaca, into which the genital, urinary, and intestinal tubes empty. This is covered by a cloacal membrane. The urorectal septum descends to divide this common channel by forming lateral ridges, which grow in and fuse by the middle of the seventh week. Opening of the posterior portion of the membrane (the anal membrane) occurs in the eighth week. Failures in any part of these processes can lead to the clinical spectrum of anogenital anomalies.

**Imperforate anus** can be divided into low lesions, where the rectum has descended through the sphincter complex, and high lesions, where it has not. Most patients with imperforate anus have a fistula. There is a spectrum of malformation in males and females. In males, low lesions usually manifest with meconium staining somewhere on the perineum along the median raphe (Figs. 392.2A and 392.3). Low lesions in females also manifest as a spectrum from an anus that is only slightly anterior on the perineal body to a fourchette fistula that opens on the moist mucosa of the introitus distal to the hymen (Fig. 392.4A). A high imperforate anus in a male has no apparent cutaneous opening or fistula, but it usually has a fistula to the urinary tract, either the urethra or the bladder (Fig. 392.2B). Although there is occasionally a rectovaginal fistula, in females, high lesions are usually cloacal anomalies in which the rectum, vagina, and urethra all empty into a common channel or cloacal stem of varying length (see Fig. 392.4B).



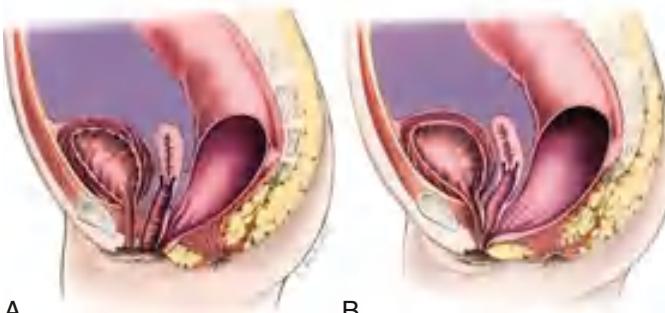
**Fig. 392.1** Normal anorectal anatomy in relation to pelvic structures. A, Male. B, Female. (From Peña A. *Atlas of Surgical Management of Anorectal Malformations*. New York: Springer-Verlag; 1989: 3.)



**Fig. 392.2** Imperforate anus in males. A, Low lesions. B, High lesions. (From Peña A. *Atlas of Surgical Management of Anorectal Malformations*. New York: Springer-Verlag; 1989:7, 26.)



**Fig. 392.3** This male infant has a rectoperineal fistula with a subepithelial tract filled with either mucus or meconium that extends into the scrotal raphe. (From Rentea RM, Levitt MA. *Anorectal atresia and cloacal malformations*. In Holcomb III GW, Murphy JP, St. Peter SD, eds. *Holcomb and Ashcraft's Pediatric Surgery*, 7th ed. Philadelphia: Elsevier; 2020: Fig. 35.2, p. 578.)



**Fig. 392.4** Imperforate anus in females. A, Vestibular fistula. B, Cloaca. (From Peña A. *Atlas of Surgical Management of Anorectal Malformations*. New York: Springer-Verlag; 1989: 50, 60.)

The interesting category of males with imperforate anus and no fistula occurs mainly in children with trisomy 21. The most common lesions are the rectourethral bulbar fistula in males and the rectovestibular fistula in females; the second most common lesion in both sexes is the perianal fistula (Fig. 392.5).

### ASSOCIATED ANOMALIES

Many anomalies are associated with anorectal malformations (Table 392.1). The most common are anomalies of the kidneys and urinary tract in conjunction with abnormalities of the sacrum. This complex is often referred to as *caudal regression syndrome*. Males with a rectovesical fistula and patients with a persistent cloaca have a 90% risk of urologic defects. Other common associated anomalies are cardiac anomalies and esophageal atresia with or without tracheoesophageal fistula. These can cluster in any combination in a patient. When combined, they are often accompanied by abnormalities of the radial aspect of the upper extremity and are termed the *VACTERL* (vertebral, anal, cardiac, tracheal, esophageal, renal, limb) *anomalad*.

Anorectal malformations, particularly anal stenosis and rectal atresia, can also present as the Currarino triad, which includes sacral agenesis, a presacral mass, and anorectal stenosis. These patients present with a funnel-appearing anus, have sacral bony defects on plain x-ray, and have a presacral mass (teratoma, meningocele, dermoid cyst, enteric cyst) on exam or imaging. It is an autosomal dominant disorder caused in most patients by a pathogenic variant in the *MNX1* gene.

A good correlation exists between the degree of sacral development and future function. Patients with an absent sacrum usually have permanent fecal and urinary incontinence. Spinal abnormalities and different degrees of dysraphism are often associated with these defects. Tethered cord occurs in approximately 25% of patients with anorectal malformations. Untethering of the cord can lead to improved urinary and rectal continence in some patients, although it seldom reverses established neurologic defects. The diagnosis of spinal defects can be screened for in the first 3 months of life by spinal ultrasound, although MRI is the imaging method of choice if a lesion is suspected. In older patients, MRI is needed.

### MANIFESTATIONS AND DIAGNOSIS

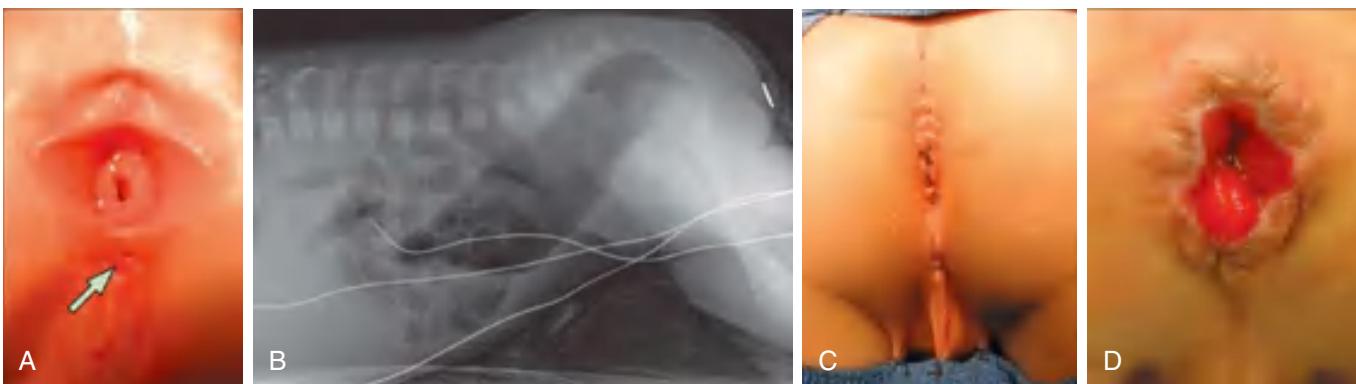
#### Low Lesions

Examination of a newborn includes the inspection of the perineum. The absence of an anal orifice in the correct position leads to further evaluation. Mild forms of imperforate anus are often called *anal stenosis* or *anterior ectopic anus*. These are typically cases of an imperforate anus with a perineal fistula. The normal position of the anus on the perineum is approximately halfway (0.5 ratio) between the coccyx and the scrotum or introitus. Although symptoms, primarily constipation, have been attributed to anterior ectopic anus (ratio: <0.34 in females, <0.46 in males), many patients have no symptoms.

If no anus or fistula is visible, there may be a low lesion or *covered anus*. In these cases, there are well-formed buttocks and often a thickened raphe or *bucket handle*. After 24 hours, meconium bulging may be seen, creating a blue or black appearance. In these cases, an immediate perineal procedure can often be performed, followed by a dilation program.

In a male, the perineal (cutaneous) fistula can track anteriorly along the median raphe across the scrotum and even down the penile shaft (see Fig. 392.3). This is usually a thin track, with a normal rectum often just a few millimeters from the skin. Extraintestinal anomalies are seen in <10% of these patients.

In a female, a low lesion enters the vestibule or fourchette (the moist mucosa outside the hymen but within the introitus). In this case, the rectum has descended through the sphincter complex. Children with a low lesion can usually be treated initially with perineal manipulation and dilation. Visualizing these low fistulas is so important in the evaluation and treatment that one should avoid passing a nasogastric tube for the first 24 hours to allow the abdomen and bowel to distend, pushing meconium down into the distal rectum.



**Fig. 392.5** Preoperative and postoperative images of anorectal malformations. A, Preoperative rectoperineal fistula. B, Radiograph with cross-table lateral film showing neonate in prone position and gas below the coccyx. C, Postoperative appearance after a posterior sagittal anorectoplasty. D, Postoperative large, patulous, and prolapsed anoplasty. (From Bischoff A, Bealer J, Pená A. Controversies in anorectal malformations. Lancet Child Adolesc. 2017;1:323–330.)

**Table 392.1** Associated Malformations

#### GENITOURINARY

- Vesicoureteric reflux
- Renal agenesis
- Renal dysplasia
- Ureteral duplication
- Cryptorchidism
- Hypospadias
- Bicornuate uterus
- Vaginal septa

#### VERTEBRAL

- Spinal dysraphism
- Tethered chord
- Presacral masses
- Meningocele
- Lipoma
- Dermoid
- Teratoma

#### CARDIOVASCULAR

- Tetralogy of Fallot
- Ventricular septal defect
- Transposition of the great vessels
- Hypoplastic left-heart syndrome

#### GASTROINTESTINAL

- Tracheoesophageal fistula
- Duodenal atresia
- Malrotation
- Hirschsprung disease

#### CENTRAL NERVOUS SYSTEM

- Spina bifida
- Tethered cord

In females with high imperforate anus, there may be the appearance of a rectovaginal fistula. A true rectovaginal fistula is rare. Most are either the fourchette fistulas described earlier or are forms of a cloacal anomaly.

#### Persistent Cloaca

In persistent cloaca, the embryologic stage persists in which the rectum, urethra, and vagina communicate in a common orifice, the cloaca. It is important to realize this anomaly, because the repair often requires repositioning the urethra and vagina as well as the rectum. Children of both sexes with a high lesion require a colostomy before repair.

#### Rectal Atresia

Rectal atresia is a rare defect occurring in only 1% of anorectal anomalies. It has the same characteristics in both sexes. The unique feature of this defect is that affected patients have a normal anal canal and a normal anus. The defect is often discovered while rectal temperature is being taken. An obstruction is present approximately 2 cm above the skin level. These patients need a protective colostomy. The functional prognosis is excellent because they have a normal sphincteric mechanism (and normal sensation), which resides in the anal canal.

#### APPROACH TO THE PATIENT

Evaluation includes identifying associated anomalies (see Table 392.1). Careful inspection of the perineum is important to determine the presence or absence of a fistula. If the fistula can be seen, it is a low lesion. The invertogram, or upside-down x-ray, is of little value, but a prone cross-table lateral plain x-ray at 24 hours of life (to allow time for bowel distention from swallowed air) with a radiopaque marker on the perineum can demonstrate a low lesion by showing the rectal gas bubble <1 cm from the perineal skin (see Fig. 392.5). A plain x-ray of the entire sacrum, including both iliac wings, is important to identify sacral anomalies and the adequacy of the sacrum. An abdominal-pelvic ultrasound and voiding cystourethrogram must be performed. The clinician should also pass a nasogastric tube to identify esophageal atresia and should obtain an echocardiogram. In males with a high lesion, the voiding cystourethrogram often identifies the rectourinary fistula. In females with a high lesion, more invasive evaluation, including vaginogram and endoscopy, is often necessary for careful detailing of the cloacal anomaly.

Good clinical evaluation and a urinalysis provide enough data in 80–90% of male patients to determine the need for a colostomy. Voluntary sphincteric muscles surround the most distal part of the bowel in cases of perineal and rectourethral fistulas, and the intraluminal bowel pressure must be sufficiently high to overcome the tone of those muscles before meconium can be seen in the urine or on the perineum. The presence of meconium in the urine and a flat bottom are considered indications for the creation of a colostomy. Clinical findings consistent with the diagnosis of a perineal fistula represent an indication

#### High Lesions

In a male with a high imperforate anus, the perineum appears flat. There may be air or meconium passed via the urethra when the fistula is high, entering the bulbous or prostatic urethra, or even the bladder. In *rectobulbar urethral fistulas* (the most common in males), the sphincter mechanism is satisfactory, the sacrum may be underdeveloped, and an anal dimple is present. In *rectoprostatic urethral fistulas*, the sacrum is poorly developed, the scrotum may be bifid, and the anal dimple is near the scrotum. In *rectovesicular fistulas*, the sphincter mechanism is poorly developed, and the sacrum is hypoplastic or absent. In males with trisomy 21, all the features of a high lesion may be present, but there is no fistula, the sacrum and sphincter mechanisms are usually well developed, and the prognosis is good.

for an anoplasty without a protective colostomy. Ultrasound is valuable not only for the evaluation of the urinary tract, but it can also be used to investigate spinal anomalies in the newborn and to determine how close to the perineum the rectum has descended.

More than 90% of the time, the diagnosis in females can be established on perineal inspection. The presence of a single perineal orifice is a cloaca. A palpable pelvic mass (hydrocolpos) reinforces this diagnosis. A vestibular fistula is diagnosed by careful separation of the labia, exposing the vestibule. The rectal orifice is located immediately in front of the hymen within the female genitalia and in the vestibule. A perineal fistula is easy to diagnose. The rectal orifice is located somewhere between the female genitalia and the center of the sphincter and is surrounded by skin. Less than 10% of these patients fail to pass meconium through the genitalia or perineum after 24 hours of observation. Those patients can require a prone cross-table lateral film.

### OPERATIVE REPAIR

Sometimes a perineal fistula, if it opens in a good position, can be treated by simple dilation. Hegar dilators are employed, starting with a No. 5 or 6 and letting the baby go home when the mother can use a No. 8. Twice-daily dilatations are done at home, increasing the size every few weeks until a No. 14 is achieved. By 1 year of age, the stool is usually well formed and further dilation is not necessary. By the time No. 14 is reached, the examiner can usually insert a little finger. If the anal ring is soft and pliable, dilation can be reduced in frequency or discontinued.

Occasionally, there is no visible fistula, but the rectum can be seen to be filled with meconium bulging on the perineum, or a covered anus is otherwise suspected. If confirmed by plain x-ray or ultrasound of the perineum that the rectum is <1 cm from the skin, the clinician can do a minor perineal procedure to perforate the skin and then proceed with dilation or do a simple perineal anoplasty.

When the fistula orifice is close to the introitus or scrotum, it is often appropriate to move it back surgically. This also requires postoperative dilation to prevent stricture formation. This procedure can be done any time from the newborn period to 1 year. It is preferable to wait until dilatations have been done for several weeks and the child is bigger. The anorectum is a little easier to dissect at this time. The posterior sagittal approach of Peña is used, making an incision around the fistula and then in the midline to the site of the posterior wall of the new location. The dissection is continued in the midline, using a muscle stimulator to be sure there is adequate muscle on both sides. The fistula must be dissected cephalad for several centimeters to allow posterior positioning without tension. If appropriate, some of the distal fistula is resected before the anastomosis to the perineal skin.

In children with a high lesion, a double-barrel colostomy is performed. This effectively separates the fecal stream from the urinary tract. It also allows the performance of an augmented pressure colostogram before repair to identify the exact position of the distal rectum and the fistula. The definitive repair or posterior sagittal anorectoplasty (PSARP) is performed at about 1 year of age. A midline incision is made, often splitting the coccyx and even the sacrum. Using a muscle stimulator, the surgeon stays strictly in the midline and divides the sphincter complex and identifies the rectum. The rectum is then opened in the midline, and the fistula is identified from within the rectum. This allows a division of the fistula without injury to the urinary tract. The rectum is then dissected proximally until enough length is gained to suture it to an appropriate perineal position. The muscles of the sphincter complex are then sutured around (and especially behind) the rectum.

Other operative approaches (such as an anterior approach) are used, but the most popular procedure is by laparoscopy. This operation allows division of the fistula under direct visualization and identification of the sphincter complex by transillumination of perineum. Other imaging techniques in the management of anorectal malformations include 3D endorectal ultrasound, intraoperative MRI, and colonoscopy-assisted PSARPs, which may help perform a technically better operation. None of these other procedures or innovations has demonstrated improved outcomes.

A similar procedure can be done for female high anomalies with variations to deal with separating the vagina and rectum from within

the cloacal stem. When the stem is longer than 3 cm, this is an especially difficult and complex procedure.

Usually the colostomy can be closed 6 weeks or more after the PSARP. Two weeks after any anal procedure, twice-daily dilatations are performed by the family. By doing frequent dilatations, each one is not so painful and there is less tissue trauma, inflammation, and scarring.

### OUTCOME

The ability to achieve rectal continence depends on both motor and sensory elements. There must be adequate muscle in the sphincter complex and proper positioning of the rectum within the complex. There must also be intact innervation of the complex and of sensory elements, as well as the presence of these sensory elements in the anorectum. Patients with low lesions are more likely to achieve true continence. They are also, however, more prone to constipation, which leads to overflow incontinence. It is very important that all these patients are followed closely and that the constipation and anal dilation are well managed until toilet training is successful. Tables 392.2 and 392.3 outline the results of continence and constipation in relation to the malformation encountered.

Children with high lesions, especially males with rectoprostatic urethral fistulas and females with cloacal anomalies, have a poorer chance of being continent, but they can usually achieve a socially acceptable defecation (without a colostomy) pattern with a bowel management

**Table 392.2** Types of Anorectal Malformation by Sex

#### MALE (PERCENTAGE CHANCE OF BOWEL CONTROL\*)

- Rectoperineal fistula (100%)
- Rectourethral bulbar fistula (85%)
- Imperforate anus without fistula (90%)
- Rectourethral prostatic fistula (65%)
- Rectobladder neck fistula (15%)

#### FEMALE (PERCENTAGE CHANCE OF BOWEL CONTROL\*)

- Rectoperineal fistula (100%)
- Rectovestibular fistula (95%)
- Imperforate anus without fistula (90%)
- Rectovaginal fistula (rare anomaly)<sup>†</sup>
- Cloaca (70%)<sup>‡</sup>

\*Provided patients have a normal sacrum, no tethered cord, and they receive a technically correct operation without complications.

<sup>†</sup>Rectovaginal anomalies are extremely unusual; usually their prognosis is like rectovestibular fistula.

<sup>‡</sup>Cloaca represents a spectrum; those with a common channel length <3 cm have the best functional prognosis.

From Bischoff A, Bealer J, Peña A. Controversies in anorectal malformations. *Lancet Child/Adolesc*. 2017;1:323–330.

**Table 392.3** Constipation and Type of Anogenital Malformation

TYPE	PERCENTAGE
Vestibular fistula	61
Bulbar urethral fistula	64
Rectal atresia/stenosis	50
Imperforate with no fistula	55
Perineal fistula	57
Long cloaca	35
Prostatic fistula	45
Short cloaca	40
Bladder neck fistula	16

Modified from Levitt MA, Peña A. Outcomes from the correction of anorectal malformations. *Curr Opin Pediatr*. 2005;17:394–401.

program. Often, the bowel management program consists of a daily enema to keep the colon empty and the patient clean until the next enema. If this is successful, an *antegrade continence enema* (ACE) procedure, sometimes called the *Malone* or *Malone antegrade continence enema* (MACE) procedure, can improve the patient's quality of life. These procedures provide access to the right colon either by bringing the appendix out the umbilicus in a nonrefluxing fashion or by putting a plastic button in the right lower quadrant to access the cecum. The patient can then sit on the toilet and administer the enema through the ACE, thus flushing out the entire colon. Antegrade regimens can produce successful 24-hour cleanliness rates of up to 95%. Of special interest is the clinical finding that most patients improve their control with growth. Patients who wore diapers or pull-ups to primary school are often in regular underwear by high school. Some groups have taken advantage of this evidence of psychologic influences to initiate behavior modification early with good results.

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## 392.2 Anal Fissure

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Anal fissure is a laceration of the anal mucocutaneous junction. It is an acquired lesion of unknown etiology. Although likely secondary to the forceful passage of a hard stool, it is mainly seen in infants younger than 1 year of age when the stool is frequently quite soft. Fissures may be the consequence and not the cause of constipation.

### CLINICAL MANIFESTATIONS

A history of constipation is often described, with a recent painful bowel movement corresponding to the fissure formation after passing of hard stool. The patient then voluntarily retains stool to avoid another painful bowel movement, exacerbating the constipation, resulting in harder stools. Complaints of pain on defecation and bright red blood on the surface of the stool are often elicited.

The diagnosis is established by inspection of the perineal area. The infant's hips are held in acute flexion, the buttocks are separated to expand the folds of the perianal skin, and the fissure becomes evident as a minor laceration. Often a small skin appendage is noted peripheral to the lesion. This *skin tag* represents epithelialized granulomatous tissue formed in response to chronic inflammation. Findings on rectal examination can include hard stool in the ampulla and rectal spasm.

### TREATMENT

The parents must be counseled as to the origin of the laceration and the mechanism of the cycle of constipation. The goal is to ensure that the patient has soft stools to avoid overstressing the anus. The healing process can take several weeks or even several months. A single episode of impaction with passing of hard stool can exacerbate the problem. Treatment requires that the primary cause of the constipation be identified (see Chapter 378.3). The use of dietary and behavioral modification and a stool softener is indicated. Parents should titrate the dose of the stool softener based on the patient's response to treatment. Stool softening is best done by increasing water intake or using an oral polyethylene glycol such as MiralAX or GlycoLax. Surgical intervention, including stretching of the anus, "internal" anal sphincterotomy, or excision of the fissure, is not indicated or supported by scientific evidence.

*Chronic anal fissures* in older patients are associated with constipation, prior rectal surgery, Crohn disease, and chronic diarrhea. They are managed initially like fissures in infants, with stool softeners with the addition of sitz baths. Topical 0.2% glyceryl trinitrate reduces anal spasm and heals fissures, but it is often associated with headaches. Calcium channel blockers, such as 2% diltiazem ointment and 0.5% nifedipine cream, are more effective and cause fewer headaches than glyceryl trinitrate. Injection of botulinum toxin from 12.5 to 25 units

is also effective and probably chemically replicates the action of internal sphincterotomy, which is the most effective treatment in adults, although seldom used in children.

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## 392.3 Perianal Abscess and Fistula

Christina M. Shanti

Perianal abscesses usually manifest in *infancy* (~75%  $\leq 1$  year) and are of unknown etiology. Fistula appears to be secondary to the abscess rather than the cause. Links to congenitally abnormal crypts of Morgagni have been proposed, suggesting that deeper crypts (3-10 mm rather than the normal 1-2 mm) lead to trapped debris and cryptitis (Fig. 392.6).

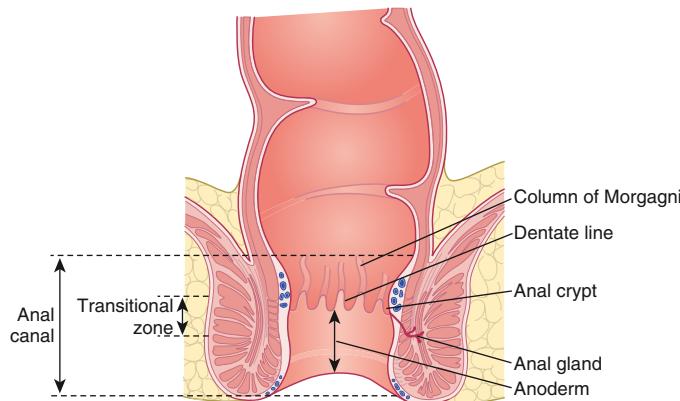
Conditions associated with the risk of an anal fistula in *older children* include Crohn disease, tuberculosis, pilonidal disease, hidradenitis, HIV, trauma, foreign bodies, dermal cysts, sacrococcygeal teratoma, actinomycosis, lymphogranuloma venereum, and radiotherapy.

The most common organisms isolated from perianal abscesses are mixed aerobic (*Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*) and anaerobic (*Bacteroides* spp., *Clostridium*, *Veillonella*) flora. A total of 10–15% yield pure growth of *E. coli*, *S. aureus*, or *Bacteroides fragilis*. There is a strong male predominance in those affected who are younger than 2 years of age, whereas the distribution is more equal in older patients, where the etiology shifts to associated conditions such as inflammatory bowel disease, leukemia, or immunocompromised states.

### CLINICAL MANIFESTATIONS

In younger patients, symptoms are usually mild and can consist of low-grade fever, mild rectal pain, and an area of perianal cellulitis (Fig. 392.7). Often these spontaneously drain and resolve without treatment. In older patients with underlying predisposing conditions, the clinical course may be more serious. A compromised immune system can mask fever and allow rapid progression to toxicity and sepsis. Abscesses in these patients may be deeper in the ischiorectal fossa or even supralevator in contrast to those in younger patients, which are usually adjacent to the involved crypt.

Progression to fistula in patients with perianal abscesses occurs in 20–50% of cases and usually manifests with drainage from the perineal skin or multiple recurrences. Similar to abscess formation, fistulas have a strong male predominance. Histologic evaluation of fistula tracts typically reveals an epithelial lining of stratified squamous cells associated with chronic inflammation. It might also reveal an alternative etiology such as the granulomas of Crohn disease or even evidence of tuberculosis.



**Fig. 392.6** Anatomy of the anal canal. (Adapted from Brunicardi FC, Anderson DK, Billiar TR, et al. Schwartz's Principles of Surgery, 8th ed. New York: McGraw-Hill; 2004.)



**Fig. 392.7** Perianal abscesses are often seen in male infants. The abscess typically presents as a fluctuant, tender mass in the perianal region. Incision and drainage is the initial management of these abscesses if conservative measures have failed. (From Sullins VF, Jarboe M, Calkins CM. Acquired anorectal disorders. In: Holcomb III GW, Murphy JP, St. Peter SD, eds. Holcomb and Ashcraft's Pediatric Surgery, 7th ed. Philadelphia: Elsevier; 2020: Fig. 37.1, p. 613.)

## TREATMENT

Treatment is rarely indicated in infants with no predisposing disease because the condition is often self-limited. Even in cases of fistulization, conservative management (observation) is advocated because the fistula often disappears spontaneously. In one study, 87% of fistulas (in 97/112 infants) closed after a mean of 5 months of observation and conservative management (sitz baths). Antibiotics are not useful in these patients. When dictated by patient discomfort, abscesses may be incised and drained under local anesthesia. Fistulas requiring surgical intervention may be treated by fistulotomy (unroofing or opening), fistulectomy (excision of the tract leaving it open to heal secondarily), or placement of a seton (heavy suture threaded through the fistula, brought out the anus, and tied tightly to itself). In patients with inflammatory bowel disease, topical tacrolimus has been effective.

Older children with predisposing diseases might also do well with minimal intervention. If there is little discomfort and no fever or other sign of systemic illness, local hygiene and antibiotics may be best. The danger of surgical intervention in an immunocompromised patient is the creation of an even larger, nonhealing wound. There certainly are such patients with serious systemic symptoms who require more aggressive intervention along with treatment of the predisposing condition. Broad-spectrum antibiotic coverage must be administered, and wide excision and drainage are mandatory in cases involving sepsis and expanding cellulitis.

Fistulas in older patients are mainly associated with Crohn disease, a history of pull-through surgery for the treatment of Hirschsprung disease, or, in rare cases, tuberculosis. Those fistulas are often resistant to therapy and require treatment of the predisposing condition.

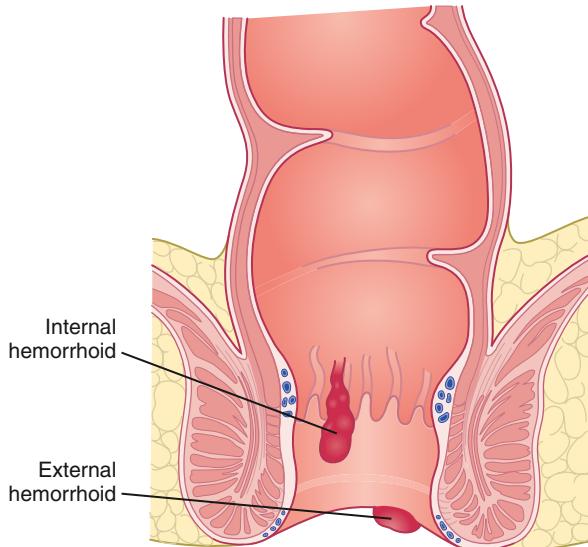
Complications of treatment include recurrence and, rarely, incontinence.

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## 392.4 Hemorrhoids

Christina M. Shanti

Hemorrhoidal disease occurs in both children and adolescents, often related to a diet deficient in fiber and poor hydration. In younger



**Fig. 392.8** Formation of hemorrhoids.

children, the presence of hemorrhoids should also raise the suspicion of portal hypertension. A third of patients with hemorrhoids require treatment.

## CLINICAL MANIFESTATIONS

Presentation depends on the location of the hemorrhoids. External hemorrhoids occur below the dentate line (Fig. 392.8; see Fig. 392.6) and are associated with extreme pain and itching, often because of acute thrombosis. Internal hemorrhoids are located above the dentate line and manifest primarily with bleeding, prolapse, and occasional incarceration.

## TREATMENT

In most cases, conservative management with dietary modification, decreased straining, and avoidance of prolonged time spent sitting on the toilet results in resolution of the condition. Discomfort may be treated with topical analgesics or antiinflammatories such as Anusol (pramoxine) and Anusol-HC (hydrocortisone) and sitz baths. The natural course of thrombosed hemorrhoid involves increasing pain, which peaks at 48–72 hours, with gradual remission as the thrombus organizes and involutes over the next 1–2 weeks. In cases where the patient with external hemorrhoids presents with excruciating pain soon after the onset of symptoms, thrombectomy may be indicated. This is best accomplished with local infiltration of bupivacaine 0.25% with epinephrine 1:200,000, followed by incision of the vein or skin tag and extraction of the clot. This provides immediate relief; recurrence is rare, and further follow-up is unnecessary.

Internal hemorrhoids can become painful when prolapse leads to incarceration and necrosis. Pain usually resolves with reduction of hemorrhoidal tissue. Surgical treatment is reserved for patients failing conservative management. Techniques described in adults include excision, rubber banding, stapling, and excision using the LigaSure device. Complications are rare (<5%) and include recurrence, bleeding, infection, nonhealing wounds, and fistula formation.

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### 392.5 Rectal Mucosal Prolapse

Christina M. Shanti

Rectal mucosal prolapse is the exteriorization of the rectal mucosa through the anus. In the unusual occurrence when all the layers of the rectal wall are included, it is called *procidentia* or *rectocele*. Most cases of rectal tissue protruding through the anus are prolapse and not polyps, hemorrhoids, intussusception, or other tissue.

Most cases of prolapse are idiopathic. The onset is often between 1 and 5 years of age. It usually occurs when the child begins standing and then resolves by approximately 3-5 years of age when the sacrum has taken its more adult shape and the anal lumen is oriented posteriorly. Thus the entire weight of the abdominal viscera is not pushing down on the rectum, as it is earlier in development.

Other predisposing factors include intestinal parasites (particularly in endemic areas), malnutrition, diarrhea, ulcerative colitis, pertussis, Ehlers-Danlos syndrome, meningocele (more often associated with procidentia owing to the lack of perineal muscle support), cystic fibrosis, and chronic constipation. Patients treated surgically for imperforate anus can also have varying degrees of rectal mucosal prolapse. This is particularly common in patients with poor sphincteric development. Rectal prolapse is also seen with higher incidence in patients with mental issues and behavior problems. These patients are particularly difficult to manage and are more likely to fail medical treatment.

#### CLINICAL MANIFESTATIONS

Rectal mucosal prolapse usually occurs during defecation, especially during toilet training. Reduction of the prolapse may be spontaneous or accomplished manually by the patient or parent. In severe cases, the prolapsed mucosa becomes congested and edematous, making it more difficult to reduce (Fig. 392.9). Rectal prolapse is usually painless or produces mild discomfort. If the rectum remains prolapsed after defecation, it can be traumatized by friction with undergarments, with resultant bleeding, wetness, and potentially ulceration. The appearance of the prolapse varies from bright red to dark red and resembles a beehive. It can be as long as 10-12 cm. See Chapter 393 for a distinction from a prolapsed polyp.

#### TREATMENT

Initial evaluation should include tests to rule out any predisposing conditions, especially cystic fibrosis and sacral root lesions. Reduction of protrusion is aided by pressure with warm compresses. An easy method of reduction is to cover the finger with a piece of toilet paper, introduce it into the lumen of the mass, and gently push it into the patient's rectum. The finger is then immediately withdrawn. The toilet paper adheres to the mucous membrane, permitting release of the finger. The paper, when softened, is later expelled.

Conservative treatment consists of careful manual reduction of the prolapse after defecation, attempts to avoid excessive pushing during bowel movements (with the patient's feet off the floor), use of laxatives and stool softeners to prevent constipation, avoidance of inflammatory conditions of the rectum, and treatment of intestinal parasitosis when present. If all this fails, surgical treatment may be indicated. Existing surgical options are associated with some morbidity, and therefore medical treatment should always be attempted first.



**Fig. 392.9** This 2-year-old child developed persistent rectal prolapse. The prolapse occurred several times daily and was not responsive to medical management. The child underwent submucosal sclerotherapy with 5% morrhuate sodium and the prolapse resolved. (From Sullins VF, Jarboe M, Calkins CM. Acquired anorectal disorders. In Holcomb III GW, Murphy JP, St. Peter SD, eds. *Holcomb and Ashcraft's Pediatric Surgery*, 7th ed. Philadelphia: Elsevier; 2020: Fig. 37.8, p. 616.)

Sclerosing injections have been associated with complications such as neurogenic bladder. We have found linear cauterization effective and with few complications other than recurrence. In the operating room, the prolapse is re-created by traction on the mucosa. Linear burns are made through nearly the full thickness of the mucosa using electrocautery. One can usually make eight linear burns on the outside and four on the inside of the prolapsed mucosa. In the immediate postoperative period, prolapse can still occur, but in the next several weeks, the burned areas contract and keep the mucosa within the anal canal. The Delorme mucosal sleeve resection addresses mucosal prolapse via a transanal approach by incising, prolapsing, and amputating the redundant mucosa. The resulting mucosal defect is then approximated with absorbable suture.

For patients with procidentia or full-thickness prolapse or intussusception of the rectosigmoid (usually from myelodysplasia or other sacral root lesions), other, more invasive options exist. Those most commonly in use by pediatric surgeons today include a modification of the Thiersch procedure, which involves placing a subcutaneous suture to narrow the anal opening. Complications include obstruction, fecal impaction, and fistula formation. Laparoscopic rectopexy is effective and can be performed as an outpatient. The Altemeier perineal rectosigmoidectomy is a transanal, full-thickness resection of redundant bowel with a primary anastomosis to the anus.

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## Chapter 393

# Tumors of the Digestive Tract

Stacey G. Zahler, Mohammad Nasser Kabbany, and Karen F. Murray

Tumors of the digestive tract in children are also commonly syndromic tumors and tumors with known genetic association (Table 393.1). They usually manifest as painless rectal bleeding, but when large they can cause obstruction or serve as lead points for intussusception. Most intestinal polyps in children can be generally classified into two groups: hamartomatous (as seen in juvenile polyps and Peutz-Jeghers syndrome) or adenomatous (as seen in familial adenomatous polyposis syndrome).

### HAMARTOMATOUS TUMORS

Hamartomas are benign tumors composed of tissues that are normally found in an organ but that are not organized normally. Juvenile, retention, or inflammatory polyps are hamartomatous polyps, which represent the most common intestinal tumors of childhood, occurring in 1–2% of children. Patients generally present in the first decade, most often at ages 2–5 years, and rarely at younger than 1 year. Polyps may be found anywhere in the gastrointestinal (GI) tract, most commonly in the rectosigmoid colon, with one third located proximal to splenic flexure; they are often solitary but may be multiple.

Histologically, juvenile polyps are composed of hamartomatous collections of mucus-filled glandular and stromal elements with inflammatory infiltrate, covered with a thin layer of epithelium (Fig. 393.1A). These polyps are often bulky, vascular, and prone to bleed as their growth exceeds their blood supply with resultant mucosal ulceration, or autoamputation with bleeding from a residual central artery.

Patients often present with painless rectal bleeding after defecation. Bleeding is generally scant and intermittent; rarely presenting findings can include iron-deficiency anemia and/or hypoalbuminemia. Extensive bleeding can occur but is generally self-limited, requiring supportive care until the bleeding stops spontaneously after autoamputation. Occasionally endoscopic polypectomy is required for control of bleeding. Abdominal pain or cramps are uncommon unless associated with intussusception. Patients can present with prolapse, with a dark, edematous, pedunculated mass protruding from the rectum. Mucus discharge and pruritus are associated with prolapse.

Patients presenting with rectal bleeding require a thorough workup; differential diagnosis includes anal fissure, other intestinal polyposis syndromes, Meckel's diverticulum, inflammatory bowel disease, intestinal infections, IgA vasculitis (Henoch-Schönlein purpura), angiodyplasia, or coagulopathy.

Diagnosis and therapy are best accomplished via **endoscopy**. Polyps may be visualized via ultrasound or cross-sectional imaging, but this provides no therapeutic advantage. Colonoscopy affords opportunity for biopsy, **polypectomy** by snare cautery, and visualization of synchronous lesions; up to 50% of children have one or more additional polyps, and approximately 20% may have more than five polyps. Retrieved polyps should be sent for histologic evaluation for definitive diagnosis.

### Juvenile Polyposis Syndrome

Patients with juvenile polyposis syndrome (JPS) present with multiple juvenile polyps—usually five or more—but typically 50–200 are present within the GI tract. The incidence of JPS is between 1:10,000 and 1:160,000. Polyps are most likely isolated to the colon (98%) but may be distributed throughout the GI tract. There is often a family history (20–50%) with an autosomal dominant pattern of variable penetrance. Alterations in transforming growth factor- $\beta$  pathways have been

identified in some JPS patients and families; pathogenic variants in *SMAD4* or *BMPR1A* are found in 50–60% of patients with JPS. Genetic testing is available for both of these variants. Patients with the *SMAD4* pathogenic variant may have hereditary hemorrhagic telangiectasia and should be evaluated for brain and lung vascular malformations. A clinical diagnosis of JPS is established by the presence of one of the following: a lifetime total of five or more juvenile polyps in the colon, juvenile polyps outside the colon, or any number of juvenile polyps in a patient with a family history of JPS.

Histologically, these polyps are identical to solitary juvenile polyps; however, the risk of malignant transformation is greatly increased (10–50%). Malignancy occurs most commonly in the colorectal region, although gastric, upper GI, and pancreatic tumors have been described. The risk of malignancy is greater in patients with increased polyp burden and a positive family history. These patients should therefore undergo routine esophagogastroduodenoscopy and colonoscopy starting at 12–15 years of age. Age at which surveillance of the upper GI tract should begin varies between guidelines. It is not required during teenage years per current published pediatric guidelines unless symptomatic. Serial polypectomy or polyp biopsy should be undertaken if possible. If dysplasia or malignant degeneration is found, a total colectomy is indicated.

Juvenile polyposis of infancy is characterized by early polyp formation (in patients younger than 2 years of age) and may be associated with protein-losing enteropathy, hypoproteinemia, anemia, failure to thrive, and intussusception. Early **endoscopic or surgical intervention** may be needed.

### Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant disorder (incidence: ~1:120,000 total population) characterized by mucocutaneous pigmentation and extensive GI hamartomatous polyposis. Macular pigmented lesions may be dark brown to dark blue and are found primarily around the lips and oral mucosa, although these lesions may also be found on the hands, feet, or perineum (Fig. 393.2). Lesions can fade by puberty or adulthood, though buccal pigmentation can persist.

Polyps are primarily found in the small intestine (in order of prevalence: jejunum, ileum, duodenum) but may also infiltrate gastric or colonic regions. Histologically, polyps are defined by normal epithelium surrounding bundles of smooth muscle arranged in a branching or frondlike pattern called *arborization* (see Fig 393.1B). They may show “pseudo-invasion,” which may be mistaken for malignancy. Symptoms arising from GI polyps in PJS are similar to those of other polyposis syndromes—namely bleeding and abdominal cramping from obstruction or recurrent intussusception. Patients have a 68% risk of intussusception during childhood and may require repeated laparotomies and intestinal resections.

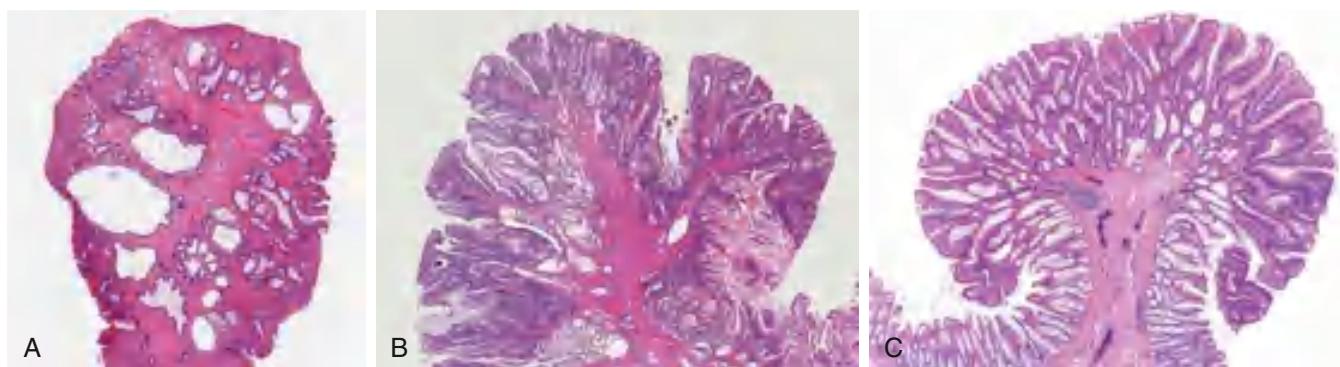
The diagnosis of PJS is made clinically in patients with at least two histologically proven PJS polyps or any number of PJS polyps in patients with a known family history. Diagnosis also can be made in individuals with a family history of PJS with characteristic mucocutaneous hyperpigmentation. Genetic testing can reveal pathogenic variants in *LKB1/STK11* (19p13.3), a serine-threonine kinase that acts as a tumor suppressor gene. Up to 94% of patients with clinical characteristics of PJS have a pathogenic variant at this locus. Only 50% of patients with PJS have an affected family member, suggesting a high rate of de novo mutations.

Patients with PJS have increased risk of GI and extraintestinal malignancies. Lifetime cancer risk has been reported to be in the range of 47–93%. Colorectal, breast, and reproductive tumors are most common. Even though risk of GI malignancy in childhood is quite low, GI surveillance for polyps should begin in childhood (by age 8 years of age or when symptoms occur) with upper and lower endoscopy. The small bowel may be evaluated radiographically, with magnetic resonance enterography, endoscopically with balloon or push enteroscopy, or with video capsule endoscopy. Polyps larger than 1.5 cm should be removed, although resection does not lower the cancer risk and is mainly to avoid complications. Patients with PJS should be monitored for signs of precocious puberty given their risk of having sex cord/

**Table 393.1** General Features of the Inherited Colorectal Cancer Syndromes

SYNDROME	POLYP DISTRIBUTION	AGE OF ONSET	RISK OF COLON CANCER	GENETIC LESION	CLINICAL MANIFESTATIONS	ASSOCIATED LESIONS
<b>HAMARTOMATOUS POLYPS</b>						
Juvenile polyposis	Large and small intestine, gastric polyps	First decade	~10–50%	<i>SMAD4, BMPR1A</i> Autosomal dominant	Possible rectal bleeding, abdominal pain, intussusception	Congenital abnormalities in 20% of the nonfamilial type, clubbing, AV malformations
Peutz-Jeghers syndrome	Small and large intestine	First decade	Increased	<i>LKB1/STK11</i> Autosomal dominant	Possible rectal bleeding, abdominal pain, intussusception	Orocutaneous melanin pigment spots
Cowden syndrome	Colon	Second decade	13–18%	<i>PTEN</i> gene	Macrocephaly, breast/thyroid/endometrial cancers, developmental delay	
Bannayan-Riley-Ruvalcaba syndrome	Colon	Second decade	Increased	<i>PTEN</i> gene	Macrocephaly, speckled penis, thyroid/breast cancers, hemangiomas, lipomas	
<b>ADENOMATOUS POLYPS</b>						
Familial adenomatous polyposis (FAP)	Large intestine, often >100	16yr (range: 8–34yn)	100%	5q (APC gene), autosomal dominant	Rectal bleeding, abdominal pain, bowel obstruction	Desmoids, CHRPE, upper GI polyps, osteoma, hepatoblastoma, thyroid cancer
Attenuated familial adenomatous polyposis (AFAP)	Colon (fewer in number)	>18yr	Increased	APC gene	Same as FAP	Fewer associated lesions
MYH-associated polyposis	Colon	>20yr	High risk	MYH autosomal recessive	Same as FAP	May be confused with sporadic FAP or AFAP; few extraintestinal findings
Gardner syndrome	Large and small intestine	16yr (range: 8–34yn)	100%	5q (APC gene)	Rectal bleeding, abdominal pain, bowel obstruction	Desmoid tumors, multiple osteomas, fibromas, epidermoid cysts
Hereditary nonpolyposis colon cancer (Lynch syndrome)	Large intestine	40yr	30%	DNA mismatch repair genes (MMR) Autosomal dominant	Rectal bleeding, abdominal pain, bowel obstruction	Other tumors (e.g., ovary, ureter, pancreas, stomach)

APC, adenomatous polyposis coli; AV, arteriovenous; CHRPE, congenital hypertrophy of the retinal pigment epithelium; GI, gastrointestinal; PTEN, phosphatase and tensin homolog.



**Fig. 393.1** Representative histologic sections of commonly found polyps in pediatric patients. A, Juvenile polyp. Cystically dilated and irregular colonic crypts within an inflamed, expanded stroma. B, Peutz-Jeghers polyp. Small bowel with large arborizing bundles of smooth muscle and otherwise normal epithelial component. C, Adenomatous polyp. Enlarged, hyperchromatic, and stratified nuclei confined to a tubular configuration. (Images courtesy Dr. Thomas Plesec, Cleveland Clinic.)



**Fig. 393.2** Peutz-Jeghers syndrome. Characteristic bluish brown to black spots were first noted in early childhood on the lips of this boy who later developed hamartomatous gastrointestinal polyps. (From Paller AS, Mancini AJ, eds. Hurwitz Clinical Pediatric Dermatology, 6th ed. Philadelphia: Elsevier; 2022: Fig. 11.46, p. 312.)

stromal tumors, particularly large-cell calcifying Sertoli cell tumors. Screening for breast, gynecologic, and testicular cancers should be routine after age 18 years.

### Phosphatase and Tensin Homolog Hamartoma Tumor Syndromes

Pathogenic variants in the tumor suppressor gene *PTEN* are associated with several rare autosomal dominant syndromes, including Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and Proteus and Proteus-like syndrome. These patients present with multiple hamartomas in the skin (99%), brain, breast, thyroid, endometrium, and GI tract (60%). Other extraintestinal manifestations include macrocephaly, developmental delay, lipomas, and genital pigmentation. Patients have 9–18% lifetime risk of colorectal cancer. However, this risk is low in childhood. They also have increased risk of thyroid, breast, uterine, renal, and skin malignancies.

## ADENOMATOUS TUMORS

### Adenomatous Polyposis Coli-Associated Polyposis Syndromes

Familial adenomatous polyposis (FAP) is the most common genetic polyposis syndrome (incidence 1:5,000–1:17,000 persons) and is characterized by numerous adenomatous polyps throughout the colon and extraintestinal manifestations. FAP and related syndromes (attenuated FAP; Gardner and Turcot syndromes) are linked to pathogenic variants in the *APC* gene, a tumor suppressor mapped to 5q21, which is part of the WNT signaling pathway. *APC* regulates degradation of  $\beta$ -catenin, a protein with roles in regulation of the cytoskeleton, tissue architecture organization, cell migration and adherence, and numerous other functions. Intracellular accumulation of  $\beta$ -catenin may be responsible for colonic epithelial cell proliferation and adenoma formation. More than 400 pathogenic variants in the *APC* gene have been described, and up to 30% of patients present with no family history (sporadic variants). There is an association between disease phenotype and the location of the *APC* gene alteration. For example, a more severe colonic phenotype is associated with pathogenic variants between codons 1250 and 1464, specifically variants that include codon 1309.

Polyps generally develop late in the first or second decades of life (mean age of presentation is 16 years). At the time of diagnosis, five or more adenomatous polyps are present in the colon and rectum. By young adulthood, the number of polyps typically increases to hundreds or even thousands. Adenomatous polyps (or adenomas) are precancerous lesions within the surface epithelium of the intestine, displaying various degrees of dysplasia (see Fig. 393.1C). Without intervention,

the risk of developing colon cancer is 100% by the fifth decade of life (average age of cancer diagnosis is 40 years). Other GI adenomas can develop, particularly in the stomach and duodenum (50–90%). The risk of periampullary or duodenal carcinoma is significantly elevated (4–12% lifetime risk) and represents, along with desmoid tumors, the most common cause of death after colorectal cancer. Extraintestinal malignancies occur at an increased rate in FAP, including hepatoblastoma in young patients (1.6% before age 5 years) and follicular or papillary thyroid cancer in adolescents.

Extraintestinal manifestations of FAP may be present from birth or develop in early childhood. Lesions include congenital hypertrophy of retinal pigment epithelium, desmoid tumors, epidermoid cysts, osteomas, fibromas, lipomas, and supernumerary, impacted, or missing teeth. Many of these nonmalignant soft tissue tumors appear before intestinal polyps develop. Expression of extraintestinal findings can depend on the location of the *APC* gene alteration.

Other syndromes associated with *APC* pathogenic variants include *Gardner syndrome*, classically characterized by multiple colorectal polyps, desmoid tumors, and soft tissue tumors, including fibromas, osteomas (typically mandibular), epidermoid cysts, and lipomas. Once thought to be a distinct clinical entity, *Gardner syndrome* shares many characteristics with FAP. Up to 20% of FAP patients present with the classic extraintestinal manifestations once associated with *Gardner syndrome*. Some (but not all) cases of *Turcot syndrome* are also related to *APC*. These patients present with colorectal polyposis and primary brain tumors (medulloblastoma). Attenuated FAP is characterized by a significantly increased risk of colorectal cancer but fewer polyps than classic FAP (average: 30 polyps). The average age of cancer diagnosis in this form of FAP is 50–55 years. Upper GI tumors and extraintestinal manifestations may be present but are less common.

The clinical presentation of FAP is variable. Polyps are generally sessile, of variable size, and initially asymptomatic. If symptoms develop, they can include rectal bleeding (possibly with secondary anemia), cramping, and diarrhea. The presence of symptoms at presentation does not correlate with malignant changes. Diagnosis should be suspected from family history, and ensuing colonoscopy is confirmatory. Histologic examination of biopsied polyps reveals adenomatous architecture (as opposed to inflammatory or hamartomatous polyps found in other polyposis syndromes) with varying degrees of dysplasia. Genetic testing for *APC* variants is clinically available, and index patients should be tested. If a pathogenic variant is identified, affected family members should be screened and appropriate genetic counseling should be provided. If the index patient does not demonstrate a defined variant, family members may undergo genetic testing, which might identify novel *APC* alterations. Children with identified *APC* mutations must undergo careful surveillance, with colonoscopy every 1–2 years starting early in the second decade of life or earlier if symptomatic. Once polyps are identified, colonoscopy should be performed annually. Patients should also have upper endoscopy in the third decade of life to monitor for gastric and especially duodenal lesions, earlier if symptomatic or if there is family history of aggressive duodenal adenoma burden or cancer.

Treatment of FAP requires **prophylactic proctocolectomy** to prevent inevitable colon cancer. Prophylactic colectomy should be planned in the late teens or early twenties, earlier if significant polyposis burden or malignancy is suspected. Ileorectal pull-through procedures restore bowel continuity, with acceptable functional outcomes. Surgical approaches include ileal pouch anal anastomosis (with J-pouch) versus ileorectal anastomosis; the type of surgery depends on rectal and colonic polyp burden and surgeon preference. It is very important to note that ongoing surveillance of the ileal pouch or rectal cuff is warranted after surgery. **Nonsteroidal antiinflammatory agents**, such as sulindac, and cyclooxygenase-2 inhibitors, such as celecoxib, might inhibit polyp progression. No guidelines have been established, however, and their efficacy in preventing malignant transformation of existing polyps is unknown.

### Carcinoma

Primary carcinomas of the esophagus, stomach, or colon are extremely rare in children. Development of adenocarcinoma in adolescence or

early adulthood may be associated with a genetic predisposition or syndrome such as FAP, hereditary nonpolyposis colon carcinoma, PJS, radiation exposure, or inflammatory bowel disorders such as Crohn disease or ulcerative colitis.

Colorectal carcinoma (CRC), though rare (reported incidence of 1 case per 1,000,000 persons younger than 19 years of age), is the most common primary GI carcinoma in children. Patients with long-standing ulcerative colitis are at increased risk. Many cases are spontaneous (i.e., not associated with a genetic predisposition or syndrome); associated genetic syndromes occur in 3–5% of all CRC cases (see Table 393.1). Histologically, tumors tend to be poorly differentiated and pathologically aggressive. Patients may be asymptomatic, or they present with nonspecific signs and symptoms such as abdominal pain, constipation, and vomiting. Delay in diagnosis is common. Adolescents and young adults present with advanced-stage disease more often than in older patients; microscopic or gross metastases are often present at the time of diagnosis. **Surgical resection** is the primary treatment modality, although with delayed presentation and advanced-stage disease, complete resection may not be possible. Complete resection is necessary for cure, however. **Chemotherapy** is standard treatment for patients with more advanced, surgically unresectable disease, though its efficacy is variable. Targeted immunotherapy agents such as monoclonal antibodies against epidermal growth factor receptor or vascular endothelial growth factor receptor are gaining traction as useful systemic therapies. **Radiation therapy** has a limited role in patients with metastatic disease.

## OTHER GASTROINTESTINAL TUMORS

### Lymphoma

Lymphoma is the most common GI malignancy in the pediatric population. Approximately 30% of children with non-Hodgkin lymphoma present with abdominal tumors. Immunocompromised patients have an increased incidence of lymphoma. Predisposing conditions include HIV/AIDS, agammaglobulinemia, long-standing celiac disease, and bone marrow or solid-organ transplantation. Examples of non-Hodgkin lymphoma subtypes that commonly occur in the GI tract are Burkitt lymphoma and posttransplant lymphoproliferative disorder (PTLD). Lymphoma can occur anywhere in the GI tract, but it most commonly occurs in the distal small bowel and ileocecal region; for instance, Burkitt lymphoma is classically located at the terminal ileum. Presenting symptoms include crampy abdominal pain, vomiting, obstruction, bleeding, or palpable mass. Lymphoma should be considered in patients older than 3 years of age who present with intussusception. Treatment consists of a combination of **surgical resection** and **chemotherapy**, and the intensity of chemotherapy regimens depends on the extent of the tumor burden.

### Nodular Lymphoid Hyperplasia

Lymphoid follicles in the lamina propria and submucosa of the gut normally aggregate in Peyer patches, most prominently in the distal ileum. These follicles can become hyperplastic, forming nodules that protrude into the lumen of the bowel during times of developmental lymphoid proliferation such as early childhood and adolescence. Some suggested etiologies are infectious (classically *Giardia*), allergic, or immunologic. Nodular lymphoid hyperplasia has been described in infants with enterocolitis secondary to dietary protein sensitivity. This phenomenon has also been described in patients with inflammatory bowel disease and Castleman disease. Patients may be asymptomatic or, especially in cases of immunodeficiency, may present with abdominal pain, rectal bleeding, diarrhea, or intussusception. Nodular lymphoid hyperplasia usually resolves spontaneously. The use of antiinflammatory medications or elimination diets is unlikely to change the clinical course, although in cases with severe pain or bleeding, **corticosteroids** may be effective.

### Gastroenteric Neuroendocrine Tumors

Gastroenteric neuroendocrine tumors (NETs) arise from neuroendocrine cells found in the intestines (and in the pancreas; however, pancreatic NETs will not be discussed here). These tumors can be low, intermediate, or high-grade tumors, depending on the Ki-67

proliferative index on histopathology (i.e., how rapidly the cells proliferate). The World Health Organization (WHO) classification separates NETs from “neuroendocrine carcinomas.” NETs can be functional or nonfunctional; some NETs overproduce and secrete hormones such as gastrin, serotonin, or ectopic hormones such as adrenocorticotrophic hormone (ACTH). Several heritable tumor syndromes are associated with gastroenteric NETs, including multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau (VHL) disease, tuberous sclerosis (TSC), or neurofibromatosis type 1 (NF1). Two of the most common NETs of the GI tract in children and adolescents are carcinoid tumors and gastrinomas.

### Carcinoid Tumor

Carcinoid tumors are neuroendocrine tumors of enterochromaffin cells, which can occur throughout the GI tract, but in children they are typically found in the appendix. This is often an incidental diagnosis at the time of appendectomy. **Complete surgical resection** of small tumors (<1 cm) with clear surgical margins is curative. Appendiceal tumors >1.5 cm are at increased risk for nodal metastasis and thus mandate further bowel resection, typically a right hemicolectomy.

Carcinoid tumors outside the appendix (small intestine, rectum, stomach) are more likely to metastasize. Serum tumor markers may be helpful in monitoring for development of metastatic disease—chromogranin A is the most sensitive tumor marker for intestinal NETs. Carcinoid tumors of the midgut can metastasize to the liver and give rise to a constellation of symptoms called **carcinoid syndrome**. Serotonin, 5-hydroxytryptophan, or histamine may be secreted by the tumor, and elevated serum levels cause cramps, diarrhea, vasomotor disturbances (flushing), bronchoconstriction, and right heart failure. The diagnosis is confirmed by elevated urinary 5-hydroxyindoleacetic acid (5-HIAA). Symptomatic relief of carcinoid syndrome may be achieved with administration of **somatostatin analogs** (i.e., octreotide). Treatment of metastatic NETs is again **surgical resection**, and the extent of resection may be curative or palliative, depending on the goals of care and risk of surgical morbidity. Because NETs tend to be slow-growing, some patients may be closely monitored for periods without surgical intervention. **Chemotherapy** has been used, including medications such as temozolamide, 5-fluorouracil, and cisplatin. Clinical trials studying various targeted systemic therapies are ongoing. A mammalian target of rapamycin (mTOR) inhibitor, called **everolimus**, is FDA-approved for the treatment of nonfunctional NETs based on the results of several clinical trials.

### Gastrinoma

A malignant NET that arises in the duodenum or the pancreas is called **gastrinoma**, and these tumors secrete gastrin, which causes gastric acid hypersecretion and Zollinger-Ellison syndrome. Clinical symptoms of gastrinoma include diarrhea (because of large amounts of acid secretion into the duodenum), abdominal pain, peptic ulcer disease, and bleeding. Strictures and perforation may develop with more severe disease. Unfortunately, about 75–80% of patients with gastrinoma present with metastases to the liver or lymph nodes at diagnosis, and approximately 12% can have bone metastases at diagnosis as well. Treatment of gastrinoma includes **proton pump inhibitors** and **surgical resection**.

### Leiomyoma

Leiomyomas are rare benign tumors that can arise anywhere in the GI tract, although most often in the stomach, jejunum, or distal ileum. Age of presentation is variable, from the newborn period through adolescence. Patients may be asymptomatic or can present with an abdominal mass, obstruction, intussusception, volvulus, or pain and bleeding from central necrosis of the tumor. **Surgical resection** is the treatment of choice. Pathologically, these tumors may be difficult to distinguish from malignant leiomyosarcomas. Smooth muscle tumors occur with increased incidence in children with HIV or those requiring immunosuppression after transplantation.

### Gastrointestinal Stromal Cell Tumors

Gastrointestinal stromal cell tumors (GISTs) are intestinal mesenchymal tumors that probably arise from interstitial cells of Cajal or their

precursors. Historically, these may have been diagnosed as tumors of smooth muscle or neural cell origin. The WHO recognized GIST in 1990 as a distinct neoplasm. Typically, GISTs arise in adults, after the third decade of life. Cases have also been reported in the pediatric population, generally in adolescents with a female predominance. A minority of pediatric cases were reported with Carney's triad (gastric gastrointestinal stromal tumor, pulmonary chondroma, and extraadrenal paraganglioma) or a history of neurofibromatosis. In children, tumors are most commonly found in the stomach, though they can occur anywhere in the GI tract or even the mesentery or omentum. Many patients (~45%) present with metastatic disease primarily to the lymph nodes, although metastases to the peritoneum or liver occur as well. Patients may be asymptomatic for years to decades or can present with an abdominal mass, lower GI bleeding, or obstruction. Treatment consists of **surgical resection** of local disease. Recurrence rates are high, and early postoperative surveillance is recommended. GISTs occurring in adults are typically associated with pathogenic variants in the *KIT* oncogene. This alteration is less commonly found in pediatric GISTs (~15%). Adjuvant systemic therapy for *KIT<sup>+</sup>* lesions can be given, and typically **tyrosine kinase inhibitors (such as imatinib, sunitinib, or dasatinib)** are used. These medications are conveniently available as oral therapy. Patients with persistent, recurrent, or metastatic disease may benefit from treatment.

### Vascular Tumors

Vascular malformations and hemangiomas are rare in children. The usual presentation is painless rectal bleeding, which may be chronic or acute, with massive or even fatal hemorrhage. There are usually no associated symptoms, although intussusception has been described. Half of patients have associated cutaneous hemangiomas or telangiectasia. These lesions may be associated with blue rubber bleb nevus syndrome, hereditary hemorrhagic telangiectasia, and other syndromes. About half of these lesions are in the colon and can be identified on colonoscopy. During acute bleeding episodes, bleeding can be localized via nuclear medicine bleeding scans, mesenteric angiography, or endoscopy. Colonic bleeding may be controlled by endoscopic means. Surgical intervention is required occasionally for isolated lesions.

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the first 6 months. The incidence of incarceration in untreated hernias varies between 6% and 18% across ages. The risk of incarceration is greatest in infancy, with some reports of incarceration rates of 30–40% in the first year of life, mandating prompt identification and operative repair to minimize morbidity and complications related to incarceration and strangulation. Laparoscopic hernia (LH) repair has increasingly emerged in many pediatric centers as an effective alternative to traditional open hernia (OH) repair.

### EMBRYOLOGY AND PATHOGENESIS

Indirect inguinal hernias in infants and children are congenital and result from an arrest of embryologic development—failure of obliteration of the PV rather than a weakness in the abdominal wall musculature. The pertinent developmental anatomy of indirect inguinal hernia relates to development of the gonads and descent of the testes through the inguinal canal and into the scrotum late in gestation. The testes descend from the urogenital ridge in the retroperitoneum to the area of the internal ring by about 28 weeks of gestation. The final descent of the testes into the scrotum occurs late in gestation, between weeks 28 and 36, guided by the PV and the gubernaculum. The PV, an outpouching of peritoneum in the inguinal region, is present in the developing fetus at 12 weeks of gestation. The PV develops lateral to the deep inferior epigastric vessels and descends anteriorly along the spermatic cord within the cremasteric fascia through the internal inguinal ring. The testis accompanies the PV as it exits the abdomen and descends into the scrotum. The gubernaculum testis forms from the mesonephros (developing kidney), attaches to the lower pole of the testis, and directs the testis through the internal ring, inguinal canal, and into the scrotum. The testis passes through the inguinal canal in a few days but takes about 4 weeks to migrate from the external ring to its final position in the scrotum. The cordlike structures of the gubernaculum occasionally pass to ectopic locations (perineum or femoral region), resulting in ectopic testes.

In the last few weeks of gestation or shortly after birth, the layers of the PV normally fuse together and obliterate the patency from the peritoneal cavity through the inguinal canal to the testis. The PV also obliterates distally just above the testes, and the portion of the PV that envelops the testis becomes the tunica vaginalis. In females, the PV obliterates earlier, at approximately 7 months of gestation, and may explain why females demonstrate a much lower incidence of inguinal hernia. Proper closure of the PV effectively *seals off* the opening from the abdominal cavity into the inguinal region, containing the abdominal viscera within the abdominal cavity. Failure of the PV to close permits fluid or abdominal viscera to escape the abdominal cavity into the extraabdominal inguinal canal and accounts for a variety of inguinal-scrotal abnormalities commonly seen in infancy and childhood. Involution of the left-sided PV precedes that of the right, which is consistent with the increased incidence of indirect inguinal hernias on the right side (60%).

The ovaries descend into the pelvis from the urogenital ridge but do not exit from the abdominal cavity. The cranial portion of the gubernaculum in females differentiates into the ovarian ligament, and the inferior aspect of the gubernaculum becomes the round ligament, which passes through the internal ring and terminates in the labia majora. The PV in females is also known as the *canal of Nuck*.

Androgenic hormones produced by the fetal testis, adequate end-organ receptors, and mechanical factors such as increased intraabdominal pressure combine to regulate complete descent of the testis. The testes and spermatic cord structures (spermatic vessels and vas deferens) are located in the retroperitoneum but are affected by increases in intraabdominal pressure as a consequence of their intimate attachment to the descending PV. The genitofemoral nerve also has an important role: it innervates the cremaster muscle, which develops within the gubernaculum, and experimental division or injury to both nerves in the fetus prevents testicular descent. Failure of regression of smooth muscle (present to provide the force for testicular descent) has also been postulated to play a role in the development of indirect inguinal hernias. Several studies have investigated genes involved in the control of testicular descent for their role in closure of

## Chapter 394

# Inguinal Hernias

José H. Salazar and John J. Aiken

Inguinal hernias are one of the most common conditions seen in pediatric practice, with an overall incidence of 0.8–4.5% in term infants and children and increasing to nearly 30% in premature and low birth-weight (<1 kg) infants. Most inguinal hernias in infants and children are **congenital indirect** hernias (99%) because of a patent processus vaginalis (PV), an evagination of peritoneum in the inguinal area important in testicular descent. There is rarely any defect or deficiency in the abdominal wall musculature in congenital indirect inguinal hernia. Inguinal hernias are more common in males compared with females (8:1 ratio), but females have a higher incidence of bilateral inguinal hernias (~25%) compared with males (~12%). Two other types of inguinal hernia are seen rarely in children: **direct** (acquired) hernia (0.5–1.0%) and **femoral** hernia (<0.5%). Femoral hernias are substantially more common in females (2:1 ratio). Approximately 50% of inguinal hernias manifest clinically in the first year of life, most in

precursors. Historically, these may have been diagnosed as tumors of smooth muscle or neural cell origin. The WHO recognized GIST in 1990 as a distinct neoplasm. Typically, GISTs arise in adults, after the third decade of life. Cases have also been reported in the pediatric population, generally in adolescents with a female predominance. A minority of pediatric cases were reported with Carney's triad (gastric gastrointestinal stromal tumor, pulmonary chondroma, and extraadrenal paraganglioma) or a history of neurofibromatosis. In children, tumors are most commonly found in the stomach, though they can occur anywhere in the GI tract or even the mesentery or omentum. Many patients (~45%) present with metastatic disease primarily to the lymph nodes, although metastases to the peritoneum or liver occur as well. Patients may be asymptomatic for years to decades or can present with an abdominal mass, lower GI bleeding, or obstruction. Treatment consists of **surgical resection** of local disease. Recurrence rates are high, and early postoperative surveillance is recommended. GISTs occurring in adults are typically associated with pathogenic variants in the *KIT* oncogene. This alteration is less commonly found in pediatric GISTs (~15%). Adjuvant systemic therapy for *KIT<sup>+</sup>* lesions can be given, and typically **tyrosine kinase inhibitors (such as imatinib, sunitinib, or dasatinib)** are used. These medications are conveniently available as oral therapy. Patients with persistent, recurrent, or metastatic disease may benefit from treatment.

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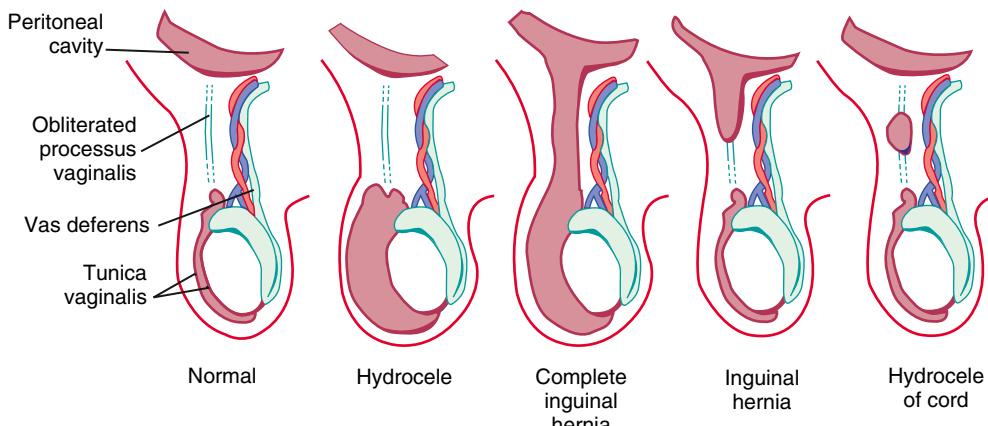
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**Fig. 394.1** Hernia and hydroceles. (Modified from Scherer LR III, Grosfeld JL. Inguinal and umbilical anomalies. *Pediatr Clin North Am.* 1993;40:1121–1131.)

the patent PV—for example, hepatocyte growth factor and calcitonin gene-related peptide. Unlike in adult hernias, there does not appear to be any deficiency in collagen synthesis associated with inguinal hernia in children (Fig. 394.1).

A **direct inguinal hernia** results from a weakness in the abdominal wall musculature in the inguinal region, specifically the transverse abdominis muscle, which forms the floor of the inguinal canal. A direct inguinal hernia originates **medial** to the deep inferior epigastric vessels and is external to the cremasteric fascia; the hernia sac protrudes directly through the posterior wall of the inguinal canal and does not protrude through the external ring. A **femoral hernia** originates medial to the femoral vein and descends inferior to the inguinal ligament along the femoral canal.

### Incidence

The incidence of congenital indirect inguinal hernia in full-term newborn infants is estimated at 3.5–5.0%. The incidence of hernia in preterm and low birthweight infants is considerably higher, ranging from 9% to 11%, and approaches 30% in very low birthweight infants (<1,000 g) and preterm infants (<28 weeks of gestation). Inguinal hernia is much more common in males than in females, with a male-to-female ratio of approximately 8:1. Approximately 60% of inguinal hernias occur on the right side, 30% are on the left side, and 10% are bilateral. The incidence of bilateral hernias is higher in females (20–40%) and young children (<2 years). An increased incidence of congenital inguinal hernia has been documented in twins and in family members of patients with inguinal hernia. There is a history of another inguinal hernia in the family in 11.5% of patients. The sisters of affected females are at the highest risk, with a relative risk of 17.8. In general, the risk of brothers of a sibling is approximately 4–5, as is the risk of a sister of an affected brother. Both a multifactorial threshold model and autosomal dominance with incomplete penetrance and sex influence have been suggested as an explanation for this pattern of inheritance.

Inguinal hernia, scrotal hydrocele (communicating and noncommunicating), and hydrocele of the spermatic cord are conditions resulting from varying degrees of failure of closure of the PV. Closure of the PV is often incomplete at birth and continues postnatally; the rate of patency is inversely proportional to the age of the child. It has been estimated that the patency rate of the PV is as high as 80% at birth and decreases to ~40% during the first year of life and that ~20% of males have a persistent patency of the PV at 2 years of age. Patency of the PV after birth is an opening from the abdominal cavity into the inguinal region, and therefore a potential hernia, but not all patients will develop a clinical hernia. An inguinal hernia occurs clinically when intraabdominal contents escape the abdominal cavity and enter the inguinal region through the PV patency. Depending on the extent of patency of the PV, the hernia may be confined to the inguinal region or pass down into the scrotum. Complete failure of obliteration of the PV, mostly seen in infants, predisposes to a complete inguinal hernia

**Table 394.1** Predisposing Factors for Hernias

Prematurity	
Urogenital	<ul style="list-style-type: none"> <li>• Cryptorchidism</li> <li>• Extrophy of the bladder or cloaca</li> <li>• Ambiguous genitalia</li> <li>• Hypospadias/epispadias</li> </ul>
Increased peritoneal fluid	<ul style="list-style-type: none"> <li>• Ascites</li> <li>• Ventriculoperitoneal shunt</li> <li>• Peritoneal dialysis catheter</li> </ul>
Increased intraabdominal pressure	<ul style="list-style-type: none"> <li>• Repair of abdominal wall defects</li> <li>• Severe ascites (chylous)</li> <li>• Meconium peritonitis</li> </ul>
Chronic respiratory disease	<ul style="list-style-type: none"> <li>• Cystic fibrosis</li> </ul>
Connective tissue disorders	<ul style="list-style-type: none"> <li>• Ehlers-Danlos syndrome</li> <li>• Hunter-Hurler syndrome</li> <li>• Marfan syndrome</li> <li>• Mucopolysaccharidosis</li> </ul>

characterized by a protrusion of abdominal contents into the inguinal canal and extending into the scrotum. Obliteration of the PV distally (around the testis) with patency proximally results in the classic indirect inguinal hernia with a bulge in the inguinal canal.

A **hydrocele** occurs when only fluid enters the patent PV; the swelling may exist only in the scrotum (scrotal hydrocele), only along the spermatic cord in the inguinal region (hydrocele of the spermatic cord), or extend from the scrotum through the inguinal canal and even into the abdomen (abdominal-scrotal hydrocele). A hydrocele is termed a **communicating hydrocele** if it demonstrates fluctuation in size, often increasing in size after activity and, at other times, being smaller when the fluid decompresses into the peritoneal cavity often after lying recumbent. Occasionally, hydroceles develop in older children after trauma, inflammation, torsion of the appendix testis, or in association with tumors affecting the testis.

Although reasons for failure of closure of the PV are unknown, it is more common in cases of testicular nondesccent (cryptorchidism) and prematurity. In addition, persistent patency of the PV is twice as common on the right side, presumably related to later descent of the right testis and interference with obliteration of the PV from the developing inferior vena cava and external iliac vein. Table 394.1 lists the risk factors identified as contributing to failure of closure of the PV and to the development of clinical inguinal hernia. The incidence of inguinal hernia in patients with cystic fibrosis is approximately 15%, believed to be related to an altered embryogenesis of the Wolffian duct structures, which

leads to an absent vas deferens and infertility in males with this condition. There is also an increased incidence of inguinal hernia in patients with **testicular feminization syndrome** and other disorders of sexual development. The rate of recurrence after repair of an inguinal hernia in patients with a connective tissue disorder approaches 50%, and often the diagnosis of connective tissue disorders in children results from investigation after development of a recurrent inguinal hernia.

### Clinical Presentation and Diagnosis

An inguinal hernia typically appears as an intermittent, asymptomatic bulge or mass in the inguinal region or scrotum, most often noted on routine physical examination or by a parent; after bathing or urination are classic presentations. In females, the mass typically occurs in the upper portion of the labia majora. The bulge or mass is most visible at times of irritability or increased intraabdominal pressure (crying, straining, coughing). Most inguinal hernias present clinically in young children, approximately 50% in the first year, and most are asymptomatic or minimally symptomatic. The classic history from the parents is of intermittent groin, labial, or scrotal swelling that spontaneously reduces but that is gradually enlarging or is more persistent and is becoming more difficult to reduce. *Rarely an incarcerated hernia may present in an infant with emesis, dehydration, and abdominal distention suggestive of gastroenteritis or a bowel obstruction.* The **hallmark sign** of an inguinal hernia on physical examination is a smooth, firm mass that emerges through the external inguinal ring lateral to the pubic tubercle and enlarges with increased intraabdominal pressure. When the child relaxes, the hernia typically reduces spontaneously or can be reduced by gentle pressure, first posteriorly to free it from the external ring and then upward toward the peritoneal cavity. In males, the hernia sac contains intestines; female infants often have an ovary and fallopian tube in the hernia sac.

The diagnosis of inguinal hernia is clinical and generally is made by history and physical examination. Methods used to demonstrate the hernia on examination vary depending on the age of the child. A quiet infant can be made to strain the abdominal muscles by stretching the infant out supine on the bed with legs extended and arms held straight above the head. Most infants struggle to get free, thus increasing the intraabdominal pressure and pushing out the hernia. Older children can be asked to perform the Valsalva maneuver by blowing up a balloon or coughing. The older child should be examined while standing, and examination after voiding also can be helpful. With increased intraabdominal pressure, the protruding mass is obvious on inspection of the inguinal region or can be palpated by an examining finger invaginating the scrotum to palpate at the external ring. Another subtle and less definitive test is the *silk glove sign*, which describes the feeling of the layers of the hernia sac as they slide over the spermatic cord structures with rolling of the spermatic cord beneath the index finger at the pubic tubercle. In the absence of a bulge, the finding of increased thickness of the inguinal canal structures on palpation also suggests the diagnosis of an inguinal hernia. It is important on examination to note the position of the testes because retractile testes are common in infants and young males and can mimic an inguinal hernia with a bulge in the region of the external ring. Because in the female patient approximately 20–25% of inguinal hernias are **sliding** hernias (the contents of the hernia sac are adherent within the sac and therefore not reducible), a fallopian tube or ovary can be palpated in the inguinal canal as a firm, slightly mobile, nontender mass in the labia or inguinal canal. A **femoral** hernia appears as a protrusion on the medial aspect of the thigh, below the inguinal region, and does not enter the scrotum or labia.

Because most hernias in young children reduce spontaneously, the physical examination in the office can be equivocal. Infants and children with a strong history suggestive of inguinal hernia and an equivocal clinical examination may be offered ultrasound or referral to a pediatric surgeon. Diagnostic laparoscopy has been increasingly used to evaluate for suspected inguinal hernia; particularly in infants where the risk of incarceration and potential injury to the intestines or testis is high. In an older child with low risk of incarceration, the parents can be reassured and educated relative to the low risk of incarceration and morbidity. If an inguinal hernia is present, it will predictably become

increasingly observed. A plan for a period of observation is thoughtful and safe, and the parents can be asked to take a digital image at home if the bulge is noted.

### EVALUATION OF ACUTE INGUINAL-SCROTAL SWELLING

Commonly in pediatric practice, an inguinal-scrotal mass appears suddenly in an infant or child and is associated with pain and discomfort. The differential diagnosis includes incarcerated inguinal hernia, acute hydrocele, torsion of an undescended testis, infection (epididymitis/orchitis), and suppurative inguinal lymphadenitis. Differentiating between the incarcerated inguinal hernia and the acute hydrocele is probably the most difficult. The infant or child with an incarcerated inguinal hernia is likely to have associated findings suggesting intestinal obstruction, such as colicky abdominal pain, abdominal distention, vomiting, and cessation of stool, and may appear ill. Plain radiographs, if obtained, typically demonstrate distended intestines with multiple air-fluid levels. The infant with an acute hydrocele may have discomfort but is consolable and tolerates feedings without signs or symptoms suggesting intestinal obstruction.

On examination of the child with the acute scrotal hydrocele, the clinician may note that the mass is somewhat mobile. In addition, the inguinal region is flat and the mass confined to the scrotum. With the incarcerated hernia, there is a lack of mobility of the groin mass and marked swelling or a mass extending from the scrotal mass through the inguinal area and up to and including the internal ring. An experienced clinician can selectively use a bimanual examination to help differentiate groin abnormalities. The examiner palpates the internal ring per rectum, with the other hand placing gentle pressure on the inguinal region over the internal ring. In cases of an indirect inguinal hernia, intraabdominal viscera can be palpated extending through the internal ring.

Another method used in diagnostic evaluation is **transillumination** to ascertain if the mass contains only fluid (hydrocele) versus intestine (hernia); however, it must be noted that transillumination can be misleading because the thin wall of the infant's intestine can approximate that of the hydrocele wall, and both may transilluminate. This is also the reason aspiration to assess the contents of a groin mass is discouraged. **Ultrasonography** can help distinguish between a hernia, a hydrocele, and lymphadenopathy and is a simple and well-tolerated test. An expeditious diagnosis is important to avoid the potential complications of an incarcerated hernia, which can develop rapidly. Diagnostic laparoscopy is an effective and reliable tool in this setting by pediatric surgeons but requires general anesthesia.

The occurrence of suppurative adenopathy in the inguinal region can be confused with an incarcerated inguinal hernia. Examination of the watershed area of the inguinal lymph nodes might reveal a superficial infected or crusted skin lesion. In addition, the swelling associated with inguinal lymphadenopathy is typically located more inferior and lateral than the mass of an inguinal hernia, and there may be other associated enlarged nodes in the area. Torsion of an undescended testis can manifest as a painful erythematous mass in the groin. The absence of a gonad in the scrotum in the ipsilateral side should clinch this diagnosis. Infectious etiologies typically demonstrate swelling and tenderness of the testis, but often there is associated urinary symptoms and the swelling is confined to the scrotum and does not extend into the inguinal canal.

### Incarcerated Hernia

Incarceration is a common consequence of untreated inguinal hernia in infants and presents as a *nonreducible* mass in the inguinal canal, scrotum, or labia. Contained structures can include the small bowel, appendix, omentum, colon, bladder, or, rarely, Meckel diverticulum. In females, the ovary, fallopian tube, or both are commonly incarcerated. Rarely, the uterus in infants can also be pulled into the hernia sac. A **strangulated hernia** is one that is tightly constricted in its passage through the inguinal canal, and as a result, the hernia contents have become ischemic or gangrenous. The incidence of incarceration of an inguinal hernia is between 6% and 18% throughout childhood

years, and two thirds of incarcerated hernias occur in the first year of life. The greatest risk is in infants younger than 6 months of age, with reported incidences of incarceration between 25% and 30%. Reports vary, but many believe a history of prematurity imparts an increased risk of incarceration in the first year of life.

Although incarceration may be tolerated in adults for years, most nonreducible inguinal hernias in children, unless treated, rapidly progress to *strangulation* with potential infarction of the hernia contents or intestinal obstruction. Initially, pressure on the herniated viscera leads to impaired lymphatic and venous drainage. This leads to swelling of the herniated viscera, which further increases the compression in the inguinal canal, ultimately resulting in total occlusion of the arterial supply to the trapped viscera. Progressive ischemic changes take place, culminating in gangrene and/or perforation of the herniated viscera. The testis is at risk of ischemia because of compression of the testicular blood vessels by the strangulated hernia. In females, herniation/incarceration of the ovary places it at risk of torsion with resultant ischemia.

The symptoms of an incarcerated hernia are irritability, feeding intolerance, and abdominal distention in the infant; pain presents in the older child. Within a few hours, the infant becomes inconsolable; lack of flatus or stool signals complete intestinal obstruction. A somewhat tense, nonfluctuant mass is present in the inguinal region and can extend down into the scrotum or labia. The mass is well defined, firm, and does not reduce. With the onset of ischemic changes, the pain intensifies, and the vomiting becomes bilious or feculent. Blood may be noted in the stools. The mass is typically markedly tender, and there is often edema and erythema of the overlying skin. The testes may be normal, demonstrate a reactive hydrocele, or may be swollen and hard on the affected side because of venous congestion resulting from compression of the spermatic veins and lymphatic channels at the inguinal ring by the tightly strangulated hernia mass. Abdominal radiographs demonstrate features of partial or complete intestinal obstruction, and gas within the incarcerated bowel segments may be seen below the inguinal ligament or within the scrotum.

### Ambiguous Genitalia

Infants with disorders of sexual development commonly present with inguinal hernias, often containing a gonad, and require special consideration. In female infants with inguinal hernias, particularly if the presentation is bilateral inguinal masses, **testicular feminization syndrome** should be suspected (>50% of patients with testicular feminization have an inguinal hernia; see Chapter 628). Conversely, the true incidence of testicular feminization in all female infants with inguinal hernias is difficult to determine but is approximately 1%. In phenotypic females, if the diagnosis of testicular feminization is suspected preoperatively, the child should be screened with a buccal smear for Barr bodies and appropriate genetic evaluation before proceeding with the hernia repair. The diagnosis of testicular feminization is occasionally made at the time of operation by identifying an abnormal gonad (testis) within the hernia sac or absence of the uterus on laparoscopy or rectal exam. In the normal female infant, the uterus is easily palpated as a distinct midline structure beneath the symphysis pubis on rectal examination. Preoperative diagnosis of testicular feminization syndrome or other disorders of sexual development such as mixed gonadal dysgenesis and selected pseudohermaphrodites enables the family to receive genetic counseling, and gonadectomy can be accomplished at the time of the hernia repair if indicated.

### Indications for Surgery

*The presence of an inguinal hernia in the pediatric age-group constitutes the indication for operative repair.* An inguinal hernia does not resolve spontaneously, and prompt repair eliminates the risk of incarceration and the associated potential complications, particularly in the first 6–12 months of life. The timing of operative repair depends on several factors, including age, general condition of the patient, and comorbid conditions. In full-term, healthy infants (younger than 1 year) with an inguinal hernia, repair should proceed promptly (within 2–3 weeks) after diagnosis because as many as 70% of incarcerated inguinal hernias requiring emergency operation occur in infants younger than 11

months. In addition, the incidence of complications associated with elective hernia repair (intestinal injury, testicular atrophy, recurrent hernia, wound infection) are low (~1%) but rise to as high as 18–20% when repair is performed emergently at the time of incarceration. The incidence of testicular atrophy after incarceration in infants younger than 3 months of age has been reported as high as 30%. Therefore an approach emphasizing prompt elective repair in infants is warranted; anesthetic risks must be considered when determining timing of elective surgery for inguinal hernia repair. The risk factors for apnea after general anesthesia include prematurity, multiple congenital anomalies, history of apnea and bradycardia, chronic lung disease, postconceptual age <60 weeks at the time of surgery, and anemia. Unfortunately, although this group of patients would be ideal for inguinal hernia repair under regional (spinal/caudal) anesthesia, inguinal hernia repair in this group is often remarkably technically challenging even for experienced pediatric surgeons, and success is elusive under regional techniques. The outcome advantage of a regional technique is lost if additional intravenous sedation is required. Institutional policies vary, but in general, full-term infants <50 weeks postconceptual age and preterm infants <55 weeks postconceptual age should be observed after repair for a minimum of 12 hours postoperatively and potentially overnight after general anesthesia for the development of apnea and bradycardia.

In children older than 1 year, the risk of incarceration is less, and the repair can be scheduled with less urgency. For the routine reducible hernia, the operation should be carried out electively shortly after diagnosis. Elective inguinal hernia repair in healthy children can be safely performed in an outpatient setting, with an expectation for full recovery within 48 hours. A regional caudal block or local inguinal nerve block using local anesthetic is useful to diminish perioperative pain and optimize recovery. Prophylactic antibiotics are not routinely used except for associated conditions, such as congenital heart disease or the presence of a ventriculoperitoneal shunt. *The operation should be performed at a facility with the ability to admit the patient to an inpatient unit as needed should concerns or complications arise.*

There is controversy as to the optimal timing of inguinal herniorrhaphy in preterm and low birthweight infants. In the past 2 decades, most pediatric surgeons have planned hernia repair shortly before discharge from the neonatal intensive care unit. This group has a high rate of incarceration but also a high risk of anesthesia-related postoperative complications with elective surgery, such as apnea, bradycardia, inability to extubate, hemodynamic instability (5–10%), and even cardiopulmonary arrest. In addition, this group has an increased rate of postoperative surgical-related complications such as wound infection (5–10%) and recurrent hernia (10%). At present, studies to develop evidence-based data for timing of inguinal hernia repair in premature infants are ongoing, but there is a lack of consensus, and patients should be individualized, with important consultation with both neonatology and pediatric anesthesia. The operation for inguinal hernia repair is most often performed under general anesthesia, but it can be performed under spinal/caudal anesthesia in selected high-risk infants in whom avoidance of intubation is preferable (e.g., because of chronic lung disease or bronchopulmonary dysplasia). In this setting, open repair (OH) is preferable to the laparoscopic approach, as it can be performed under local/regional techniques.

An incarcerated, irreducible hernia without evidence of strangulation in a clinically stable patient should initially be managed nonoperatively, unless there is evidence of bowel obstruction, peritonitis, or hemodynamic instability, because 70–95% of incarcerated inguinal hernias are successfully reduced. Manual reduction is performed using a surgical technique called *taxis*, first with traction caudad and posteriorly to free the mass from the external inguinal ring, and then upward to reduce the contents back into the peritoneal cavity. Reduction attempts usually require sedation (intravenous) and analgesics, and thus appropriate experience with monitoring and airway management are critical concerns. In addition, if reduction of the incarcerated hernia is successful, the infant may rapidly become somnolent and apneic, requiring important supportive measures by skilled personnel. Other techniques advocated to assist in the nonoperative reduction of an incarcerated inguinal hernia include elevation of the lower torso

and legs. Ice packs should be avoided in infants because of the risk of hypothermia but may be used for brief periods in the older child. If reduction is successful but difficult, the patient should be observed for several hours to ensure that feedings are tolerated and there is no concern that necrotic intestine was reduced; fortunately, this is an uncommon occurrence. Given the risk of early recurrent incarceration after a successful reduction, it is recommended that herniorrhaphy be performed after a brief period (1-4 days), by which time there is less edema, handling of the sac is easier, and the risk of complications is reduced.

If the inguinal hernia is unable to be reduced, or there is concern for an incomplete reduction, then operative reduction should be performed emergently. In addition, for any patient who presents with a prolonged history of incarceration of an inguinal hernia, signs of peritoneal irritation, or small bowel obstruction, surgery and operative reduction and repair of the hernia should be urgently performed. Initial management includes nasogastric intubation, intravenous fluids, and administration of broad-spectrum antibiotics. When fluid and electrolyte imbalance has been corrected and the child's condition is satisfactory, exploration is undertaken. In current practice, the laparoscopic approach may have advantages, as the abdominal cavity insufflation expands the internal ring, potentially aiding reduction of the incarcerated viscera and enabling visualization of the viscera for possible ischemic injury and/or perforation. The risk of postoperative complications such as testicular atrophy, bowel ischemia, wound infections, and recurrence of hernia is increased after emergency inguinal hernia repair: 4.5–33% compared with 1% in elective hernia repairs in healthy, full-term infants.

A common presentation in female patients is an irreducible ovary in the inguinal hernia in an otherwise asymptomatic patient. The inguinal mass is soft and nontender to gentle exam, and there is no swelling or edema; thus there are no findings suggesting strangulation. This represents a *sliding* hernia, with the fallopian tube and ovary fused to the wall of the hernia sac preventing reduction to the abdominal cavity. Overzealous attempts to reduce the hernia are unwarranted and potentially harmful to the tube and ovary. The risk that incarceration, most often resulting from torsion of the ovary in this setting, will lead to strangulation is not known. Most pediatric surgeons recommend elective repair of the hernia within 24–48 hours.

The appearance of necrotic ovaries and testes at the time of operation does not consistently provide evidence of irreversible damage or predict future functionality. Multiple studies report that even when ovaries appear persistently ischemic after relief of incarceration and detorsion, most ovaries, if preserved, will recover and demonstrate evidence of follicular development. Similarly, ischemic-appearing testes after relief of incarceration survive in as much as 50% of cases. Testicular atrophy occurs in 2.5–15% of incarcerated hernias. Given the potential for retained functionality, the current recommendation is to avoid testicular resection unless frank necrosis is present.

### Open Inguinal Hernia Repair

The operation is performed through a small (2–3 cm) inguinal skin crease incision. The procedure involves opening of the inguinal canal; reduction of the contents of the hernia sac if present, careful separation of the hernia sac from the cremasteric muscle fibers, spermatic cord vessels, and vas deferens to avoid injury to these structures in the inguinal canal, division of the hernia sac, and high ligation of the hernia sac at the internal ring, thus preventing protrusion of abdominal contents into the inguinal canal. A communicating hydrocele is approached with the same technique, separation of the spermatic cord structures from the hernia sac, high ligation of the proximal portion of the hernia sac, and opening of the distal sac to relieve the hydrocele. In older children with a noncommunicating hydrocele, the approach may be through a scrotal incision with avoidance of manipulation of the spermatic cord vessels and vas deferens. Open inguinal hernia repair has a low rate of recurrence, vas deferens injury, and testicular atrophy (~1–2%).

In females, surgical repair is technically simpler because the hernia sac and round ligament can be ligated without concern for injury to the ovary and its blood supply, which generally remain within the

abdomen. The hernia sac and round ligament are divided from their distal attachment in the labia majora, proximal dissection away from the cremasteric muscle fibers to the internal ring, and high ligation at the internal ring. In female infants, opening of the sac to visualize the ovary and fallopian tube may help avoid injury to these structures during suture ligation of the sac and also rule out testicular feminization syndrome. If the ovary and fallopian tube are within the sac and not reducible, the sac is suture ligated distal to these structures, and the internal ring is closed after reducing the sac and its contents to the abdominal cavity.

### Laparoscopic Inguinal Hernia Repair

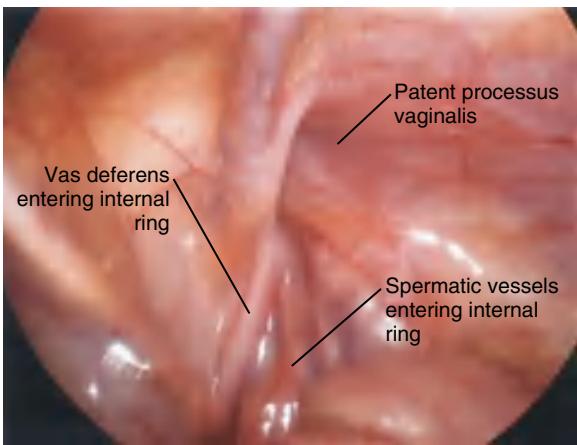
Laparoscopic repair (LH) is used by most pediatric surgeons. There are several techniques described, both transperitoneal and preperitoneal, depending on surgeon preference. The laparoscopic technique is fundamentally a high ligation of the indirect inguinal hernia sac (PV) at the internal ring to prevent protrusion of abdominal viscera into the inguinal canal. The laparoscopic technique affords confirmation of the diagnosis and inspection of the contralateral side for the presence of a hernia or a patent PV (potential hernia). Reported advantages of laparoscopic repair (LH) compared with open repair (OH) include better cosmesis, shorter length of stay (LOS), faster recovery, and greater ability to visualize and repair a contralateral hernia.

In LH, the inguinal canal is not explored, and the spermatic cord structures are not manipulated, which may portend reduced risk to the testicular blood supply or vas deferens, particularly in younger patients. Disadvantages of LH in infants and younger children are the increased risk associated with general anesthesia, the potential hemodynamic effects of abdominal insufflation (e.g., acidosis, compromised venous return), and technical challenges of the LH technique. Operative times have been similar for the OH and LH approaches; however, there is wide variability with the LH technique based on the experience of the surgeon and surgical team. Laparoscopic procedures in infants should always be performed expeditiously and with low insufflation pressure to avoid the risk of cardiorespiratory compromise and development of acidosis. Postoperative pain in both techniques is managed with oral acetaminophen for 24–48 hours; older children may require a brief period of postoperative NSAIDs or narcotics. In a prospective, randomized study, the laparoscopic approach was associated with decreased pain, parental perception of faster recovery, and parental perception of better wound cosmesis. At present, outcomes, recurrence rates, recovery metrics, complications, and family satisfaction appear similar for both approaches (OH and LH), and evidence is lacking to recommend one approach over the other.

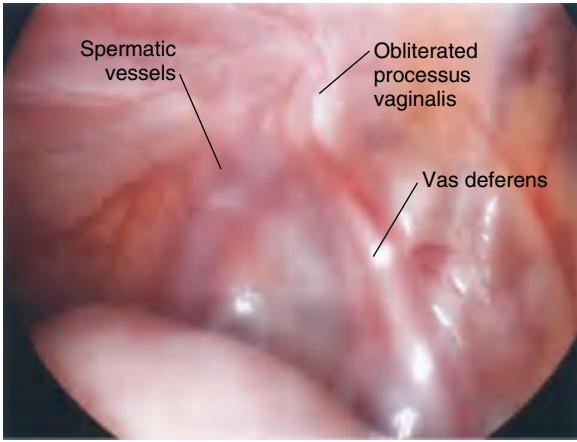
### Contralateral Inguinal Exploration

Most children (85%) present with a unilateral inguinal hernia. Controversy exists regarding when to proceed with contralateral groin exploration. The only purpose of contralateral exploration is to avoid the occurrence of a hernia on that side at a later date. The advantages of contralateral exploration include avoidance of parental anxiety and possibly a second anesthesia, the cost of additional surgery, and the risk of contralateral incarceration. The disadvantages of exploration include potential injury to the spermatic cord vessels, vas deferens, and testis and increased operative and anesthesia time.

Laparoscopy enables assessment of the contralateral side without risk of injury to the spermatic cord structures or testis. When performing OH repair, the laparoscope can be introduced through an umbilical incision or by passing a 30-degree or 70-degree oblique scope through the OH sac before ligation of the hernia sac on the involved side. If patency of the contralateral side is demonstrated, the surgeon can proceed with bilateral hernia repair, and if the contralateral side is properly obliterated, exploration and potential complications are avoided. When performing LH, visualization of the contralateral side is easily performed. The downside of this approach includes the risks associated with laparoscopy and that laparoscopy cannot differentiate between a patent PV and a true hernia (Figs. 394.2 and 394.3). In experienced hands, ultrasound has been proven to be a good alternative to surgical approaches to explore the contralateral groin. Infants and children



**Fig. 394.2** Laparoscopic image of patent processus vaginalis on right side.



**Fig. 394.3** Diagnostic laparoscopic image of obliterated processus vaginalis on left side.

with risk factors for development of an inguinal hernia or with medical conditions that increase the risk of general anesthesia should be approached with a low threshold for routine contralateral exploration.

### DIRECT INGUINAL HERNIA

Direct inguinal hernias are rare in children, approximately 0.5–1%. Direct hernias appear as groin masses that extend toward the femoral vessels with exertion or straining. The etiology is from a muscular defect or weakness in the floor of the inguinal canal *medial* to the epigastric vessels. Thus direct inguinal hernias in children are generally considered an acquired problem. In one third of cases, the patient has a history of a prior indirect hernia repair on the side of the direct hernia, which suggests a possible missed direct hernia at the initial surgery or injury to the floor muscles of the inguinal canal at the time of the first herniorrhaphy. Patients with **connective tissue disorders** such as Ehlers-Danlos syndrome or Marfan syndrome and mucopolysaccharidosis such as Hunter-Hurler syndrome are at increased risk for the development of direct inguinal hernias either independently or after indirect inguinal hernia repair.

Operative repair of a direct inguinal hernia involves strengthening of the floor of the inguinal canal, and many standard techniques have been described, similar to repair techniques used in adults. The repair can be performed through a single limited incision, and therefore LH does not offer a significant advantage. Recurrence after repair, in contrast to that in adults, is extraordinarily rare. Because typically the area

of muscular weakness is small and pediatric tissues have greater elasticity, primary repair is usually possible. Prosthetic material (mesh) for direct hernia repair or other approaches, such as preperitoneal repair, are rarely required in the pediatric age-group. The older child with a direct inguinal hernia and a connective tissue disorder may be the exception, and a laparoscopic approach and prosthetic material in such a case can be useful for repair.

### FEMORAL HERNIA

Femoral hernias are rare in children (<1% of groin hernias in children). They are more common in females than in males (2:1 ratio). They are extremely rare in infancy and occur typically in older children, believed to most often be an acquired defect. Femoral hernias represent a protrusion through the femoral canal. The bulge of a femoral hernia is located below the inguinal ligament and typically projects on the medial aspect of the proximal thigh. Femoral hernias are more often missed clinically than direct hernias on physical examination or at the time of indirect hernia repair. Repair of a femoral hernia involves closure of the defect at the femoral canal, generally suturing the inguinal ligament to the pecten ligament/fascia.

### COMPLICATIONS

Complications after elective inguinal hernia repair are uncommon (~1.5%) but significantly higher in association with incarceration (~10%). The major risk of elective inguinal hernia repair in infants and children relates to the need for general anesthesia, and spinal/caudal anesthesia should be considered based on the experience of the surgeon and anesthesia team. Surgical complications can be related to technical factors (recurrence, iatrogenic cryptorchidism or *trapped testicle*, inadvertent injury to the vas deferens or spermatic vessels) or to the underlying process, such as bowel ischemia, gonadal infarction, and testicular atrophy after incarceration. Because LH repair generally does not involve inguinal exploration or manipulation of the testicular vessels or vas deferens, the risk of injury is potentially lower, but supportive data are unavailable at present.

### Wound Infection

Wound infection occurs in <1% of elective inguinal hernia repairs in infants and children, but the incidence increases to 5–7% in association with incarceration and emergent repair. The patient typically develops fever and irritability 3–5 days after the surgery, and the wound demonstrates warmth, erythema, and fluctuance. Management consists of opening and draining the wound, a short course of antibiotics, and a daily wound dressing. The most common organisms are gram-positive (*Staphylococcus* and *Streptococcus* spp.), and consideration should be given to coverage of methicillin-resistant *Staphylococcus aureus*. The wound generally heals in 1–2 weeks with low morbidity and a good cosmetic result.

### Recurrent Hernia

The recurrence rate of inguinal hernias after elective inguinal hernia repairs is generally reported as 0.5–1.0%, with rates as high as 2% for premature infants. The rate of recurrence after emergency repair of an incarcerated hernia is much higher, reported as 3–6% in most large series. The true incidence of recurrence is most certainly even higher, given the problem of accurate long-term follow-up. In the group of patients who develop recurrent inguinal hernia, the recurrence occurs in 50% within 1 year of the initial repair and in 75% by 2 years. Recurrence of an indirect hernia may be the result of a technical problem in the original procedure, such as failure to identify the sac properly, failure to perform high ligation of the sac at the level of the internal ring, or a tear in the sac that leaves a strip of peritoneum along the cord structures. Recurrence as a direct hernia can result from injury to the inguinal floor (transversalis fascia) during the original procedure or, more likely, failure to identify a direct hernia during the original exploration. Patients with **connective tissue disorders** (collagen deficiency) or

conditions that cause *increased intraabdominal pressure* (ventriculo-peritoneal shunts, ascites, chronic lung disease, peritoneal dialysis) are at increased risk for recurrence.

### Iatrogenic Cryptorchidism (Trapped Testicle)

Iatrogenic cryptorchidism describes malposition of the testis after inguinal hernia repair. This complication is usually related to disruption of the testicular attachment in the scrotum at the time of hernia repair or failure to recognize an undescended testis during the original procedure, allowing the testes to retract, typically to the region of the external ring. At the completion of inguinal hernia repair, the testis should be placed in a dependent intrascrotal position. If the testis will not remain in this position, proper fixation in the scrotum should be performed at the time of the hernia repair.

### Incarceration

Incarceration of an inguinal hernia can result in injury to the intestines, the fallopian tube and ovary, or the ipsilateral testis. The incidence of incarceration of a congenital indirect inguinal hernia is reported as 6–18% throughout childhood and as high as 30% for infants younger than 6 months of age. Intestinal injury requiring bowel resection is uncommon, occurring in only 1–2% of incarcerated hernias. In cases of incarceration in which the hernia is reduced nonoperatively, the likelihood of intestinal injury is low; however, these patients should be observed closely for 6–12 hours after reduction of the hernia for signs and symptoms of intestinal obstruction, such as fever, vomiting, abdominal distention, or bloody stools. Laparoscopy affords the opportunity to inspect the reduced viscera for injury or necrosis in select cases.

The reported incidence of testicular infarction and subsequent testicular atrophy with incarceration is 4–12%, with higher rates among the irreducible cases requiring emergency operative reduction and repair. The testicular insult can be caused by compression of the gonadal vessels by the incarcerated hernia mass or as a result of damage incurred during operative repair. Young infants are at highest risk, with testicular infarction rates reported as high as 30% in infants younger than 2–3 months of age. These problems underscore the need for prompt reduction of incarcerated hernias and early repair once the diagnosis is known to avoid repeat episodes of incarceration.

### Injury to the Vas Deferens and Male Fertility

Similar to the gonadal vessels, the vas deferens can be injured as a consequence of compression from an incarcerated hernia or during operative repair. This injury is almost certainly underreported because it is unlikely to be recognized until adulthood and, even then, possibly only if the injury is bilateral. Although the vulnerability of the vas deferens has been documented in many studies, no good data exist as to the actual incidence of this complication. One review reported an incidence of injury to the vas deferens of 1.6% based on pathology demonstrating segments of the vas deferens in the hernia sac specimen; this may be overstated, because others have shown that small glandular inclusions found in the hernia sac can represent müllerian duct remnants and are of no clinical importance. The relationship between male fertility and previous inguinal hernia repair is also unknown. There appears to be an association between infertile males with testicular atrophy and abnormal sperm count and a previous hernia repair. A relationship has also been reported between infertile males with spermatic autoagglutinating antibodies and previous inguinal hernia repair. The proposed etiology is that operative injury to the vas deferens during inguinal hernia repair might result in obstruction of the vas with diversion of spermatozoa to the testicular lymphatics, and this breach of the blood-testis barrier produces an antigenic challenge, resulting in formation of spermatic autoagglutinating antibodies.

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## Section 5

# Exocrine Pancreas

## Chapter 395

# Embryology, Anatomy, and Physiology of the Pancreas

Steven L. Werlin and Michael Wilschanski

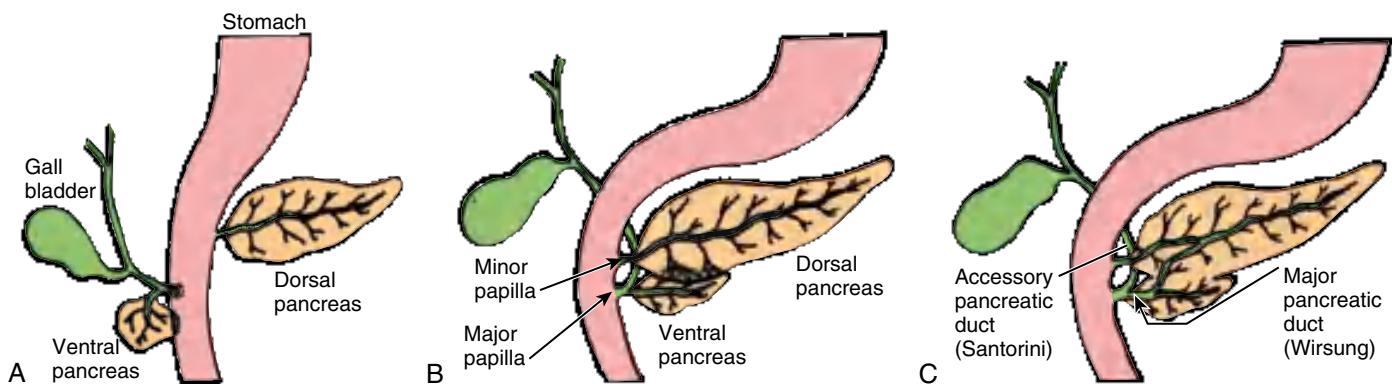
### INTRODUCTION

The human pancreas develops from the ventral and dorsal domains of the primitive duodenal endoderm beginning at about the fifth week of gestation (Fig. 395.1). The larger dorsal anlage, which develops into the tail, body, and part of the head of the pancreas, grows directly from the duodenum. The smaller ventral anlage develops as one or two buds from the primitive liver and eventually forms the major portion of the head of the pancreas. At about the 17th week of gestation, the dorsal and ventral anlagen fuse as the buds develop and the gut rotates. The ventral duct forms the proximal portion of the major pancreatic duct of Wirsung, which opens into the ampulla of Vater. The dorsal duct forms the distal portion of the duct of Wirsung and the accessory duct of Santorini, which empties independently in approximately 5% of people. Variations in fusion might account for pancreatic developmental anomalies. Pancreatic agenesis has been associated with a base pair deletion in the insulin promoter factor 1-HOX gene, *PDX1* (*PAGEN1*), *PTF1A* (*PAGEN2*), and *GATA 6 haploinsufficiency* genes. Other genes involved in pancreatic organogenesis include the *IHH*, *SHH* or sonic hedgehog gene, *SMAD2*, and *TGF-1 $\beta$*  genes.

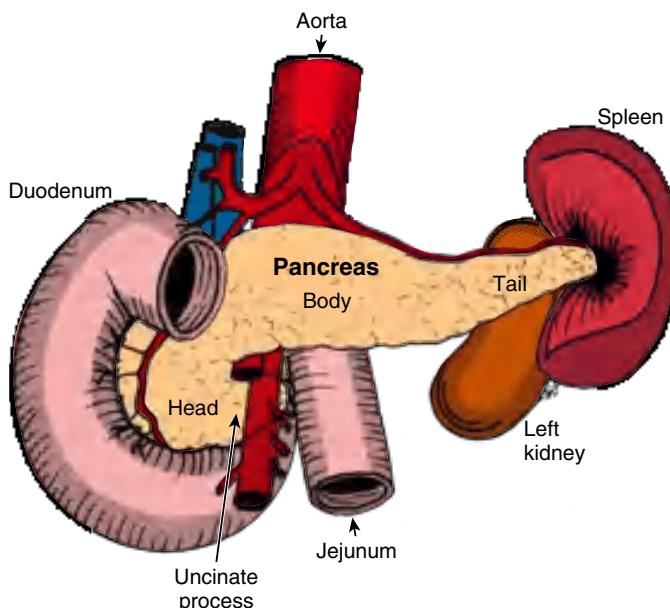
The pancreas lies transversely in the upper abdomen between the duodenum and the spleen in the retroperitoneum (Fig. 395.2). The head, which rests on the vena cava and renal vein, is adherent to the C loop of the duodenum and surrounds the distal common bile duct. The tail of the pancreas reaches to the left splenic hilum and passes above the left kidney. The lesser sac separates the tail of the pancreas from the stomach.

By the 13th week of gestation, exocrine and endocrine cells can be identified. Primitive acini containing immature zymogen granules are found by the 16th week. Mature zymogen granules containing amylase, trypsinogen, chymotrypsinogen, and lipase are present at the 20th week. Centroacinar and duct cells, which are responsible for water, electrolyte, and bicarbonate secretion, are also found by the 20th week. The final three-dimensional structure of the pancreas consists of a complex series of branching ducts surrounded by grapelike clusters of epithelial cells. Cells containing glucagon are present at the 8th week. Islets of Langerhans appear between the 12th and 16th weeks.

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**Fig. 395.1** Development of the exocrine pancreas. A, Gestational age 6 wk. B, Gestational age 7-8 wk. The ventral pancreas has rotated but has not yet fused with the dorsal pancreas. C, The ventral and dorsal pancreatic ductal systems have fused. (From Werlin SL. The exocrine pancreas. In: Kelly VC, ed. Practice of Pediatrics, vol 3. Hagerstown, MD: Harper and Row, 1980: Fig. 16.1.)



**Fig. 395.2** Anterior view of the pancreas and relationship to neighboring structures. (From Werlin SL. The exocrine pancreas. In: Kelly VC, ed. Practice of Pediatrics, vol 3. Hagerstown, MD: Harper and Row, 1980: Fig. 16.2.)

### 395.1 Pancreatic Anatomic Abnormalities

Steven L. Werlin and Michael Wilschanski

Complete or partial **pancreatic agenesis** is a rare condition. Complete agenesis is associated with severe neonatal diabetes and usually death at an early age (see Chapter 629). Partial or dorsal pancreatic agenesis is often asymptomatic but may be associated with diabetes, congenital heart disease, polysplenia, and recurrent pancreatitis. Pancreatic agenesis is also associated with malabsorption.

An **annular pancreas** results from incomplete rotation of the left (ventral) pancreatic anlage, which may be a result of recessive pathogenic variants in the *IHH* or *SHH* genes. Patients usually present in infancy with symptoms of complete or partial bowel obstruction or in the fourth or fifth decade. There is often a history of maternal

polyhydramnios. Other congenital anomalies, such as Down syndrome, tracheoesophageal fistula, intestinal atresia, imperforate anus, malrotation and cardiorenal abnormalities, and pancreatitis, may be associated with annular pancreas. Some children present with chronic vomiting, pancreatitis, or biliary colic. The treatment of choice is duodenaljejunostomy. Division of the pancreatic ring is not attempted because a duodenal diaphragm or duodenal stenosis often accompanies annular pancreas.

**Ectopic pancreatic rests** in the stomach or small intestine occur in approximately 3% of the population. Most cases (70%) are found in the upper intestinal tract. Recognized on barium contrast studies by their typical umbilicated appearance, they are rarely of clinical importance. On endoscopy, they are irregular, yellow nodules 2-4 mm in diameter. A pancreatic rest may rarely be the lead point of an intussusception, produce hemorrhage, or cause bowel obstruction.

**Pancreas divisum**, which occurs in 5-15% of the population, is the most common pancreatic developmental anomaly. Because of the failure of the dorsal and ventral pancreatic anlagen to fuse, the tail, body, and part of the head of the pancreas drain through the small accessory duct of Santorini rather than the main duct of Wirsung. Some researchers believe that this anomaly may be associated with recurrent pancreatitis when there is relative obstruction of the outflow of the ventral pancreas. Diagnosis is made by endoscopic retrograde cholangiopancreatography or by magnetic resonance cholangiopancreatography. Pancreatitis in patients with pancreas divisum may be associated with pathogenic *CFTR* variants. Sphincterotomy is not recommended unless other anomalies are present or the patient has classic pancreatobiliary-type pain, recurrent pancreatitis, or chronic pancreatitis, and no other etiology is found.

**Choledochal cysts** are dilations of the biliary tract and usually cause biliary tract symptoms, such as jaundice, pain, and fever. On occasion, the presentation may be pancreatitis. The diagnosis is usually made with ultrasonography, CT or biliary scanning, or magnetic resonance cholangiopancreatography. Similarly, a choledochocele—an intraduodenal choledochal cyst—may manifest with pancreatitis. The diagnosis can be difficult and require magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, or endoscopic ultrasound.

A number of rare conditions, such as Ivemark (pathogenic variant in *GDF* gene) and Johanson-Blizzard (pathogenic variant in *UBR1* gene) syndromes, include pancreatic dysgenesis or dysfunction among their features. Many of these syndromes include renal and hepatic dysgenesis along with the pancreatic anomalies.

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## 395.2 Pancreatic Physiology

Steven L. Werlin and Michael Wilschanski

The acinus is the functional unit of the exocrine pancreas. Acinar cells are arrayed in a semicircle around a lumen. Ducts that drain the acini are lined by centroacinar and ductular cells. This arrangement allows the secretions of the various cell types to mix.

The acinar cell synthesizes, stores, and secretes more than 20 enzymes, which are stored in zymogen granules, some in inactive forms. The relative concentration of the various enzymes in pancreatic juice is affected and perhaps controlled by the diet, probably by regulating the synthesis of specific messenger RNA. The main enzymes involved in digestion include *amylase*, which splits starch into maltose, isomaltose, and maltotriose; dextrins; and *trypsin* and *chymotrypsin*, endopeptidases secreted by the pancreas as inactive proenzymes. Trypsinogen is activated in the gut lumen by enterokinase, a brush-border enzyme. Trypsin can then activate trypsinogen, chymotrypsinogen, and procarboxypeptidase into their respective active forms. Pancreatic lipase requires *colipase*, a coenzyme also found in pancreatic fluid, for activity. Lipase liberates fatty acids from the 1 and 3 positions of triglycerides, leaving a monoglyceride.

The stimuli for exocrine pancreatic secretion are neural and hormonal. Acetylcholine mediates the cephalic phase; cholecystokinin (CCK) mediates the intestinal phase. CCK is released from the duodenal mucosa by luminal amino acids and fatty acids. Feedback regulation of pancreatic secretion is mediated by pancreatic proteases in the duodenum. Secretion of CCK is inhibited by the digestion of a trypsin-sensitive, CCK-releasing peptide released in the lumen of the small intestine or by a monitor peptide released in pancreatic fluid.

Centroacinar and duct cells secrete water and bicarbonate. Bicarbonate secretion is under feedback control and is regulated by duodenal intraluminal pH. The stimulus for bicarbonate production is secretin in concert with CCK. Secretin cells are abundant in the duodenum.

Although normal pancreatic function is required for digestion, malabsorption occurs only after considerable reduction in pancreatic function; lipase and colipase secretion must be decreased by 90–98% before fat malabsorption occurs.

Although amylase and lipase are present in the pancreas early in gestation, secretion of both amylase and lipase is low in infants. Adult levels of these enzymes are not reached in the duodenum until late in the first year of life. Digestion of the starch found in many infant formulas depends in part on the low levels of salivary amylase that reach the duodenum. This explains the diarrhea that may be seen in infants who are fed formulas high in glucose polymers or starch. Neontal secretion of trypsinogen and chymotrypsinogen is at approximately 70% of the level found in the 1-year-old infant. The low levels of amylase and lipase in duodenal contents of infants may be partially compensated by salivary amylase and lingual lipase. This explains the relative starch and fat intolerance of premature infants.

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>90%. When compared with a 72-hour fecal fat content in both pancreatic insufficient and sufficient patients, an elastase value of 100 µg/g stool has a 99% predictive value in ruling out pancreatic insufficiency based on an abnormal fecal fat finding. Falsely abnormal results can occur in many enteropathies and when the stool is very loose.

### DIRECT TESTS

Classically, a triple-lumen tube was used to isolate the pancreatic secretions in the duodenum. Measurement of bicarbonate concentration and enzyme activity (*trypsin*, *chymotrypsin*, *lipase*, and *amylase*) is performed on the aspirated secretions. This test is cumbersome and infrequently used in children. Endoscopic collection of pancreatic secretions after stimulation with secretin and/or cholecystokinin is the commonly used direct test.

A 72-hour stool collection for quantitative analysis of fat content is the gold standard for the diagnosis of *malabsorption*. The collection can be performed at home, and the parent is asked to keep a careful dietary record, from which fat intake is calculated. A preweighed, sealable plastic container is used, which the parent keeps in the freezer. Freezing helps to preserve the specimen and reduce odor. Infants are dressed in disposable diapers with the plastic side facing the skin so that the complete sample can be transferred to the container. Normal fat absorption is >93% of intake. The presence of fat malabsorption does not differentiate between pancreatic dysfunction and enteropathies, such as celiac disease. Qualitative examination of the stool for microscopic fat globules can give false-positive and false-negative results.

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## Chapter 397

# Disorders of the Exocrine Pancreas

Steven L. Werlin and Michael Wilschanski

### DISORDERS ASSOCIATED WITH PANCREATIC INSUFFICIENCY

Other than cystic fibrosis (CF), conditions that cause pancreatic insufficiency are very rare in children. They include Shwachman-Diamond syndrome (SDS), Johanson-Blizzard syndrome, Ivemark syndrome, Pearson syndrome, isolated enzyme deficiencies (see Chapter 385.8), enterokinase deficiency, chronic pancreatitis, protein-calorie malnutrition (see Chapters 64 and 385.7), and IMNEPD (infantile onset multisystem neurologic, endocrine, and pancreatic disease).

### CYSTIC FIBROSIS

See Chapter 454.

By the end of the first year of life, 85–90% of children with CF have pancreatic insufficiency, which, if untreated, will lead to malnutrition. Treatment of the associated pancreatic insufficiency leads to improvement in absorption, better growth, and more normal stools. Pancreatic function can be monitored in children with CF with serial measurements of fecal elastase. Between 10–15% of children present with a *neonatal* intestinal obstruction called **meconium ileus**; in later life, a common intestinal complication is **distal intestinal obstruction syndrome**, which is unique to CF.

## Chapter 396

# Pancreatic Function Tests

Michael Wilschanski and Steven L. Werlin

Pancreatic function can be measured by direct and indirect methods. An indirect test, the measurement of *fecal elastase*, which is the standard screening test for pancreatic insufficiency, has a sensitivity and specificity

Ten percent of CF patients develop severe liver disease. Between 10–15% of CF patients are pancreatic sufficient, and their presentation tends to be later in life, including recurrent pancreatitis, male infertility, and chronic bronchiectasis. CF is part of the newborn screen in every state in the United States and in most countries in the Western world. Pathogenic gene variant specific therapy has caused great improvements in pulmonary function and weight gain, which is probably a direct effect on the gastrointestinal tract. The first drug to be released, Ivacaftor, reduced the number of episodes of pancreatitis in CF patients who were prone to recurrent pancreatitis; in younger patients, fecal elastase was significantly increased.

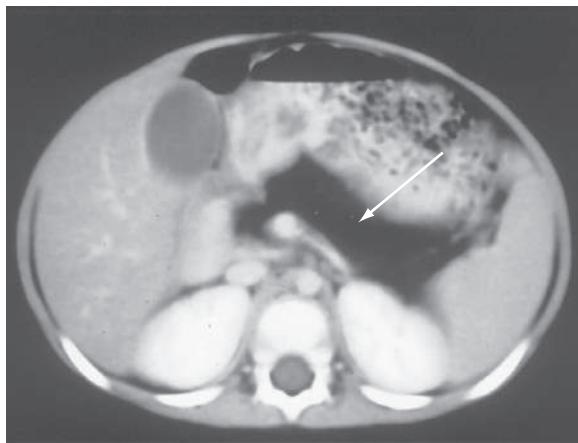
### SHWACHMAN-DIAMOND SYNDROME

See Chapter 171.

SDS is an autosomal recessive syndrome (1/20,000 births) caused by a pathogenic variant of the Shwachman-Bodian-Diamond syndrome (*SBDS*) gene on chromosome 7, which causes ribosomal dysfunction in 90–95% of patients. Signs and symptoms of SDS include pancreatic insufficiency, neutrophil chemotaxis defects, metaphyseal dysostosis, failure to thrive, short stature, and neutropenia, which may be cyclic. Some patients with SDS have liver or kidney involvement, dental disease, or learning difficulty. SDS is a common cause of congenital neutropenia.

Patients typically present in infancy with poor growth and steatorrhea. More varied phenotypes have been described, including absence of pancreatic lipomatosis on imaging, normal fecal elastase levels, and normal skeletal survey. These children can be readily differentiated from those with CF by their normal sweat chloride levels, lack of pathogenic variants in the CF gene, characteristic metaphyseal lesions, and fatty pancreas characterized by a hypodense appearance on CT and MRI scans (Fig. 397.1).

Despite adequate pancreatic replacement therapy and correction of malabsorption, poor growth commonly continues. Pancreatic insufficiency is often transient, and steatorrhea frequently spontaneously improves with age. Recurrent pyogenic infections (otitis



**Fig. 397.1** CT appearance of the pancreas in a patient with Shwachman-Diamond syndrome. Note that the pancreas (arrow) retains a typical size and shape, but it is highly fatty and therefore appears as a very low-density structure. (Courtesy Prof. Peter Durie, Hospital for Sick Children, Toronto, Ontario.)

media, pneumonia, osteomyelitis, dermatitis, sepsis) are frequent and are a common cause of death. Thrombocytopenia is found in 70% of patients and anemia in 50%. Development of aplastic anemia or a *myelodysplastic syndrome* can occur, with transformation to *acute myeloid leukemia* in 24%. The pancreatic acini are replaced by fat with little fibrosis. Islet cells and ducts are normal. Bone marrow transplant is the treatment of choice in patients who develop acute myeloid leukemia.

### PEARSON SYNDROME

Pearson (marrow-pancreas) syndrome is caused by a contiguous mitochondrial gene depletion involving several mitochondrial genes affecting oxidative phosphorylation, which manifests in infants with severe macrocytic anemia and variable thrombocytopenia. The bone marrow demonstrates vacuoles in erythroid and myeloid precursors as well as ringed sideroblasts. In addition to its role in severe bone marrow failure, pancreatic insufficiency contributes to growth failure. Mitochondrial DNA mutations are transmitted through maternal inheritance to both sexes or are sporadic.

### JOHANSON-BLIZZARD SYNDROME

The features of Johanson-Blizzard syndrome include exocrine pancreatic deficiency, aplasia or hypoplasia of the alae nasi, congenital deafness, hypothyroidism, developmental delay, short stature, ectodermal scalp defects, absence of permanent teeth, urogenital malformations, and imperforate anus. This syndrome is caused by a pathogenic variant in the *UBR1* gene found on chromosome 15.

### ISOLATED ENZYME DEFICIENCIES

Isolated deficiencies of trypsinogen, enterokinase, lipase, and colipase have been reported. Although enterokinase is a brush-border enzyme, deficiency causes pancreatic insufficiency because enterokinase is required to activate trypsinogen to trypsin in the duodenum. Deficiencies of trypsinogen or enterokinase manifest with failure to thrive, hypoproteinemia, and edema. Isolated amylase deficiency is typically developmental and resolves by age 2–3 years.

### OTHER SYNDROMES ASSOCIATED WITH PANCREATIC INSUFFICIENCY

Pancreatic agenesis, congenital pancreatic hypoplasia, and congenital rubella are rare causes of pancreatic insufficiency. Pancreatic insufficiency has also been reported in celiac disease and inflammatory bowel disease. It may occur in duodenal atresia and stenosis and may also be seen in infants with familial or nonfamilial hyperinsulinemic hypoglycemia after a 95–100% pancreatectomy to control hypoglycemia. Pathogenic variants in at least six genes have been described. Pancreatic insufficiency, which may be found in children with celiac disease and undernutrition, recovers with nutritional rehabilitation.

**Infantile onset multisystem neurology endocrine and pancreatic disease (IMNEPD)** is a rare disease caused by pathogenic variants in the *PTRH2* gene. Neurologic features dominate the phenotype (microcephaly, intellectual disability, cerebellar atrophy, deafness, and neuropathy), but pancreatic insufficiency is seen in most patients.

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## Chapter 398

# Treatment of Pancreatic Insufficiency

Michael Wilschanski and Steven L. Werlin

The most important treatment of pancreatic insufficiency (PI) is pancreatic enzyme replacement therapy (PERT). In modern enzyme capsules, the enzymes are enterically coated to protect the enzymes from degradation by gastric acid and from autodigestion in the small intestine. It is common for patients to change from one product to another using a 1:1 lipase ratio and then titrating for maximum efficacy (Table 398.1).

The North American CF Foundation has published dosing guidelines based on age and fat ingestion (Table 398.2). Because these products contain excess protease compared with lipase, the dosage is estimated from the lipase requirement. The final dosage of PERT for children is often established by trial and error. An adequate dose is one that is followed by resumption of normal growth and the return of stools to normal fat content, which, when desired, can be verified by a 72-hour fecal fat collection and normalization of stool consistency and color. Because there is no elastase in enzyme preparations, fecal elastase

**Table 398.1** FDA-Approved Pancreatic Enzyme Replacement Products for Exocrine Pancreatic Insufficiency\*

DRUG	AVAILABLE STRENGTHS
<b>IMMEDIATE-RELEASE</b>	
Viokace (Allergan) <sup>†,§,  </sup>	10,440 or 20,880 units of lipase <sup>¶</sup>
<b>DELAYED-RELEASE</b>	
Creon (AbbVie)	3,000, 6,000, 12,000, 24,000, or 36,000 USP units of lipase <sup>¶,  ,**</sup>
Pancreaze (Janssen)	2,600, 4,200, 10,500, 16,800, or 21,000 units of lipase <sup>¶,  ,**</sup>
Pertzye (Digestive Care)	4,000, 8,000, 16,000, or 24,000 units of lipase <sup>¶,  ,**</sup>
Zenpep (Allergan)	3,000, 5,000, 10,000, 15,000, 20,000, 25,000, or 40,000 units of lipase <sup>¶,  ,**</sup>

\*Pancrelipase products are not interchangeable. All of these products contain a combination of porcine-derived lipases, proteases, and amylases.

†Viokace is only approved for use in adults.

§Should be used in combination with a proton pump inhibitor to maximize absorption in the duodenum.

||FDA-approved only for treatment of adults with EPI because of chronic pancreatitis or pancreatectomy.

¶Should not be crushed or chewed.

\*\*Capsules can be opened and contents sprinkled on soft acidic food ( $\text{pH} \leq 4.5$ ) such as applesauce.

From The Medical Letter. Pancreatic enzyme replacement products. Med Lett. 2017;59(1531):170.

**Table 398.2**

## Pancreatic Enzyme Replacement Therapy: North American CF Foundation Consensus Statement

Infants (up to 12 mo)	2,000-4,000 U lipase/120 mL breast milk or formula
12 mo to 4 yr	1,000 U lipase/kg/meal initially, then titrate per response
Children >4 yr and adults	500 U lipase/kg/meal initially, up to maximum of 2,500 U lipase/kg/meal or 10,000 U lipase/kg/day or 4,000 U lipase/g fat ingested per day

PLUS: one half the standard meal dose to be given with snacks.

cannot be used to monitor appropriateness of PERT dosage. Enzyme replacement should be divided and given at the beginning of and during the meal. Enzymes should not be chewed, crushed, or dissolved in food, which would allow gastric acid to penetrate the enteric coating and destroy the enzymes. Enzymes must also be given with snacks that contain fat. Increasing enzyme supplements beyond the recommended dose does not improve absorption, might retard growth, and can cause fibrosing colonopathy (see later).

A major concern has been the ingestion of enzymes by infants. The importance of correct enzyme ingestion in infants and children is obvious, but there may be difficulty in feeding the infant microspheres, however small they may be. Enterically coated microspheres can be mixed with applesauce for oral use or crushed for use in tube feeding. Patients treated with this approach do achieve growth and weight gain. Pancreatic enzymes specifically prepared for infants and young children with smaller granules have been developed.

Treatment of exocrine PI by oral enzyme replacement usually corrects protein malabsorption, but steatorrhea is difficult to correct completely. Factors contributing to fat malabsorption include inadequate dosage, incorrect timing of doses in relation to food consumption or gastric emptying, lipase inactivation by gastric acid, and the observation that *chymotrypsin* in the enzyme preparation digests and thus inactivates *lipase*.

When adequate fat absorption is not achieved, gastric acid neutralization with an  $\text{H}_2$ -receptor antagonist or, more commonly, a proton pump inhibitor, decreases enzyme inactivation by gastric acid and thus improves delivery of lipase into the intestine. Enteric coating also protects lipase from acid inactivation.

Untoward effects secondary to PERT include allergic reactions and kidney stones. Fibrosing colonopathy, consisting of colonic fibrosis and strictures, can occur 7-12 months after severe overdose of PERT. This iatrogenic complication is now very uncommon.

Fat-soluble vitamin supplements are required by PI patients because of the ongoing mild to moderate fat malabsorption that occurs despite PERT.

Knowledge of novel mechanisms affecting absorption, such as intestinal microbiota, may, in the future, be therapeutic targets in the treatment of exocrine pancreatic insufficiency.

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## Chapter 399

# Pancreatitis

### 399.1 Acute Pancreatitis

Steven L. Werlin and Michael Wilschanski

Acute pancreatitis (AP) is the most common pancreatic disorder in children; 50 or more cases are usually seen in major pediatric centers per year. In children, blunt abdominal injuries, multisystem disease such as the hemolytic uremic syndrome and inflammatory bowel disease, biliary stones or microlithiasis (sludging), and drug toxicity are the most common etiologies. Although many drugs and toxins can induce AP in susceptible persons, in children, valproic acid, L-asparaginase, 6-mercaptopurine, and azathioprine are the most common causes of drug-induced pancreatitis. Alcohol should be considered in adolescents. Other cases follow organ transplantation or are caused by infections, metabolic disorders, or mutations in susceptibility genes. Only 10–20% of cases are idiopathic (*Table 399.1*).

After an initial insult, such as ductal disruption or obstruction, there is premature activation of trypsinogen to trypsin within the acinar cell. Trypsin then activates other pancreatic proenzymes, leading to autodigestion, further enzyme activation, and release of active proteases. Lysosomal hydrolases co-localize with pancreatic proenzymes within the acinar cell. Pancreastasis (similar in concept to cholestasis) with continued synthesis of enzymes occurs. Lecithin is activated by phospholipase A<sub>2</sub> into the toxic lysolecithin. Prophospholipase is unstable and can be activated by minute quantities of trypsin. After the insult, cytokines and other proinflammatory mediators are released.

The healthy pancreas is protected from autodigestion by pancreatic proteases that are synthesized as inactive proenzymes; digestive enzymes that are segregated into secretory granules at pH 6.2 by low calcium concentration, which minimizes trypsin activity; the presence of protease inhibitors both in the cytoplasm and zymogen granules; and enzymes that are secreted directly into the ducts.

Histopathologically, interstitial edema appears early. Later, as the episode of pancreatitis progresses, localized and confluent necrosis, blood vessel disruption leading to hemorrhage, and an inflammatory response in the peritoneum can develop.

The diagnosis of pancreatitis in children is made when two of three of the following are present: abdominal pain; serum amylase and/or lipase activity at least 3 times greater than the upper limit of normal; and imaging findings characteristic of, or compatible with, AP.

### CLINICAL MANIFESTATIONS

The severity of AP in children has been defined by a consensus committee.

**Mild Acute Pancreatitis:** AP that is not associated with organ failure, local or systemic complications, and usually resolves within the first week after presentation. This is the most common form of pediatric AP.

The patient with mild AP has moderate to severe abdominal pain, persistent vomiting, and possibly fever. The pain is epigastric or in either upper quadrant and steady, often resulting in the child's assuming an antalgic position with hips and knees flexed, sitting upright, or lying on the side. The child is uncomfortable, irritable, and appears acutely ill. The abdomen may be distended and tender, and a mass may be palpable. The pain can increase in intensity for 24–48 hours, during which time vomiting may increase and the patient can require hospitalization for fluid and electrolyte therapy and analgesia. There is no other organ failure, and imaging does not demonstrate peri- or pancreatic necrosis. The prognosis for

complete recovery in the acute uncomplicated case after 4–7 days is excellent.

**Moderately Severe Acute Pancreatitis:** AP with either transient organ failure/dysfunction (lasting <48 hours) or development of local or systemic complications, such as exacerbation of previously diagnosed comorbid disease (such as lung or kidney disease). Imaging may reveal sterile (peri-) pancreatic necrosis. The prognosis for these patients is also excellent, but recovery may be prolonged.

**Severe Acute Pancreatitis:** AP with development of other organ dysfunction (lung, cardiac, renal) that persists longer than 48 hours. Persistent organ failure may be single or multiple. Severe AP is uncommon in children. In this life-threatening condition, the patient is acutely ill with severe nausea, vomiting, and abdominal pain. Shock, high fever, jaundice, ascites, hypocalcemia, and pleural effusions can occur. A bluish discoloration may be seen around the umbilicus (Cullen sign) or in the flanks (Grey Turner sign). The pancreas is necrotic and can be transformed into an inflammatory hemorrhagic mass. The mortality rate, which is approximately 20%, is related to the systemic inflammatory response syndrome with multiple organ dysfunction, shock, renal failure, acute respiratory distress syndrome, disseminated intravascular coagulation, gastrointestinal bleeding, and systemic or intraabdominal infection. The percentage of necrosis seen on CT and failure of pancreatic tissue to enhance on CT (suggesting necrosis) predicts the severity of the disease.

### DIAGNOSIS

AP is usually diagnosed by measurement of serum lipase and amylase activities. Serum lipase is considered the test of choice for AP because it is more specific than amylase for acute inflammatory pancreatic disease and should be determined when pancreatitis is suspected. The serum lipase rises by 4–8 hours, peaks at 24–48 hours, and remains elevated 8–14 days longer than serum amylase. Serum lipase greater than 7 times the upper limit of normal obtained within 24 hours of presentation may predict a severe course. Serum lipase can be elevated in nonpancreatic diseases. The serum amylase level is typically elevated for up to 4 days. A variety of other conditions can also cause hyperamylasemia without pancreatitis (*Table 399.2*). Elevation of salivary amylase can mislead the clinician to diagnose pancreatitis in a child with abdominal pain. The laboratory can separate amylase isoenzymes into pancreatic and salivary fractions. Initially serum amylase levels are normal in 10–15% of patients.

Other laboratory abnormalities that may be present in AP include hemoconcentration, coagulopathy, leukocytosis, hyperglycemia, glucosuria, hypocalcemia, elevated  $\gamma$ -glutamyl transpeptidase, and hyperbilirubinemia.

X-ray of the chest and abdomen might demonstrate nonspecific findings such as atelectasis, basilar infiltrates, elevation of the hemidiaphragm, left- (rarely right-) sided pleural effusions, pericardial effusion, and pulmonary edema. Abdominal x-rays might demonstrate a sentinel loop, dilation of the transverse colon (cutoff sign), ileus, pancreatic calcification (if recurrent), blurring of the left psoas margin, a pseudocyst, diffuse abdominal haziness (ascites), and peripancreatic extraluminal gas bubbles.

CT has a major role in the diagnosis and follow-up of children with pancreatitis. Findings can include pancreatic enlargement; a hypoechoic, sonolucent edematous pancreas; pancreatic masses; fluid collections; and abscesses (*Fig. 399.1*). Normal imaging studies at the time of diagnosis are not uncommon. In adults, CT findings are the basis of a widely accepted prognostic system (*Table 399.3*). Ultrasonography is more sensitive than CT for the diagnosis of biliary stones. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) are essential in the investigation of recurrent pancreatitis, nonresolving pancreatitis, and disease associated with gallbladder pathology. Endoscopic ultrasonography also helps visualize the pancreaticobiliary system. Complications of AP are noted in *Table 399.4*.

**Table 399.1** Etiology of Acute and Recurrent Pancreatitis in Children

DRUGS AND TOXINS	OBSTRUCTIVE
Acetaminophen overdose	Ampullary disease
Alcohol	Ascariasis
Anabolic androgenic steroids	Biliary tract malformations
L-Asparaginase	Choledochal cyst
Azathioprine	Choledochocoele
Cannabis	Cholelithiasis, microlithiasis, and choledocholithiasis (stones or sludge)
Carbamazepine	Duplication cyst
Cimetidine	Endoscopic retrograde cholangiopancreatography (ERCP) complication
Cisplatin	Pancreas divisum
Corticosteroids	Pancreatic ductal abnormalities
Cytosine arabinoside	Postoperative
Dapsone	Sphincter of Oddi dysfunction
Didanosine	Tumor
Enalapril	
Erythromycin	
Estrogen	
Furosemide	
Glucagon-like peptide-1 agents	
Interferon- $\alpha$	
Isoniazid	
Lamivudine	
Lisinopril	
6-Mercaptopurine	
Methyldopa	
Mesalamine	
Metronidazole	
Organophosphate poisoning	
Pentamidine	
Procainamide	
Retrovirals: DDC (dideoxycytidine), DDI (dideoxyinosine), tenofovir	
Rifampin	
Sulfonamides: mesalamine, 5-aminosalicylates, sulfasalazine, trimethoprim-sulfamethoxazole	
Sulindac	
Tetracycline	
Thiazides	
Valproic acid	
Venom (spider, scorpion, Gila monster lizard)	
Vincristine	
Volatile hydrocarbons	
GENETIC	SYSTEMIC DISEASE
Cationic trypsinogen gene ( <i>PRSS1</i> )	Autoimmune pancreatitis (IgG4-related systemic disease)
Carboxypeptidase A1 ( <i>CPA1</i> )	Brain tumor
Chymotrypsin C gene ( <i>CTRC</i> )	Collagen vascular diseases
Cystic fibrosis gene ( <i>CFTR</i> )	Congenital partial lipodystrophy
Trypsin inhibitor gene ( <i>SPINK1</i> )	Crohn disease
	Diabetes mellitus (ketoacidosis)
INFECTIOUS	Head trauma
Ascariasis	Henoch-Schönlein purpura
COVID-19	Hemochromatosis
Coxsackie B virus	Hemolytic uremic syndrome
Echovirus	Hyperlipidemia: types I, IV, V
Enterovirus	Hyperparathyroidism/hypercalcemia
Epstein-Barr virus	Kawasaki disease
Hepatitis A, B	Malnutrition
Herpes viruses	Organic acidemia
Influenza A, B	Peptic ulcer
Leptospirosis	Periarteritis nodosa
Malaria	Renal failure
Measles	Scorpion venom
Mumps	Systemic lupus erythematosus
Mycoplasma	Transplantation: bone marrow, heart, liver, kidney, pancreas
Rabies	Vasculitis
Rubella	
Reye syndrome: varicella, influenza B	
Septic shock	
Thyroid fever	
TRAUMATIC	
	Blunt injury
	Burns
	Child abuse
	Hypothermia
	Surgical trauma
	Total-body cast

## TREATMENT

The aims of medical management are to relieve pain (often needing opioids) and restore metabolic homeostasis. Analgesia should be given in adequate doses. Fluid, electrolyte, and mineral balance should be restored and maintained. Intravenous fluids (lactated Ringer's solution)

is often required to correct hypovolemia because of poor fluid intake and the fluid losses secondary to capillary leak from the systemic inflammatory response syndrome. Excessive fluids should be avoided; fluid therapy should be titrated to improve vital signs and renal function. Nasogastric suction is useful in patients who are vomiting. Early refeeding decreases the complication rate and length of stay. In patients with pancreatitis who are not vomiting, oral nutrition should not be stopped. Recovery is usually complete within 4–5 days.

Prophylactic antibiotics are not recommended in inflammatory pancreatitis or with sterile necrosis, but broad-spectrum antibiotics are used to treat *infected* areas of pancreatic necrosis. Elevated serum procalcitonin levels suggest infection. Gastric acid secretion is suppressed with proton pump inhibitors. Enteral alimentation by mouth, nasogastric tube, or nasojejunal tube (in severe cases or for those intolerant of oral or nasogastric feedings) within 2–3 days of onset reduces the length of hospitalization, complication rate, and survival in patients with severe AP. In children, surgical therapy of nontraumatic AP is rarely required but may include drainage of necrotic material or abscesses. Endotherapy for common bile duct stones, ductal strictures, and for drainage of fluid collections is the standard of care when indicated.

## PROGNOSIS

Children with mild AP do well and recover within 4–5 days. When pancreatitis is associated with trauma or systemic disease, the prognosis is typically related to the associated medical conditions.

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**Table 399.2** Differential Diagnosis of Hyperamylasemia

### PANCREATIC PATHOLOGY

Acute or chronic pancreatitis  
Complications of pancreatitis (pseudocyst, ascites, abscess)  
Factitious pancreatitis

### SALIVARY GLAND PATHOLOGY

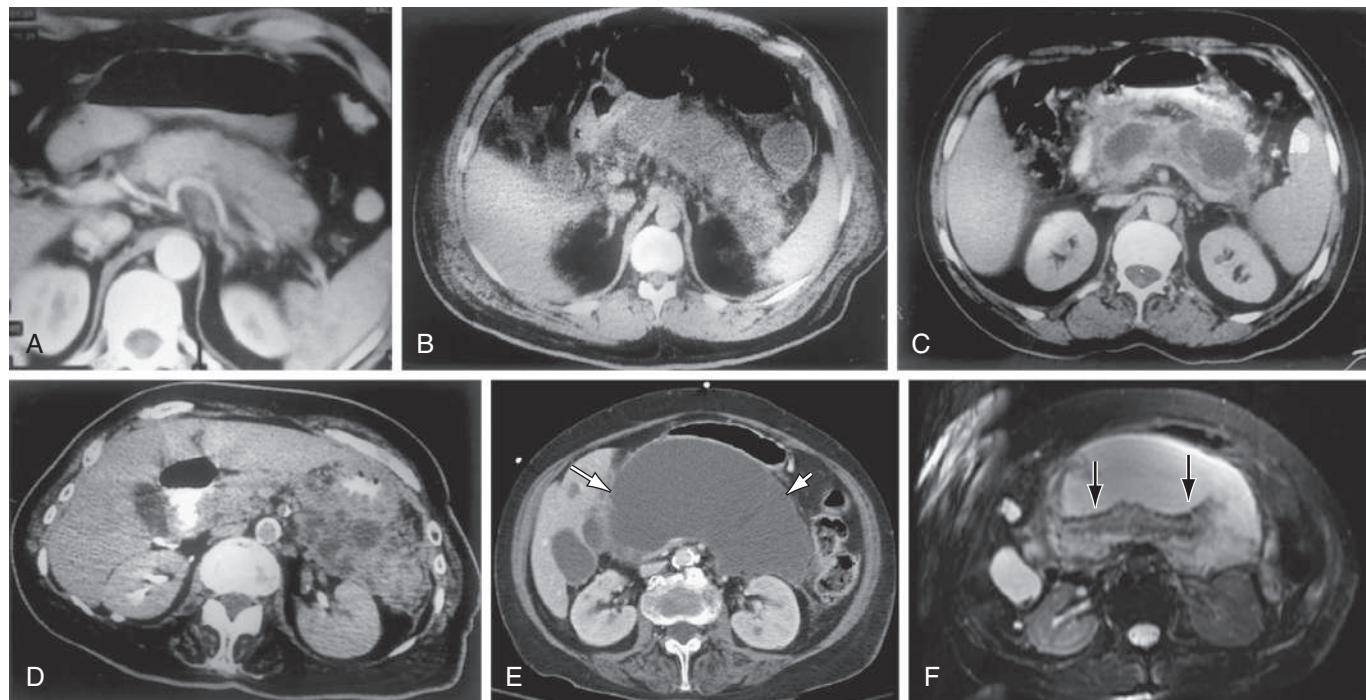
Parotitis (mumps, *Staphylococcus aureus*, cytomegalovirus, HIV, Epstein-Barr virus)  
Sialadenitis (calculus, radiation)  
Eating disorders (anorexia nervosa, bulimia)

### INTRAABDOMINAL PATHOLOGY

Biliary tract disease (cholelithiasis)  
Peptic ulcer perforation  
Peritonitis  
Intestinal obstruction  
Appendicitis

### SYSTEMIC DISEASES

Metabolic acidosis (diabetes mellitus, shock)  
Renal insufficiency, transplantation  
Burns  
Pregnancy  
Drugs (morphine)  
Head injury  
Cardiopulmonary bypass



**Fig. 399.1** CT and MRI appearance of pancreatitis. A, Mild acute pancreatitis. Arterial phase spiral CT. Diffuse enlargement of pancreas without fluid accumulation. B, Severe acute pancreatitis. Lack of enhancement of the pancreatic parenchyma because of the necrosis of the entire pancreatic gland. C, Pancreatic pseudocyst. A round fluid collection with thin capsule is seen within the lesser sac. D, Acute severe pancreatitis and peripancreatic abscess formation. Peripancreatic abscess formation is observed within the peripancreatic and the left anterior pararenal space. E, Pancreatic necrosis. A well-defined fluid attenuation collection in the pancreatic bed (white arrows) seen on contrast-enhanced CT imaging. F, The same collection is more complex appearing on the corresponding T2-weighted MR image. The internal debris and necrotic tissue are better appreciated because of the superior soft tissue contrast of MRI (black arrows). (A-D from Elmas N. The role of diagnostic radiology in pancreatitis. Eur J Radiol. 2001;38[2]:120–132. Figs. 1, 3b, 4a, and 5; E and F from Soakar A, Rabinowitz CB, Sahani DV. Cross-sectional imaging in acute pancreatitis. Radiol Clin North Am. 2007;45[3]:447–460. Fig. 14.)

Table 399.3	Revised Definitions of Morphologic Features of Acute Pancreatitis
<b>INTERSTITIAL EDEMATOUS PANCREATITIS</b>	
Acute inflammation of the pancreatic parenchyma and peripancreatic tissues but without recognizable tissue necrosis	
<b>CECT criteria</b>	
<ul style="list-style-type: none"> <li>Pancreatic parenchyma enhancement by intravenous contrast agent</li> <li>No peripancreatic necrosis</li> </ul>	
<b>NECROTIZING PANCREATITIS</b>	
Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis	
<b>CECT criteria</b>	
<ul style="list-style-type: none"> <li>Lack of pancreatic parenchymal enhancement by intravenous contrast agent</li> <li>Presence of findings of peripancreatic necrosis</li> </ul>	
<b>ACUTE PANCREATITIS FLUID COLLECTION</b>	
Peripancreatic fluid associated with interstitial edematous pancreatitis with no associated peripancreatic necrosis. Applies only to areas of peripancreatic fluid seen within the first 4 wk after onset of interstitial edematous pancreatitis and without the features of a pseudocyst.	
<b>CECT criteria</b>	
<ul style="list-style-type: none"> <li>Occurs in the setting of interstitial edematous pancreatitis</li> <li>Homogeneous collection with fluid density</li> <li>Confined by normal peripancreatic fascial planes</li> <li>No definable wall encapsulating the collection</li> <li>Adjacent to pancreas (no intrapancreatic extension)</li> </ul>	
<b>PANCREATIC PSEUDOCYST</b>	
An encapsulated collection of fluid with a well-defined inflammation wall, usually outside the pancreas, with little or no necrosis. Usually occurs more than 4 wk after onset of interstitial edematous pancreatitis.	
<b>CECT criteria</b>	
<ul style="list-style-type: none"> <li>Well circumscribed; usually round or oval</li> <li>Homogeneous fluid density</li> <li>No nonliquid component</li> <li>Well-defined wall that is wholly encapsulated</li> <li>Maturation usually needs &gt;4 wk after onset of acute pancreatitis; occurs after interstitial edematous pancreatitis</li> </ul>	
<b>ACUTE NECROTIC COLLECTION</b>	
A collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis; the necrosis can include the pancreatic parenchyma and/or the peripancreatic tissue.	
<b>CECT criteria</b>	
<ul style="list-style-type: none"> <li>Occurs only in the setting of acute necrotizing pancreatitis</li> <li>Heterogeneous and nonliquid density of varying degrees in different locations (some seem homogeneous early in their course)</li> <li>No definable wall encapsulating the collection</li> <li>Intrapancreatic and/or extrapancreatic</li> </ul>	
<b>WALLED-OFF NECROSIS</b>	
A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall. Usually occurs >4 wk after onset of necrotizing pancreatitis.	
<b>CECT criteria</b>	
<ul style="list-style-type: none"> <li>Heterogeneous with liquid and nonliquid density, with varying locations (some can seem homogeneous)</li> <li>Well-defined wall that is wholly encapsulated</li> <li>Intrapancreatic and/or extrapancreatic</li> <li>Maturation usually needs 4 wk after onset of acute necrotizing pancreatitis</li> </ul>	

CECT, Contrast-enhanced CT.

From PA Banks, TL Bollen, C Dervenis, et al. The Acute Pancreatitis Classification Working Group Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62:102–111.

Table 399.4	Complications of Acute Pancreatitis
LOCAL	
Pseudocyst	
Sterile necrosis	
Infected necrosis	
Abscess	
GI bleeding	<ul style="list-style-type: none"> <li>Pancreatitis-related</li> <li>Splenic artery or splenic artery pseudoaneurysm rupture</li> <li>Splenic vein rupture</li> <li>Portal vein rupture</li> <li>Splenic vein thrombosis leading to gastroesophageal variceal bleeding</li> <li>Pseudocyst or abscess hemorrhage</li> <li>Postnecrosectomy bleeding</li> </ul>
Nonpancreatitis-related	<ul style="list-style-type: none"> <li>Mallory-Weiss tear</li> <li>Alcoholic gastropathy</li> <li>Stress-related mucosal gastropathy</li> </ul>
Splenic complications	<ul style="list-style-type: none"> <li>Infarction</li> <li>Rupture</li> <li>Hematoma</li> <li>Splenic vein thrombosis</li> </ul>
Fistulization to or obstruction of the small intestine or colon	
Hydronephrosis	
SYSTEMIC	
Respiratory failure	
Renal failure	
Shock	
Hyperglycemia	
Hypocalcemia	
Disseminated intravascular coagulation	
Fat necrosis (subcutaneous nodules)	
Retinopathy	
PSYCHOSIS	

From Tenner S, Steinberg WM. Acute pancreatitis. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 10th ed. Philadelphia: Elsevier; 2016: Box 58.7, p. 991.

## 399.2 Acute Recurrent and Chronic Pancreatitis

Steven L. Werlin and Michael Wilschanski

Acute recurrent pancreatitis (ARP) is defined as ≥2 distinct episodes of AP with intervening return of enzymes to baseline. Chronic pancreatitis (CP) is defined as the presence of typical abdominal pain plus characteristic imaging findings including pancreatic calcifications, inflammation and fibrosis, or exocrine insufficiency plus imaging findings, or endocrine insufficiency plus imaging findings. Most children with CP describe a history of ARP and tend to be older at the time of diagnosis compared with children with ARP, suggesting that ARP and CP are a disease continuum. CP without prior AP or ARP may occur.

ARP and CP in children are often caused by pathogenic gene variants or congenital anomalies of the pancreatic or biliary ductal system ([Tables 399.5 and 399.6](#)). Variants in PRSS1 (cationic trypsinogen), SPINK1 (pancreatic trypsin inhibitor), in the cystic fibrosis gene (CFTR), CPA1, and chymotrypsin C (CTRC) may all lead to CP ([Fig. 399.2](#)).

Cationic trypsinogen has a trypsin-sensitive cleavage site. Loss of this cleavage site in the abnormal protein permits uncontrolled activation of trypsinogen to trypsin, which leads to autodigestion of the pancreas. Pathogenic variants in PRSS1 act in an autosomal dominant fashion with incomplete penetrance and variable expressivity. Symptoms often begin in the first decade but are usually mild at the onset.

Although spontaneous recovery from each attack occurs in 4–7 days, episodes become progressively more severe. Hereditary pancreatitis may be diagnosed by the presence of the disease in successive generations of a family. An evaluation during symptom-free intervals may be

<b>Table 399.5 Factors Contributing to the Etiology of Chronic Pancreatitis</b>	
	NO. (%)*
Chronic pancreatitis patients with history of ≥1 episode acute pancreatitis	73 (96)
Risk factors for pancreatitis	
<b>Genetic</b>	<b>51 (67)</b>
PRSS1	33 (43)
SPINK1	14 (19)
CFTR	11 (14)
CTRC	2 (3)
CPA1	~1%
<b>Autoimmune</b>	<b>3 (4)</b>
<b>Obstructive</b>	<b>25 (33)</b>
Pancreas divisum	15 (20)
Sphincter of Oddi dysfunction	1 (1)
Gallstones	3 (4)
Pancreatic duct malunion	2 (3)
Pancreatic duct obstruction	1 (1)
<b>Other</b>	<b>5 (7)</b>
Toxic/metabolic	8 (11)
Alcohol (determined by doctor)	1 (1)
Passive smoking (exposure)	3 (4)
Hyperlipidemia	1 (1)
Medication	1 (1)
Metabolic disease	1 (1)
None cited	8 (11)

PRSS1, serine protease 1; SPINK1, pancreatic trypsin inhibitor; CFTR, cystic fibrosis transmembrane conductance regulator; CTRC, chymotrypsin C; CPA1, carboxypeptidase A1.

\*The total exceeds 100% because some children have more than one factor.

Modified from Schwarzenberg SJ, Bellin M, Husain SZ, et al. Pediatric chronic pancreatitis is associated with genetic risk factors and substantial disease burden. *J Pediatr*. 2015;166:890–896. Table II.

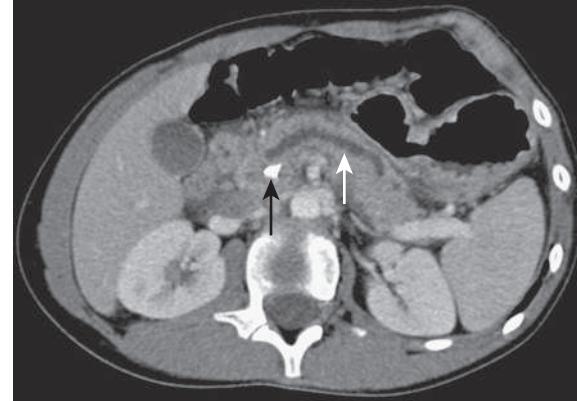
unrewarding until calcifications, pseudocysts, or pancreatic exocrine and endocrine insufficiency develop (Fig. 399.3; see Fig. 399.2). CP is a risk factor for the development of pancreatic cancer. Multiple variants of *PRSS1* associated with hereditary pancreatitis have been described.

Trypsin inhibitor acts as a fail-safe mechanism to prevent uncontrolled autoactivation of trypsin. Pathogenic variants in *SPINK1* have been associated with ARP or CP. In *SPINK1* variants, this fail-safe mechanism is lost; this gene may be a modifier gene and not the direct etiologic factor.

Pathogenic variants of *CFTR* that are associated with pancreatic sufficiency, or which do not typically produce pulmonary disease, can cause CP, possibly because of ductal obstruction. Patients with genotypes associated with mild phenotypic effects have a greater risk of developing pancreatitis than those with genotypes associated with moderate to severe phenotypes.

Pathogenic variants in the chymotrypsin C gene, which cause a loss of function, may also cause recurrent pancreatitis. Indications for genetic testing include recurrent episodes of AP, CP, a family history of pancreatitis, or unexplained pancreatitis in children. Pathogenic variants in carboxypeptidase A1 (*CPA1*) have been associated with early onset (<10 years) of CP.

Other conditions associated with chronic, relapsing pancreatitis are hyperlipidemia (types I, IV, and V), hyperparathyroidism, and ascariasis. Previously, most cases of recurrent pancreatitis in childhood were considered idiopathic; with the discovery of gene families associated with recurrent pancreatitis, this has changed. Congenital anomalies of the ductal systems, such as pancreas divisum, are also more common than previously recognized.

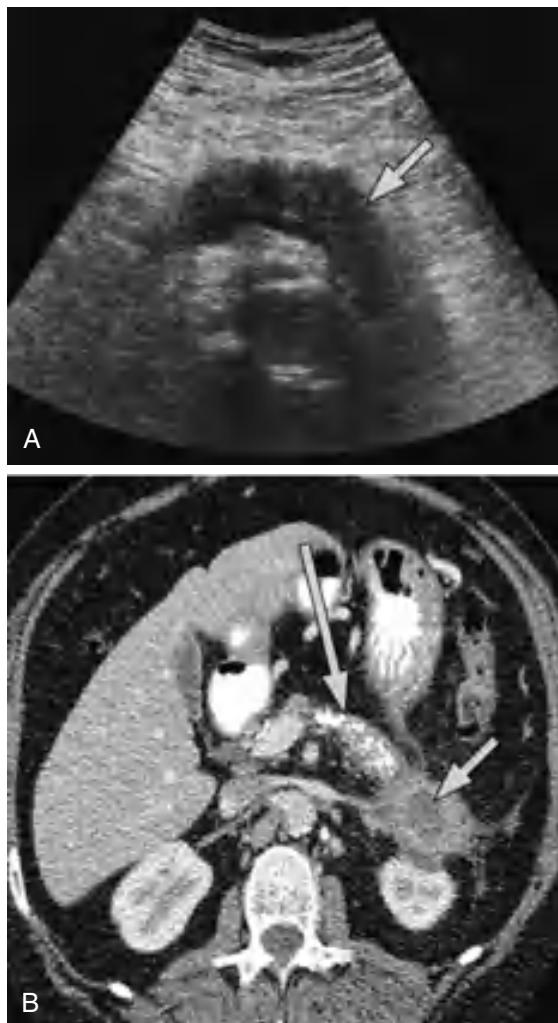


**Fig. 399.2** Chronic pancreatitis. Computed tomogram showing calcification in the head of the pancreas (black arrow) and dilated pancreatic duct (arrow) in a 12-yr-old patient. (Courtesy Dr. Janet Reid. From Wyllie R, Hyams JS, eds. *Pediatric Gastrointestinal and Liver Disease*, 3rd ed. Philadelphia: WB Saunders, 2006.)

**Table 399.6 Classification of Chronic Pancreatitis**

CHRONIC CALCIFYING PANCREATITIS	CHRONIC OBSTRUCTIVE PANCREATITIS	STEROID-RESPONSIVE PANCREATITIS
Alcohol Smoking Genetic Idiopathic Juvenile-onset Tropical	Stricture Blunt trauma Endoscopic stenting Acute pancreatitis Anastomotic stricture  Tumor Adenocarcinoma IPMN Serous cystadenoma Islet cell tumor	Autoimmune Pancreatitis Type 1 Type 2 (IDCP)

IDCP, Idiopathic duct-centric pancreatitis; IPMN, intraductal papillary mucinous neoplasm.  
From Majumder S, Chari ST. Chronic pancreatitis. *Lancet*. 2016;387:1957–1966. Fig 1.



**Fig. 399.3** Examples of ultrasound and multidetector images in patients with chronic pancreatitis. **A**, Transabdominal ultrasound scan showing a uniformly swollen, hypoechoic pancreas (arrow) typical of autoimmune pancreatitis. **B**, Multidetector CT showing pancreatic calculi in an atrophic pancreas (long arrow) and a pseudocyst at the tail of the pancreas (short arrow). (From Braganza JM, Lee SH, McCloy RF, McMahon MJ. Chronic pancreatitis. Lancet. 2011;377:1184–1197. Fig. 5.)

**Autoimmune pancreatitis (AIP)** typically manifests with jaundice, abdominal pain, and weight loss. The pancreas is typically enlarged and is hypodense on CT. The pathogenesis is unknown. **Type 1** is a systemic disease and is associated with high serum immunoglobulin G4 (IgG4). In addition to pancreatitis in type 1 disease, the patient may have retroperitoneal fibrosis, orbital inflammation, aortitis, sclerosing cholangitis, cutaneous vasculitis, pulmonary fibrosis, and sialadenitis. These extrapancreatic features may also be present in the absence of pancreatitis (Table 399.7). Tissue biopsy shows fibrosis, plasmacytosis, and positive staining for IgG4; serum IgG4 levels are not always elevated.

**Type 2** is limited to diffuse or focal involvement of just the pancreas. IgG4 levels are normal. *Both types respond to steroids.* Children with AIP typically have type 2.

**Table 399.7** Chronic Disorders Recognized to Be Part of IgG4-Related Disease

Autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis)
Eosinophilic angiocentric fibrosis (affecting the orbits and upper respiratory tract)
Fibrosing mediastinitis
Hypertrophic pachymeningitis
Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits
Inflammatory pseudotumor (affecting the orbits, lungs, kidneys, and other organs)
Küttner tumor (affecting the submandibular glands)
Mikulicz disease (affecting the salivary and lacrimal glands)
Multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs)
Periaortitis and periarteritis
Inflammatory aortic aneurysm
Retroperitoneal fibrosis (Ormond disease)
Riedel thyroiditis
Sclerosing mesenteritis
Conditions once regarded as individual disorders now recognized to be part of IgG4-related disease

From Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet. 2015;385:1460–1471. Panel 1.

**Juvenile tropical pancreatitis** is the most common form of CP in developing equatorial countries. The highest prevalence is in the Indian state of Kerala. Tropical pancreatitis occurs during late childhood or early adulthood, manifesting with abdominal pain and irreversible pancreatic insufficiency followed by diabetes mellitus within 10 years. The pancreatic ducts are obstructed with inspissated secretions, which later calcify. This condition is associated with pathogenic variants in *SPINK1* in 50% of cases.

A thorough diagnostic evaluation of every child with more than one episode of pancreatitis is indicated. Serum lipid, calcium, and phosphorus levels are determined. Stools are evaluated for ascaris, and a sweat test is performed. Plain abdominal films are evaluated for the presence of pancreatic calcifications. Abdominal ultrasound or CT scanning is performed to detect the presence of a pseudocyst. The biliary tract is evaluated for the presence of stones. After genetic counseling, evaluation of *PRSS1*, *SPINK1*, *CFTR*, *CPA1*, and *CRTC* genotypes can be measured. Electrophysiologic tests such as nasal potential difference testing may be recommended when the diagnosis of cystic fibrosis (CF) is uncertain.

MRCP and ERCP are techniques that can be used to define the anatomy of the gland and are mandatory if surgery is considered. MRCP is the test of choice when endotherapy is not being considered and should be performed as part of the evaluation of any child with idiopathic, nonresolving, or recurrent pancreatitis and in patients with a pseudocyst before drainage. In these cases, a previously undiagnosed anatomic defect that may be amenable to endoscopic or surgical therapy may be detected. Endoscopic treatments include sphincterotomy, stone extraction, drainage of pseudocysts, and insertion of pancreatic or biliary endoprosthetic stents. These treatments allow the successful nonsurgical management of conditions previously requiring surgical intervention.

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## Chapter 400

# Pancreatic Fluid Collections

Michael Wilschanski and Steven L. Werlin

Pancreatic pseudocyst formation is an uncommon sequela to acute or chronic pancreatitis. A pancreatic pseudocyst is a circumscribed collection of fluid rich in pancreatic enzymes, blood, and necrotic tissue, typically located in the lesser sac of the abdomen. Pancreatic pseudocysts are usually complications of pancreatitis, although in children they frequently occur after abdominal trauma. They can enlarge or extend in almost any direction, thus producing a wide variety of symptoms (Fig. 400.1; see also Fig. 399.1C).

A pancreatic pseudocyst is suggested when an episode of pancreatitis fails to resolve or when a mass develops after an episode of pancreatitis. Clinical features usually include pain, nausea, and vomiting, but many patients are asymptomatic. The most common signs are a palpable mass in 50% of patients and jaundice in 10%. Other findings include ascites and pleural effusions (usually left-sided).

Pancreatic pseudocysts can be detected by transabdominal ultrasonography, CT scan, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasound (EUS). Because of its ease, availability, and reliability, ultrasonography is the first choice. Sequential ultrasonography studies have demonstrated that most small pseudocysts (<6 cm)

resolve spontaneously. It is recommended that the patient with acute pancreatitis undergo an ultrasonographic evaluation 4 weeks after resolution of the acute episode for an evaluation of possible pseudocyst formation.

## TREATMENT OF FLUID COLLECTIONS AND NECROSIS

Percutaneous and endoscopic drainage of pseudocysts have replaced open surgical drainage, except for complicated or recurrent pseudocysts. Whereas a pseudocyst must be allowed to mature for 4–6 weeks before surgical drainage is attempted, percutaneous or endoscopic drainage can be attempted earlier. In some cases, endoscopic creation of a cyst-gastrostomy is performed. When a surgical treatment is planned, an MRCP or ERCP is performed to define anatomic abnormalities and aid the surgeon in planning the approach. EUS is helpful when an endoscopic approach is chosen.

**Necrotizing pancreatitis** includes both pancreatic gland necrosis and peripancreatic fat necrosis. In the initial phases, the necrotic collection is a mix of semisolid and solid tissue. Over a period of 4 weeks or longer, the collection becomes more liquid and becomes encapsulated by a visible wall. At this point, the process is termed *walled-off pancreatic necrosis*. Sterile necrosis does not require therapy except in the rare case of a collection that obstructs a nearby viscus (e.g., duodenal, bile duct, or gastric obstruction).

The development of *infected* necrosis is the main indication for broad-spectrum antibiotic therapy. The development of fever, leukocytosis, an elevated procalcitonin level, and increasing abdominal pain suggests infection of the necrotic tissue. A CT scan may reveal evidence of air bubbles in the necrotic cavity.

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	Interstitial edematous pancreatitis	Necrotizing pancreatitis
< 4 weeks	<b>Acute (peri)pancreatic fluid collection</b>  Homogenous fluid adjacent to pancreas without a recognizable wall	<b>Acute necrotic collection</b>  Intra- and/or extra-pancreatic necrotic collection without a well-defined wall
≥ 4 weeks	<b>Pancreatic pseudocyst</b>  An encapsulated, well-defined, usually extrapancreatic fluid collection with minimal solids	<b>Walled off necrosis</b>  Intra- and/or extra-pancreatic necrotic collection with a well-defined wall

**Fig. 400.1** Classification of acute pancreatitis and associated fluid collections. Based on international consensus according to the Acute Pancreatitis Classification Working Group (revised Atlanta criteria). (From Trikudanathan G, Wolbrink DRJ, van Santvoort HC, et al. Current concepts in severe acute and necrotizing pancreatitis: an evidence-based approach. *Gastroenterol*. 2019;156:1994–2007e3. Fig. 1.)

## Chapter 401

# Pancreatic Tumors

Meghen B. Browning, Steven L. Werlin, and Michael Wilschanski

Pancreatic tumors can be of either endocrine or nonendocrine origin. Tumors of endocrine origin include gastrinomas and insulinomas, which are more typically seen in nonpancreatic sites. These occur in the autosomal dominantly inherited multiple endocrine neoplasia type 1 (MEN-1) and are often benign. Hypoglycemia accompanied by higher-than-expected insulin levels or refractory gastric ulcers (Zollinger-Ellison syndrome) indicate the possibility of a functional endocrine pancreatic tumor (see Chapter 381.1). The treatment of choice is surgical removal. If the primary tumor cannot be found, or if it has metastasized, cure might not be possible. Treatment with a high dose of a proton pump inhibitor to inhibit gastric acid secretion is then indicated. Insulinomas and persistent hyperinsulinemic hypoglycemia of infancy produce symptomatic hypoglycemia caused by pathogenic variants in a variety of genes, most commonly *GUUD1* and *KATP*. Massive subtotal or total pancreatectomy is the treatment of choice when medical treatment fails. These children might then develop pancreatic insufficiency and diabetes as a complication of surgery.

Nonfunctioning pancreatic endocrine tumors make up most of the remainder of the pancreatic endocrine tumors (PETs). Diagnosis is either incidental, because they tend to be asymptomatic, or made after the tumors are large enough to have mass effects. The nonfunctioning PETs, as well as the even-more-rare functioning PETs, are less likely to be histologically benign. Pancreatic tumors secreting a variety of hormones, including glucagon, somatostatin, parathyroid hormone, adrenocorticotrophic hormone, and pancreatic polypeptide, have been described (Table 401.1). The treatment is surgical resection when possible.

The **watery diarrhea-hypokalemia-acidosis syndrome** is usually produced by the secretion of vasoactive intestinal peptide by a non- $\alpha$ -cell tumor (VIPoma). Vasoactive intestinal peptide levels are often, but not always, increased in the serum. Again, treatment is surgical removal of the tumor. When this is not possible, symptoms may be controlled by the use of octreotide acetate (cyclic somatostatin [Sandostatin]), a synthetic analog of somatostatin.

Pancreatoblastomas, pancreatic adenocarcinomas, and sarcomas of the pancreas are also rarely encountered. Pancreatoblastoma, a malignant embryonal tumor that secretes  $\alpha$ -fetoprotein and can contain both endocrine and exocrine elements, is the most common pancreatic neoplasm in young children (<10 years of age). Genetic associations include familial adenomatous polyposis and Beckwith-Wiedemann syndromes. Presurgical chemotherapy should be considered for lesions not primarily resectable. Resection can be curative. The effectiveness of adjuvant chemotherapy is less clear. Sarcomas are very rarely primarily pancreatic but may include Ewing family tumors (Ewing sarcoma and primitive neuroectodermal tumor), rhabdomyosarcoma, or undifferentiated soft tissue sarcomas. They are treated with multimodality therapy, including chemotherapy and either resection or radiation. The pancreas can be a site of metastases for any of these entities. Histologically benign tumors, such as teratomas and vascular anomalies, may also rarely involve the pancreas.

Carcinoma of the exocrine pancreas, or ductal adenocarcinoma, is a major problem in adults, accounting for 2% of diagnoses and 5% of deaths from cancer. However, it is exceptionally rare in childhood. Pathogenic variants in the *PRSS1* and *MEN-1* genes lead to an increased incidence of pancreatic cancer in adult life but do not appear to account for pediatric cases. Acinar cell carcinoma is very rarely seen in children. The solid pseudopapillary tumor of the pancreas, also called *Frantz tumor*, is the most common pancreatic tumor in adolescents. It is a more indolent pancreatic carcinoma usually found in adolescent/young adult females. Typical presenting symptoms are abdominal pain, mass, or jaundice. The treatment of choice is total surgical removal. Prognosis is very good.

Pancreatic lesions in von Hippel-Lindau disease are usually benign and cystic. Cystadenomas, familial adenocarcinomas, and islet cell tumors are less common. Metastases have been reported, but effective adjuvant therapy has not been established.

Prognosis is good for completely resected endocrine tumors but very poor for sarcomas and carcinomas, except for rare subtypes. Children who survive partial or complete pancreatectomy may have decreased pancreatic exocrine and endocrine reserve.

Inflammatory myofibroblastic tumors (resembling IgG4-related lesions) may cause obstruction and be identified during evaluation for pain or jaundice. Pancreatic tumors and other entities, including intra-pancreatic accessory spleens, may be found incidentally during imaging. Pancreatic imaging and biopsy when indicated confirm the diagnosis.

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**Table 401.1** Syndromes Associated with Pancreatic Neuroendocrine Tumors (pNETs)\*

SYNDROME	INCIDENCE/10 <sup>6</sup> /YR	MALIGNANCY (%)	HORMONE
Insulinoma	1-2	<10	Insulin
Gastrinoma (ZES)	0.5-1.5	60-90	Gastrin
VIPoma (Verner-Morrison syndrome, WDHA, pancreatic cholera)	0.05-0.2	>60	VIP
Glucagonoma	0.01-0.1	50-80	Glucagon
Somatostatinoma	Rare	>70	Somatostatin
GRFoma	Unknown	>30	GH-RF
ACTHoma	Uncommon	>95%	ACTH
pNET secreting PTH-rP	Rare	84%	PTH-rP
Pancreatic carcinoid tumor	Rare (<1% of all carcinoids)	77%	Serotonin, tachykinins
pNET secreting renin	Rare	Unknown	Renin
pNET secreting erythropoietin	Rare	Unknown	Erythropoietin
pNET secreting luteinizing hormone	Rare	Unknown	Luteinizing hormone
pNET secreting cholecystokinin (CCKoma)	Rare	Unknown	CCK

\*These syndromes may also be caused by a GI-NET (carcinoid).

GH-RF, Growth hormone-releasing factor; PP, pancreatic polypeptide; PTH-rP, parathyroid hormone-related protein; VIP, vasoactive intestinal polypeptide; WDHA, watery diarrhea, hypokalemia, achlorhydria; ZES, Zollinger-Ellison syndrome; ACTH, adrenocorticotrophic hormone.

From Jensen RT, Norton JA, Oberg K. Neuroendocrine tumors. In: Feldman M, Friedman LS, Brandt LJ, eds. Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 10th ed. Philadelphia: Elsevier; 2016: Table 33.1.

## Section 6

# The Liver and Biliary System

## Chapter 402

### Morphogenesis of the Liver and Biliary System

Stacey S. Huppert and William F. Balistreri

During the early embryonic process of gastrulation, the three embryonic germ layers (endoderm, mesoderm, and ectoderm) are formed. The definitive endoderm is an epithelial sheet that occupies the ventral surface of the early embryo by approximately the second week of human gestation. The digestive and respiratory organs, as well as the thymus and thyroid, are all derived from the definitive endoderm.

*Hepatogenesis* can be divided into three distinct processes. First, through unknown mechanisms, the ventral foregut endoderm intrinsically acquires *competence* to receive signals arising from the cardiac mesoderm and the septum transversum mesenchyme (Fig. 402.1A). The thickened epithelium of the ventral foregut endoderm is visible morphologically just before the onset of hepatic-specific gene expression. “Pioneer” transcription factors, including the Forkhead Box A (FOXA) and GATA protein families, have the unique ability to engage closed and silent chromatin locally, converting it to an open and permissive chromatin state marking genes as competent. However, hepatic-specific genes will be expressed only if they are induced by additional transcription factors. There are no known hepatic-specific molecular markers associated with the morphologic initial ventral foregut endoderm thickening.

Signals originating from the mesoderm lead to *specification* of cells that have the potential to form the liver and activate hepatic-specific genes (see Fig. 402.1B). Fibroblast growth factor (FGF) from the

cardiac mesoderm and bone morphogenetic protein (BMP) from septum transversum mesenchyme cells coordinately specify the hepatic—and suppress the pancreas—transcriptional programs in the cells of the ventral foregut endoderm.

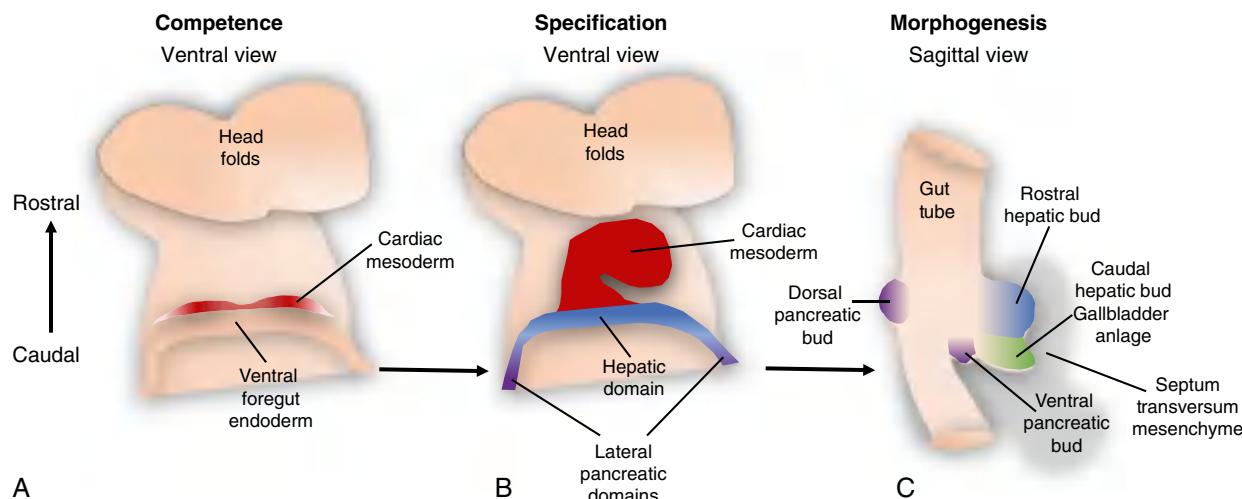
The newly specified hepatic cells initially compose a columnar epithelium that transitions to a single-layer of pseudostratified epithelium attached to a laminin-containing basement membrane. The basement membrane is then broken down, and the hepatic cells delaminate from the ventral foregut endoderm and migrate in a rostral ventral direction into the septum transversum in the third to fourth week of human gestation to initiate liver *morphogenesis* (see Fig. 402.1C). After foregut closure, the hepatic cells proliferate and continue to migrate into the surrounding mesenchyme, interacting to form a bud that becomes vascularized. The rostral hepatic bud gives rise to the liver, including the intrahepatic bile ducts, and the caudal hepatic bud develops into the gallbladder and the extrahepatic common bile duct. The gallbladder anlage is visible around the seventh week of human gestation. Careful orchestration of signals between epithelial, mesenchymal, and endothelial cells are required to guide hepatogenesis (Table 402.1).

#### HEPATIC ARCHITECTURE

Within the ventral mesentery, proliferation of migrating cells forms anastomosing hepatic cords, with the network of primitive liver progenitors (i.e., hepatoblasts), sinusoids, and septal mesenchyme establishing the basic architectural pattern of the liver lobule (Fig. 402.2). The hepatic lobules are identifiable in the sixth week of human gestation. The bile canalicular structures, including microvilli and junctional complexes, are specialized intralobular network channels; these appear very early in gestation, and large canaliculi bounded by several hepatocytes are seen by the sixth to seventh week of human gestation.

The *caudal* part (pars cystica) of the hepatic diverticulum becomes the gallbladder, cystic duct, and common bile duct. The distal portions of the right and left hepatic ducts develop from the extrahepatic ducts, whereas the proximal portions develop from the first intrahepatic ductal plates. The extrahepatic bile ducts and the developing intrahepatic biliary tree maintain luminal continuity and patency from the beginning of organogenesis (see Fig. 402.2C).

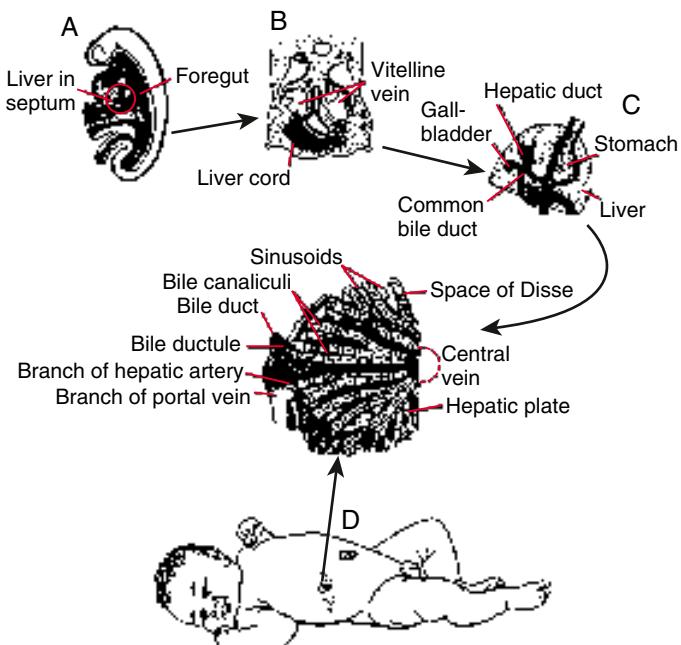
Fetal hepatic blood flow is derived from the hepatic artery and from the portal and umbilical veins, which form the portal sinus. The portal venous inflow is directed mainly to the right lobe of the liver and umbilical flow primarily to the left. The ductus venosus shunts blood from the portal and umbilical veins to the hepatic vein, bypassing the



**Fig. 402.1** Processes involved in early liver development. A, The ventral foregut endoderm acquires competence to receive signals arising from the cardiac mesoderm and septum transversum mesenchyme. B, Specific cells of the ventral foregut endoderm undergo specification and activation of liver-specific genes under the influence of mesodermal signals. C, Liver morphogenesis is initiated as the newly specified cells migrate into the septum transversum under the influence of signaling molecules and extracellular matrix released by septum transversum mesenchymal cells and of primitive endothelial cells.

**Table 402.1** Selected Growth Factors, Receptors, Protein Kinases, and Transcription Factors Required for Normal Liver Development in Animal Models

INDUCTION OF HEPATIC FATE THROUGH CARDIAC MESODERM	
• Fibroblast growth factors (FGFs) 1, 2, 8	
• FGF receptors 1, 4	
INDUCTION OF HEPATIC FATE THROUGH SEPTUM TRANSVERSUM	
• Bone morphogenetic proteins 2, 4, 7	
STIMULATION OF HEPATOBLAST GROWTH AND PROLIFERATION	
• Hepatocyte growth factor (HGF)	
• HGF receptor c-met	
• "Pioneer" transcription factors Foxa1, Foxa2, FoxA3, and Gata4, Gata6	
• Transcription factors Xbp1, Foxm1b, Hlx, Hex, Prox1, Tbx3	
• Wnt signaling pathway, $\beta$ -catenin	
SPECIFICATION OF HEPATOCYTE LINEAGE	
• HGF	
• Transcription factors	
• Hepatocyte nuclear factors (HNFs) 1 $\alpha$ , 4 $\alpha$ , 6, Cebpa	
SPECIFICATION OF CHOLANGIOCYTE LINEAGE	
• Jagged 1 (Notch ligand) and Notch receptors 1, 2	
• Transforming growth factor- $\beta$ and its downstream effectors Smad 2, Smad 3	
• Hippo/Yap	
• HNF6, HNF1 $\beta$ , Cebpb, Sox9, Sox4	



**Fig. 402.2** Hepatic morphogenesis. A, Ventral outgrowth of hepatic diverticulum from foregut endoderm in the 3.5-wk embryo. B, Between the two vitelline veins, the enlarging hepatic diverticulum buds off epithelial (liver) cords that become the liver parenchyma, around which the endothelium of capillaries (sinusoids) align (4-wk embryo). C, Hemisection of embryo at 7.5 wk. D, Three-dimensional representation of the hepatic lobule as present in the newborn. (From Andres JM, Mathis RK, Walker WA. Liver disease in infants. Part I: developmental hepatology and mechanisms of liver dysfunction. J Pediatr. 1977;90:686–697.)

sinusoidal network. After birth, the ductus venosus becomes obliterated when oral feedings are initiated. The fetal oxygen saturation is lower in portal than in umbilical venous blood; accordingly, the right

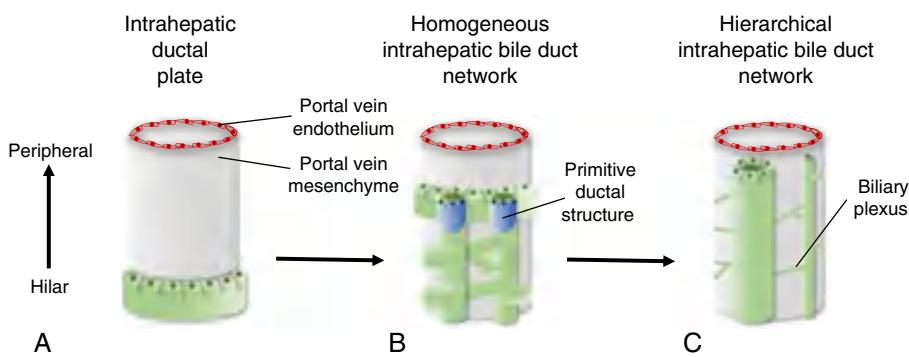
hepatic lobe has lower oxygenation and greater hematopoietic activity than the left hepatic lobe.

The transport and metabolic activities of the liver are facilitated by the structural arrangement of liver cell cords, which are formed by rows of hepatocytes, separated by sinusoids that converge toward the tributaries of the hepatic vein (the central vein) located in the center of the lobule (see Fig. 402.2D). This establishes the pathways and patterns of flow for substances to and from the liver. In addition to arterial input from the systemic circulation, the liver also receives venous input from the gastrointestinal tract via the portal system. The products of the hepatobiliary system are released by two different paths: through the hepatic vein and through the biliary system back into the intestine. Plasma proteins and other plasma components are secreted by the liver. Absorbed and circulating nutrients arrive through the portal vein or the hepatic artery and pass through the sinusoids and past the hepatocytes to the systemic circulation at the central vein. Biliary components are transported via the series of enlarging channels from the bile canaliculi through the bile ductule to the common bile duct. The intrahepatic bile duct system relies on its intricate three-dimensional structure to access all of the hepatocytes and effectively clear bile out of the liver.

Hepatocytes and cholangiocytes (i.e., bile duct epithelial cells) originate from the bipotential hepatoblast progenitor. Single-cell RNA sequencing data suggest that hepatoblasts enter the hepatocyte transcriptional program after hepatic specification from ventral foregut endodermal progenitors and transcriptionally move in unison toward the hepatocyte fate. The synchronicity suggests that the hepatocyte lineage specification is the default cell identity. Cholangiocyte differentiation is more nonsynchronous. Individual hepatoblasts upregulate the cholangiocyte transcriptional program coincident with repression of the hepatocyte transcriptional program. Cholangiocyte identity is initiated specifically in portal vein regions around the seventh to tenth week of human gestation, reinforcing that hepatoblasts are not pre-fated to the cholangiocyte transcriptional program but rather their location and signals arising from a niche influence their ultimate fate. Potential cholangiocytes form a temporary structure, termed the *intrahepatic ductal plate*, encircling the portal veins (Fig. 402.3A). Primitive ductal structures are asymmetrically composed of lumen-forming cells. The portal vein adjacent cells express early cholangiocyte markers, and parenchymal adjacent cells still express hepatoblast and hepatocyte markers. Remodeling of the ductal plate or tubulogenesis begins around the 11th to 15th week of human gestation starting at the larger hilar portal vein regions and moving toward the peripheral region of liver following the portal vein system. Newly committed cholangiocytes are incorporated into a *homogeneous intrahepatic bile duct network* encircling the portal vein (see Fig. 402.3B). The final rearrangement of the *hierarchical intrahepatic bile duct network* is thought to be associated with hepatocyte excretion of bilirubin into bile (see Fig. 402.3C). The intrahepatic bile duct architecture remains incomplete in the human liver periphery during the first years of life. If the unincorporated ductal plate or primitive ductal cells do not receive, or are unresponsive to, the proper signals, they may contribute to ductal plate malformation. This histopathologic lesion has been observed in liver biopsies of a variety of liver conditions, including congenital hepatic fibrosis, Caroli disease, biliary atresia, and autosomal dominant polycystic liver disease.

### METABOLIC FUNCTIONS OF THE LIVER

The liver reaches a peak relative size of approximately 10% of the fetal weight at the ninth week of human gestation. Early in development, the liver is a primary site of hematopoiesis. In the seventh week of human gestation, hematopoietic cells outnumber functioning hepatocytes in the hepatic anlage. These early hepatocytes are smaller than at maturity ( $\sim 20 \mu\text{m}$  vs  $30\text{--}35 \mu\text{m}$ ) and contain less glycogen. Near term, the hepatocyte mass expands to dominate the organ, as cell size and glycogen content increase. Hematopoiesis is virtually absent by the second postnatal month in full-term infants. As the density of hepatocytes increases with gestational age, the relative volume of the sinusoidal network decreases. The liver constitutes 5% of body weight at birth but only 2% in an adult.



**Fig. 402.3** Process of intrahepatic bile duct formation. A, Cholangiocytes are specified in the region adjacent to the portal vein system forming transient ductal plate. B, Ductal plates are quickly remodeled into luminal or primitive ductal structures surrounded by asymmetric gene expressing cells. These luminal structures form a dense homogeneous network that is communicating with the extrahepatic bile duct. C, Upon hepatocyte bile production, secretion, and canalicular membrane lengthening, the homogeneous network begins to reorganize into a hierarchical network.

Several metabolic processes are immature in a healthy newborn infant, owing in part to the fetal patterns of activity of various enzymatic processes. Many fetal hepatic functions are carried out by the maternal liver, which provides nutrients and serves as a route of elimination of metabolic end products and toxins. Fetal liver metabolism is devoted primarily to the production of proteins required for growth. Toward term, primary functions become production and storage of essential nutrients, excretion of bile, and establishment of processes of elimination. Extrauterine adaptation requires de novo enzyme synthesis. Modulation of these processes depends on substrate and hormonal input via the placenta and on dietary and hormonal input in the postnatal period.

### Carbohydrate Metabolism

The liver regulates serum glucose levels closely via several processes, including storage of excess carbohydrate as glycogen, a polymer of glucose readily hydrolyzed to glucose during fasting. To maintain serum glucose levels, hepatocytes produce free glucose by either glycogenolysis or gluconeogenesis. Immediately after birth, an infant is dependent on hepatic glycogenolysis. Gluconeogenic activity is present at a low level in the fetal liver and increases rapidly after birth. Fetal glycogen synthesis begins at about the ninth week of gestation, with glycogen stores most rapidly accumulated near term, when the liver contains 2-3 times the amount of glycogen of adult liver. Most of this stored glycogen is used in the immediate postnatal period. Re-accumulation is initiated at about the second week of postnatal life, and glycogen stores reach adult levels at approximately the third week in healthy full-term infants. In preterm infants, serum glucose levels fluctuate in part because efficient regulation of the synthesis, storage, and degradation of glycogen develops only near the end of full-term gestation. Dietary carbohydrates such as galactose are converted to glucose, but there is a substantial dependence on gluconeogenesis for glucose in early life, especially if glycogen stores are limited.

### Protein Metabolism

During the rapid fetal growth phase, specific decarboxylases that are rate limiting in the biosynthesis of physiologically important polyamines have higher activities than in the mature liver. The rate of synthesis of albumin and secretory proteins in the developing liver parallels the quantitative changes in the endoplasmic reticulum. Synthesis of albumin appears at the seventh to eighth week in the human fetus and increases in inverse proportion to that of  $\alpha$ -fetoprotein, which is the dominant fetal protein. By the third to fourth month of gestation, the fetal liver is able to produce fibrinogen, transferrin, and low-density lipoproteins. From this period on, fetal plasma contains each of

the major protein classes at concentrations considerably below those achieved at maturity.

The postnatal patterns of protein synthesis vary with the class of protein. Lipoproteins of each class rise abruptly in the first week after birth to reach levels that vary little until puberty. Serum albumin concentrations are low in a neonate (~2.5 g/dL), reaching adult levels (~3.5 g/dL) after several months. Levels of ceruloplasmin and complement factors increase slowly to adult values in the first year. In contrast, transferrin levels at birth are similar to those of an adult, decline for 3-5 months, and rise thereafter to achieve their final concentrations. Low levels of activity of specific proteins have implications for the nutrition of an infant. A low level of cystathione  $\gamma$ -lyase (cystathionase) activity impairs the *trans*-sulfuration pathway by which dietary methionine is converted to cysteine. Consequently, the latter must be supplied in the diet. Similar dietary requirements might exist for other sulfur-containing amino acids, such as taurine.

### Lipid Metabolism

Fatty acid oxidation provides a major source of energy in early life, complementing glycogenolysis and gluconeogenesis. Newborn infants are relatively intolerant of prolonged fasting, owing in part to a restricted capacity for hepatic ketogenesis. Rapid maturation of the ability of the liver to oxidize fatty acid occurs in the first few days after birth. Milk provides the major source of calories in newborns; this high-fat, low-carbohydrate diet mandates active gluconeogenesis to maintain blood glucose levels. When the glucose supply is limited, ketone body production from endogenous fatty acids can provide energy for hepatic gluconeogenesis and an alternative fuel for brain metabolism. When carbohydrates are in excess, the liver produces triglycerides. Metabolic processes involving lipids and lipoproteins are predominantly hepatic; liver immaturity or disease affects lipid concentrations and lipoproteins.

### Biotransformation

Newborn infants have a decreased capacity to metabolize and detoxify certain drugs, owing to underdevelopment of the hepatic microsomal component that is the site of the specific oxidative, reductive, hydrolytic, and conjugation reactions required for these biotransformations. The major components of the monooxygenase system, such as cytochrome P450, cytochrome-c reductase, and the reduced form of nicotinamide-adenine dinucleotide phosphate, are present in low concentrations in fetal microsomal preparations. In full-term infants, hepatic uridine diphosphate glucuronosyltransferase and enzymes involved in the oxidation of polycyclic aromatic hydrocarbons are expressed at very low levels.

Age-related differences in pharmacokinetics vary from compound to compound. The half-life of acetaminophen in a newborn is similar to that of an adult, whereas theophylline has a half-life of approximately 100 hours in a premature infant, as compared with 5–6 hours in an adult. These differences in metabolism, as well as factors such as binding to plasma proteins and renal clearance, determine appropriate drug dosage to maximize effectiveness and to avoid toxicity. Dramatic historical examples of the susceptibility of newborn infants to drug toxicity are the responses to chloramphenicol (the *gray baby* syndrome) or to benzoyl alcohol and its metabolic products, which involve ineffective glucuronide and glycine conjugation, respectively. The low concentrations of antioxidants (vitamin E, superoxide dismutase, glutathione peroxidase) in the fetal and early newborn liver lead to increased susceptibility to deleterious effects of oxygen toxicity and oxidant injury through lipid peroxidation.

Conjugation reactions, which convert drugs or metabolites into water-soluble forms that can be eliminated in bile, are also catalyzed by hepatic microsomal enzymes. Newborn infants have decreased activity of hepatic uridine diphosphate glucuronyltransferase, which converts unconjugated bilirubin to the readily excreted glucuronide conjugate and is the rate-limiting enzyme in the excretion of bilirubin. There is rapid postnatal development of transferase activity irrespective of gestational age, which suggests that birth-related, rather than age-related, factors are of primary importance in the postnatal development of activity of this enzyme. Microsomal activity can be stimulated by administration of phenobarbital, rifampin, or other inducers of cytochrome P450. Alternatively, drugs such as cimetidine can inhibit microsomal P450 activity.

### Hepatic Excretory Function

Hepatic excretory function and bile flow are closely related to hepatic *bile acid* excretion and enterohepatic recirculation. Bile secretion is first noted at the 12th week of human gestation. Bile acids, the major products of cholesterol degradation, are incorporated into mixed micelles with cholesterol and phospholipid. These micelles act as efficient vehicles for solubilization and intestinal absorption of lipophilic compounds, such as dietary fats and fat-soluble vitamins. Secretion of bile acids by the liver cells is the major determinant of bile flow in the mature animal. Accordingly, maturity of bile acid metabolic processes affects overall hepatic excretory function, including biliary excretion of endogenous and exogenous compounds.

In humans, the two primary bile acids, cholic acid and chenodeoxycholic acid, are synthesized in the liver. Before excretion, they are conjugated with glycine or taurine. In response to a meal, contraction of the gallbladder delivers bile acids (micelles) to the intestine to assist in fat digestion and absorption. After mediating fat digestion, the bile acids themselves are reabsorbed from the terminal ileum through specific active transport processes. They return to the liver via portal blood, are taken up by liver cells, and are re-excreted in bile. In an adult, this enterohepatic circulation involves 90–95% of the circulating bile acid pool. Bile acids that escape ileal reabsorption reach the colon, where the bacterial flora, through dihydroxylation and deconjugation, produce the secondary bile acids, deoxycholic and lithocholic acid. In an adult, the composition of bile reflects the excretion of the primary and also the secondary bile acids, which are reabsorbed from the distal intestinal tract.

Intraluminal concentrations of bile acids are low in newborn infants and increase rapidly after birth. The expansion of the bile acid pool is

**Table 402.2** Causes of Impaired Bile Acid Metabolism and Enterohepatic Circulation

#### DEFECTIVE BILE ACID SYNTHESIS OR TRANSPORT

- Inborn errors of bile acid synthesis
- Progressive familial intrahepatic cholestasis
- Intrahepatic cholestasis (neonatal hepatitis)
- Acquired defects in bile acid synthesis secondary to severe liver disease

#### ABNORMALITIES OF BILE ACID DELIVERY TO THE BOWEL

- Celiac disease (sluggish gallbladder contraction)
- Extrahepatic bile duct obstruction (e.g., biliary atresia, gallstones)

#### ALTERED ENTEROHEPATIC CIRCULATION OF BILE ACIDS

- External bile fistula
- Cystic fibrosis
- Small bowel bacterial overgrowth syndrome (with bile acid precipitation, increased jejunal absorption, and “short-circuiting”)
- Drug-induced entrapment of bile acids in intestinal lumen (e.g., cholestyramine)

#### BILE ACID MALABSORPTION

- Primary bile acid malabsorption (absent or inefficient ileal active transport)
- Secondary bile acid malabsorption
- Ileal disease or resection

#### DEFECTIVE UPTAKE OR ALTERED INTRACELLULAR METABOLISM

- Parenchymal disease
- Regurgitation from cells
- Portosystemic shunting
- Cholestasis

important because bile acids are required to stimulate bile flow and absorb lipids, a major component of the diet of a newborn. Nuclear receptors, such as farnesoid X receptor (FXR), control intrahepatic bile acid homeostasis through several mechanisms, including regulation of expression of the genes encoding two key proteins, cholesterol 7 $\alpha$ -hydroxylase (CYP7A1) and bile salt export pump (BSEP). These proteins are important for bile acid synthesis and canalicular secretion, respectively. Neonatal expression of these nuclear receptors varies depending on the studied animal model.

Because of inefficient ileal reabsorption of bile acids and the low rate of hepatic clearance of bile acids from portal blood, serum concentrations of bile acids are commonly elevated in healthy newborns, often to levels that would suggest liver disease in older persons. Transient phases of *physiologic cholestasis* and *physiologic steatorrhea* can often be observed in low birthweight infants and in full-term infants after perinatal stress, such as hypoxia or infection, but are otherwise uncommon in healthy full-term newborns.

Many of the processes related to immaturity of the newborn in liver morphogenesis and function, as discussed earlier, are implicated in the increased susceptibility of infants to liver disease associated with parenteral nutrition. The reduced bile acid pool size, hepatic glutathione depletion, and deficient sulfation contribute to production of toxic lithocholic acid and thus to cholestasis, whereas deficiencies of essential amino acids, including taurine and cysteine, and excessive lipid infusion can lead to hepatic steatosis in these infants. Beyond the neonatal period, disturbances in bile acid metabolism may be responsible for diverse effects on hepatobiliary and intestinal function (Table 402.2).

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## Chapter 403

# Manifestations of Liver Disease

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### PATHOLOGIC MANIFESTATIONS

Congenital and acquired alterations in hepatic structure and function (acute or chronic) can be manifest by varying patterns of reaction of the liver to cell injury. Hepatocyte injury can be caused by infection (viral, bacterial, parasitic), drugs or toxins, hypoxia, immunologic and structural disorders, or inborn errors of metabolism. The injury results in inflammatory cell infiltration and cell death (necrosis), which may be followed by a healing process of scar formation (fibrosis) and, potentially, nodule formation (regeneration). Cirrhosis is the result of any progressive fibrotic liver disease.

**Cholestasis** is an alternative or concomitant response to injury caused by extrahepatic or intrahepatic obstruction to bile flow. Substances that are normally excreted in bile, such as bile acids, conjugated bilirubin, cholesterol, and trace elements, accumulate in serum. Bile pigment accumulation in liver parenchyma can be seen in liver biopsy specimens. In *extrahepatic* obstruction, bile pigment may be visible in the intralobular bile ducts or throughout the parenchyma as bile lakes or infarcts. In *intrahepatic* cholestasis, an injury to hepatocytes or an alteration in hepatic physiology leads to a reduction in the rate of secretion of solute and water. Etiologies include alterations in enzymatic or canalicular transporter activity, permeability of the bile canalicular apparatus, organelles responsible for bile secretion, or ultrastructure of the cytoskeleton of the hepatocyte. The result may be clinically indistinguishable from obstructive cholestasis.

**Cirrhosis**, defined histologically by the presence of bands of fibrous tissue that link central and portal areas and form parenchymal nodules, is an end stage of any prolonged acute or chronic liver disease. Cirrhosis can be *macronodular*, with nodules of various sizes (up to 5 cm) separated by broad septa, or *micronodular*, with nodules of uniform size (<1 cm) separated by fine septa; mixed forms occur. The progressive scarring results in altered hepatic blood flow, with further impairment of liver cell function. Increased intrahepatic resistance to portal blood flow leads to portal hypertension.

The liver can be secondarily involved in neoplastic (metastatic) and nonneoplastic (storage diseases, fat infiltration) processes, as well as several systemic conditions and infectious processes. The liver can be affected by chronic passive congestion (congestive heart failure) or acute hypoxia, with hepatocellular damage.

### CLINICAL MANIFESTATIONS

#### Hepatomegaly

Enlargement of the liver can be caused by several mechanisms (Table 403.1). Normal liver size estimations are based on age-related clinical indices, such as the degree of extension of the liver edge below the costal margin, the span of dullness to percussion, or the length of the vertical axis of the liver, as estimated from imaging techniques. In children, the normal liver edge can be felt up to 2 cm below the right costal margin. In a newborn infant, extension of the liver edge more than 3.5 cm below the costal margin in the right midclavicular line suggests hepatic enlargement. Measurement of liver span is carried out by percussing the upper margin of dullness and by palpating the lower edge in the right midclavicular line. This may be more reliable than an extension of the liver edge alone. The two measurements may correlate poorly.

The liver span increases linearly with body weight and age in both sexes, ranging from approximately 4.5–5.0 cm at 1 week of age to approximately 7–8 cm in males and 6.0–6.5 cm in females by 12 years of age. The lower edge of the right lobe of the liver extends downward

(Riedel lobe) and can normally be palpated as a broad mass in some people. An enlarged left lobe of the liver is palpable in the epigastrium of some patients with cirrhosis. Downward displacement of the liver by the diaphragm (hyperinflation) or thoracic organs can create an erroneous impression of hepatomegaly.

Examination of the liver should note the consistency, contour, tenderness, and presence of any masses or bruits, as well as assessment of spleen size, along with documentation of the presence of ascites and any stigmata of chronic liver disease.

Ultrasound is useful in assessment of liver size and consistency, along with gallbladder size. Gallbladder length normally varies from 1.5 to 5.5 cm (average: 3 cm) in infants to 4 to 8 cm in adolescents; width ranges from 0.5 to 2.5 cm for all ages. Gallbladder distention may be seen in infants with sepsis. The gallbladder is often absent or abnormal in infants with biliary atresia.

#### Jaundice (Icterus)

Yellow discoloration of the sclera, skin, and mucous membranes is a sign of hyperbilirubinemia (see Chapter 137). Clinically apparent jaundice in children and adults occurs when the serum concentration of bilirubin reaches 2–3 mg/dL (34–51 µmol/L); the neonate might not appear jaundiced until the bilirubin level is >5 mg/dL (>85 µmol/L). Jaundice may be the earliest and only sign of hepatic dysfunction. Liver disease must be suspected in the infant who appears only mildly jaundiced but has dark urine or acholic (light-colored) stools. Immediate evaluation to establish the cause is required.

Measurement of the total serum bilirubin concentration allows quantitation of jaundice. Bilirubin occurs in plasma in four forms: *unconjugated* bilirubin tightly bound to albumin; *free* or *unbound bilirubin* (the form responsible for kernicterus, because it can cross cell membranes); *conjugated bilirubin* (the only fraction to appear in urine); and *δ fraction* (bilirubin covalently bound to albumin), which appears in serum when hepatic excretion of conjugated bilirubin is impaired in patients with hepatobiliary disease. The δ fraction permits conjugated bilirubin to persist in the circulation and delays resolution of jaundice. Although the terms *direct* and *indirect* bilirubin are used equivalently with *conjugated* and *unconjugated* bilirubin, this is not quantitatively correct, because the direct fraction includes both conjugated bilirubin and δ bilirubin.

Investigation of jaundice in an infant or older child must include determination of the accumulation of both unconjugated and conjugated bilirubin. Unconjugated hyperbilirubinemia might indicate increased production, hemolysis, reduced hepatic removal, or altered metabolism of bilirubin (Table 403.2). Conjugated hyperbilirubinemia reflects decreased excretion by damaged hepatic parenchymal cells or disease of the biliary tract, which may be a result of obstruction, sepsis, toxins, inflammation, and genetic or metabolic disease (Table 403.3).

#### Pruritus

Intense generalized itching can occur in patients with chronic liver disease, often in association with cholestasis (conjugated hyperbilirubinemia). Symptoms can be generalized or localized (commonly to palms and soles), are usually worse at night, are exacerbated with stress and heat, and are relieved by cool temperatures. Pruritus is unrelated to the degree of hyperbilirubinemia; deeply jaundiced patients can be asymptomatic.

The pathogenesis of pruritus remains unknown; however, multiple suspected pruritogens have been reported, including bile acids, histamine, serotonin, progesterone metabolites, endogenous opioids, the potent neuronal activator lysophosphatidic acid (LPA), and the LPA-forming enzyme, autotaxin (ATX). Ultimately, a multifactorial process is suspected, as evidenced by the symptomatic relief of pruritus after administration of various therapeutic agents, including bile acid-binding agents (cholestyramine), choleretic agents (ursodeoxycholic acid), opiate antagonists (naltrexone), antihistamines, serotonin reuptake inhibitors (sertraline), antibiotics, and ileal bile acid transporter (IBAT) inhibitors. Plasmapheresis, molecular adsorbent recirculating system therapy, and surgical diversion of bile (partial and total biliary

**Table 403.1** Causes of Hepatomegaly in Infants and Children

INFECTIVE AND INFLAMMATION	STORAGE/METABOLIC DISEASE
Viral hepatitis (hepatitis A, B, C, D, E; EBV; adenovirus, adeno-associated virus, echovirus, TORCH)	$\alpha_1$ -Antitrypsin deficiency
Autoimmune hepatitis	Wilson disease
Sepsis	Infants of diabetic mothers
Perinatal infections	Glycogen storage disease
Allograft rejection	Galactosemia
Graft-versus-host disease	Tyrosinemia
Systemic lupus erythematosus	Cystic fibrosis
Juvenile idiopathic arthritis	Gaucher disease
Primary sclerosing cholangitis	Niemann-Pick disease
Systemic granulomatous disorders with hepatic involvement	Gangliosidoses
Sarcoid	Hereditary fructose intolerance
Tuberculosis	Mitochondrial hepatic disorders including DNA depletion syndrome
Hepatic abscess (bacterial and parasitic)	Mucopolysaccharidoses
Parasitic infection	Amyloidosis
Visceral larva migrans	Hepatic porphyrias
Schistosomiasis	
Leishmaniasis	
Malaria	
Liver flukes	
Kupffer cell hyperplasia	
Macrophage activation syndrome	
Gestational alloimmune liver disease	
BILIARY OBSTRUCTION	EXPANSION OF EXTRACELLULAR MATRIX
Biliary atresia	Cirrhosis
Choledochal cysts	Fibrocystic disease (congenital hepatic fibrosis)
Stricture of common bile duct	
Primary sclerosing cholangitis	
INFILTRATION	STEATOSIS
Extramedullary hematopoiesis	Malnutrition
Erythroblastosis fetalis	Nonalcoholic steatohepatitis (obesity)
Thalassemias	Cystic fibrosis
Metastatic tumors	Parenteral nutrition
Neuroblastoma	Diabetes mellitus
Wilms tumor	Hereditary fructose intolerance
Leukemia	Galactosemia
Lymphoma	Wolman disease
Hemophagocytic lymphohistiocytosis (HLH)	Cholesterol ester storage disease
Langerhans cell histiocytosis	Mitochondrial hepatopathies
	$\beta$ -Oxidation defects
	Medication toxicity (tetracycline, valproic acid)
	HEPATIC MALIGNANCY/TUMOR
	Primary or metastatic
	VASCULAR CONGESTION
	Congestive heart failure
	Budd-Chiari syndrome
	Venoocclusive disease (VOD): radiation, high-dose chemotherapy, stem cell transplant, bush tea, pyrrolizidine alkaloids, familial VOD with immunodeficiency
	CYSTIC DISEASE
	Fibrocystic disease
	Autosomal dominant polycystic kidney disease
	Congenital hepatic fibrosis
	Caroli syndrome
	Isolated polycystic liver disease

EBV, Epstein-Barr virus; TORCH, toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex virus.

From Telega GW. Hepatomegaly. In Kliegman RM, Toth H, Bordini BJ, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis, 2nd ed. Philadelphia: Elsevier; 2023: Table 17.1, p. 307.

diversion) have been used in attempts to provide relief for medically refractory pruritus.

### Spider Angiomas

Vascular spiders (*telangiectasias*), characterized by central pulsating arterioles from which small, wiry venules radiate, may be seen in patients with chronic liver disease. These are usually most prominent in the superior vena cava distribution area (on the face and chest). Their size varies between 1 and 10 mm, and they exhibit central clearing with pressure. They presumably reflect altered estrogen metabolism in the presence of hepatic dysfunction.

### Palmar Erythema

Blotchy erythema, most noticeable over the thenar and hypothenar eminences and on the tips of the fingers, is also noted in patients with chronic liver disease. Abnormal serum estradiol levels and regional alterations in peripheral circulation have been identified as possible causes.

### Xanthomas

The marked elevation of serum cholesterol levels (to >500 mg/dL) associated with some forms of chronic cholestasis, especially Alagille syndrome, can cause the deposition of lipid in the dermis and subcutaneous tissue. Brown nodules can develop, first over the extensor surfaces of the extremities; rarely, xanthelasma of the eyelids develops.

### Portal Hypertension

Portal hypertension occurs when there is increased portal resistance and/or increased portal flow. The portal system drains the splanchnic area (abdominal portion of the gastrointestinal tract, pancreas, and spleen) into the hepatic sinusoids. Normal portal pressure is between 1 and 5 mm Hg. Portal hypertension is defined as a portal pressure greater than or equal to 6 mm Hg. Clinically significant portal hypertension exists when pressure exceeds a threshold of 10–12 mm Hg. Portal hypertension is the main complication of cirrhosis and is directly responsible for two of the most common and potentially lethal complications: ascites and variceal hemorrhage.

**Table 403.2** Differential Diagnosis of Unconjugated Hyperbilirubinemia

Physiologic Jaundice	Sepsis
Breastfeeding/Breast Milk Jaundice	Hemangioma
Polycythemia	Congenital erythropoietic porphyria
Diabetic mother	HUS
Fetal transfusion (maternal, twin)	Familial TTP (ADAM TS 13)
Intrauterine hypoxemia	Hemolysis from Wilson disease
Delayed cord clamping	
Congenital adrenal hyperplasia	
Neonatal thyrotoxicosis	
Hemolysis	
Isoimmune	
Rh incompatibility	Intestinal obstruction
ABO incompatibility	Pyloric stenosis
Other (M, S, Kidd, Kell, Duffy)	Intestinal atresia
Autoimmune	Hirschsprung disease
Cold antibody	Cystic fibrosis
Warm antibody	
Erythrocyte membrane defects	Enclosed Hematoma (Cephalohematoma, Ecchymoses)
Hereditary spherocytosis	
Hereditary elliptocytosis	Congestive Heart Failure
Infantile pyknocytosis	
Erythrocyte enzyme defects	Hypoxia
Glucose-6-phosphate dehydrogenase	
Pyruvate kinase	Acidosis
Hexokinase	Hypothyroidism or Hypopituitarism
Other	
Hemoglobinopathy	Drugs/Toxins
Thalassemia	Maternal oxytocin
Sickle cell anemia	Vitamin K
	Antibiotics
	Phenol disinfectants
	Herbs
	Familial Disorders of Bilirubin Metabolism
	Gilbert syndrome
	Crigler-Najjar syndrome types I and II
	Lucey-Driscoll syndrome

TTP, Thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome.

Modified from Telega GW. Jaundice. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis, 2nd ed. Philadelphia: Elsevier; 2023: Table 18.2, p. 326.

## Ascites

Ascites is a consequence of increased hydrostatic and osmotic pressures within the hepatic and mesenteric capillaries resulting in transfer of fluid from the blood vessels to the lymphatics that overcomes the drainage capacity of the lymphatic system. Ascites can also be associated with nephrotic syndrome and other urinary tract abnormalities, metabolic diseases (such as lysosomal storage diseases), congenital or acquired heart disease, and hydrops fetalis. Factors favoring the intraabdominal accumulation of fluid include decreased plasma colloid (albumin) osmotic pressure, increased capillary hydrostatic pressure, increased ascitic colloid osmotic fluid pressure, and decreased ascitic fluid hydrostatic pressure. Abnormal renal sodium retention plays a central role.

## Gastrointestinal Bleeding

Chronic liver disease may manifest as gastrointestinal hemorrhage. Bleeding may result from portal hypertensive gastropathy, gastric antral vascular ectasia, or varix rupture. Variceal hemorrhage is classically from an esophageal origin but may be caused by gastric, duodenal, peristomal, or rectal varices. Variceal hemorrhage results from increased pressure within the varix, which leads to changes in the diameter of the varix and increased wall tension. When the variceal wall strength is exceeded, physical rupture of the varix results. Given the high blood flow and pressure in the portosystemic collateral system, coupled with the lack of a natural mechanism to tamponade variceal bleeding, the rate of hemorrhage can be striking.

## Encephalopathy

Hepatic encephalopathy can be manifest as any neurologic dysfunction, but it is most likely to present in subtle forms such as deterioration of school performance, sleep disturbances, depression, or

emotional outbursts. It can be recurrent and precipitated by intercurrent illness, drugs, bleeding, or electrolyte and acid-base disturbances. The appearance of hepatic encephalopathy depends on the presence of portosystemic shunting, alterations in the blood-brain barrier, and the interactions of toxic metabolites with the central nervous system. Postulated causes include altered ammonia metabolism, synergistic neurotoxins, decreased cerebral oxygen metabolism and blood flow, or false neurotransmitters with plasma amino acid imbalance.

## Endocrine Abnormalities

Endocrine abnormalities are more common in older adolescents and adults with hepatic disease than in children. They reflect alterations in hepatic synthetic, storage, and metabolic functions, including those concerned with hormonal metabolism in the liver. Proteins that bind hormones in plasma are synthesized in the liver, and steroid hormones are conjugated in the liver and excreted in the urine; failure of such functions can have clinical consequences. Endocrine abnormalities can also result from malnutrition or specific deficiencies.

## Renal Dysfunction

Systemic disease or toxins can affect the liver and kidneys simultaneously, or parenchymal liver disease can produce secondary impairment of renal function. In hepatobiliary disorders, there may be renal alterations in sodium and water economy, impaired renal concentrating ability, and alterations in potassium metabolism. Ascites in patients with cirrhosis may be related to inappropriate retention of sodium by the kidneys and expansion of plasma volume, or it may be related to sodium retention mediated by diminished effective plasma volume.

**Hepatorenal syndrome (HRS)** is defined as functional renal failure in patients with end-stage liver disease. The pathophysiology of

**Table 403.3** Mechanistic Classification of the Etiologies of Cholestasis

<b>EXTRAHEPATIC DUCTS</b>	<b>PROTOZOAL</b> Toxoplasmosis
Biliary atresia	
Choledochal cyst	<b>TOXIC</b>
Spontaneous bile duct perforation	Parenteral nutrition-associated liver disease
Choledocholithiasis, biliary sludge	Fetal alcohol syndrome
Duct compression (may also be intrahepatic; e.g., hepatoblastoma, neuroblastoma, rhabdomyosarcoma, neonatal leukemia, systemic juvenile xanthogranuloma, Langerhans cell histiocytosis)	Drugs: maternal amphetamines, anticonvulsants; infant antifungals
Bile duct stenosis, stricture	
<b>INTRAHEPATIC DUCT OBSTRUCTION/FORMATION</b>	<b>ENDOCRINE</b>
Alagille syndrome	Panhypopituitarism
"Nonsyndromic paucity of interlobular bile ducts" (e.g., Williams syndrome)	Hypothyroidism, cortisol deficiency
Cystic fibrosis	McCune-Albright syndrome
Ductal plate malformations: congenital hepatic fibrosis; ARPKD; Caroli disease; Ivemark, Jeune, Joubert, Bardet-Biedl syndromes	Donohue syndrome (leprechaunism)
Sclerosing cholangitis	
<b>CANALICULAR MEMBRANE TRANSPORTERS</b>	<b>METABOLIC</b>
PFIC type 1, BRIC, Nielsen syndrome (familial Greenland cholestasis)	$\alpha_1$ -Antitrypsin deficiency
PFIC type 2 (bile salt export pump deficiency)	Galactosemia
PFIC type 3 (MDR3 deficiency)	Fructosemia (hereditary fructose intolerance)
Tight junction protein 2 deficiency	Glycogen storage disease type IV (Andersen disease)
Farnesoid X receptor variants	Congenital disorders of glycosylation
MYO5B deficiency	Tyrosinemia type I
Neonatal Dubin-Johnson syndrome	Niemann-Pick disease type C
Villin functional defect	Gaucher disease
Overload of excretory mechanism capacity: ABO blood group incompatibility with hemolysis	Cerebrotendinous xanthomatosis
<b>HEPATOCYTE TIGHT JUNCTIONS</b>	Farber disease
Neonatal ichthyosis–sclerosing cholangitis syndrome–claudin-1 protein	Wolman disease
Familial hypercholanemia caused by TJP2 (zonulin-2) deficiency	$\beta$ -Oxidation defects: short- and long-chain acyl-CoA dehydrogenase deficiencies
<b>BILE ACID SYNTHESIS</b>	Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome)
First-degree: BASD	Mucolipidosis II (I-cell disease)
3-Oxo- $\Delta$ 4-steroid 5 $\beta$ -reductase deficiency	Urea cycle defects
3 $\beta$ -Hydroxy- $\Delta$ 5-C27-steroid dehydrogenase/isomerase deficiency	Citrin deficiency (formerly type II citrullinemia)
Oxysterol 7 $\alpha$ -hydroxylase deficiency	Mitochondrial respiratory chain disorders
Familial hypercholanemia due to BAAT deficiency	Growth retardation, amino aciduria, cholestasis, iron overload, lactic acidosis, and early death (GRACILE)
Second-degree: organelle dysfunction	Wilson disease (>5 yr)
Smith-Lemli-Opitz syndrome (cholesterol formation)	
Peroxisomal disorders: Zellweger, infantile Refsum, neonatal ALD	<b>IMMUNE MEDIATED</b>
<b>INFECTIOUS</b>	Gestational alloimmune liver disease
Bacterial: sepsis (endotoxemia, e.g., UTI, gastroenteritis)	Neonatal or acquired lupus erythematosus
Listeria	Autoimmune hemolytic anemia with giant cell hepatitis
Syphilis	Hemophagocytic lymphohistiocytosis
TB	Autoimmune hepatitis
<b>VIRAL</b>	
Herpes viruses: CMV, HSV, HHV-6, varicella	<b>OTHER</b>
Parvovirus B19	Hypoxic/ischemic/vascular
Hepatitis A, B, C	Shock/hypoperfusion/hypoxia
Enterovirus: coxsackieviruses, echoviruses, "numbered" enteroviruses	Budd-Chiari syndrome
Adenovirus	Cardiac insufficiency (congenital heart disease, arrhythmia)
Adeno-associated virus	Multiple hemangioma
Rubella	Sinusoidal obstruction syndrome
HIV	ARC syndrome (arthrogryposis-renal tubular dysfunction–cholestasis; defective vacuolar protein sorting)
Paramyxovirus	Chromosomal: trisomy 17, 18, 21
	Congenital disorders of glycosylation
	Hardikar syndrome
	Lymphedema cholestasis syndrome (Aagenes syndrome)
	Kabuki syndrome
	North American Indian childhood cirrhosis (UTP4 variant)
	Pseudo-TORCH (PTORCH-1) syndrome ( <i>OCLN</i> variant)
	"Idiopathic neonatal hepatitis"
	COACH syndrome (coloboma, oligophrenia, ataxia, cerebellar vermis hypoplasia, hepatic fibrosis)

ALD, Adrenoleukodystrophy; ARC, arthrogryposis-renal-cholestasis; ARPKD, autosomal recessive polycystic kidney disease; BAAT, bile acid coenzyme A: amino acid N-acyltransferase; BASD, bile acid synthetic defects; BRIC, benign recurrent intrahepatic cholestasis; CMV, cytomegalovirus; HHV-6, human herpesvirus type 6; HIV, human immunodeficiency virus; HSV, herpes simplex virus; PFIC, progressive familial intrahepatic cholestasis; TORCH, toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes infections; UTI, urinary tract infection.

Modified from Telega GW, Jaundice. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis*, 2nd ed. Philadelphia: Elsevier; 2023: Table 18.3, p. 327.

hepatorenal syndrome is related to splanchnic vasodilation, mesenteric angiogenesis, and decreased effective blood volume with resulting decreased renal perfusion. The hallmark is intense renal vasoconstriction (mediated by hemodynamic, humoral, or neurogenic mechanisms) with coexistent systemic vasodilation. The diagnosis is supported by the findings of oliguria (<1 mL/kg/day), a characteristic pattern of urine electrolyte abnormalities (urine sodium <10 mEq/L, fractional excretion of sodium of <1%, urine:plasma creatinine ratio <10, and normal urinary sediment), absence of hypovolemia, and exclusion of other kidney pathology. Both acute (HRS-AKI) and chronic (HRS-CKD) forms have been described. The best treatment of HRS is timely liver transplantation, with complete renal recovery expected.

### Pulmonary Involvement

**Hepatopulmonary syndrome** (HPS) is characterized by the typical triad of hypoxemia, intrapulmonary vascular dilations, and liver disease. There is intrapulmonic right-to-left shunting of blood resulting from enlarged pulmonary vessels that prevents adequate exposure to oxygen-rich alveoli of red blood cells traveling through the center of the vessel. Shunting of vasodilatory mediators from the mesentery away from the liver is thought to contribute. HPS should be suspected and investigated in the child with chronic liver disease with a history of shortness of breath or exercise intolerance and clinical examination findings of cyanosis (particularly of the lips and fingers), digital clubbing, and oxygen saturations <96%, particularly in the upright position. Treatment is timely liver transplantation; resolution of pulmonary involvement usually follows.

**Portopulmonary hypertension** is a condition characterized by an increase in the resistance to pulmonary arterial blood flow in the setting of portal hypertension. It is defined by a pulmonary arterial pressure >25 mm Hg at rest and above 30 mm Hg with exercise, elevated pulmonary vascular resistance with pulmonary arterial occlusion pressure, or a left ventricular end diastolic pressure of <15 mm Hg. Although the pathophysiology is unclear, deficiency in endothelial prostacyclin synthase and increased circulating endothelin-1 have been implicated as a cause for the vasculopathy. Autopsy studies have demonstrated the coexistence of portal hypertension, microscopic pulmonary artery thromboembolism, endothelial and smooth muscle proliferation, and platelet aggregates contributing to portopulmonary hypertension development. Symptoms suggesting a diagnosis include exertional dyspnea, fatigue, syncope, palpitations, and chest pain. Pulmonary artery-directed therapy is the cornerstone of management, along with consideration of liver transplant.

### Recurrent Cholangitis

Ascending infection of the biliary system is often seen in pediatric cholestatic disorders, most commonly because of gram-negative enteric organisms such as *Escherichia coli*, *Klebsiella*, *Pseudomonas*, and *Enterococcus*. Liver transplantation is the definitive treatment for recurrent cholangitis, especially when medical therapy is not effective.

### Miscellaneous Manifestations of Liver Dysfunction

Nonspecific signs of acute and chronic liver disease include anorexia, which often affects patients with anicteric hepatitis and with cirrhosis associated with chronic cholestasis; abdominal pain or distention resulting from ascites, spontaneous peritonitis, or visceromegaly; malnutrition and growth failure; and bleeding, which may be a result of altered synthesis of coagulation factors (biliary obstruction with vitamin K deficiency or excessive hepatic damage) or to portal hypertension with hypersplenism. In the presence of hypersplenism, there can be decreased synthesis of specific clotting factors, production of qualitatively abnormal proteins, or alterations in platelet number and function. Altered drug metabolism can prolong the biologic half-life of commonly administered medications.

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## 403.1 Evaluation of Patients with Possible Liver Dysfunction

James E. Squires and William F. Balistreri

Adequate evaluation of an infant, child, or adolescent with suspected liver disease begins with an appropriate and accurate history, a carefully performed physical examination, and skillful interpretation of signs and symptoms. Further evaluation is aided by judicious selection of diagnostic tests, followed using imaging modalities and/or a liver biopsy (Fig. 403.1). Most of the so-called liver “function” tests do not measure any specific hepatic function: a rise in serum aminotransferase levels reflects liver cell *injury*, an increase in immunoglobulin levels reflects an immunologic response to injury, or an elevation in serum bilirubin levels can reflect any of several disturbances of bilirubin metabolism (see Tables 403.2 and 403.3). Any single biochemical assay provides limited information, which must be placed in the context of the entire clinical picture. The most cost-efficient approach is to become familiar with the rationale, implications, and limitations of a selected group of tests so that specific questions can be answered. Young infants with cholestatic jaundice should be evaluated promptly to identify patients needing specific medical treatment or surgical intervention.

For a patient with suspected liver disease, evaluation addresses the following issues in sequence: Is liver disease present? If so, what is its nature? What is its severity? Is specific treatment available? How can we monitor the response to treatment? What is the prognosis? Importantly, more recent rapid genotype testing and gene chip technologies have transformed the field of diagnostics. These advances, paired with a greater understanding of the genetic basis for many pediatric liver diseases, are enabling more accurate and timely diagnoses while simultaneously eliminating the need for more invasive, costly, and time-intensive testing.

### BIOCHEMICAL TESTS

Laboratory tests commonly used to screen for or to confirm a suspicion of liver disease include measurements of serum aminotransferase (Table 403.4), bilirubin (total and fractionated), alkaline phosphatase (AP), and gamma glutamyl-transpeptidase (GGT) levels, as well as determinations of prothrombin time (PT) or international normalized ratio (INR) and serum albumin level. These tests are complementary, provide an estimation of synthetic and excretory functions, and might suggest the nature of the disturbance (inflammation or cholestasis).

The severity of the liver disease may be reflected in clinical signs or biochemical alterations. Clinical signs include encephalopathy, variceal hemorrhage, worsening jaundice, apparent shrinkage of liver mass owing to massive necrosis, or onset of ascites. Biochemical alterations reflective of severity include hypoglycemia, acidosis, hyperammonemia, electrolyte imbalance, continued hyperbilirubinemia, marked hypoalbuminemia, or a prolonged PT or INR that is unresponsive to parenteral administration of vitamin K.

Acute liver cell injury (parenchymal disease) caused by viral hepatitis, drug- or toxin-induced liver disease, shock, hypoxemia, or metabolic disease is best suggested by a marked increase in serum aminotransferase levels. Cholestasis (obstructive disease) involves regurgitation of bile components into serum; the serum levels of total and conjugated bilirubin and serum bile acids are elevated. Elevations in serum AP, 5' nucleotidase, and GGT levels are also sensitive indicators of obstruction or inflammation of the biliary tract. Fractionation of the total serum bilirubin level into conjugated and unconjugated bilirubin fractions helps to distinguish between elevations caused by processes such as hemolysis and those caused by hepatic dysfunction. A predominant elevation in the conjugated bilirubin level provides a relatively sensitive index of hepatocellular disease or hepatic excretory dysfunction.

Alanine aminotransferase (ALT, serum glutamate pyruvate transaminase) is *liver* specific, whereas aspartate aminotransferase (AST, serum glutamic-oxaloacetic transaminase) is derived from other

differences in density of liver parenchyma, the average liver attenuation coefficient being reduced with fatty infiltration.

*MRI* is a useful alternative that limits radiation exposure. Magnetic resonance cholangiography can be of value in differentiating biliary tract lesions. MRI with Eovist (gadoxetate disodium) can assist in the detection and characterization of known or suspected focal liver lesions. In differentiating obstructive from nonobstructive cholestasis, CT scanning or MRI identifies the precise level of obstruction more often than ultrasound. Either CT scanning or ultrasound may be used to guide percutaneously placed fine needles for biopsies, aspiration of specific lesions, or cholangiography.

*Elastography* is a novel noninvasive method to assess for liver stiffness, a measure of the development of hepatic fibrosis in patients with liver disease. Both ultrasound and MR methods have been developed. These noninvasive techniques allow for monitoring fibrosis progression and development of cirrhosis, characterization of hepatic tumors, improved diagnostic capabilities in certain disease processes such as biliary atresia, and prognostic stratification of diseases such as nonalcoholic fatty liver disease and NASH.

*Radionuclide scanning* relies on selective uptake of a radiopharmaceutical agent. Commonly used agents include technetium-99m-labeled sulfur colloid, which undergoes phagocytosis by Kupffer cells; <sup>99m</sup>Tc-iminodiacetic acid agents, which are taken up by hepatocytes and excreted into bile in a fashion similar to bilirubin; and gallium-67, which is concentrated in inflammatory and neoplastic cells. The anatomic resolution possible with hepatic scintiscans is generally less than that obtained with CT scanning, MRI, or ultrasound.

The <sup>99m</sup>Tc-sulfur colloid scan can detect focal lesions (tumors, cysts, abscesses) >2-3 cm in diameter. This modality can help to evaluate patients with possible cirrhosis and with patchy hepatic uptake and a shift of colloid uptake from liver to bone marrow.

*Cholangiography*, direct visualization of the intrahepatic and extrahepatic biliary tree after injection of opaque material, may be required in some patients to evaluate the cause, location, or extent of biliary obstruction. Percutaneous transhepatic cholangiography with a fine needle is the technique of choice in infants and young children. The likelihood of opacifying the biliary tract is excellent in patients in whom CT scanning, MRI, or ultrasound demonstrates dilated ducts. Percutaneous transhepatic cholangiography has been used to outline the biliary ductal system.

*Endoscopic retrograde cholangiopancreatography* is an alternative method of examining the bile ducts in older children. The papilla of Vater is cannulated under direct vision through a fiberoptic endoscope, and contrast material is injected into the biliary and pancreatic ducts to outline the anatomy. The advantage of endoscopic retrograde cholangiopancreatography is that it allows therapeutic interventions of the extrahepatic biliary tree (stone extraction, stent placement).

Selective angiography of the celiac, superior mesenteric, or hepatic artery can be used to visualize the hepatic or portal circulation. Both arterial and venous circulatory systems of the liver can be examined. Angiography is often required to define the blood supply of tumors before surgery and is useful in the study of patients with known or presumed portal hypertension. The patency of the portal system, the extent of collateral circulation, and the caliber of vessels under consideration for a shunting procedure can be evaluated. MRI can provide similar information.

## DIAGNOSTIC APPROACH TO INFANTS WITH JAUNDICE

Well-appearing infants can have cholestatic jaundice. Biliary atresia and neonatal hepatitis are the most common causes of cholestasis in early infancy. Biliary atresia portends a poor prognosis unless it is identified early. The best outcome for this disorder is with early surgical reconstruction (45-60 days of age). History, physical examination, and the detection of a conjugated hyperbilirubinemia via examination of total and direct bilirubin are the first steps in evaluating the jaundiced infant (see Fig. 403.1). Consultation with a pediatric gastroenterologist should be sought early in the course of the evaluation.

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# Chapter 404

## Cholestasis

Simon Lam and William F. Balistreri

### 404.1 Neonatal Cholestasis

Simon Lam and William F. Balistreri

Neonatal cholestasis is defined as conjugated hyperbilirubinemia occurring within the neonatal period. Cholestasis implies impediment to normal bile flow. In contrast to unconjugated hyperbilirubinemia, cholestasis (conjugated bilirubin elevation of any degree) in the neonate is *always pathologic*, and prompt differentiation of the cause is imperative.

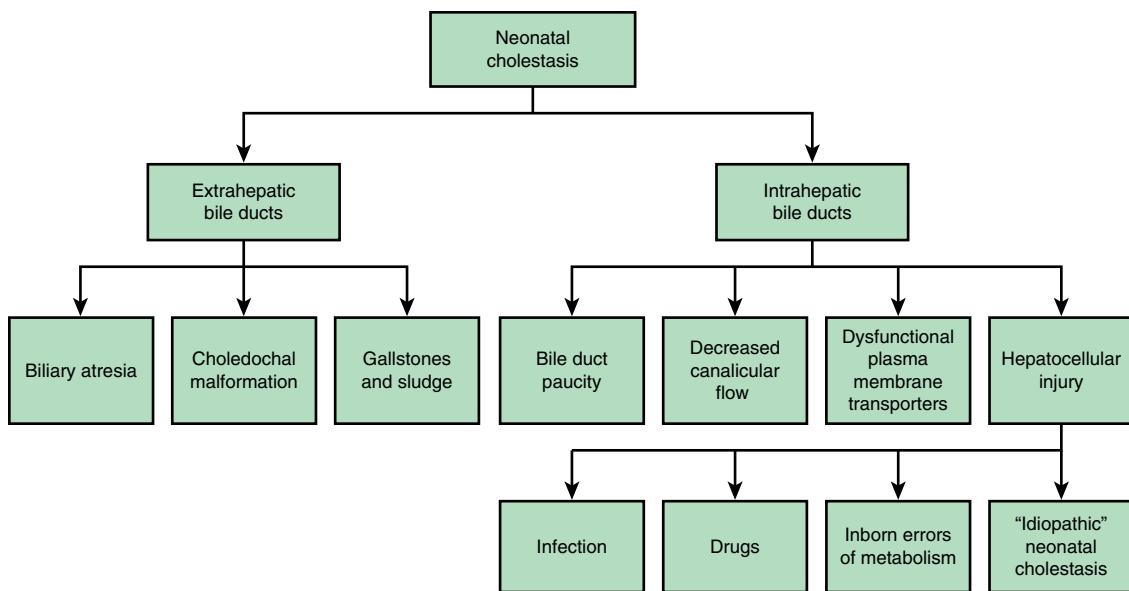
Neonatal cholestasis occurs in approximately 1 in 2,500 live births. Although the clinical features for the diverse causes of neonatal cholestasis can be similar, the differential diagnosis remains broad, including infections, endocrine disorders, genetic/metabolic conditions, and various forms of mechanical obstruction. One approach is to evaluate the pathologies of the biliary system with an anatomic perspective, from the large extrahepatic bile ducts, to the smaller intrahepatic bile ducts, to the bile canaliculus, to the membrane transporters on the hepatocyte, and finally to the level of the hepatocyte (Fig. 404.1).

## DISORDERS OF THE EXTRAHEPATIC BILE DUCTS

### Biliary Atresia

Biliary atresia is an important cause of neonatal cholestasis and the leading indication for pediatric liver transplantations worldwide. The prevalence of biliary atresia varies from 1 in 3,000 in French Polynesia to 1 in 12,000-22,000 in North America and Europe. In most cases, infants with biliary atresia appear well but are jaundiced with a history of acholic stools (i.e., stools devoid of pigment appearing white or pale colored) (Fig. 404.2). **Biliary atresia splenic malformation (BASM)** syndrome affects 15% of patients with biliary atresia and is associated with other congenital abnormalities, including situs inversus (heterotaxia syndrome), congenital heart disease, intestinal malformation, primary ciliary dyskinesia, Kabuki syndrome, caudal regression syndrome, and polysplenia. The pathogenesis of biliary atresia is unknown. For nonsyndromic biliary atresia, it appears that bile duct destruction may be initiated in utero but is primarily a progressive postnatal event. Evidence for this includes elevated levels of conjugated/direct bilirubin in the first 1-3 days after birth. Leading hypotheses include (1) a complex interplay between genetic predisposition/susceptibility, (2) prenatal or postnatal biliary injury from viruses, toxins, or vascular insults, (3) increased susceptibility to ongoing biliary injury caused by a descending glycocalyx on the apical surface of the cholangiocytes or abnormal intracellular glutathione production, and (4) aberrant immune responses. Biliary atresia has been discordant among identical twins. The final common pathway is an *obliterative cholangiopathy*, leading to the destruction of the biliary tree, most commonly at the porta hepatis. Bile is therefore unable to flow through the atretic region of the *extrahepatic* bile ducts, causing increased pressure and reflux of biliary contents back into the *intrahepatic* biliary system resulting in hepatic injury, inflammation, and fibrosis (Fig. 404.3). Because bile is not excreted into the small bowel, fat/fat-soluble vitamin digestion is impaired, and stools are acholic. If left untreated, end-stage liver disease usually occurs by 2 years of life.

Typical abdominal ultrasound findings include nonvisualization of the gallbladder, a small-contracted gallbladder, and nonvisualization of the common bile duct. The triangular cord sign has also been reported as a specific ultrasound finding for biliary atresia, but may lack sensitivity. Notably, dilation of intrahepatic ducts is not a feature consistent with biliary atresia. Characteristic features on liver biopsy include bile duct proliferation, bile duct plugs, and portal stromal edema. Although abdominal ultrasonography and liver biopsies are helpful in the diagnostic workup for biliary atresia, an intraoperative cholangiogram remains the gold standard for diagnosis. After catheterization of the

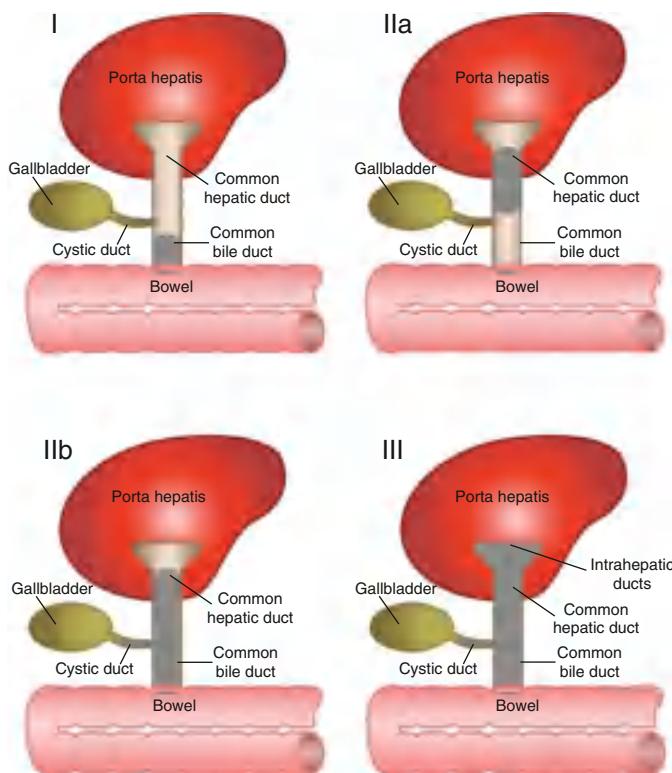


**Fig. 404.1** Conceptual approach to neonatal cholestasis. There are areas of overlap: patients with biliary atresia will have some degree of intrahepatic/hepatocellular injury. Additional patients with “idiopathic” neonatal hepatitis may be determined in the future to be related to an enzyme or membrane transporter defect.

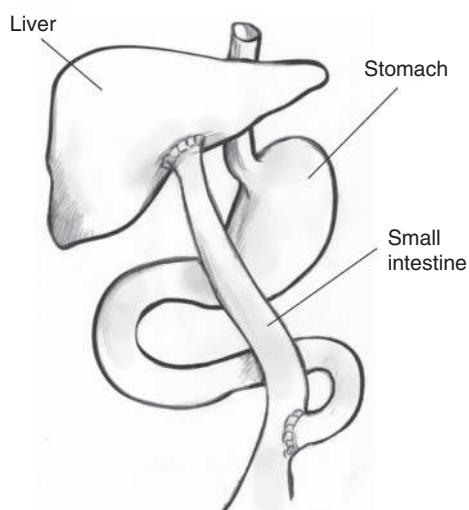


**Fig. 404.2** Acholic stools from a 1-mo-old patient with biliary atresia. (Courtesy Dr. S. Lam.)

gallbladder, a diagnosis of biliary atresia is made if contrast does not fill the intrahepatic biliary tree or drain into the small bowel. After the diagnosis is confirmed, the Kasai hepatoperoenterostomy (KPE) is typically performed. The atretic biliary remnant is removed and a Roux-en-Y jejunostomy is anastomosed to the biliary hilum to reestablish bile flow; this remains the accepted surgical intervention for patients with biliary atresia (Fig. 404.4). A prompt diagnosis of biliary atresia is key because the timing of surgical correction is strongly linked to the prognosis. Historically, KPE performed before 60 days



**Fig. 404.3** Biliary atresia classified according to the area of involvement (gray colored). Type I: Atresia of the distal bile duct with patent proximal extrahepatic bile duct. Type IIa: Atresia of the common hepatic duct. Type IIb: Atresia of the common hepatic duct, cystic duct, and common bile duct. Type III: Nonpatency of the entire extrahepatic biliary system and intrahepatic bile ducts at the hilum. (Modified from A-Kader HH, Feerick J, Rodriguez-Davalos M. After two centuries biliary atresia remains the darkest chapter in pediatric hepatology. Ann Pediatr Child Health. 2015;3:1044, Fig. 2.)



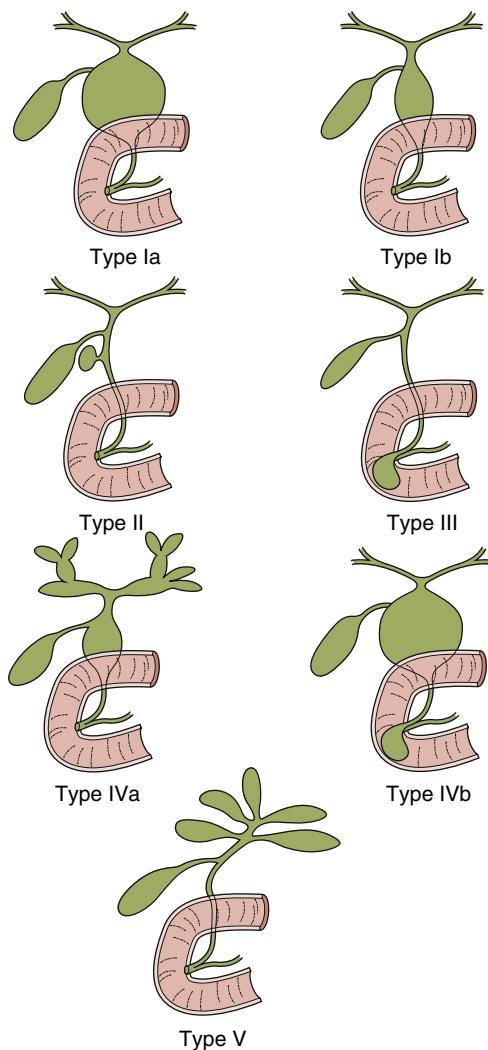
**Fig. 404.4** Hepatportoenterostomy (Kasai procedure). The atretic biliary remnant is removed and a Roux-en-Y jejunostomy is anastomosed to the biliary hilum to reestablish bile flow. (Courtesy National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. <https://www.niddk.nih.gov/news/media-library/18094>.)

of life was used as the benchmark surgical intervention. However, the earlier that the KPE is established, the better the outcome. A national study across all Canadian centers showed that when the KPE was performed at  $\leq 30$  days of age, survival with the native liver at 4 years of age was higher than when the surgery was performed between 31 and 90 days. Given the strong impact of early intervention with KPE, biliary atresia screening programs have been implemented in select countries. Clearly any infant with jaundice persisting beyond the first few weeks of life should have serum total and conjugated bilirubin levels assessed. In Taiwan, the national rate of KPE before 60 days of age increased from 60% to 74% after the implementation of a biliary atresia stool card screening program. Similarly, the proportion of patients with total bilirubin  $<2$  mg/dL 3 months post-KPE, an important prognostic marker for survival with native liver, significantly increased from 37% to 60% after the implementation of the program. A two-stage screening protocol assessing conjugated bilirubin levels in the state of Texas also led to a significant decrease in the age at which patients with biliary atresia underwent the KPE. The first stage was performed before 60 hours of life; the second stage was performed at 2 weeks of age if an elevated conjugated bilirubin was detected in the first stage. Stage two conjugated bilirubin levels that were increasing or were greater than 1 mg/dL were considered positive and underwent further testing. A novel serum biomarker, matrix metalloproteinase 7 (MMP7), has been identified as a possible sensitive and specific marker for biliary atresia.

### Choledochal Malformations

Choledochal malformations, formerly known as *choledochal cysts*, are rare congenital dilations of the biliary tree (Fig. 404.5). With a 4:1 female predominance, these malformations have also been reported to be more common in the Asian population, with an incidence of approximately 1 in 13,000 compared with 1 in 100,000–150,000 in Western populations. The underlying pathogenesis is unknown; however, the presence of an anomalous pancreaticobiliary ductal union present in approximately 90% of patients may contribute to the development of choledochal malformations. Leading hypotheses suggest that an anomalous pancreaticobiliary union leads to reflux of pancreatic contents into the common bile duct, causing chronic inflammation and biliary damage leading to cystic changes.

Approximately 80% of choledochal malformations are detected in infancy and early childhood. Although these lesions are often first discovered by ultrasonography, magnetic resonance cholangiopancreatography (MRCP) and, less commonly, an endoscopic retrograde cholangiopancreatography, may be needed to further characterize the malformation according to the Todani classification (see Fig. 405.5).



**Fig. 404.5** These diagrams depict the five classifications for choledochal cyst according to Todani. (From Todani T, Watanabe Y, Narusue M, et al. Congenital bile duct cysts: classification, operative procedures, and review of thirty-seven cases including cancer arising from choledochal cyst. Am J Surg. 1977;134:263–269.)

In the neonatal period, choledochal malformations present with cholestasis and clay-colored stools; duodenal obstruction has also been reported. If untreated, long-term complications include cholangitis, pancreatitis, portal hypertension, and liver dysfunction. Importantly, biliary malignancies have also been associated with choledochal malformations, particularly with type I and IV malformations. Therefore although the approach differs based on subtype, surgical excision is the treatment of choice. The exceptions are type III cysts (choledochocele), which may be managed by endoscopic sphincterotomy. In those with extensive intrahepatic involvement (type IVa and V) not amenable to surgical resection, orthotopic liver transplantation may be required if symptomatic chronic liver disease develops.

### Choledocholithiasis and Biliary Sludge

Choledocholithiasis in the neonatal age-group is rare. The incidence of biliary sludge or inspissated bile causing cholestasis has been reported to affect 1 in 175,000 births. Both choledocholithiasis and biliary sludge are often detected by abdominal ultrasound. In patients with choledocholithiasis, a stone is typically visualized, whereas biliary sludge is suspected when low-level echoes are seen without evidence of choledocholithiasis on abdominal ultrasound. Factors altering bile acid composition, such as hemolytic disease, or bile flow, such as fasting or use of parenteral nutrition, contribute to the formation of sludge and stones. Ceftriaxone, a third-generation cephalosporin, has been identified as a risk factor in neonates;

**Table 404.1** Classic Criteria Based on Five Body Systems for a Diagnosis of Alagille Syndrome

SYSTEM/PROBLEM	DESCRIPTION
Liver/cholestasis	Usually presenting as jaundice with conjugated hyperbilirubinemia in the neonatal period, often with pale stools
Dysmorphic facies	Broad forehead; deep-set eyes, sometimes with upslanting palpebral fissures; prominent ears; straight nose with bulbous tip; and pointed chin giving the face a somewhat triangular appearance
Congenital heart disease	Most frequently peripheral pulmonary artery stenosis, but also pulmonary atresia, atrial septal defect, ventricular septal defect, and tetralogy of Fallot
Axial skeleton/vertebral anomalies	"Butterfly" vertebrae may be seen on an anteroposterior radiograph and occasionally hemivertebrae, fusion of adjacent vertebrae, and spina bifida occulta
Eye/posterior embryotoxon	Anterior chamber defects, most commonly posterior embryotoxon, which is prominence of the Schwalbe ring at the junction of the iris and cornea

From Turnpenny PD, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. *Eur J Hum Genet*. 2012;20(3):251–257, Table 1.



**Fig. 404.6** Posterior embryotoxon. (From Turnpenny PD, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. *Eur J Hum Genet*. 2012;20:251–257, Fig. 1.)



**Fig. 404.7** Butterfly vertebrae seen in the thoracic and upper lumbar regions. The child had undergone cardiac surgery, hence the presence of visible wires. (From Turnpenny PD, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. *Eur J Hum Genet*. 2012;20:251–257, Fig. 2.)

biliary sludge has been reported to occur in 30–46% of children after a mean of 9 days. It is thought that high drug concentrations in the biliary system may precipitate with calcium salts, causing sludge or gallstones.

Both choledocholithiasis and biliary sludge in the infant is usually managed conservatively because cholestasis usually resolves with spontaneous passage of the stone or sludge. Ursodeoxycholic acid has also been used to treat gallstones and sludge. However, its ability to significantly alter the natural history has not been demonstrated. Endoscopic or surgical interventions are rarely required, but may be reserved for those with severe disease.

## INTRAHEPATIC DISORDERS

### Alagille Syndrome

Alagille syndrome (ALGS) is a multisystem autosomal dominant disorder with hepatic, ophthalmologic (i.e., posterior embryotoxon), cardiac (i.e., peripheral pulmonary stenosis), skeletal (i.e., butterfly vertebrae), renal, and vascular involvement (i.e., moyamoya or aneurysms) (Table 404.1). Characteristic triangular facies, a prominent forehead, deep-set eyes, bulbous nose tip, and pointed chin may be noted. ALGS is caused by pathogenic variants in the *JAG1* gene in 98% of patients and the *NOTCH2* gene in the remaining 2%. Other genes associated with paucity of bile ducts, but not typical ALGS, include *KDM6A* and *HNF1β*. The estimated prevalence of ALGS is approximately 1 in 30,000 live births. A clinical diagnosis can also be made in the presence of cholestatic liver disease and associated eye (Fig. 404.6), heart, skeletal (Fig. 404.7), and facial features.

The majority of patients with ALGS are diagnosed within the first year of life, with many presenting with cholestasis and elevated liver enzymes. Cholestasis is thought to be a result of the paucity of intrahepatic bile ducts, a characteristic hepatic manifestation of AGLS, defined as an intrahepatic bile duct-to-hepatic artery ratio in the portal areas of <0.5; this is present in 75–100% of patients. However, bile duct paucity may not be present in the newborn period, and the liver biopsy may show inflammation and bile ductular proliferation. In addition, nonvisualization of the extrahepatic biliary tree because of intrahepatic disease may lead to a misdiagnosis of biliary atresia in some cases. Therefore expert review of histologic and

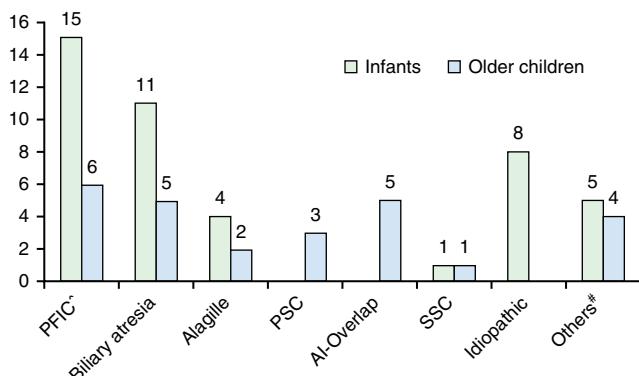
radiographic studies is essential to making the correct diagnosis. The spectrum of bile duct paucity is noted in Figure 404.8.

In general, cholestasis in patients with ALGS typically worsens until 5–6 years of age and then stabilizes or improves in some children. Pruritus, a prominent and debilitating complication of this condition, can be noted within the first 6 months of life. Choleretics, rifampin, sertraline, and naltrexone have been traditionally used in attempts to reduce pruritus in patients with ALGS. Clinical approval of apical sodium-dependent bile acid transporter inhibitors (also known as *ileal bile acid cotransporters*) (such as maralixibat and odevixibat) offers an option for debilitating pruritis and reducing serum bile acid levels.

End-stage liver disease develops in approximately 18% of children, but cardiac and vascular complications are the leading causes of mortality. Therefore a multisystem approach is critical to ensure adequate care for a patient with ALGS.

## CYSTIC FIBROSIS-ASSOCIATED LIVER DISEASE

Cystic fibrosis (CF) is caused by a pathogenic variant in the *CFTR* gene. The incidence of CF varies based on ethnicity, from 1 in 2,500 in Northern Europe to 1 in 350,000 in the Japanese population. In Europe and North America, newborn screening for CF is widely available. Sweat chloride measurements and genetic testing are required to confirm



**Fig. 404.8** Etiologic spectrum of ductal paucity. <sup>a</sup>PFIC type 2 and type 3 were present in 14 and 1 infants and 3 and 3 older children, respectively. SSC was secondary to Langerhans cell histiocytosis in 2 children. <sup>#</sup>Other etiologies included in infants: cystic fibrosis ( $n=1$ ), giant cell hepatitis ( $n=1$ ), cytomegalovirus infection ( $n=1$ ), Caroli syndrome ( $n=1$ ), and Niemann-Pick type C ( $n=1$ ), whereas in older children: oxcarbazepine-induced vanishing bile duct syndrome ( $n=1$ ), congenital portosystemic shunt ( $n=1$ ), myeloproliferative disorder ( $n=1$ ), and hereditary fructose intolerance ( $n=1$ ). AI-Overlap, Autoimmune-overlap; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis; SSC, secondary sclerosing cholangitis. (From Meena BL, Khanna R, Bihari C, et al. Bile duct paucity in childhood – spectrum, profile, and outcome. Eur J Pediatr. 2018;177:1261–1289.)

the diagnosis. Cholestasis can be the first presenting symptom of CF-associated liver disease and has been reported to be present in approximately 6% of infants with CF. Infants with meconium ileus have been identified to be at increased risk for developing cholestasis in the neonatal period.

The cystic fibrosis transmembrane conductance regulator (CFTR), expressed on the apical surface of the biliary epithelial cells, functions to regulate chloride and bicarbonate secretion into the biliary canalculus to provide adequate hydration for bile flow. When CFTR is nonfunctional or dysfunctional, the secretions become thick, leading to biliary obstruction. Postmortem examination of infants with CF revealed excessive mucus within the biliary tree.

Cholestasis in most infants with CF resolves by 9–10 months of age without significant sequelae. However, reports of clinically significant CF-associated liver disease causing liver failure and death have been reported in early childhood.

## DISORDERS OF PLASMA MEMBRANE TRANSPORTERS

### Progressive Familial Intrahepatic Cholestasis

Progressive familial intrahepatic cholestasis (PFIC) is the term used to denote a group of autosomal recessive disorders affecting bile acid transport (Table 404.2). Notably, all PFIC disorders typically present with low or normal GGT cholestasis except for PFIC3, which is associated with high GGT concentrations. Genetic testing is available to aid in the diagnosis of these disorders. **PFIC1** is caused by a pathogenic variant in *ATP8B1* encoding for a P-type ATPase (FIC1) highly expressed on the apical membrane of epithelial cells. Although its exact role is unknown, it likely functions as an aminophospholipid flippase to maintain homeostasis within the phospholipid bilayer by translocating phospholipids from the outer leaflet into the inner leaflet of the plasma membrane. Loss of *ATP8B1* may result in an imbalance in the distribution of phospholipids, leading to instability of the canalicular membrane and decreased function of the transmembrane proteins, including the bile acid transporter (i.e., *ABCB11*). *ATP8B1* is expressed on other epithelial cells, including the pancreas and small intestines. Therefore extrahepatic manifestations of *ATP8B1* (FIC1) deficiency include diarrhea, pancreatic exocrine insufficiency, and sensorineural hearing loss. The liver histology was first described in Amish descendants with the surname Byler. Characteristic findings of “bland cholestasis” include preserved liver architecture with canalicular cholestasis and mild ductular proliferation. Inflammation is typically not a

prominent feature with the absence of giant cells. On electron microscopy, the bile has a granular appearance and has been referred to as *Byler bile*. Progression to end-stage liver disease may occur. Significant diarrhea and hepatic steatosis have been reported in children after liver transplantation.

**PFIC2** is caused by a pathogenic variant in *ABCB11* encoding the bile salt export pump (BSEP) located on the canalicular membrane of the hepatocyte. BSEP actively transports bile acids out of the hepatocyte into the canalculus against a large concentration gradient. Pathogenic variants in *ABCB11* (*BSEP deficiency*) lead to the inability to transport bile acids, resulting in cholestasis. In contrast to PFIC1, liver histology shows features of neonatal hepatitis with disruption of the liver architecture and giant cell transformation. Immunohistochemistry (IHC) may reveal the absence of the BSEP protein; however, the presence of staining does not exclude a dysfunctional protein. Medical therapies are generally supportive; there are currently no proven approaches to halt progression toward cirrhosis. Hepatocellular carcinoma is a recognized complication of this condition, with 10 patients diagnosed before 5 years of age in one report. Most children will eventually require liver transplantation. Notably, recurrence of BSEP deficiency has been reported in the liver allograft, likely the result of recipient antibody production against the BSEP protein in the transplanted liver.

**PFIC3** is caused by a pathogenic variant in *ABCB4* encoding the class III multidrug resistance P-glycoprotein (MDR3) located on the canalicular membrane of the hepatocyte. MDR3 functions as an aminophospholipid floppase, transporting phosphatidylcholine (PC) from the inner leaflet to the outer leaflet (canalicular lumen) of the plasma membrane. With an abundance of PC in the canalicular lumen, mixed micelles containing PC, cholesterol, and excreted bile acids can be formed, thus protecting the biliary tree against the detergent properties of the bile acids. In the absence of available PC, biliary injury results from exposure to inadequately solubilized bile acids. Unlike other forms of PFIC, *MDR3 deficiency* is associated with elevated serum  $\gamma$ -glutamyl transferase (GGT) concentrations. Liver biopsies may show portal inflammation, fibrosis, and prominent ductal proliferation. Medical and surgical therapies are limited; however, ursodeoxycholic acid (UDCA), a hydrophilic bile acid, may have a role. In a single-center study, 77% of children with a clinical diagnosis of PFIC3 showed normalization or improvement in liver enzymes during treatment with UDCA. Furthermore, patients who responded to UDCA also showed resolution of hepatosplenomegaly and pruritus. Liver histology in four children also showed decreased fibrosis after 2 years of UDCA administration. However, response to UDCA has been linked to the type of pathogenic variant, with no response in children with a truncated protein from premature stop codons.

**PFIC4** is caused by a pathogenic variant in *TJP2* encoding the tight junction protein 2, a cytosolic component for several classes of cell-cell junctions; TJP2 plays an important role in the localization of paracellular structures. When dysfunctional, the tight junctions between hepatocytes are impaired, predisposing to reflux of bile into the paracellular spaces and resulting in hepatocellular injury. Hepatocellular carcinoma has been reported. Extrahepatic manifestations include neurologic and respiratory involvement, thought to be related to the widespread distribution of the TJP2 protein. Histologic characteristics include nonspecific features with intracellular cholestasis and scant giant cells. There are no proven effective medical therapies, and liver transplantation has only been reported in a small number of patients.

**PFIC5** is caused by a pathogenic variant in *NR1H4* encoding for the farnesoid X receptor (FXR), a master regulator of bile acid homeostasis. All patients described had severe liver dysfunction and coagulopathy not responsive to vitamin K beginning within the first several months of life. Progression to liver failure has been reported within the first 2 years of life with worsening coagulopathy, hypoglycemia, and hyperammonemia. Liver biopsy features include ductular reaction, diffuse giant cell transformation, intralobular cholestasis with variable degrees of inflammation, and fibrosis. None of the reported patients showed BSEP expression. Outcomes are universally poor, necessitating liver transplantation. Survival after liver transplantation has been reported to be satisfactory, but graft steatosis has been noted.

**Table 404.2** Progressive Intrahepatic Familial Cholestasis Genetics and Transporter Defects and Associated  $\gamma$ -Glutamyl Transferase Levels

	<b>LOCUS</b>	<b>GENE</b>	<b>DEFECT</b>	<b>GGT</b>
PFIC-1 BRIC-1	18q21-22	ATP8B1/FIC1	ATP-dependent amino-phospholipid transport	Normal
PFIC-2 BRIC-2	2q24	ABCB11/BSEP	ATP-dependent bile acid transport	Normal
PFIC-3	7q21	ABCB4/MDR3	ATP-dependent translocation of phosphatidylcholine	High
PFIC-4		TJP2	Tight junction protein	Normal
PFIC-5		NR1H4/FXR	Nuclear bile acid receptor	Normal
PFIC-6		MYO5B	Myosin 5b	Normal

BRIC, Benign recurrent intrahepatic cholestasis; GGT,  $\gamma$ -glutamyl transferase; PFIC, progressive familial intrahepatic cholestasis.

From Loomes KM, Emerick KM. Pediatric cholestatic liver disease. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*, 6th ed. Philadelphia: Elsevier; 2021: Table 70.2, p. 771.

**PFIC6** is caused by a pathogenic variant in *MYO5B* encoding for myosin 5B. *MYO5B* deficiency has also been linked to **microvillus inclusion disease**, in which some patients develop low GGT cholestasis. It is recognized that a form of low GGT cholestasis, resembling other PFIC disorders, can develop in the absence of intestinal disease in patients with *MYO5B* defects. Histologic features show giant cell hepatitis, fibrosis, and hepatocellular cholestasis. IHC reveals abnormal organization of both BSEP and MDR3 in the canalicular and a granular and patchy pattern in the subcanalicular area. The prognosis for patients with PFIC6 appears to be better than with other forms of PFIC, with the median age of 5 years without progressive liver failure in the first case series reported. Cholestatic liver disease has developed in some patients who had undergone isolated intestinal transplant because of intestinal failure. This has prompted some to advocate for the consideration of a combined liver-intestine transplant in this patient population.

### Endocrinopathies

Congenital hypothyroidism has long been associated with neonatal cholestasis. In a single-center study, 35% of patients with congenital hypothyroidism presented with cholestasis. Liver biopsies in these infants revealed intracellular bile pigment accumulation and variable giant cell formation. The pathogenesis remains unknown, but it is postulated that hormones, including thyroid hormone, regulate bile production and flow. Although screening for congenital hypothyroidism using thyroid-stimulating hormone (TSH) is common in many countries, central hypothyroidism resulting from pan-hypopituitarism (i.e., septo-optic dysplasia) may be missed because of a falsely low TSH. Prompt recognition and treatment are vital, as delayed treatment in congenital hypothyroidism may have severe neurodevelopmental consequences and lead to death in those with adrenal insufficiency. Fortunately, cholestasis usually resolves after appropriate hormone supplementation, and progression of liver disease is not expected.

### HEPATOCYTE INJURY

Infections, drugs, metabolic disorders, and genetic conditions should also be considered as causes of cholestasis in an infant.

### Infections

Bacterial, fungal, and viral infections may manifest as neonatal cholestasis. In a single-center study, urinary tract infections were found in 7.5% of asymptomatic, afebrile infants less than 8 weeks of age presenting with jaundice. Infections may result in hepatic injury through direct invasion from hepatotrophic microorganisms (i.e., cytomegalovirus [CMV]), or secondarily by exposure to endotoxins released from microbe membranes. In animal models, endotoxin has been shown to decrease bile flow. In sepsis, perfusion to the liver may also be impaired.

Congenital infections are unique to neonates and require particular attention. The so-called “TORCHes” infections (*Toxoplasma gondii*, rubella, CMV, herpes simplex virus, and syphilis) are recognized causes

of neonatal cholestasis. Although some affected infants are born with stigmata of a congenital infection, such as thrombocytopenic purpura in congenital rubella syndrome, others may present with neonatal cholestasis alone. Therefore it is important to assess for congenital infections in the cholestatic infant, as treatment and additional screening may be necessary upon diagnosis (i.e., hearing tests in congenital CMV infection).

### Infusions, Drugs, and Medications

Although a multitude of drugs and medications can cause cholestasis, parenteral nutrition-associated liver disease (PNALD) is a common iatrogenic cause of cholestasis, particularly in the neonatal intensive care unit. Typically observed in infants requiring parenteral nutrition for more than 2 weeks, other risk factors for the development of PNALD include prematurity, low birthweight, nil per os (NPO), long duration of parenteral nutrition, imbalanced amino acid composition, bacteremia, and abdominal surgeries. The lipid emulsion used also has a significant impact on the development of PNALD. Specifically, soybean lipid emulsions contain  $\omega$ -6 fatty acids and plant-based cholesterol products called phytosterols.  $\omega$ -6 Fatty acids are thought to be proinflammatory, whereas phytosterols can impair bile flow caused by inefficient metabolism in the liver. In contrast, fish oil emulsions are rich in  $\omega$ -3 fatty acids, which are antiinflammatory and do not contain phytosterols, thus protecting the liver against PNALD. The availability of SMOF—a soy, medium-chain triglyceride (MCT), olive oil, and fish oil emulsion—also offers the benefits of an  $\omega$ -3 rich emulsion but also contains adequate essential fatty acids. Clinical trials have shown that SMOF was hepatoprotective in preterm infants, resulting in a lower incidence of PNALD with a lower peak bilirubin level and was associated with decreased hospital length of stay. UDCA may also provide some benefit to patients with PNALD; it was well tolerated without reported adverse events. Therefore the benefits of reducing liver enzymes must be weighed against the unknown efficacy of UDCA. Fortunately, as parenteral nutrition is weaned and enteral feeds are increased, PNALD resolves in most patients without long-term sequelae.

### Alpha<sub>1</sub>-Antitrypsin Deficiency

$\alpha_1$ -Antitrypsin (A1AT) deficiency is the most common form of inherited neonatal cholestasis, occurring in approximately 1 in 2,000–3,500 live births in North America. This autosomal recessive disorder is diagnosed by a low serum A1AT level, protein electrophoresis to identify pathologic phenotypes—most commonly ZZ—and molecular testing. Pathogenic variants in the *SERPINA1* gene may result in abnormal folding of the A1AT protein within the rough endoplasmic reticulum. The misfolded A1AT protein is unable to be secreted out of the hepatocyte, and intracellular accumulation leads to autophagy, mitochondrial injury, and progression to hepatocellular injury. It should be noted that A1AT is also an acute-phase reactant and may be falsely elevated during systemic inflammation; therefore a normal A1AT level in this clinical context may not exclude a diagnosis of A1AT deficiency.

A large Swedish study prospectively screened 200,000 newborns to identify those with A1AT deficiency; neonatal cholestasis occurred in ~11% of infants with the ZZ phenotype. A multicenter study of 350 patients with A1AT deficiency with a mean follow-up time of 2.5 years reported a slightly increased risk of developing portal hypertension in those with a history of neonatal cholestasis compared with those without, although there was no difference in the risk of liver transplantation or death.

### Inborn Errors of Metabolism

**Galactosemia** is a rare inborn error of galactose metabolism caused by a deficiency in the galactose-1-phosphate uridylyltransferase (GALT), galactokinase (GALK), or UDP-galactose-4'-epimerase (GALE) enzyme. As such, galactose cannot be metabolized to glucose, leading to hypoglycemia and accumulation of toxic intermediate metabolites causing vomiting; feed intolerance; and hepatic, neurologic, ocular, and renal injury. An association between galactosemia and *Escherichia coli* sepsis has also been reported. Although rare, neonatal cholestasis may be the presenting symptom of an infant with galactosemia. Early diagnosis with enzyme and genetic testing and treatment with a strict galactose-free diet are essential to preserving neurologic function. Fortunately, many countries have adopted galactosemia as part of their newborn metabolic screen, which has aided in the early diagnosis and improved outcomes of these patients.

**Type I tyrosinemia** is an autosomal recessive disorder caused by a defect in the fumarylacetoacetate hydrolase (FAH) enzyme required for tyrosine metabolism. Accumulation of metabolites upstream of the FAH enzyme, including fumarylacetoacetate, succinylacetate, and succinylacetone, may precipitate hepatic and renal injury. Infants with tyrosinemia can be present with cholestasis, but usually also have evidence of hepatic dysfunction, including severe coagulopathy out of keeping with the degree of hepatocellular injury. High urine succinylacetone levels are highly suggestive of tyrosinemia type I. Treatment with nitisinone, a potent inhibitor of tyrosine degradation, and dietary therapy are the mainstays of therapy to prevent acute and chronic complications of tyrosinemia type I.

**Hereditary fructose intolerance** (HFI) is an autosomal recessive disorder caused by the deficiency of aldolase B enzyme. In the absence of aldolase B activity, large amounts of fructose-1-phosphate accumulate in the liver, leading to depletion of inorganic phosphate and adenosine triphosphate (ATP). As a result of depleted inorganic phosphate, new ATP cannot be generated, leading to hepatocyte necrosis and liver dysfunction. Although breast milk is fructose free, common infant formulas may contain fructose in various forms. Furthermore, sucrose, a disaccharide made up of glucose and fructose monosaccharides, is a common component of oral medications for infants. Therefore a careful review of unexpected fructose exposure should be undertaken in infants with liver dysfunction in which HFI is suspected. A diagnosis is confirmed by measuring enzyme activity or through molecular testing. Symptoms resolve with the institution of a strict fructose-free diet, and patients are expected to develop normally.

**Lysosomal and peroxisomal disorders**, including Niemann-Pick type A and C and Zellweger syndrome, respectively, are another group of conditions that may present with neonatal cholestasis. Typically, these conditions are multisystemic resulting in neurologic, cardiac, and hematologic manifestations depending on the disorder. Liver biopsies may show accumulation of storage materials within organelles on electron microscopy. The diagnosis is usually confirmed by genetic testing.

**Mitochondrial hepatopathies** result from deletion or depletion of mitochondrial genes including *POLG1*, *DGUOK*, and *MPV17* (Table 404.3). These conditions typically present with neonatal cholestasis and may evolve into neonatal acute liver failure characterized by lactic acidosis, coagulopathy, hypoglycemia, and hyperammonemia. An elevated lactate-to-pyruvate ratio >25 mol/mol is suggestive of a mitochondrial disorder. Liver biopsy may reveal microsteatosis and abnormal mitochondrial staining or abnormal architecture on electron microscopy. There is often multisystem involvement, including neurologic, cardiac, and musculoskeletal

Table 404.3

## Phenotypic Classification of Primary Mitochondrial Hepatopathies

RC (electron transport) defects (OXPHOS)

- Neonatal liver failure
  - Complex I deficiency
  - Complex IV deficiency (*SCO1* variants)
  - Complex III deficiency (*BCS1L* variants)
  - Coenzyme Q deficiency
  - Multiple complex deficiencies (transfer and elongation factor variants)
  - mtDNA depletion syndrome (*DUGOK*, *MPV17*, *POLG*, *SUCLG1*, *C10orf2/Twinkle* variants)
- Later-onset liver dysfunction or failure
  - Alpers-Huttenlocher disease (*POLG* variants)
  - Pearson marrow pancreas syndrome (mtDNA deletion)
  - Mitochondrial neurogastrointestinal encephalopathy (*TYMP* variants)
  - NHH (*MPV17* variants)

Fatty acid oxidation defects

- Long-chain 3 hydroxyacyl-coenzyme A dehydrogenase
- Carnitine palmitoyltransferase I and II deficiencies
- Carnitine-acylcarnitinetranslocase deficiency

Urea cycle enzyme deficiencies

Electron transfer flavoprotein and electron transfer flavoprotein dehydrogenase deficiencies

Phosphoenol pyruvate carboxykinase (mitochondrial) deficiency; nonketotic hyperglycemia

Citrin deficiency; neonatal intrahepatic cholestasis caused by citrin deficiency (*SLC25A13* variants)

NN, Navajo neurohepatopathy; OXPHOS, oxidative phosphorylation; RC, respiratory chain.

From Lee WS, Sokol RJ. Mitochondrial hepatopathies: advances in genetics, therapeutic approaches, and outcomes. *J Pediatr*. 2013;163(4):942–948, Table 1.

manifestations of mitochondrial dysfunction. Prognosis is poor with limited proven therapies.

### Bile Acid Synthesis Defects

**Bile acid synthesis** defects are a rare cause of neonatal cholestasis. Liver injury is postulated to result from the accumulation of hepatotoxic intermediate metabolites and absence of the normal trophic and choleretic effects of primary bile acids. Inborn errors of bile acid biosynthesis typically present with a form of low GGT cholestasis and low serum bile acid levels. Clinical presentation may vary from neonatal cholestasis to neonatal acute liver failure. Characteristic urine bile acid profiles may indicate specific enzyme defects. Supplementation with cholic acid may be helpful; however, patients who do not respond to bile acid replacement therapy may require liver transplantation.

### Gestational Alloimmune Liver Disease

**Gestational alloimmune liver disease** (GALD) is a rapidly progressive disease characterized by iron deposition in the liver, heart, salivary glands, and endocrine organs without increased iron stores in the reticuloendothelial system. Infants present with liver dysfunction within the first few days of life. Familial cases and repeated miscarriages are commonly reported. The postulated pathophysiology involves maternal sensitization to fetal liver antigens. As a result, maternal antibodies against the fetal liver are transported across the placenta causing fetal liver injury in utero. Liver injury results in decreased hepatic hepcidin expression and thus dysregulated iron update into the developing fetus. Laboratory findings include hypoglycemia, hyperbilirubinemia, hypoalbuminemia, elevated ferritin, and coagulopathy. The diagnosis is usually confirmed by salivary biopsy or MRI demonstrating extrahepatic siderosis in the pancreas, myocardium, or thyroid follicles. Liver biopsies almost universally show cirrhosis, and positive staining for C5b-9 membrane attack complex has also been reported. The differential diagnosis is noted in Table 404.4. Treatment with exchange transfusion and intravenous immunoglobulin (IVIG) has been shown to

**Table 404.4** Typical Laboratory Findings in Neonatal Liver Failure

	GALD	HLH	MITOCHONDRIAL	VIRAL	ISCHEMIC
Transaminase levels (IU/L)	Normal/mild increase (<100)	Moderate/significant increase (>1,000)	Moderate increase (100–500)	Significant increase (>1,000)	Significant increase (>1,000–6,000)
INR	Significant increase	Moderate/significant increase	Moderate/significant increase	Moderate/significant increase	Moderate/significant increase
Ferritin level (ng/mL)	800–7,000	Significant increase (>20,000)	Variable	Significant increase (>20,000)	Variable depending on underlying cause of ischemia
Triglyceride levels	Normal	Increased	Normal	Normal	Normal
Hypoglycemia	Yes	Often	Yes	Often	Variable
Lactic acidosis	Normal	Normal	Increased	Normal	Often
α-Fetoprotein level (for age)	Increased	Normal	Normal/increased	Normal	Normal
Cholestasis	Progressive after birth	Moderate/significant	Moderate	None/mild at presentation	Mild/moderate

HLH, Hemophagocytic lymphohistiocytosis.

From Larson-Nath C, Vitola BE. Neonatal acute liver failure. *Clin Perinatol*. 2020;47:25–39; Table 2; with data from Sundaram et al. *J Pediatr*. 2011;159:813–818; Taylor et al. *Liver Transpl*. 2016;22(5):677–685; Bitar et al. *J Pediatr Gastroenterol Nutr*. 2017;64(1):70–75; Fellman et al. *Semin Fetal Neonatal Med*. 2011;16(4):222–228.

improve outcomes and reduce the need for liver transplantation. Given the high rate of recurrence of GALD in future pregnancies of affected mothers, maternal treatment with weekly IVIG beginning at 18 weeks gestational age should be considered and has been shown to decrease GALD in the developing fetus.

### OTHER SYNDROMES ASSOCIATED WITH NEONATAL CHOLESTASIS

#### Neonatal Ichthyosis and Sclerosing Cholangitis

**Neonatal ichthyosis and sclerosing cholangitis (NISCH) syndrome** is a rare autosomal recessive condition caused by pathogenic variants in claudin-1 (*CLDN1*), a membrane protein needed for the formation of tight junctions between cells. Infants may present with dry scaly skin, alopecia, and jaundice within the first few weeks of life. Defects in *CLDN1* (similar to *TJP2* deficiency) increase paracellular leakage and regurgitation of the toxic components of bile, leading to bile duct injury and cholestasis. Liver histology is variable, with most infants having evidence of hepatocellular cholestasis and bile duct plugs. Ductular proliferation, portal fibrosis, ductopenia, and characteristic findings of sclerosing cholangitis on cholangiogram have been described later in adolescence. Severity of liver disease is also variable ranging from transient neonatal cholestasis to progressive cirrhosis requiring liver transplantation.

#### Lymphedema-Cholestasis Syndrome (Aagenaes Syndrome)

**Lymphedema-cholestasis syndrome** is a rare cholestatic disorder manifest by cholestasis with pale stools by 1 week of life. On liver biopsy, multinucleated giant cell hepatitis was described in affected patients. The clinical course is variable, but jaundice reportedly resolves by 1–5 years of age. Intermittent episodes of cholestasis may recur but typically resolve in a period of months. Lower extremity lymphedema develops during the prepuberty period in all patients and can be disfiguring. Pathogenesis remains unknown, but a locus has been mapped to chromosome 15q and is thought to play a role in the abnormal development of lymphatic structures. The natural history of liver disease has been reported to be favorable, with cirrhosis developing in a small minority of patients.

### Arthrogryposis, Renal Dysfunction, and Cholestasis

**Arthrogryposis, renal dysfunction, and cholestasis (ARC) syndrome** is a rare and autosomal recessive disorder caused by *VPS33B* or *VIPAR* pathogenic variants. Prominent clinical features include arthrogryposis, renal tubular acidosis, and a low GGT cholestasis. Additional features include agenesis of the corpus callosum, deafness, hypothyroidism, ichthyosis, recurrent infections, and congenital cardiac defects. With abnormal platelet count and function having also been described, life-threatening bleeding has been reported both spontaneously and after liver biopsy in affected patients. *VPS33B* or *VIPAR* plays a role in intracellular vesicular trafficking pathways, cell polarity, and membrane protein localization. As such, abnormal localization of canalicular membrane proteins, including *BSEP* and *MDR3*, have been reported in liver biopsies of patients with ARC syndrome and may contribute to the pathogenesis of cholestasis. Although the prognosis has been reported to be poor, successful liver transplantation for severe intractable pruritus and poor quality of life has been reported.

### IDIOPATHIC NEONATAL HEPATITIS

*Idiopathic neonatal hepatitis* was a term used to describe infants with neonatal cholestasis for which a specific cause could not be determined. However, with the advent of molecular testing, the number of patients with “idiopathic neonatal hepatitis” is decreasing owing to the expanding knowledge of the molecular causes of cholestasis.

### Management

Management of patients with neonatal cholestasis requires the clinician to identify the cause of cholestasis while ruling out conditions that require prompt intervention. Delayed diagnosis of sepsis, pan-hypopituitarism, or inborn errors of metabolism may have fatal consequences. Similarly, failure to promptly treat galactosemia or congenital hypothyroidism can have devastating neurologic sequelae. In patients with biliary atresia, the most common indication for pediatric liver transplant worldwide, early surgical intervention with KPE has been shown to improve survival with the native liver. **Table 404.5** provides a framework for the initial investigation of a patient with neonatal cholestasis.

**Table 404.5** Etiologies and Suggested Investigations for Patients with Neonatal Cholestasis

Etiology	Recommended Investigations
General investigations for all infants with cholestasis	CBC and differential, ALT, AST, total and conjugated bilirubin, GGT and ALP, INR, albumin, blood glucose Abdominal ultrasound with Doppler Review newborn metabolic screen Urinalysis
<b>DISORDERS OF EXTRAHEPATIC BILE DUCTS</b>	
Biliary atresia	MMP7, liver biopsy, intraoperative cholangiogram, examination of the biliary remnant
Choledochal malformation and choledocholithiasis/microlithiasis	Abdominal US, MRCP
<b>INTRAHEPATIC DISORDERS</b>	
Alagille syndrome	Ophthalmologic examination, chest x-ray, echocardiogram, liver biopsy, and genetic testing for JAG1 and NOTCH2
Cystic fibrosis	Sweat chloride, CFTR testing
Membrane transporter defects	<ul style="list-style-type: none"> <li>• PFIC1 ATP8B1 genetic testing</li> <li>• PFIC2 ABCB11 genetic testing</li> <li>• PFIC3 MDR3 genetic testing</li> <li>• PFIC4 TJP2 genetic testing</li> <li>• PFIC5 NR1H4 (FXR) genetic testing</li> <li>• PFIC6 MYO5B genetic testing</li> <li>• ARC syndrome VPS33B and VIPAR genetic testing</li> <li>• NISCH syndrome CLDN1 genetic testing</li> </ul>
Endocrinopathies	<ul style="list-style-type: none"> <li>• Hypothyroidism TSH, free T<sub>4</sub></li> <li>• Hypopituitarism TSH, free T<sub>4</sub>, cortisol and electrolytes, MRI brain</li> </ul>
Hepatocyte injury	<ul style="list-style-type: none"> <li>• Infection Complete blood count and differential, blood and urine cultures, urinalysis, "ToRCHes" screen</li> <li>• Total parental nutrition History</li> </ul>
Inborn errors of metabolism	<ul style="list-style-type: none"> <li>• Galactosemia Galactose-1-phosphate uridyltransferase enzyme activity, genetic testing for GALT, GALK, or GALE</li> <li>• Tyrosinemia Urine succinylacetone, FAH genetic testing</li> <li>• Hereditary fructose intolerance Aldolase B (ALDOB) enzyme activity and genetic testing</li> </ul>
Bile acid synthesis defect	Serum bile acids, urine bile acid profile, genetic testing
$\alpha_1$ -Antitrypsin deficiency	Blood $\alpha_1$ -antitrypsin concentrations, electrophoretic phenotyping, SERPINA1 genetic testing
Lysosomal disorders	<ul style="list-style-type: none"> <li>• Niemann Pick A and C Genetic testing for SMPD1 for Niemann Pick A and NPC1 or NPC2 genes for Niemann Pick C</li> <li>• Cholesterol esterase storage disease/Wolman Liposomal acid lipase enzyme testing and LIPA genetic testing</li> <li>• Mucopolysaccharidoses Urine screen for glycosaminoglycans. Genetic testing for specific pathogenic variants associated with mucopolysaccharidoses</li> </ul>
Peroxisomal biogenesis disorders	Very long-chain fatty acid concentrations, genetic testing for PEX genes
Mitochondrial hepatopathy	Ammonia, lactate, pyruvate, creatinine kinase, echocardiogram, genetic testing for mitochondrial genes
Gestational alloimmune liver disease	MRI, buccal biopsy, serum ferritin, total iron-binding capacity ammonia

CBC, Complete blood count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; INR, international normalized ratio; MMP7, matrix metalloproteinase 7; US, ultrasound; MRCP, magnetic resonance cholangiopancreatography; JAG1, jagged-1; NOTCH2, notch receptor 2; CFTR, cystic fibrosis transmembrane conductance regulator; ATP8B1, ATPase phospholipid transporting 8B1; ABCB11, ATP-binding cassette subfamily B member 11; MDR3, class III multidrug resistance P-glycoproteins; TJP2, tight junction protein 2; NR1H4, nuclear receptor subfamily 1 group H member 4; MYO5B, myosin VB; VPS33B, vacuolar protein sorting-associated protein 33B; VIPAR, VPS33B interacting protein, apical-basolateral polarity regulator, Spe-39 homolog; CLDN1, claudin 1; TSH, thyroid-stimulating hormone; GALT, galactose-1-phosphate uridyl transferase; GALK, galactokinase; GALE, UDP-galactose-4'-epimerase; FAH: fumarylacetoacetate hydrolase; SERPINA1, serpin family A member 1; SMPD1, sphingomyelin phosphodiesterase 1; NPC1, NPC intracellular cholesterol transporter 1; NPC2, NPC intracellular cholesterol transporter 2; LIPA, lysosomal acid lipase.

**Table 404.6** Recommended Nutritional Support for Children with Cholestasis

ENERGY/NUTRIENT	REQUIREMENT
Energy	~130% of requirement for age
Fat	30–50% of total calories Start with MCT/LCT = 30%/70% of total fat calories
Protein	~130–150% of requirement for age
Carbohydrate	40–60% of total calories
Vitamin A	<10 kg: 5,000 IU/day >10 kg: 10,000 IU/day
Vitamin D	Cholecalciferol: 2,000–5,000 IU/day
Vitamin E	D-alpha-tocopheryl polyethylene glycol 1000 succinate: 15–25 IU/kg/day
Vitamin K	2–5 mg/day
Calcium	Meet DRI

Adapted from Mouzaki M, Bronsky J, Gupte G, et al. Nutrition support of children with chronic liver diseases: a joint position paper of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr.* 2019;69(4):498–511.

In infants with chronic cholestasis, growth failure and malnutrition are major concerns. Bile is an essential component of lipid digestion; therefore cholestasis leads to fat maldigestion and fat-soluble vitamin deficiencies (i.e., vitamin A, D, E, and K). Caloric support by an MCT-containing formula may be helpful, as MCT can be absorbed in a bile acid-independent manner. Supplementation with aqueous vitamin A, D, E, and K formations should be considered to avoid the complications of fat-soluble vitamin deficiencies. Table 404.6 has been adapted to provide initial guidance toward nutritional support in children with neonatal cholestasis. Regular monitoring of anthropometrics and fat-soluble vitamin levels is needed to ensure patients are provided with adequate nutrition for growth and development.

## 404.2 Cholestasis in the Older Child

Simon Lam and William F. Balistreri

Cholestasis with onset after the neonatal period is most often caused by acute viral hepatitis or exposure to hepatotoxic drugs. However, many of the conditions causing neonatal cholestasis can also cause chronic cholestasis in older patients (see Table 403.3). Consequently, older children and adolescents with conjugated hyperbilirubinemia should be evaluated for acute and chronic viral hepatitis,  $\alpha_1$ -antitrypsin deficiency, Wilson disease, liver disease associated with inflammatory bowel disease, sclerosing cholangitis, autoimmune hepatitis, drug-induced liver injury, and the syndromes of intrahepatic cholestasis. Other causes include obstruction related to cholelithiasis, abdominal tumors, enlarged lymph nodes, or hepatic inflammation resulting from drug ingestion. Management of cholestasis in the older child is similar to that proposed for neonatal cholestasis.

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## Chapter 405

# Metabolic Diseases of the Liver

Julie Bonn and William F. Balistreri

## INTRODUCTION

Metabolic liver diseases in children, although individually rare, altogether represent a significant cause of morbidity and mortality. This is because the liver has a central role in synthetic, degradative, and regulatory pathways involving carbohydrate, protein, lipid, trace element, and vitamin metabolism. Therefore inborn errors of metabolism will result in metabolic abnormalities, specific enzyme deficiencies or defects, and disorders of protein transport that can have primary or secondary effects on the liver (Table 405.1). Liver disease can arise when absence of an enzyme produces a block in a metabolic pathway, when unmetabolized substrate accumulates proximal to a block, when deficiency of an essential substance produced distal to an aberrant chemical reaction develops, or when synthesis of an abnormal metabolite occurs. The spectrum of pathologic changes includes **hepatocyte injury**, with subsequent failure of other metabolic functions, often resulting in cirrhosis and/or liver cancer; abnormal **storage** of lipid, glycogen, or other products manifested as hepatomegaly, often with complications specific to deranged metabolism (hypoglycemia with glycogen storage disease); and absence of structural change despite profound **metabolic effects**, as seen in patients with urea cycle defects. Clinical manifestations of metabolic diseases of the liver mimic infections, intoxications, and hematologic and immunologic diseases (Table 405.2).

Many metabolic diseases are detected in expanded newborn metabolic screening programs (see Chapter 104). Clues are provided by family history of a similar illness or by the observation that the onset of symptoms is closely associated with a change in dietary habits; in patients with hereditary fructose intolerance, symptoms follow ingestion of fructose (sucrose). Clinical and laboratory evidence often guides the evaluation. Liver biopsy offers morphologic study and permits enzyme assays, as well as quantitative and qualitative assays of various other constituents (e.g., hepatic copper content in Wilson disease). Genetic/molecular diagnostic approaches are also available. Such studies require cooperation of experienced laboratories and careful attention to collection and handling of specimens. Treatment depends on the specific type of defect, and although relatively uncommon, altogether metabolic diseases of the liver account for up to 10% of the indications for liver transplantation in children, a number that may be underestimated given the acute nature of some of these conditions, precluding complete diagnostic investigation before transplantation.

## 405.1 Inherited Deficient Conjugation of Bilirubin (Familial Nonhemolytic Unconjugated Hyperbilirubinemia)

Julie Bonn and William F. Balistreri

Bilirubin is the metabolic end product of heme. Before excretion into bile, it is first glucuronidated and made water-soluble by the enzyme bilirubin-uridine diphosphoglucuronate glucuronosyltransferase (UDPGT). UDPGT activity is deficient or altered in three genetically and functionally distinct disorders (Crigler-Najjar [CN] syndromes type I and II and Gilbert syndrome), producing congenital nonobstructive, nonhemolytic, **unconjugated** hyperbilirubinemia. UGT1A1

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**Table 405.1** Inborn Errors of Metabolism that Affect the Liver

#### COMMON DISORDERS OF CARBOHYDRATE METABOLISM

##### Disorders of galactose metabolism

- Galactosemia (galactose-1-phosphate uridyltransferase deficiency)

##### Disorders of fructose metabolism

- Hereditary fructose intolerance (aldolase deficiency)
- Fructose-1,6 diphosphatase deficiency

##### Glycogen storage diseases

- Type I
- Von Gierke Ia (glucose-6-phosphatase deficiency)
- Type Ib (glucose-6-phosphatase transport defect)
- Type III Cori/Forbes (glycogen debrancher deficiency)
- Type IV Andersen (glycogen branching enzyme deficiency)
- Type VI Hers (liver phosphorylase deficiency)

##### Congenital disorders of glycosylation (multiple subtypes)

#### DISORDERS OF AMINO ACID AND PROTEIN METABOLISM

##### Disorders of tyrosine metabolism

- Hereditary tyrosinemia type I (fumarylacetoacetate hydrolase deficiency)
- Tyrosinemia, type II (tyrosine aminotransferase deficiency)

##### Inherited urea cycle enzyme defects

- CPS deficiency (carbamoyl phosphate synthetase I deficiency)
- OTC deficiency (ornithine transcarbamoylase deficiency)
- Citrullinemia type I (argininosuccinate synthetase deficiency)
- Argininosuccinic aciduria (argininosuccinate deficiency)
- Argininemia (arginase deficiency)
- N-AGS deficiency (*N*-acetylglutamate synthetase deficiency)

##### Maple serum urine disease (multiple possible defects\*)

#### DISORDERS OF LIPID METABOLISM

##### Wolman disease (lysosomal acid lipase deficiency)

##### Cholesteryl ester storage disease (lysosomal acid lipase deficiency)

##### Homozygous familial hypercholesterolemia (low-density lipoprotein receptor deficiency)

##### Gaucher disease type I ( $\beta$ -glucocerebrosidase deficiency)

##### Niemann-Pick type C (NPC 1 and 2 variants)

#### DISORDERS OF BILE ACID METABOLISM

##### Defects in bile acid synthesis (several specific enzyme deficiencies)

##### Zellweger syndrome—cerebrohepatorenal (multiple pathogenic variants in peroxisome biogenesis genes)

#### DISORDERS OF METAL METABOLISM

##### Wilson disease (ATP7B pathogenic variants)

##### Hepatic copper overload

##### Indian childhood cirrhosis

##### Neonatal hemochromatosis

#### DISORDERS OF BILIRUBIN METABOLISM

##### Crigler-Najjar (bilirubin-uridine diphosphoglucuronate glucuronyltransferase pathogenic variants)

- Type I
- Type II

##### Gilbert disease (bilirubin-uridine diphosphoglucuronate glucuronyltransferase polymorphism)

##### Dubin-Johnson syndrome (multiple drug-resistant protein 2 pathogenic variants)

##### Rotor syndrome

#### MISCELLANEOUS

##### $\alpha_1$ -Antitrypsin deficiency

##### Citrullinemia type II (citrin deficiency)

##### Cystic fibrosis (cystic fibrosis transmembrane conductance regulator pathogenic variants)

##### Erythropoietic protoporphyrinia (ferrochelatase deficiency)

##### Polyzystic kidney disease

##### Mitochondrial hepatopathies (see Table 404.4 and Chapter 409)

\*Maple syrup urine disease can be caused by mutations in branched-chain  $\alpha$ -keto dehydrogenase, keto acid decarboxylase, lipoamide dehydrogenase, or dihydrolipoamide dehydrogenase.

is the primary UDPGT isoform needed for bilirubin glucuronylation. Complete absence of UGT1A1 activity causes CN type I, while CN type II is caused by decreased UGT1A1 activity to ~10% of normal.

**Table 405.2** Clinical Manifestations that Suggest the Possibility of Metabolic Disease

Recurrent vomiting, failure to thrive, short stature

Dysmorphic features

Jaundice, hepatomegaly ( $\pm$  splenomegaly), fulminant hepatic failure, edema/anasarca

Hypoglycemia, organic acidemia, lactic acidemia, hyperammonemia, bleeding (coagulopathy)

Developmental delay, hypotonia, progressive neuromuscular deterioration, seizures, myopathy, neuropathy

Cardiac dysfunction/failure

Unusual odors

Rickets

Cataracts

Multiorgan involvement

Family history

**Gilbert syndrome**, the most common hereditary hyperbilirubinemia syndrome, occurs in 5–10% of the White population. Common polymorphisms resulting in a TA insertion in the promoter region of *UGT1A1* lead to decreased binding of the TATA binding protein and decrease normal gene activity by ~30%. Snapback primer genotyping can distinguish all *UGT1A1* promoter genotypes and can provide a definitive diagnosis. Unlike the CN syndromes, Gilbert syndrome usually occurs after puberty, is not associated with chronic liver disease, and no treatment is required. Disease manifestations include fluctuating mild elevations in total serum bilirubin concentration from 1 to 6 mg/dL with no evidence of liver injury or hemolysis. Fasting or dehydration may result in visible jaundice. Because *UGT1A1* catalyzes water-soluble glucuronidation and detoxification of multiple substrates other than bilirubin (i.e., drugs, hormones, environmental toxins, and aromatic hydrocarbons), pathogenic variants in the *UGT1A1* gene are implicated in cancer risk and predispose to drug toxicity and episodic jaundice specifically in cancer chemotherapy.

#### CRIGLER-NAJJAR SYNDROME TYPE I (GLUCURONYL TRANSFERASE DEFICIENCY)

CN type I is a rare, autosomal recessive disease caused by homozygous or compound heterozygous pathogenic variants in the *UGT1A1* gene that result in a premature stop codon or frameshift pathogenic variant and complete absence of *UGT1A1* activity. At least 59 pathogenic variants have been identified to date. Parents of affected children have partial defects in conjugation, as determined by hepatic-specific enzyme assay or by measurement of glucuronide formation, but have normal serum unconjugated bilirubin levels.

#### Clinical Manifestations

Severe unconjugated hyperbilirubinemia develops in homozygous affected infants in the first 3 days of life. Without treatment, serum unconjugated bilirubin concentrations reach 25–35 mg/dL in the first month, which can cause **kernicterus**. Stools are pale yellow. Persistent unconjugated hyperbilirubinemia at levels >20 mg/dL without hemolysis after the first week of life should suggest the syndrome.

#### Diagnosis

The diagnosis of CN type I is based on the early age of onset and the extreme level of bilirubin elevation in the absence of hemolysis. In affected infants, bile contains no bilirubin glucuronide and bilirubin concentration in bile is <10 mg/dL compared with normal concentrations of 50–100 mg/dL. The diagnosis is established by measuring hepatic glucuronyl transferase activity in a liver specimen obtained by percutaneous liver biopsy; open liver biopsy should be avoided because surgery and anesthesia can precipitate kernicterus. DNA diagnosis is also available and may be preferable. Identification of the heterozygous state in parents also strongly suggests the diagnosis. The differential diagnosis of unconjugated hyperbilirubinemia is discussed in Chapter 137.

### Treatment

The serum unconjugated bilirubin concentration should be maintained at <20 mg/dL for the first few weeks of life, and even lower in low birthweight infants. This usually requires repeated exchange transfusions and phototherapy in the immediate neonatal period. Oral calcium phosphate supplementation renders phototherapy more effective, as it forms complexes with bilirubin in the gut. Phenobarbital therapy, through CYP450 enzyme induction, should be considered to determine responsiveness and differentiation between CN types I and II. In patients with type I, there is no response to phenobarbital treatment.

The risk of kernicterus persists into adult life, although the serum bilirubin levels required to produce brain injury beyond the neonatal period are considerably higher (usually >35 mg/dL). Therefore phototherapy is generally continued through the early years of life. In older infants and children, phototherapy is used mainly during sleep so as not to interfere with normal activities. Despite the administration of increasing intensities of light for longer periods, the serum bilirubin response to phototherapy decreases with age. Additional adjuvant therapy using agents that bind photobilirubin products such as cholestyramine or agar can also be used to interfere with the enterohepatic recirculation of bilirubin.

Prompt treatment of intercurrent infections, febrile episodes, and other types of illness might help prevent the later development of kernicterus, which can occur at bilirubin levels of 45–55 mg/dL. All reported patients with CN type I have eventually experienced severe kernicterus by young adulthood.

Orthotopic liver transplantation cures the disease and has been successful in a small number of patients. Isolated hepatocyte transplantation has been reported as bridge therapy to liver transplantation, with most, but not all, patients eventually requiring orthotopic transplantation. Other therapeutic modalities have included plasmapheresis and limitation of bilirubin production. The latter option, inhibiting bilirubin generation, is possible via inhibition of heme oxygenase using metalloporphyrin therapy. Finally, gene therapy using adenovirus-associated viral vectors has shown promise in a murine model and is in clinical trials in humans.

### CRIGLER-NAJJAR SYNDROME TYPE II (PARTIAL GLUCURONYL TRANSFERASE DEFICIENCY)

CN type II is an autosomal recessive disease caused by homozygous missense pathogenic variants in *UGT1A1* resulting in reduced (partial) enzymatic activity. More than 45 pathogenic variants have been identified to date. Type II disease can be distinguished from type I by the marked decline in serum bilirubin level that occurs in type II disease after treatment with phenobarbital secondary to an inducible phenobarbital response element on the *UGT1A1* promoter.

### Clinical Manifestations

When this disorder appears in the neonatal period, unconjugated hyperbilirubinemia usually occurs in the first 3 days of life; serum bilirubin concentrations can be in a range compatible with physiologic jaundice or can be at pathologic levels. The concentrations characteristically remain elevated into and after the third week of life, persisting in a range of 1.5–22 mg/dL; concentrations in the lower part of this range can create uncertainty about whether chronic hyperbilirubinemia is present. Development of kernicterus is unusual. Stool color is normal, and the infants are without clinical signs or symptoms of disease. There is no evidence of hemolysis. Liver enzymes, albumin, and prothrombin time/international normalized ratio (PT/INR) are typically normal.

### Diagnosis

The concentration of bilirubin in the bile is nearly normal in patients with CN type II. Jaundiced infants and young children with type II respond readily to 5 mg/kg/day of oral phenobarbital, with a decrease in serum bilirubin concentration to 2–3 mg/dL in 7–10 days.

### Treatment

Long-term reduction in serum bilirubin levels can be achieved with continued administration of phenobarbital at 5 mg/kg/day. Therapy must be lifelong. The cosmetic and psychosocial benefit should be weighed against the risks of an effective dose of the drug because there is a small long-term risk of kernicterus even in the absence of hemolytic disease. Orlistat, an irreversible inhibitor of intestinal lipase, increases fecal fat excretion and may decrease plasma unconjugated bilirubin concentrations (~10%) in patients with CN types I and II.

### INHERITED CONJUGATED HYPERBILIRUBINEMIA

Conjugated hyperbilirubinemia can be caused by rare autosomal recessive conditions characterized by asymptomatic mild jaundice. In these conditions, the transfer of bilirubin and other organic anions from the hepatocyte into bile is defective. Chronic mild conjugated hyperbilirubinemia is usually detected during adolescence or early adulthood but can occur as early as 2 years of age. The results of other routine liver tests are normal. Jaundice can be exacerbated by infection, pregnancy, oral contraceptives, alcohol consumption, and surgery. There is usually no morbidity, and life expectancy is normal.

### DUBIN-JOHNSON SYNDROME

Dubin-Johnson syndrome is an autosomal recessive inherited defect in hepatocyte secretion of bilirubin glucuronide. The defect in hepatic excretory function is not limited to conjugated bilirubin excretion but also involves several organic anions normally excreted from the liver cell into bile. Disease results from absent function of MRP2, encoded by the gene *ABCC2*, an adenosine triphosphate-dependent canalicular transporter. More than 10 different pathogenic variants, including compound heterozygous pathogenic variants in the *CMOAT* gene, have been identified and either affect localization of MRP2 with resultant increased degradation or impair MRP2 transporter activity in the canalicular membrane. Bile acid excretion and serum bile acid levels are normal. Total urinary coproporphyrin excretion is normal in quantity, but coproporphyrin I excretion increases to approximately 80% with a concomitant decrease in coproporphyrin III excretion. Normally, coproporphyrin III is >75% of the total. Cholangiography fails to visualize the biliary tract, and x-ray of the gallbladder is also abnormal. Liver histology demonstrates normal architecture, but hepatocytes contain black pigment similar to melanin. Liver function is normal, and the prognosis is excellent. The most commonly reported symptoms are abdominal pain and fatigue, jaundice, dark urine, and slight enlargement of the liver. Jaundice fluctuates in intensity and is aggravated by intercurrent disease. Rarely, Dubin-Johnson can present in the neonatal period with severe conjugated hyperbilirubinemia with serum bilirubin >20 mg/dL and hepatosplenomegaly. No treatment is indicated for disease that presents outside of the neonatal period.

### Rotor Syndrome

Rotor syndrome is an autosomal recessive disease resulting from biallelic inactivating pathogenic variants in *SLCO1B1* and *SLCO1B3* that result in functional deficiencies of both OATP1B1 and OATP1B protein. Importantly, these pathogenic variants may confer significant drug toxicity risk. These patients present similarly to Dubin-Johnson syndrome, with asymptomatic mild and fluctuating conjugated hyperbilirubinemia, with total serum bilirubin levels between 2 and 5 mg/dL. Unlike Dubin-Johnson syndrome, total urinary coproporphyrin excretion is elevated with a relative increase in the amount of the coproporphyrin I isomer. If liver biopsy is performed, there is no abnormal pigmentation, in contrast to Dubin-Johnson. The gallbladder is normal by roentgenography. Rotor syndrome is benign, and no treatment is indicated.

## 405.2 Wilson Disease

Julie Bonn and William F. Balistreri

Wilson disease (hepatolenticular degeneration) is an autosomal recessive disorder that can be associated with liver disease, degenerative changes in the brain, psychiatric symptoms, and Kayser-Fleischer (K-F) rings in the cornea (Fig. 405.1 and Table 405.3). The incidence is approximately 1/30,000 births worldwide. Specific treatment is available; however, this disease is progressive and potentially fatal if untreated. Prompt diagnostic evaluation for Wilson disease in all patients over age 5 presenting with any form of liver disease facilitates expeditious initiation of treatment of the disease, appropriate genetic counseling, and screening of first-degree relatives and also allows appropriate treatment of non-Wilsonian liver disease once copper toxicosis is ruled out.

### PATHOGENESIS

The variant gene for Wilson disease is found on chromosome 13 (13q14.3) and encodes ATP7B, a copper transporting P-type adenosine triphosphatase (ATPase), which is mainly expressed in hepatocytes and is critical for biliary copper excretion and for copper incorporation into ceruloplasmin. Absence or malfunction of ATP7B results in decreased biliary copper excretion and diffuse accumulation of copper in the cytosol of hepatocytes. With time, liver cells become overloaded and copper is redistributed to other tissues, including the brain and kidneys, causing toxicity, primarily as a potent inhibitor of enzymatic processes. Ionic copper inhibits pyruvate oxidase in the brain and ATPase in membranes, leading to decreased adenosine triphosphate-phosphocreatine and potassium content of tissue.

More than 500 pathogenic variants have been identified, of which >380 have a confirmed role in disease pathogenesis; genetic testing should be able to identify a pathologic variant. Most patients are compound heterozygotes. Pathogenic variants that abolish gene function are associated with an onset of disease symptoms as early as 3 years of age, when Wilson disease might not typically be considered in the differential diagnosis. Milder variants can be associated with neurologic symptoms or liver disease as late as 80 years of age. The most commonly occurring disease-causing ATP7B pathogenic variants result in a protein that binds copper but is unable to effectively traffic to the apical surface of hepatocytes to perform its copper-exporting function.

### CLINICAL MANIFESTATIONS

Forms of Wilsonian hepatic disease include asymptomatic hepatomegaly (with or without splenomegaly), subacute or chronic hepatitis, and acute hepatic failure (with or without hemolytic anemia). Cryptogenic cirrhosis, portal hypertension, ascites, edema, variceal bleeding,



**Fig. 405.1** Kayser-Fleischer ring. Brown discoloration at the outer margin of the cornea caused by deposition of copper in Descemet's membrane. Here it is clearly seen against the light green iris. Slit-lamp examination is required for secure detection. (From Ala A, Walker AP, Ashkan K, et al. Wilson's disease. Lancet. 2007;369:397–408.)

**Table 405.3** The Most Common Clinical Manifestations of WD and Their Frequency of Disease Diagnosis

WD PRESENTATION AND FREQUENCY	SYMPTOMS
Hepatic (40–60%)	Asymptomatic elevation of liver enzymes (aminotransferases) Acute hepatitis (e.g., jaundice, abdominal pain) Acute liver failure (coagulopathy, jaundice, encephalopathy) Liver cirrhosis symptoms (compensated or decompensated) (fatigue, spider naevi, portal hypertension, splenomegaly, bleeding)
Neurologic (40–50%)	Involuntary movements (tremor, dystonia, ataxia, ballism, chorea, parkinsonian syndrome) Speech disturbances: dysarthria (extrapyramidal, dystonic, cerebellar, mixed, unclassified) Dysphagia Autonomic dysfunction (e.g., salivation, electrocardiographic abnormalities, orthostatic hypotension) Gait and balance disturbances
Psychiatric (10–25%)	Personality disorders (e.g., abnormal, antisocial behavior, irritability, disinhibition) Mood disorders (bipolar disorders, depression, suicidal attempts) Psychosis and other psychiatric alterations (rarely: e.g., psychosis, anorexia, sleep disturbances) Cognitive impairment
Ophthalmologic (K-F ring: 90–100% in neurologic patients, 40–50% in hepatic and 20–30% in presymptomatic); SC (1,2–25%)	Kayser-Fleischer ring (K-F ring); sunflower cataract (SC)
Other (lack of systematic multicenter data, mostly case reports, series reports, or single-center studies)	Renal (tubular dysfunction, nephrolithiasis and nephrocalcinosis, aminocycluria, hypercalciuria, hyperphosphaturia) Bone (osteoporosis, chondrocalcinosis, osteoarthritis, joints pain) Heart (cardiac arrhythmia, cardiomyopathy, myopathy) Skin (hyperpigmentation of lower legs, azure lunulae ("sky-blue moon") of the nails, anetoderma, xerosis, acanthosis nigricans, subcutaneous lipomas, dermatomyositis) Hematopoietic system (thrombocytopenia, hemolytic anemia, leukopenia) Gynecologic abnormalities (menstrual irregularity, delayed puberty, gynecomastia) Endocrinologic abnormalities (glucose intolerance, parathyroid insufficiency, disorders of growth)

From Litwin T, Dusek P, Szafranski T, et al. Psychiatric manifestations in Wilson's disease: possibilities and difficulties for treatment. Therap Adv Psychopharmacol. 2018;8(7):199–221, Table 1.

or other effects of hepatic dysfunction (delayed puberty, amenorrhea, coagulation defects) can be manifestations of Wilson disease.

Disease presentations are variable, with a tendency to familial patterns. Liver disease is the most common disease manifestation in children and can precede neurologic symptoms by as long as 10 years. Females are 3 times more likely than males to present with acute hepatic failure. When Wilson disease presents after age 20, *neurologic symptoms* are the most common manifestation.

**Neurologic disorders** can develop insidiously or precipitously, with intention tremor, dysarthria, rigid dystonia, parkinsonism, choreiform movements, lack of motor coordination, deterioration in school performance, psychosis, or behavioral changes. K-F rings are absent in young patients with hepatic Wilson disease up to 50% of the time but are present in 95% of patients with neurologic symptoms. **Psychiatric manifestations** include depression, personality changes, anxiety, obsessive-compulsive behavior, or psychosis.

Coombs-negative **hemolytic anemia** may be an initial manifestation, possibly related to the release of large amounts of copper from damaged hepatocytes; this form of Wilson disease is usually fatal without liver transplantation. During hemolytic episodes, urinary copper excretion and serum free copper levels are markedly elevated. Manifestations of renal Fanconi syndrome and progressive renal failure with alterations in tubular transport of amino acids, glucose, and uric acid may be present. Unusual manifestations include arthritis, pancreatitis, nephrolithiasis, infertility or recurrent miscarriages, cardiomyopathy, and hypoparathyroidism.

## PATHOLOGY

All grades of hepatic injury occur in patients with Wilson disease, with steatosis, hepatocellular ballooning and degeneration, glycogen granules, minimal inflammation, and enlarged Kupffer cells being most common. The earliest histologic feature of Wilson disease is mild steatosis, which may mimic nonalcoholic fatty liver disease or nonalcoholic steatohepatitis. Additionally, the lesion may be indistinguishable from that of autoimmune hepatitis. With progressive parenchymal damage, fibrosis and cirrhosis develop. Ultrastructural changes primarily involve the mitochondria and include increased density of the matrix material, inclusions of lipid and granular material, and increased intracristal space with dilation of the tips of the cristae.

## DIAGNOSIS

Wilson disease should be considered in children and teenagers with unexplained acute or chronic liver disease, neurologic symptoms of unknown cause, acute hemolysis, psychiatric illnesses, behavioral changes, Fanconi syndrome, or unexplained bone (osteoporosis, fractures) or muscle disease (myopathy, arthralgia). The clinical suspicion is confirmed by study of indices of copper metabolism.

Most patients with Wilson disease have decreased serum ceruloplasmin levels ( $<20$  mg/dL). The failure of copper to be incorporated into ceruloplasmin leads to a plasma protein with a shorter half-life and therefore a reduced steady-state concentration of ceruloplasmin in the circulation. *Serum ceruloplasmin levels should be interpreted with caution.* Acute inflammatory states and elevated estrogen levels (pregnancy, hormone therapy, or use of oral contraception) can falsely increase ceruloplasmin levels. Additionally, serum ceruloplasmin may be low in autoimmune hepatitis, celiac disease, familial aceruloplasminemia, or carriers of ATP7B pathogenic variants (mild variants of Menkes disease: occipital horn syndrome) who do not show copper overload disease. The serum free copper level may be elevated in early Wilson disease ( $>1.6$   $\mu$ mol/L), and urinary copper excretion (normally  $<40$   $\mu$ g/day) is increased to  $>100$   $\mu$ g/day and often up to 1,000  $\mu$ g or more per day. Typical urinary copper excretion in patients with untreated Wilson disease is  $>1.6$   $\mu$ mol/24 hr in adults and  $>0.64$   $\mu$ mol/24 hr in children. In equivocal cases, the response of urinary copper output to chelation may be of diagnostic help. Before a 24-hour urine collection patients

are given two 500-mg oral doses of D-penicillamine 12 hours apart; affected patients excrete  $>1,600$   $\mu$ g/24 hr.

Demonstration of K-F rings, which might not be present in younger children, requires a slit-lamp examination by an ophthalmologist. After adequate treatment, K-F rings resolve. Liver biopsy can determine the extent and severity of liver disease and for measuring the hepatic copper content (normally  $<10$   $\mu$ g/g dry weight) but is only required if clinical signs and noninvasive tests do not allow a final diagnosis or if another liver disorder is suspected. Hepatic copper accumulation is the hallmark of Wilson disease, and measurement of hepatic parenchymal copper concentration is the method of choice for diagnosis. Hepatic copper content  $>250$   $\mu$ g/g dry weight ( $>4$   $\mu$ mol/g dry weight) is the best biochemical evidence for Wilson disease, but lowering the threshold to 1.2  $\mu$ mol/g dry weight improves sensitivity without significantly affecting specificity. Intermediate levels of hepatic copper may be present in asymptomatic carriers. In later stages of Wilson disease, hepatic copper content can be unreliable because cirrhosis leads to variable hepatic copper distribution and sampling error.

First-degree relatives of patients with Wilson disease should be screened for presymptomatic disease. This screening should include determination of the serum ceruloplasmin level and 24-hr urinary copper excretion. If these results are abnormal or equivocal, liver biopsy should be carried out to determine morphology and hepatic copper content. Genetic screening by either linkage analysis or direct DNA gene analysis is possible, especially if the mutation for the proband case is known or the patient is from an area where a specific gene variant is prevalent, such as in Central and Eastern Europe, where the H1069Q variant is present in 50–80% of patients.

## TREATMENT

Once the diagnosis of Wilson disease is made, lifelong treatment should be initiated and is focused on limiting copper uptake and promoting copper excretion through dietary and pharmacologic measures. The normal diet contains 2–5 mg of copper per day. For patients with Wilson disease, the dietary intake of copper should be restricted to  $<1$  mg/day. High copper content foods such as liver, shellfish, nuts, and chocolate should be avoided. If the copper content of the drinking water exceeds 0.1 mg/L, it may be necessary to demineralize the water.

The initial treatment in symptomatic patients is the administration of copper-chelating agents, which leads to rapid excretion of excess deposited copper. Chelation therapy is managed with oral administration of triethylene tetramine dihydrochloride (Trien, TETA, trientine) at a dose of 750–1500 mg/day in two or three divided doses, with 750 or 1000 mg used for maintenance therapy, for adults and 20 mg/kg/day rounded to the nearest 250 mg, given in two or three divided doses for children. D-penicillamine ( $\beta,\beta$ -dimethylcysteine) can be used as an alternative at a maximum of 1000–1500 mg/day in two to four divided doses before meals for adults and 20 mg/kg/day, rounded to the nearest 250 mg and given in two or three divided doses for pediatric patients. In response to chelation, urinary copper excretion increases, with marked improvement in hepatic and neurologic function and the disappearance of K-F rings.

Approximately 10–50% of patients initially treated with penicillamine for *neurologic* symptoms have a worsening of their condition. Toxic effects of penicillamine occur in 10–20% and consist of hypersensitivity reactions (i.e., Goodpasture syndrome, systemic lupus erythematosus, and polymyositis), interaction with collagen and elastin, deficiency of other elements such as zinc, and aplastic anemia and nephrosis. Because penicillamine is an antimetabolite of vitamin B<sub>6</sub>, additional amounts of this vitamin are necessary. For these reasons, trientine is the preferred alternative and is considered first-line therapy for some patients. Trientine has few known side effects. Ammonium tetrathiomolybdate is another alternative chelating agent under investigation for patients with neurologic disease; initial results suggest that significantly fewer patients

experience neurologic deterioration with this drug compared to penicillamine. The initial dose is 120 mg/day (20 mg between meals 3 times daily and 20 mg with meals 3 times daily). Side effects include anemia, leukopenia, thrombocytopenia, and mild elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Because of its extensive decoppering effect, ammonium tetrathiomolybdate also has antiangiogenic effects.

Zinc has also been used as adjuvant therapy, maintenance therapy, or primary therapy in presymptomatic patients, owing to its unique ability to impair the gastrointestinal absorption of copper. Zinc acetate can be given to adults at a dose of 50 mg of elemental zinc 3 times a day, and 25 mg 3 times a day in children over age 5 years. Side effects are predominantly limited to gastric irritation but also include reduced leukocyte chemotaxis and elevations in serum lipase and/or amylase. Guidelines recommend that all symptomatic patients with Wilson disease receive a chelating agent (penicillamine or trientine). Patients should be counseled not to suddenly stop these medications, because sudden discontinuation of therapy can precipitate fulminant Wilson disease. Zinc may have a role as a first-line therapy in patients with neurologic disease, but exclusive monotherapy with zinc in symptomatic liver disease is controversial and not recommended. Antioxidants (vitamin E and curcumin) and pharmacologic chaperones (4-phenylbutyrate and curcumin) may have a role as adjunctive treatment, but more research is needed.

### PROGNOSIS

Untreated patients with Wilson disease can die of hepatic, neurologic, renal, or hematologic complications. Medical therapy is rarely effective in those presenting with acute liver failure. The prognosis for patients receiving prompt and continuous penicillamine is variable and depends on the time of initiation of and the individual response to chelation. Liver transplantation should be considered for patients with acute liver failure or decompensated cirrhosis caused by Wilson disease. Liver transplantation for progressive neurologic disease remains controversial. Liver transplantation is curative, with a 5-year survival rate of 85–90%. In asymptomatic siblings of affected patients, early institution of chelation or zinc therapy can prevent disease manifestations.

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### 405.3 Indian Childhood Cirrhosis

Julie Bonn and William F. Balistreri

Indian childhood cirrhosis (ICC) is a chronic liver disease of infants and young children unique to the Indian subcontinent, but variants of this syndrome have been described in other populations and have been named accordingly (Tyrolean or North American childhood cirrhosis). ICC-like disease has also been reported in the Middle East, West Africa, and Central America. Affected children present with jaundice, pruritus, lethargy, and hepatosplenomegaly with rapid progression to cirrhosis. Untreated severe ICC has a mortality of 40–50% within 4 weeks. Histologically, ICC is characterized by hepatocyte necrosis, Mallory bodies, intralobular fibrosis, inflammation, and excess hepatic copper deposition. Treatment is supportive, especially in the late stages of disease. Copper chelation with D-penicillamine has been beneficial in open-label preicteric cases of ICC; however, it is unclear whether these cases were simply less severely affected and would have spontaneously improved without treatment.

The etiology of ICC has remained elusive. It was once believed that excess copper ingestion in the setting of a genetic susceptibility to copper toxicosis was the most likely cause. Epidemiologic data demonstrate that the copper toxicity theory is unlikely. The increased hepatic copper content, usually >700 µg/g dry weight, seen in ICC is only seen

in the late stages of disease and is accompanied by even higher levels of zinc, a non-hepatotoxic metal. Furthermore, the copper-contaminated utensils used to feed babies and implicated in excess copper ingestion are found in only 10–15% of all cases. The current hypothesis implicates the postnatal use of local hepatotoxic therapeutic remedies, although the exact causative agent is unknown. North American ICC is caused by pathogenic variants in the *UTP4* gene; it is seen in the Ojibway-Cree nation of Quebec.

Over the past few decades, as the awareness of the disease has increased, the incidence of ICC has decreased to the point of being virtually eliminated in some areas of India. However, established and atypical cases are probably being missed because of lack of histologic confirmation and lack of awareness of the protean manifestations and natural history of this disease.

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### 405.4 Neonatal Hemochromatosis

Julie Bonn and William F. Balistreri

See Chapter 404.

Neonatal hemochromatosis (NH) is a rare form of fulminant liver disease that manifests in the first few days of life. NH is associated with siderosis of extrahepatic tissues, similar to hereditary hemochromatosis, but is unrelated to the familial forms of hereditary hemochromatosis that occur in adulthood. **Gestational alloimmune liver disease (GALD)** has been identified as the cause of nearly all cases of NH, but they are not synonymous. GALD has a high rate of recurrence in families, with over 90% probability that subsequent infants will be affected. During gestation, the maternal immune system becomes sensitized to an unknown fetal hepatocyte cell surface antigen. Maternal immunoglobulin G (IgG) to this fetal antigen then crosses the placenta and induces hepatic injury via immune system activation. The defining feature of GALD is complement-mediated hepatocyte injury, the evidence for which comes from detection of the C5b-9 complex by immunohistochemistry on liver tissue of affected infants. Additional evidence of a gestational insult is given by the fact that affected infants may be born prematurely or with intrauterine growth restriction. Severely affected infants may also have renal hypoplasia and dysgenesis.

Excess non-transferrin-bound iron in GALD results from fetal liver injury that causes reduced synthesis of key iron regulatory and transport proteins. The pattern of extrahepatic siderosis appears to be determined by the normal capacity of various tissues to import non-transferrin-bound iron and not export cellular iron. It is thought that fetal liver injury is the primary event leading to the development of the NH phenotype, providing further evidence that this is not a primary iron overload disease.

GALD can be a rapidly fatal, progressive illness characterized by hepatomegaly, hypoglycemia, hypoprothrombinemia, hypoalbuminemia, hyperferritinemia, and hyperbilirubinemia (see Table 404.4). The coagulopathy is refractory to therapy with vitamin K. Liver biopsy demonstrates severe liver injury with acute and chronic inflammation, fibrosis, and cirrhosis; in some cases there are no surviving hepatocytes. The diagnosis is established in the neonate with severe liver injury and evidence of extrahepatic siderosis either by MRI indicating increased iron deposition in organs such as the pancreas or heart or by increased iron staining in oral submucosal gland biopsy. The differential diagnosis includes other causes of neonatal hepatic failure such as citrin deficiency, herpes simplex virus (HSV) hepatitis, and familial hemophagocytic lymphohistiocytosis (see Table 404.4).

The survival rate (50–80%) depends on the severity of the initial presentation and response to therapy. Intravenous immunoglobulin (IVIG) combined with double volume exchange transfusion has been shown to remove the injury-causing maternal IgG and

improve outcomes in infants with GALD. Liver transplantation should also be an early consideration. Recurrences of GALD in subsequent pregnancies may be modified with IVIG administered to the mother once weekly from the 18th week of gestation until delivery. The largest experience reports 48 women with previous infants with GALD who successfully delivered 52 babies after IVIG treatment. The majority of infants had biochemical evidence of liver disease with elevated serum  $\alpha$ -fetoprotein and ferritin. All infants survived with medical therapy or no therapy.

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## 405.5 Miscellaneous Metabolic Diseases of the Liver

Julie Bonn and William F. Balistreri

### $\alpha_1$ -ANTITRYPSIN DEFICIENCY

$\alpha_1$ -Antitrypsin deficiency is an autosomal recessive disorder caused by a pathogenic variant in the *SERPINA1* gene.  $\alpha_1$ -Antitrypsin, a protease inhibitor (Pi) synthesized by the liver, protects lung alveolar tissues from destruction by neutrophil elastase (see Chapter 442).  $\alpha_1$ -Antitrypsin is present in more than 20 different codominant alleles, only a few of which are associated with defective Pis. The most common allele of the Pi system is M, and the normal phenotype is PiMM. The Z allele predisposes to clinical deficiency; patients with liver disease are usually PiZZ homozygotes and have serum  $\alpha_1$ -antitrypsin levels <2 mg/mL (~10–20% of normal). The incidence of the PiZZ genotype in the White population is estimated at 1 in 2,000–4,000 live births. A small percentage of patients homozygous for deficiency of the major serum Pi  $\alpha_1$ -antitrypsin develop neonatal cholestasis or later-onset childhood cirrhosis. Compound heterozygotes PiZ, PiSZ, and PiZI are not a cause of liver disease alone but can act as modifier genes, increasing the risk of progression in other liver diseases such as nonalcoholic fatty liver disease and hepatitis C. The null phenotype only causes lung disease and results from either stop codons in the coding exon of the *SERPINA1* gene or complete deletion of *SERPINA1* coding exons leading to the absence of  $\alpha_1$ -antitrypsin protein.

Newly formed  $\alpha_1$ -antitrypsin polypeptide normally enters the endoplasmic reticulum, where it undergoes enzymatic modification and folding before transport to the plasma membrane, where it is excreted as a 55-kDa glycoprotein. In affected patients with PiZZ, the rate at which the  $\alpha_1$ -antitrypsin polypeptide folds is decreased, and this delay allows the formation of polymers that are retained in the endoplasmic reticulum. How the polymers cause liver damage is not completely elucidated, but research indicates that accumulation of abnormally folded protein leads to activation of stress and proinflammatory pathways in the endoplasmic reticulum and hepatocyte programmed cell death. In liver biopsies from patients, polymerized  $\alpha_1$ -antitrypsin peptides can be seen by electron microscopy and histochemically as periodic acid–Schiff-positive diastase-resistant globules, primarily in periportal hepatocytes, but also in Kupffer cells and biliary epithelial cells. The pattern of neonatal liver injury can be highly variable, and liver biopsies might

demonstrate hepatocellular necrosis, inflammatory cell infiltration, bile duct proliferation, periportal fibrosis, or cirrhosis.

The course of liver disease is highly variable in patients with  $\alpha_1$ -antitrypsin deficiency. Prospective studies in Sweden have shown that only 10% of patients develop clinically significant liver disease by their fourth decade, indicating that other genetic traits or environmental factors likely influence the development of liver disease. Infants with liver disease are indistinguishable from other infants with “idiopathic” neonatal hepatitis, of whom they constitute approximately 5–10%. Jaundice, acholic stools, and hepatomegaly are present in the first week of life, but the jaundice usually clears by 2–4 months of age. Complete resolution, persistent liver disease, or the development of cirrhosis can follow. Older children can present with asymptomatic hepatomegaly or manifestations of chronic liver disease or cirrhosis with evidence of portal hypertension. Patients with cirrhosis due to  $\alpha_1$ -antitrypsin deficiency are at high risk for developing hepatocellular carcinoma. Emphysema is not typically observed in children, but an increased risk for developing asthma is reported. Cigarette smoking promotes development of lung disease, so parents should be counseled on smoking cessation and exposure reduction as part of their anticipatory guidance, and older children and adolescents should be advised not to smoke or use electronic cigarettes and given cessation counseling if they do (see Chapter 157.2).

Treatment is supportive, although research is ongoing to develop therapies for  $\alpha_1$ -antitrypsin deficiency-associated liver disease that stimulate intracellular degradation of the abnormally folded Z protein polymers. Liver transplantation is indicated for hepatocellular carcinoma or end-stage liver disease with portal hypertension, with survival rates of ~90%.

### CITRIN DEFICIENCY

Neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) presents in the first few months of life with manifestations that initially may be indistinguishable from other causes of neonatal cholestasis, especially biliary atresia. Patients may have jaundice, hepatomegaly, liver dysfunction with coagulopathy, fatty liver infiltration, and hyperammonemia with or without hypoglycemia. Presymptomatic patients may be identified from the newborn metabolic screen with hypergalactosemia, hypermethionine, and hyperphenylalaninemia, but not all patients are identified by newborn screening.

Pathogenic variants in the *SLC25A13* gene cause NICCD with an autosomal recessive pattern of inheritance. *SLC25A13* encodes citrin, a mitochondrial carrier protein (calcium binding aspartate-glutamate carrier) involved in the urea cycle, gluconeogenesis, and glycolysis. Pathogenic variants are more common in those of East Asian descent. Affected infants have hypergalactosemia, elevated bile acids, vitamin K-dependent coagulopathy, and elevated levels of citrulline and methionine. Treatment is supportive in the form of providing fat-soluble vitamin supplementation and dietary feeding with a low-galactose-/lactose formula enriched with medium-chain triglycerides. More severely affected patients can develop liver failure requiring liver transplantation in the first year of life.

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## Chapter 406

# Viral Hepatitis

Michael E. Rogers and William F. Balistreri

Viral hepatitis continues to be a major health problem in both developing and developed countries, but there has been significant progress in efforts to recognize and to treat infected subjects. This disorder is caused by at least five known pathogenic hepatotropic viruses: hepatitis A (HAV), B (HBV), C (HCV), D (HDV), and E (HEV) viruses (Table 406.1). Many other viruses (and diseases) can cause hepatitis, usually as a component of a multisystem disease. These include herpes simplex viruses (1, 2, 6a, 6b), cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, HIV, rubella, measles, adenoviruses, adeno-associated virus, enteroviruses, parvovirus B19, arboviruses, and perhaps SARS-CoV-2 (Table 406.2).

The hepatotropic viruses are a heterogeneous group of infectious agents that cause similar acute clinical illness. In most pediatric patients, the acute phase causes no or mild clinical disease. Morbidity is related to rare cases of **acute liver failure (ALF)** in susceptible patients or to the development of a chronic disease state and attendant complications that several of these viruses (HBV, HCV, HDV) may cause.

### ISSUES COMMON TO ALL FORMS OF VIRAL HEPATITIS

#### Differential Diagnosis

Although often asymptomatic or nonspecific, the clinical features that may raise the suspicion of viral hepatitis is clinical icterus, with yellow skin and/or mucous membranes. The liver is usually enlarged and tender to palpation and percussion. Splenomegaly and lymphadenopathy may be present. Clinical signs of bleeding, altered sensorium, or hyperreflexia should be carefully sought, because they mark the onset of encephalopathy and ALF.

The differential diagnosis varies with the age of presentation. In the newborn period, infection is a common cause of conjugated hyperbilirubinemia; the infectious cause is either a bacterial agent (e.g., *Escherichia coli*, *Listeria*, syphilis) or a nonhepatotropic virus (e.g., enteroviruses, cytomegalovirus, and herpes simplex virus, which may also cause a nonicteric severe hepatitis). Metabolic diseases ( $\alpha_1$ -antitrypsin deficiency, cystic fibrosis, tyrosinemia), anatomic causes (biliary atresia, choledochal cysts), and inherited forms of intrahepatic cholestasis should always be excluded.

In later childhood, extrahepatic obstruction (gallstones, primary sclerosing cholangitis, pancreatic pathology), inflammatory conditions (autoimmune hepatitis, juvenile inflammatory arthritis, Kawasaki

disease), immune dysregulation (hemophagocytic lymphohistiocytosis), infiltrative disorders (malignancies), toxins and medications, metabolic disorders (Wilson disease, cystic fibrosis), and infection (Epstein-Barr virus, varicella, malaria, leptospirosis, syphilis) should be ruled out.

#### Pathogenesis

The acute response of the liver to hepatotropic viruses involves a direct cytopathic and/or an immune-mediated injury. The entire liver is involved. Necrosis is usually most marked in the centrilobular areas. An acute mixed inflammatory infiltrate predominates in the portal areas but also affects the lobules. The lobular architecture remains intact, although balloon degeneration and necrosis of single cells or groups of parenchymal cells commonly occur. Fatty change is rare. Bile duct proliferation, but not bile duct damage, is common. Diffuse Kupffer cell hyperplasia is noticeable in the sinusoids. Neonates often respond to hepatic injury by forming *giant cells*. In fulminant hepatitis, parenchymal collapse occurs on the described background. With recovery, the liver morphology returns to normal within 3 months of the acute infection. If chronic hepatitis develops, the inflammatory infiltrate settles in the periportal areas and often leads to progressive scarring.

#### Common Biochemical Profiles in the Acute Infectious Phase

Acute liver injury caused by these viruses manifests in three main liver biochemical profiles. These serve as an important guide to diagnosis, supportive care, and monitoring in the acute phase of the infection for all viruses. As a reflection of *cytopathic injury* to the hepatocytes, there is a rise in serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The magnitude of enzyme elevation does not correlate with the extent of hepatocellular necrosis and has little prognostic value. There is usually slow improvement over several weeks, but AST and ALT levels *lag* the serum bilirubin level, which tends to normalize first. Rapidly falling aminotransferase levels can predict a poor outcome, particularly if their decline occurs in conjunction with a rising bilirubin level and a prolonged international normalized ratio (INR) or prothrombin time (PT); this combination of findings usually indicates that massive hepatic injury has occurred.

*Cholestasis*, defined by elevated serum conjugated bilirubin levels, results from abnormal bile flow at the canalicular and cellular level because of hepatocyte damage and inflammatory mediators. Elevation of serum alkaline phosphatase, 5-nucleotidase, and  $\gamma$ -glutamyl transpeptidase levels marks cholestasis. Absence of cholestatic markers does not rule out progression to chronicity in HCV or HBV infections.

*Altered synthetic function* is the most important marker of liver injury. Synthetic dysfunction is reflected by abnormal protein synthesis (prolonged PT, high INR, low serum albumin levels), metabolic disturbances (hypoglycemia, lactic acidosis, hyperammonemia), poor clearance of medications dependent on liver function, and altered sensorium with increased deep tendon reflexes (hepatic encephalopathy). Monitoring of synthetic function should be the main focus in clinical follow-up to define the severity of the disease. In the acute phase, the degree of liver synthetic dysfunction guides treatment and helps to establish intervention criteria. *Abnormal liver synthetic function is a marker of liver failure and is an indication for prompt referral to a transplant center.* Serial assessment is necessary because liver dysfunction does not progress linearly.

#### HEPATITIS A

Hepatitis A virus is responsible for most forms of acute and benign hepatitis. Although fulminant hepatic failure caused by HAV can occur, it is rare (<1% of cases in the United States) and occurs more often in adults than in children and in hyperendemic communities.

#### Etiology

HAV is an RNA virus, a member of the picornavirus family. It is heat stable and has a limited host range—namely, the human and other primates.

**Table 406.1** Features of the Hepatotropic Viruses

VIROLOGY	HAV RNA	HBV DNA	HCV RNA	HDV RNA	HEV RNA
Incubation (days)	15-19	60-180	14-160	21-42	21-63
Transmission					
Parenteral	Rare	Yes	Yes	Yes	No
Fecal-oral	Yes	No	No	No	Yes
Sexual	No	Yes	Rare	Yes	No
Perinatal	No	Yes	Uncommon (5-15%)	Yes	No
Chronic infection	No	Yes	Yes	Yes	No
Fulminant disease	Rare	Yes	Rare	Yes	Yes

HAV, Hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus.

**Table 406.2** Causes and Differential Diagnosis of Hepatitis in Children

INFECTIOUS	
Hepatotropic viruses	Tuberculosis
HAV	Other
HBV	
HCV	
HEV	
HDV	
HFV	
HGV	
TT virus	
Non-hepatitis A-E viruses	
SYSTEMIC INFECTION THAT MAY INCLUDE HEPATITIS	
Adenovirus	
Arbovirus	
Coxsackievirus	
Cytomegalovirus	
Dengue virus	
Enterovirus	
Epstein-Barr virus	
Herpes simplex viruses (1, 2, 6)	
Human immunodeficiency virus	
Lassa fever	
Paramyxovirus (measles)	
Parvovirus	
Rubella	
Varicella-zoster	
Yellow fever	
Unknown	
NONVIRAL LIVER INFECTIONS	
Abscess	
Amebiasis	
Bacterial sepsis	
Brucellosis	
Fitz-Hugh-Curtis syndrome	
Histoplasmosis	
Leptospirosis	
Syphilis	
AUTOIMMUNE/INFLAMMATORY	
	Chronic autoimmune hepatitis
	Other (e.g., systemic lupus erythematosus, juvenile idiopathic arthritis)
	Celiac disease
	Hemophagocytic lymphohistiocytosis
METABOLIC	
	$\alpha_1$ -Antitrypsin deficiency
	Glycogen storage disease
	Tyrosinemia
	Wilson disease
	Other
TOXIC	
	Iatrogenic/drug induced (e.g., acetaminophen)
	Environmental (e.g., pesticides)
	Mushroom poisoning
	Hepatotoxic herbal agents (pyrrolizidine alkaloids, other toxins)
ANATOMIC	
	Choledochal cyst
	Biliary atresia
	Other
HEMODYNAMIC	
	Shock
	Congestive heart failure
	Budd-Chiari syndrome
	Venoocclusive disease
	Other
NONALCOHOLIC FATTY LIVER DISEASE	
	Idiopathic
	Sclerosing cholangitis
	Reye syndrome
	Other

Modified from Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*, 6th ed. Philadelphia: Elsevier; 2021: Box 75.1, p. 820.

## Epidemiology

HAV infection occurs throughout the world but is most prevalent in developing countries. In the United States, 30–40% of the adult population has evidence of previous HAV infection. In 2018, more than 12,000 cases of HAV were reported in the United States to the Centers for Disease Control and Prevention (CDC). The overall incidence rate was 3.8 cases per 100,000 population, an increase from recent years (specifically in patients over the age of 20 years). However, as a result of aggressive implementation of childhood vaccination programs, the prevalence of symptomatic HAV cases worldwide has declined significantly. Nonetheless, outbreaks in developing countries and in daycare centers (where the spread of HAV from young, nonicteric, infected children can occur easily) as well as multiple foodborne and waterborne outbreaks have justified the implementation of intensified universal vaccination programs.

HAV is highly contagious. Transmission is almost always by person-to-person contact through the fecal-oral route. Perinatal transmission occurs rarely. HAV infection during pregnancy or at the time of delivery does not appear to result in increased complications of pregnancy or clinical disease in the newborn. In the United States, increased risk of infection is found in contacts with infected persons, childcare centers, and household contacts. Infection is also associated with contact

with contaminated food or water and after travel to endemic areas. Common-source foodborne and waterborne outbreaks continue to occur, including several caused by contaminated shellfish, frozen berries, and raw vegetables; no known source is found in about half of the cases.

The mean incubation period for HAV is approximately 3 weeks. Fecal excretion of the virus starts late in the incubation period, reaches its peak just before the onset of symptoms, and resolves by 2 weeks after the onset of jaundice in older subjects. The duration of fecal viral excretion is prolonged in infants. The patient is therefore contagious before clinical symptoms are apparent and remains so until viral shedding ceases.

## Clinical Manifestations

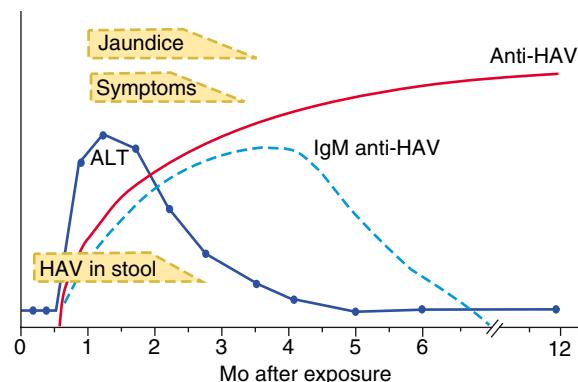
HAV is responsible for acute hepatitis only. Often, this is an *anicteric* illness, with clinical symptoms indistinguishable from other forms of viral gastroenteritis, particularly in young children.

The illness is more likely to be symptomatic in older adolescents or adults, in patients with underlying liver disorders, and in those who are immunocompromised. It is characteristically an acute febrile illness with an abrupt onset of anorexia, nausea, malaise, vomiting, and jaundice. The typical duration of illness is 7–14 days (Fig. 406.1).

Other organ systems can be affected during acute HAV infection. Regional lymph nodes and the spleen may be enlarged. The bone marrow may be moderately hypoplastic, and aplastic anemia has been reported. Tissue in the small intestine might show changes in villous structure, and ulceration of the gastrointestinal tract can occur, especially in fatal cases. Acute pancreatitis and myocarditis have been reported, though rarely, and nephritis, arthritis, leukocytoclastic vasculitis, and cryoglobulinemia can result from circulating immune complexes.

### Diagnosis

Acute HAV infection is diagnosed by detecting antibodies to HAV, specifically, anti-HAV (immunoglobulin [Ig] M) by radioimmunoassay or, rarely, by identifying viral particles in stool. An HAV viral polymerase chain reaction (PCR) assay is commercially available (Table 406.3). Anti-HAV is detectable when the symptoms are clinically apparent, and it remains positive for 4–6 months after the acute infection. A neutralizing anti-HAV (IgG) is usually detected within 8 weeks of symptom onset and is measured as part of a total anti-HAV in the serum. Anti-HAV (IgG) confers long-term protection. Rises in serum levels of ALT, AST, bilirubin, alkaline phosphatase, 5'-nucleotidase, and  $\gamma$ -glutamyl transpeptidase are almost universally found and do not help to differentiate the cause of hepatitis.



**Fig. 406.1** The serologic course of acute hepatitis A. ALT, Alanine aminotransferase; HAV, hepatitis A virus; IgM, immunoglobulin class M. (From Goldman L, Ausiello D, eds. *Cecil Textbook of Medicine*, 22nd ed. Philadelphia: WB Saunders; 2004:913.)

### Complications

Although most patients achieve full recovery, distinct complications can occur. ALF from HAV infection is an infrequent complication. Those at risk for this complication are elderly adults, but also immunocompromised patients or those with underlying liver disorders. The height of HAV viremia may be linked to the severity of hepatitis. In the United States, HAV represents <0.5% of pediatric-age ALF; HAV is responsible for up to 3% mortality in the adult population with ALF. In endemic areas of the world, HAV constitutes up to 40% of all cases of pediatric ALF. HAV can also progress to a *prolonged cholestatic syndrome* that waxes and wanes over several months. Pruritus and fat malabsorption are problematic and require symptomatic support with antipruritic medications and fat-soluble vitamin supplementation. This syndrome occurs in the absence of any liver synthetic dysfunction and resolves without sequelae.

### Treatment

There is no specific treatment for hepatitis A. Supportive treatment consists of intravenous hydration as needed and antipruritic agents and fat-soluble vitamins for the prolonged cholestatic form of disease. There is no benefit to the use of corticosteroid treatment during acute illness. Serial monitoring for signs of ALF is prudent and, if ALF is diagnosed, a prompt referral to a transplantation center can be lifesaving.

### Prevention

Patients infected with HAV are contagious for 2 weeks before and approximately 7 days after the onset of jaundice and should be excluded from school, childcare, or work during this period. Careful hand-washing is necessary, particularly after changing diapers and before preparing or serving food. In hospital settings, contact and standard precautions are recommended for 1 week after onset of symptoms.

### Immunoglobulin

Indications for intramuscular administration of Ig include preexposure and postexposure prophylaxis (Table 406.4). Ig is recommended for *preexposure* prophylaxis for susceptible travelers to countries where HAV is endemic, and it provides effective protection for up to 2 months. *HAV vaccine* given any time before travel is preferred for *preexposure* prophylaxis in healthy persons, but Ig ensures an appropriate prophylaxis in children *younger than 6 months* old, patients allergic to a vaccine component, or those who elect not to receive the vaccine. If travel is planned in <2 weeks, older patients, immunocompromised

**Table 406.3** Diagnostic Blood Tests: Serology and Viral Polymerase Chain Reaction

HAV	HBV	HCV	HDV	HEV
<b>ACUTE/ACTIVE INFECTION</b>				
Anti-HAV IgM (+)	Anti-HBc IgM (+)	Anti-HCV (+)	Anti-HDV IgM (+)	Anti-HEV IgM (+)
Blood PCR positive*	HBsAg (+) Anti-HBs (−) HBV DNA (+) (PCR)	HCV RNA (+) (PCR)	Blood PCR positive HBsAg (+) Anti-HBs (−)	Blood PCR positive*
<b>PAST INFECTION (RECOVERED)</b>				
Anti-HAV IgG (+)	Anti-HBs (+) Anti-HBc IgG (+) <sup>†</sup>	Anti-HCV (+) Blood PCR (−)	Anti-HDV IgG (+) Blood PCR (−)	Anti-HEV IgG (+) Blood PCR (−)
<b>CHRONIC INFECTION</b>				
N/A	Anti-HBc IgG (+) HBsAg (+) Anti-HBs (−) PCR (+) or (−)	Anti-HCV (+) Blood PCR (+)	Anti-HDV IgG (+) Blood PCR (−) HBsAg (+) Anti-HBs (−)	N/A
<b>VACCINE RESPONSE</b>				
Anti-HAV IgG (+)	Anti-HBs (+) Anti-HBc (−)	N/A	N/A	N/A

\*Research tool.

<sup>†</sup>Still poses a risk for reactivation.

HAV, Hepatitis A virus; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; Ig, immunoglobulin; PCR, polymerase chain reaction.

**Table 406.4**

Indications and Updated Dosage Recommendations for GamaSTAN S/D Human Immune Globulin for Preexposure and Postexposure Prophylaxis Against Hepatitis A Infection

INDICATION	UPDATED DOSAGE RECOMMENDATION
Preexposure prophylaxis	
Up to 1 mo of travel	0.1 mL/kg
Up to 2 mo of travel	0.2 mL/kg
2 mo of travel or longer	0.2 mL/kg (repeat every 2 mo)
Postexposure prophylaxis	0.1 mL/kg

From Nelson NP. Updated dosing instruction for immune globulin (human) GamaSTAN S/D for hepatitis A virus prophylaxis. MMWR. 2017;66(36):959–960.

hosts, and those with chronic liver disease or other medical conditions should receive *both* Ig and the HAV vaccine.

Ig prophylaxis in *postexposure* situations should be used as soon as possible (it is not effective if administered more than 2 weeks after exposure). It is exclusively used alone for children younger than 12 months old or in whom vaccine is contraindicated (e.g., serious allergy to the vaccine). Ig in combination with HAV vaccine may be used in patients older than 40 years of age, with HAV vaccine preferred in healthy persons 12 months to 40 years old. An alternative approach is to immunize previously unvaccinated patients who are 12 months old or older with the age-appropriate vaccine dosage as soon as possible. Ig is not routinely recommended for sporadic nonhousehold exposure (e.g., protection of hospital personnel or schoolmates). The vaccine has several advantages over Ig, including long-term protection, availability, and ease of administration, with cost similar to, or less than, that of Ig.

### Vaccine

The availability of at least three inactivated, highly immunogenic, and safe HAV vaccines has had a major impact on the prevention of HAV infection. These vaccines are approved for children older than 12 months. They are administered intramuscularly in a two-dose schedule, with the second dose given 6–12 months after the first dose. Seroconversion rates in children exceed 90% after an initial dose and approach 100% after the second dose; protective antibody titer persists for longer than 10 years in most patients. The immune response in immunocompromised persons, older patients, and those with chronic illnesses may be suboptimal; in those patients, combining the vaccine with Ig for preexposure and postexposure prophylaxis is indicated. HAV vaccine may be administered simultaneously with other vaccines. A combination HAV and HBV vaccine is approved in adults older than age 18. For healthy persons at least 12 months old, vaccine is preferable to Ig for preexposure and postexposure prophylaxis (see Table 406.3).

In the United States and some other countries, universal vaccination is recommended for all children older than 12 months. Nevertheless, studies show <50% of U.S. adolescents have received even a single dose of the vaccine and <30% have received the complete vaccine series. The vaccine is effective in curbing outbreaks of HAV because of rapid seroconversion and the long incubation period of the disease.

### Prognosis

The prognosis for the patient with HAV is excellent, with no long-term sequelae. The only feared complication is ALF. Nevertheless, HAV infection remains a major cause of morbidity; it has a high socioeconomic impact during epidemics and in endemic areas.

## HEPATITIS B

### Etiology

HBV, a member of the Hepadnaviridae family, has a circular, partially double-stranded DNA genome composed of approximately 3,200 nucleotides. Four constitutive genes have been identified: the S (surface),

C (core), X, and P (polymer) genes. The surface of the virus includes particles, designated as the hepatitis B surface antigen (HBsAg), which consist of 22-nm-diameter spherical particles and 22-nm-wide tubular particles with a variable length of up to 200 nm. The inner portion of the virion contains the hepatitis B core antigen (HBcAg), the nucleocapsid that encodes the viral DNA, and a nonstructural antigen called the hepatitis B e antigen (HBeAg), a nonparticulate soluble antigen derived from HBcAg by proteolytic self-cleavage. HBeAg serves as a marker of active viral replication and usually correlates with the HBV DNA levels. Replication of HBV occurs predominantly in the liver but also occurs in the lymphocytes, spleen, kidney, and pancreas.

### Epidemiology

HBV has been detected worldwide, with an estimated 250 million persons chronically infected. The areas of highest prevalence of HBV infection are sub-Saharan Africa, China, parts of the Middle East, the Amazon basin, and the Pacific Islands. In the United States, the indigenous population in Alaska had the highest prevalence rate before the implementation of their universal vaccination programs. An estimated 1.25 million persons in the United States are chronic HBV carriers, with approximately 300,000 new cases of HBV occurring each year, the highest incidence being among adults 20–39 years of age. One in four chronic HBV carriers will develop serious sequelae in their lifetime. The number of new cases in children reported each year is thought to be low but is difficult to estimate because many infections in children are asymptomatic. In the United States, since the first vaccine for HBV was introduced, the overall incidence of HBV infection has been reduced by more than half. Since the implementation of universal vaccination programs in Taiwan and the United States, substantial progress has been made toward eliminating HBV infection in children in these countries. In fact, in Alaska, where HBV neared epidemic proportions, universal newborn vaccination with mass screening and immunization of susceptible Alaska indigenous peoples virtually eliminated symptomatic HBV and secondary hepatocellular carcinoma (HCC).

HBV is present in high concentrations in blood, serum, and serous exudates and in moderate concentrations in saliva, vaginal fluid, and semen. Efficient transmission occurs through blood exposure and sexual contact. Risk factors for HBV infection in children and adolescents include acquisition by intravenous drugs or blood products, contaminated needles used for acupuncture or tattoos, sexual contact, institutional care, and intimate contact with carriers. No risk factors are identified in approximately 40% of cases. HBV is not thought to be transmitted via indirect exposure, such as sharing toys. After infection, the incubation period ranges from 45 to 160 days, with a mean of approximately 120 days. In children, the most important risk factor for acquisition of HBV remains perinatal exposure to an HBsAg-positive mother. The risk of transmission is greatest if the mother is HBeAg-positive; up to 90% of these infants become chronically infected if untreated. Additional risk factors include high maternal HBV viral load (HBeAg/HBV DNA titers) and delivery of a prior infant who developed HBV despite appropriate prophylaxis. In most perinatal cases, serologic markers of infection and antigenemia appear 1–3 months after birth, suggesting that transmission occurred at the time of delivery. Virus contained in amniotic fluid or in maternal feces or blood may be the source. Immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and the HBV immunization, given within 12 hours of delivery, is highly effective in preventing infection and protects >95% of neonates born to HBsAg-positive mothers. Of the ~22,000 infants born each year to HBsAg-positive mothers in the United States, >98% receive immunoprophylaxis and are thus protected. Infants who fail to receive the complete vaccination series (e.g., homeless children, international adoptees, and children born outside the United States) have the highest incidence of developing chronic HBV. These and all infants born to HBsAg-positive mothers should have follow-up HBsAg and anti-HBs testing to determine appropriate follow-up. The mothers (HBeAg positive) of these infants who develop chronic HBV infection should receive antiviral therapy during the third trimester for subsequent pregnancies.

HBsAg is inconsistently recovered in human milk of infected mothers. Breastfeeding of nonimmunized infants by infected mothers does not seem to confer a greater risk of hepatitis than does formula feeding.

The risk of developing **chronic HBV infection**, defined as being positive for HBsAg for longer than 6 months, is inversely related to the age of acquisition. In the United States, although <10% of infections occur in children, these infections account for 20–30% of all chronic cases. This risk of chronic infection is 90% in children younger than 1 year; the risk is 30% for those 1–5 years of age and 2% for adults. Chronic HBV infection is associated with the development of chronic liver disease and HCC. The carcinoma risk is independent of the presence of cirrhosis and was the most prevalent cancer-related death in young adults in Asia, where HBV was endemic.

HBV has 10 genotypes (A–J). A is pandemic, B and C are prevalent in Asia, D is seen in Southern Europe, E in Africa, F in the United States, G in the United States and France, H in Central America, I in Southeast Asia, and J in Japan. Genetic variants have become resistant to some antiviral agents.

### Pathogenesis

The acute response of the liver to HBV is similar to that of other viruses. Persistence of histologic changes in patients with hepatitis B indicates development of chronic liver disease. HBV, unlike the other hepatotropic viruses, is a predominantly noncytopathogenic virus that causes injury mostly by immune-mediated processes. The severity of hepatocyte injury reflects the degree of the immune response, with the most complete immune response associated with the greatest likelihood of viral clearance but also the most severe injury to hepatocytes. The first step in the process of acute hepatitis is infection of hepatocytes by HBV, resulting in expression of viral antigens on the cell surface. The most important of these viral antigens may be the nucleocapsid antigens—HBcAg and HBeAg. These antigens, in combination with class I major histocompatibility proteins, make the cell a target for cytotoxic T-cell lysis.

The mechanism for development of chronic hepatitis B is less well understood. To permit hepatocytes to continue to be infected, the core protein or major histocompatibility class I protein might not be recognized, the cytotoxic lymphocytes might not be activated, or some other, yet unknown mechanism might interfere with destruction of hepatocytes. This tolerance phenomenon predominates in the perinatally acquired cases, resulting in a high incidence of persistent HBV infection in children with no or little inflammation in the liver, normal liver enzymes, and markedly elevated HBV viral load. Although end-stage

liver disease rarely develops in those patients, the inherent HCC risk is high, possibly related, in part, to uncontrolled viral replication cycles.

ALF has been seen in infants of chronic carrier mothers who have anti-HBe or are infected with a precore-variant strain. This fact led to the postulate that HBeAg exposure in utero in infants of chronic carriers likely induces tolerance to the virus once infection occurs postnatally. In the absence of this tolerance, the liver is massively attacked by T cells and the patient presents with ALF.

Immune-mediated mechanisms are also involved in the extrahepatic conditions that can be associated with HBV infections. Circulating immune complexes containing HBsAg can result in polyarteritis nodosa, membranous or membranoproliferative glomerulonephritis, polymyositis, rheumatoma, leukocytoclastic vasculitis, and Guillain-Barré syndrome.

### Clinical Manifestations

Many acute cases of HBV infection in children are asymptomatic, as evidenced by the high carriage rate of serum markers in persons who have no history of acute hepatitis (Table 406.5). The usual acute symptomatic episode is similar to that of HAV and HCV infections but may be more severe and is more likely to include involvement of the skin and joints (Fig. 406.2).

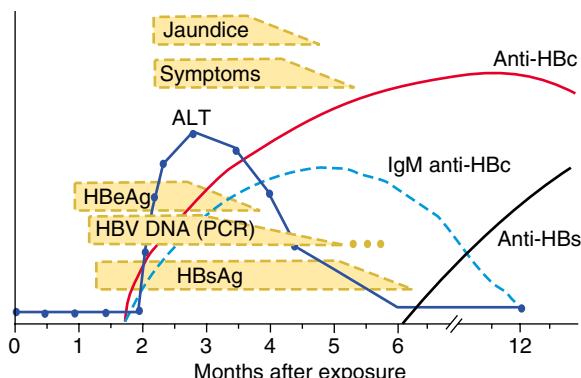
The first biochemical evidence of HBV infection is elevation of serum ALT levels, which begin to rise just before development of fatigue, anorexia, and malaise, at approximately 6–7 weeks after exposure. The illness is preceded, in a few children, by a serum sickness-like prodrome marked by arthralgia or skin lesions, including urticarial, purpuric, macular, or maculopapular rashes. Papular acrodermatitis, Gianotti-Crosti syndrome, can also occur. Other extrahepatic conditions associated with HBV infections in children include polyarteritis nodosa, glomerulonephritis, and aplastic anemia. Jaundice is present in approximately 25% of acutely infected patients and usually begins approximately 8 weeks after exposure and lasts approximately 4 weeks. In the usual course of resolving HBV infection, symptoms persist for 6–8 weeks. The percentage of children in whom clinical evidence of hepatitis develops is higher for HBV than for HAV, and the rate of ALF is also greater. Most patients do recover, but the chronic carrier state complicates up to 10% of cases acquired in adulthood. The rate of development of chronic infection depends largely on the mode and age of acquisition and occurs in up to 90% of perinatally infected cases. Cirrhosis and HCC are only seen with chronic infection. Chronic HBV infection has three identified phases: immune tolerant, immune active, and inactive. Most children fall in the immune-tolerant phase, against

**Table 406.5** Typical Interpretation of Test Results for Hepatitis B Virus Infection

HBsAg	TOTAL ANTI-HBc	IgM ANTI-HBc	ANTI-HBs	HBV DNA	INTERPRETATION
–	–	–	–	–	Never infected
+	–	–	–	+ or –	Early acute infection; transient (up to 18 days) after vaccination
+	+	+	–	+	Acute infection
–	+	+	+ or –	+ or –	Acute resolving infection
–	+	–	+	–	Recovered from past infection and immune
+	+	–	–	+	Chronic infection
–	+	–	–	+ or –	False-positive (i.e., susceptible), past infection, "low-level" chronic infection, or passive transfer of anti-HBc to infant born to HBsAg-positive mother
–	–	–	+	–	Immune if anti-HBs concentration is $\geq 10$ mIU/mL after vaccine series completion; passive transfer after hepatitis B immune globulin administration

–, Negative; +, positive; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; IgM, immunoglobulin class M.

From Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. MMWR. 2018;67(1):1–29, Table 1.



**Fig. 406.2** The serologic course of acute hepatitis B. ALT, Alanine aminotransferase; HBc, hepatitis B core; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; IgM, immunoglobulin class M; PCR, polymerase chain reaction. (From Goldman L, Ausiello D, eds. Cecil Textbook of Medicine, 22nd ed. Philadelphia: WB Saunders; 2004:914.)

which no effective therapy has been developed. Most treatments target the immune active phase of the disease, characterized by active inflammation, elevated ALT/AST levels, and progressive fibrosis. Spontaneous HBeAg seroconversion, defined as the development of anti-HBe and loss of HBeAg, occurs in the immune-tolerant phase, albeit at low rates of 4–5% per year. It is more common in childhood-acquired HBV rather than in perinatally transmitted infections. Seroconversion can occur over many years, during which time significant damage to the liver may take place. There are no large studies that accurately assess the lifetime risks and morbidities of children with chronic HBV infection, making decisions regarding the rationale, efficacy, and timing of still less-than-ideal treatments difficult. Reactivation of chronic infection has been reported in immunosuppressed children treated with chemotherapy, biologic immunomodulators such as infliximab, or T-cell-depleting agents, leading to an increased risk of ALF or to rapidly progressing fibrotic liver disease (Table 406.6).

### Diagnosis

The serologic profile of HBV infection is more complex than for HAV infection and differs depending on whether the disease is acute or chronic (Fig. 406.3, see Table 406.5). Several antigens and antibodies are used to confirm the diagnosis of acute HBV infection (see Table 406.3). Routine screening for HBV infection requires assay of multiple serologic markers (HBsAg, anti-HBc, anti-HBs). HBsAg is an early serologic marker of infection and is found in almost all infected persons; its rise closely coincides with the onset of symptoms. Persistence of HBsAg beyond 6 months defines the chronic infection state. During recovery from acute infection, because HBsAg levels fall before symptoms wane, IgM antibody to HBcAg (anti-HBc IgM) might be the only marker of acute infection. Anti-HBc IgM rises early after the infection and remains positive for many months before being replaced by anti-HBc IgG, which then persists for years. Anti-HBs marks serologic recovery and protection. Only anti-HBs is present in persons immunized with hepatitis B vaccine, whereas both anti-HBs and anti-HBc are detected in persons with resolved infection. HBeAg is present in active acute or chronic infection and is a marker of infectivity. The development of anti-HBe, termed *seroconversion*, marks improvement and is a goal of therapy in chronically infected patients. HBV DNA can be detected in the serum of acutely infected patients and chronic carriers. High DNA titers are seen in patients with HBeAg, and they typically fall once anti-HBe develops.

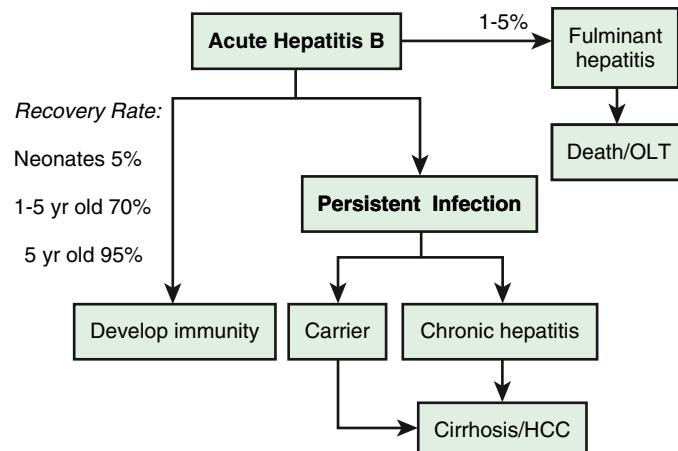
### Complications

ALF with coagulopathy, encephalopathy, and cerebral edema occurs more commonly with HBV than the other hepatotropic viruses. The risk of ALF is further increased when there is coinfection or superinfection with HDV or in an immunosuppressed host. Mortality

**Table 406.6** Causes of Hepatitis Flares in Patients with Chronic Hepatitis B

CAUSE OF FLARE	COMMENT
Spontaneous	Factors that precipitate viral replication are unclear
Immunosuppressive therapy	Flares are often observed during withdrawal of the agent; preemptive antiviral therapy is required
Antiviral therapy for HBV	
Interferon	Flares are often observed during the second to third month of therapy in 30% of patients; may herald virologic response
Nucleoside analog	
During treatment	Flares are no more common than with placebo
Drug-resistant HBV	Severe consequences can occur in patients with advanced liver disease
On withdrawal	Flares are caused by the rapid reemergence of wild-type HBV; severe consequences can occur in patients with advanced liver disease
HIV treatment	Flares can occur as a result of the direct toxicity of HAART or with immune reconstitution; HBV increases the risk of antiretroviral drug hepatotoxicity
Genotypic variation	
Precore and core promoter variants	Fluctuations in serum alanine aminotransferase levels are common with precore variants
Superinfection with other hepatitis viruses	May be associated with suppression of HBV replication

HAART, Highly active antiretroviral therapy; HBV, hepatitis B virus.  
From Wells JT, Perillo R. Hepatitis B. In Feldman M, Friedman LS, Brandt LJ, eds. Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 10th ed. Philadelphia: Elsevier; 2016: Table 79.1.



**Fig. 406.3** Natural history of hepatitis B virus infection. HCC, Hepatocellular carcinoma; OLT, orthotopic liver transplant.

from ALF is >30%, and liver transplantation is the only effective intervention. Supportive care aimed at sustaining patients and early referral to a liver transplantation center can be lifesaving. As mentioned, HBV infection can also result in chronic hepatitis, which can lead to cirrhosis, end-stage liver disease complications, and HCC. Membranous glomerulonephritis with deposition of complement and HBeAg in glomerular capillaries is a rare complication of HBV infection.

## Treatment

Treatment of *acute* HBV infection is largely supportive. Close monitoring for liver failure and extrahepatic morbidities is key. Treatment of *chronic* HBV infection is in evolution; no drug currently achieves consistent, complete eradication of the virus. The natural history of chronic HBV infection in children is complex, and there is a lack of reliable long-term outcome data on which to base treatment recommendations. Treatment of chronic HBV infection in children should be individualized and done under the care of a pediatric hepatologist experienced in treating the disease.

The goal of treatment is to reduce viral replication, defined by having undetectable HBV DNA in the serum and development of anti-HBe, termed *seroconversion*. The development of anti-HBe transforms the disease into an inactive form, thereby decreasing infectivity, active liver injury and inflammation, fibrosis progression, and the risk of HCC. Treatment is only indicated for patients in the immune-active form of the disease, as evidenced by elevated ALT and/or AST, who have fibrosis on liver biopsy, putting the child at higher risk for cirrhosis during childhood.

## Treatment Strategies

**Interferon- $\alpha 2b$**  (IFN- $\alpha 2b$ ) has immunomodulatory and antiviral effects. It has been used in children, with long-term viral response rates similar to the 25% rate reported in adults. IFN use is limited by its subcutaneous administration, treatment duration of 24 weeks, and side effects (flulike symptoms, marrow suppression, depression, retinal changes, autoimmune disorders). IFN is further contraindicated in decompensated cirrhosis. One advantage of IFN, compared with other treatments, is that viral resistance does not develop with its use.

**Lamivudine** is an oral synthetic nucleoside analog that inhibits the viral enzyme reverse transcriptase. In children older than 2 years of age, its use for 52 weeks resulted in HBeAg clearance in 34% of patients with an ALT >2 times normal; 88% remained in remission at 1 year. It has a good safety profile. Lamivudine must be used for  $\geq 6$  months after viral clearance, and the emergence of a variant viral strain (YMDD) poses a barrier to its long-term use. Combination therapy in children using IFN and lamivudine did not seem to improve the rates of response in most series.

**Adefovir** (a purine analog that inhibits viral replication) is approved for use in children older than 12 years of age, in whom a prospective 1-year study showed 23% seroconversion. No viral resistance was noted in that study but has been reported in adults.

**Entecavir** (a nucleoside analog that inhibits replication) is currently approved for use in children older than 2 years of age. Prospective data have shown a 21% seroconversion rate in adults with minimal resistance developing. Patients in whom resistance to lamivudine developed have an increased risk of developing resistance to entecavir.

**Tenofovir** (a nucleotide analog that inhibits viral replication) is also approved for use in children older than 12 years of age. Prospective data have shown a 21% seroconversion rate with a very low rate of developing resistance. Patients with lamivudine-resistant variants do not appear to have an increased rate of resistance. Concern exists over long-term use and bone mineral density.

**Peginterferon- $\alpha_2$**  has the same mechanism of action as IFN but is given once weekly. This formulation has not been approved in the United States but is recommended for the treatment of chronic HBV in other countries. Patients most likely to respond to currently available drugs have low serum HBV DNA titers, are HBeAg-positive, have active hepatic inflammation (ALT greater than twice the upper limit of normal for at least 6 months), and have recently acquired disease.

Immune-tolerant patients—those with normal ALT and AST and who are HBeAg-positive with elevated viral load—are currently not considered for treatment, although the emergence of new treatment paradigms is promising for this large, yet hard-to-treat, subgroup of patients.

## Prevention

The most effective prevention strategies have resulted from the screening of pregnant mothers and the use of HBIG and hepatitis B vaccine in infants (Tables 406.7 to 406.10). In HBsAg-positive and

**Table 406.7**

### Strategy to Eliminate Hepatitis B Virus Transmission in the United States\*

- Screening of all pregnant women for HBsAg
- HBV DNA testing for HBsAg-positive pregnant women, with suggestion of maternal antiviral therapy to reduce perinatal transmission when HBV DNA is  $>200,000$  IU/mL
- Prophylaxis (HepB vaccine and hepatitis B immunoglobulin) for infants born to HBsAg-positive<sup>†</sup> women
- Universal vaccination of all infants beginning at birth<sup>‡,§</sup> as a safeguard for infants born to HBV-infected mothers not identified prenatally
- Routine vaccination of previously unvaccinated children age <19 yr
- Vaccination of adults at risk for HBV infection, including those requesting protection from HBV without acknowledgment of a specific risk factor

\*Sources: Mast EE, Margolis HS, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). Part 1: immunization of infants, children, and adolescents, *MMWR Recomm Rep*. 2005;54(No. RR-16):1–31; Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). Part II: immunization of adults, *MMWR Recomm Rep*. 2006;55(No. RR-16):1–33.

<sup>†</sup>Refer to Table 406.8 for prophylaxis recommendations for infants born to women with unknown HBsAg status.

<sup>‡</sup>Within 24 hr of birth for medically stable infants weighing  $\geq 2,000$  g.

<sup>§</sup>Refer to Table 406.8 for birth dose recommendations for infants weighing <2,000 g. HBsAg, Hepatitis B surface antigen; HBV, hepatitis B virus.

From Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR*. 2018;67(1):1–29, Box 2.

HBeAg-positive mothers, a 10% risk of chronic HBV infection exists compared with 1% in HBeAg-negative mothers. This knowledge offers screening strategies that may affect both mother and infant by using antiviral medications during the third trimester. Guidelines suggest that mothers with an HBV DNA viral load  $>200,000$  IU/mL receive an antiviral such as telbivudine, lamivudine, or tenofovir during the third trimester, especially if they had a previous child who developed chronic HBV after receiving HBIG and the hepatitis B vaccine. This practice has proven safe, with normal growth and development in infants of treated mothers.

Household, sexual, and needle-sharing contacts of patients with chronic HBV infection should be identified and vaccinated if they are susceptible to HBV infection. Patients should be advised about the perinatal and intimate contact risk of transmission of HBV. HBV is not spread by breastfeeding, kissing, hugging, or sharing water or utensils. Children with HBV should not be excluded from school, play, childcare, or work, unless they are prone to biting. A support group might help children to cope better with their disease. Families should not feel obligated to disclose the diagnosis, as this information may lead to prejudice or mistreatment of the patient or the patient's family. All patients positive for HBsAg should be reported to the state or local health department.

HBIG is indicated only for specific *postexposure* circumstances and provides only temporary protection (3–6 months). It plays a pivotal role in preventing *perinatal* transmission when administered within 12 hours of birth.

## Universal Vaccination

Two single-antigen vaccines (Recombivax HB and Engerix-B) are approved for children and are the only preparations approved for infant dosing under 6 weeks of life. Heplisav-B is approved only for people 18 years of age and older. Combination vaccines can be used for subsequent immunization dosing and enable integration of the HBV vaccine into the regular immunization schedule. The safety profile of the HBV vaccine is excellent. The most reported side effects are pain at the

**Table 406.8** Hepatitis B Vaccine Schedules for Infants by Infant Birthweight and Maternal Hepatitis B Surface Antigen Status

BIRTHWEIGHT	MATERNAL HBsAg STATUS	SINGLE-ANTIGEN VACCINE		SINGLE-ANTIGEN + COMBINATION VACCINE <sup>t</sup>	
		DOSE	AGE	DOSE	AGE
≥2,000 g	Positive	1	Birth (≤12 hr)	1	Birth (≤12 hr)
		HBIG <sup>‡</sup>	Birth (≤12 hr)	HBIG	Birth (≤12 hr)
		2	1-2 mo	2	2 mo
	Unknown*	3	6 mo <sup>§</sup>	3	4 mo
				4	6 mo <sup>§</sup>
		1	Birth (≤12 hr)	1	Birth (≤12 hr)
	Negative	2	1-2 mo	2	2 mo
		3	6-18 mo <sup>§</sup>	3	4 mo
				4	6 mo <sup>§</sup>
<2,000 g	Positive	1	Birth (≤12 hr)	1	Birth (≤12 hr)
		HBIG	Birth (≤12 hr)	HBIG	Birth (≤12 hr)
		2	1 mo	2	2 mo
		3	2-3 mo	3	4 mo
	Unknown	4	6 mo <sup>§</sup>	4	6 mo <sup>§</sup>
		1	Birth (≤12 hr)	1	Birth (≤12 hr)
		HBIG	Birth (≤12 hr)	HBIG	Birth (≤12 hr)
		2	1 mo	2	2 mo
	Negative	3	2-3 mo	3	4 mo
		4	6 mo <sup>§</sup>	4	6 mo <sup>§</sup>
		1	Hospital discharge or age 1 mo	1	Hospital discharge or age 1 mo
		2	2 mo	2	2 mo
		3	6-18 mo <sup>§</sup>	3	4 mo
				4	6 mo <sup>§</sup>

\*Mothers should have blood drawn and tested for HBsAg as soon as possible after admission for delivery; if the mother is found to be HBsAg positive, the infant should receive HBIG as soon as possible but no later than age 7 days.

<sup>†</sup>Pediarix should not be administered before age 6 wk.

<sup>‡</sup>HBIG should be administered at a separate anatomic site from the vaccine.

<sup>§</sup>The final dose in the vaccine series should not be administered before age 24 wk (164 days).

HBIG, Hepatitis B immune globulin; HBsAg, hepatitis B surface antigen.

From Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. MMWR. 2018;67(1):1–29, Table 3.

**Table 406.9** Recommended Doses of Hepatitis B Vaccine by Group and Vaccine Type

	SINGLE-ANTIGEN VACCINE				COMBINATION VACCINE			
	RECOMBIVAX		ENGERIX		PEDIARIX*	TWINRIX <sup>†</sup>		
Age-Group (yr)	Dose (μg)	Vol (mL)	Dose (μg)	Vol (mL)	Dose (μg)	Vol (mL)	Dose (μg)	Vol (mL)
Birth-10	5	0.5	10	0.5	10*	0.5	N/A	N/A
11-15	10 <sup>‡</sup>	1	N/A	N/A	N/A	N/A	N/A	N/A
11-19	5	0.5	10	0.5	N/A	N/A	N/A	N/A
≥20	10	1	20	1	N/A	N/A	20 <sup>†</sup>	1
<b>HEMODIALYSIS PATIENTS AND OTHER IMMUNE-COMPROMISED PERSONS</b>								
<20	5	0.5	10	0.5	N/A	N/A	N/A	N/A
≥20	40	1	40	2	N/A	N/A	N/A	N/A

\*Pediarix is approved for use in persons age 6 wk through 6 yr (before the seventh birthday).

<sup>†</sup>Twinrix is approved for use in persons age ≥18 yr.

<sup>‡</sup>Adult formulation administered on a two-dose schedule.

N/A, Not applicable.

From Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. MMWR. 2018;67(1):1–29, Table 2.

**Table 406.10**

Hepatitis B Vaccine Schedules for Children, Adolescents, and Adults

AGE GROUP	SCHEDULE* (INTERVAL REPRESENTS TIME IN MONTHS FROM FIRST DOSE)
Children (1-10 yr)	0, 1, and 6 mo 0, 1, 2, and 12 mo
Adolescents (11-19 yr)	0, 1, and 6 mo 0, 12, and 24 mo 0 and 4-6 mo <sup>†</sup> 0, 1, 2, and 12 mo 0, 7 days, 21-30 days, 12 mo <sup>‡</sup>
Adults ( $\geq 20$ yr)	0, 1, and 6 mo 0, 1, 2, and 12 mo 0, 1, 2, and 6 mo <sup>§</sup> 0, 7 days, 21-30 days, 12 mo <sup>‡</sup>

\*Refer to package inserts for further information. For all ages, when the hepatitis B vaccine schedule is interrupted, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be administered as soon as possible, and the second and third doses should be separated by an interval of at least 8 wk. If only the third dose has been delayed, it should be administered as soon as possible. The final dose of the vaccine must be administered at least 8 wk after the second dose and should follow the first dose by at least 16 wk; the minimum interval between the first and second doses is 4 wk. Inadequate doses of hepatitis B vaccine or doses received after a shorter-than-recommended dosing interval should be readministered, using the correct dosage or schedule. Vaccine doses administered  $\leq 4$  days before the minimum interval or age are considered valid. Because of the unique accelerated schedule for Twinrix, the 4-day guideline does not apply to the first three doses of this vaccine when administered on a 0-day, 7-day, 21 to 30-day, and 12-mo schedule (new recommendation).

<sup>†</sup>A two-dose schedule of Recombivax adult formulation (10  $\mu$ g) is licensed for adolescents age 11-15 yr. When scheduled to receive the second dose, adolescents age  $>15$  yr should be switched to a three-dose series, with doses two and three consisting of the pediatric formulation administered on an appropriate schedule.

<sup>‡</sup>Twinrix is approved for use in persons age  $\geq 18$  yr and is available on an accelerated schedule with doses administered at 0, 7, 21-30 days, and 12 mo.

<sup>§</sup>A four-dose schedule of Engerix administered in two-1 mL doses (40  $\mu$ g) on a 0-, 1-, 2-, and 6-mo schedule is recommended for adult hemodialysis patients.

From Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR*. 2018;67(1):1-29, Table 4.

injection site (up to 29% of cases) and fever (up to 6% of cases). Seropositivity is 90–95% with all vaccines, achieved after the second dose in most patients. The third dose serves as a booster and may have an effect on maintaining long-term immunity. For immunocompromised individuals, annual anti-HBs testing should be considered, with a fourth booster dose given when anti-HBs concentrations are  $<10$  mIU/mL. Similar consideration may be given to children with cystic fibrosis, liver disease, or celiac disease if there is an ongoing risk for HBV exposure. In infants whose birthweight is  $<2,000$  g born to HBsAg-positive mothers (or if their HBsAg status remains unknown), a fourth dose is recommended at 6 months of age (the birth dose does not count as part of the three-dose series) and these infants should be checked for anti-HBs and HBsAg after completing these shots. In this group of infants, if the anti-HBs level is  $<10$  mIU/mL, they should repeat the three-dose series. Despite declines in the anti-HBs titer in time, most healthy vaccinated persons remain protected against HBV infection.

HBV vaccination recommendations are as noted in Tables 406.8 to 406.10.

Postvaccination testing for HBsAg and anti-HBs should be done at 9–18 months. If the result is positive for anti-HBs, the child is immune to HBV. If the result is positive for HBsAg only, the parent should be counseled and the child evaluated by a pediatric hepatologist. If the result is negative for both HBsAg and anti-HBs, a second complete hepatitis B vaccine series should be administered, followed by testing for anti-HBs to determine if subsequent doses are needed.

Administration of four doses of vaccine is permissible when combination vaccines are used after the birth dose; this does not affect vaccine response.

## Postexposure Prophylaxis

Recommendations for postexposure prophylaxis for prevention of hepatitis B infection depend on the conditions under which the person is exposed to HBV (see Table 406.10). Vaccination should never be postponed if written records of the exposed person's immunization history are not available, but every effort should still be made to obtain those records.

## Special Populations

Patients with cirrhosis may not respond as well to the HBV vaccine, and repeat anti-HBs titers should be performed. Adult studies suggest a higher dosage or shorter interval between dosages may increase immunization effectiveness. Patients with inflammatory bowel disease frequently have not been immunized or did not develop complete immunity to HBV, as demonstrated by inadequate anti-HBs levels. These patients may be at risk for fulminant HBV (reactivation) when immunosuppression is started as part of their treatment regimen, specifically with biologic agents such as infliximab.

## Prognosis

In general, the outcome after acute HBV infection is favorable, despite a risk of ALF. The risk of developing chronic infection brings the risks of liver cirrhosis and HCC to the forefront. Perinatal transmission leading to chronicity is responsible for the high incidence of HCC in young adults in endemic areas. Importantly, HBV infection and its complications are effectively controlled and prevented with vaccination, and multiple clinical trials are ongoing in an effort to improve and guide treatment regimens.

## HEPATITIS C

### Etiology

HCV is a single-stranded RNA virus, classified as a separate genus within the Flaviviridae family, with marked genetic heterogeneity. It has at least six major genotypes and numerous subtypes and quasi-species, which permit the virus to escape host immune surveillance. Genotype variation might partially explain the differences in clinical course and response to treatment. Genotype 1 (a and b) is the most common genotype in the United States. The advent of direct-acting antiviral (DAA) therapy has brought a new and highly successful approach to the treatment and cure of hepatitis C.

### Epidemiology

DAA therapy has made a major impact on decreasing the prevalence of HCV in the United States. However, HCV continues to be a major cause of chronic liver disease in adults and is associated with  $>10,000$  deaths per year. Approximately 2.5 million people in the United States and 70 million people worldwide are estimated to be currently infected with HCV. The reported global estimated viremic prevalence in children with HCV (age 0–17 years) is hypothesized to be around 3.25 million children as of 2018. Appropriate identification and screening for infected individuals should be implemented.

Risk factors for HCV transmission in the United States included blood transfusion before 1992; with current blood donor screening practices, the risk of HCV transmission is approximately 0.001% per unit transfused. Illegal drug use with exposure to blood or blood products from HCV-infected persons accounts for the majority of adult cases in the United States. Sexual transmission, especially through multiple sexual partners, is the second most common cause of infection. Other risk factors include occupational exposure, but approximately 10% of new infections have no known transmission source. In children, perinatal transmission is the *most* prevalent mode of transmission (see Table 406.1). HCV infection rates in the United States in women of childbearing age and those who are pregnant have increased in parallel with the rising opioid epidemic. Based on the most recent census data, an estimated 29,000 women with HCV infection give birth each year in the United States, with the majority of their infants being infected with HCV. HIV coinfection and high viremia titers (HCV RNA-positive) in the mother can increase the transmission rate to 20%. The incubation period is 7–9 weeks (range: 2–24 weeks).

In 2020, the United States Preventive Services Task Force (USPSTF) and the CDC issued updated recommendations that encourage clinicians to screen all adults age 18–79 years for HCV infection. The USPSTF recommendations specifically suggest HCV screening for all pregnant women. This is important because the rate of HCV infection in pregnant women has continued to increase, with an associated increase in the number of infants exposed to HCV. The mode of delivery (vaginal vs cesarean section) does not typically affect risk of transmission. HCV RNA may be detected in breast milk and colostrum; however, breastfeeding does not appear to increase the rate of HCV transmission (with the exception of HIV coinfected mothers).

### Pathogenesis

The pattern of acute hepatic injury is indistinguishable from that of other hepatotropic viruses. In chronic cases, lymphoid aggregates or follicles in portal tracts are found, either alone or as part of a general inflammatory infiltrate of the portal areas. HCV appears to cause injury primarily by cytopathic mechanisms, but immune-mediated injury can also occur. The cytopathic component appears to be mild because the acute illness is typically the least severe of all hepatotropic virus infections.

### Clinical Manifestations

Acute HCV infection tends to be mild and insidious in onset (Fig. 406.4; see also Table 406.1). ALF rarely occurs. HCV is the most likely of all these viruses to cause chronic infection (Fig. 406.5). Of affected adults, <15% clear the virus; the rest develop chronic hepatitis. In pediatric studies, 20–40% of children achieved spontaneous sustained clearance of the virus within the first 5 years of life.

Chronic HCV infection is also clinically silent until a complication develops. Serum aminotransferase levels fluctuate and are sometimes normal, but histologic inflammation is universal. Progression of liver fibrosis is slow over several years, unless comorbid factors are present, which can accelerate fibrosis progression. Approximately 25% of infected patients ultimately progress to cirrhosis, liver failure, and, occasionally, primary HCC within 20–30 years of the acute infection. Although progression is rare within the pediatric age range, cirrhosis and HCC from HCV have been reported in children. The long-term morbidities constitute the rationale for diagnosis and treatment in children with HCV.

Chronic HCV infection can be associated with small vessel vasculitis and is a common cause of essential mixed cryoglobulinemia. Other extrahepatic manifestations predominantly seen in adults include cutaneous vasculitis, porphyria cutanea tarda, lichen planus, peripheral neuropathy, cerebritis, polyarthritis, membranoproliferative

glomerulonephritis, and nephrotic syndrome. Antibodies to smooth muscle, antinuclear antibodies, and low thyroid hormone levels may also be present.

### Diagnosis

In children older than 18 months of age, diagnostic criteria are the same as those established for adults. Clinically available assays for detection of HCV infection are based on detection of antibodies to HCV antigens (anti-HCV) or detection of viral RNA (see Table 406.3); neither can predict the severity of liver disease.

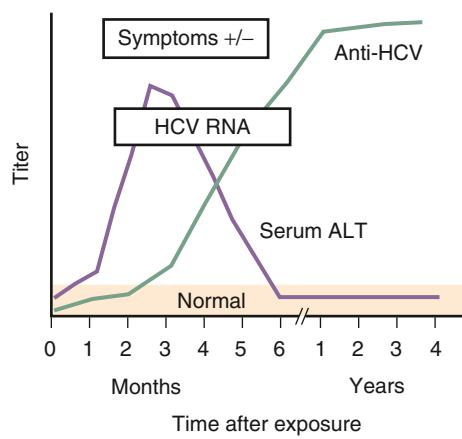
The most widely used serologic test is the third-generation enzyme immunoassay to detect anti-HCV. The predictive value of this assay is greatest in high-risk populations, but the false-positive rate can be as high as 50–60% in low-risk populations. False-negative results also occur because antibodies remain negative for as long as 1–3 months after clinical onset of illness. Anti-HCV is not a protective antibody and does not confer immunity; it is usually present simultaneously with the virus. The next step is to verify viral infection by detecting HCV RNA. This is accomplished via PCR testing. The diagnosis of chronic HCV infection is made based on the presence of detectable HCV RNA for more than 6 months. The quantitative PCR also aids in monitoring response to therapy.

For infants under 18 months of age, the diagnosis may be confounded by the passive transfer of maternal antibodies, which can last for 1 year or more postnatally. Thus anti-HCV testing is of limited value during the first year of life. Diagnosis in this age-group can be reliably established by HCV RNA positivity on two or more occasions after 2 months of age. Criteria for spontaneous clearance requires two negative HCV RNA tests spread at least 6 months apart, followed by negative anti-HCV testing after 18 months of age.

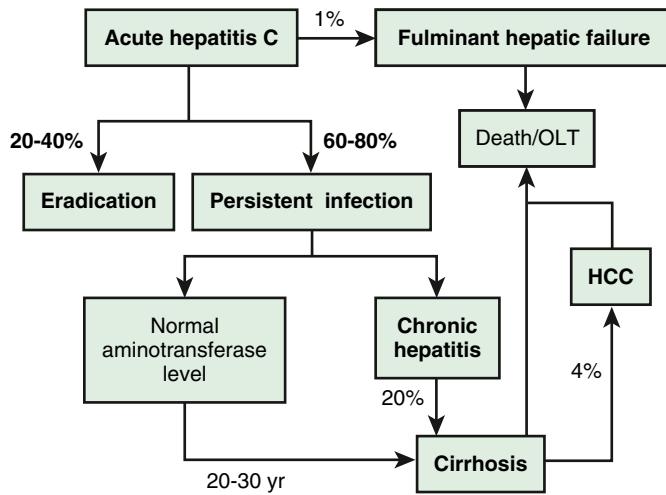
Screening for HCV should include all patients with the following risk factors: history of illegal drug use (even if only once), receiving clotting factors made before 1987 (when inactivation procedures were introduced) or blood products before 1992, hemodialysis, idiopathic liver disease, and children born to HCV-infected women (qualitative PCR in infancy and anti-HCV after 12–18 months of age). In children, it is also important to consider whether the mother has any of the risk factors noted earlier that would increase her possibility of developing HCV.

Determining HCV genotype is also important, particularly when therapy is considered, as certain DAA therapies may only target specific genotypes. Newer pangenotypic DAA agents, however, will hopefully lead to the practice of genotyping becoming moot in the near future (as discussed later).

Aminotransferase levels typically fluctuate during HCV infection and do not correlate with the degree of liver fibrosis. A liver biopsy was



**Fig. 406.4** Typical course of acute hepatitis C virus infection followed by recovery. Symptoms may or may not be present during acute infection. Anti-HCV, Antibody to HCV; ALT, alanine aminotransferase. (Modified from the Centers for Disease Control and Prevention, [www.cdc.gov/hepatitis/Resources/Professionals/Training/Serology/training.htm#one](http://www.cdc.gov/hepatitis/Resources/Professionals/Training/Serology/training.htm#one).)



**Fig. 406.5** Natural history of hepatitis C virus infection. HCC, Hepatocellular carcinoma; OLT, orthotopic liver transplant. (From Hochman JA, Balistreri WF. Chronic viral hepatitis: always be current! Pediatr Rev. 2003;24[12]:399–410.)

previously the only means to assess the presence and extent of hepatic fibrosis, outside of overt signs of chronic liver disease. Newer noninvasive modalities using ultrasound or magnetic resonance elastography, however, are now used to estimate the degree of fibrosis and decrease the need for biopsy. This technology, coupled with newer drug regimens, has eliminated the need for liver biopsy in many cases of HCV infection. A liver biopsy is now primarily indicated to rule out other causes of overt liver disease.

### Complications

The risk of ALF caused by HCV is low, but the risk of chronic hepatitis is the highest of all the hepatitis viruses. In adults, risk factors for progression to hepatic fibrosis include older age, obesity, being male, and even moderate alcohol ingestion (two 1-oz. drinks per day). Progression to cirrhosis or HCC is a major cause of morbidity and one of the most common indications for liver transplantation in adults in the United States.

### Treatment

The arrival of DAA therapies has led to a paradigm shift in the treatment and eradication of HCV in all populations. These DAAs are now available and have been shown to be as safe and effective in children (>3 years) and adolescents as in the adult populations. Pegylated-interferon (PEG-IFN) and ribavirin (RBV), the initial recommended combination for treatment of HCV in children and adolescents, are no longer recommended.

The goal of treatment is to achieve a sustained viral response (SVR), defined as the absence of viremia at a variable period after stopping the medications. SVR is associated with improved histology and decreased risk of morbidities. DAA therapies can achieve SVR after 8-12 weeks of treatment, as compared with the RBV and PEG-IFN combination, which required 48 weeks of treatment, close monitoring, and significant side effect profiles including pancytopenia. Furthermore, regimens of PEG-IFN have sustained efficacy of 50% in achieving SVR, whereas DAA regimens have been shown to be consistently more effective (SVR >95%) in children.

DAAs target three HCV proteins involved in the life cycle of this virus: (1) the nonstructural protein 3/4A (NS3/4A) protease inhibitors (PIs), which work by inhibiting HCV polyprotein processing; (2) NS5A inhibitors, which inhibit viral replication and assembly; and (3) NS5B polymerase inhibitors, which block HCV RNA replication. By combining two or more of these classes of drugs with different mechanisms attacking HCV, DAAs are able to achieve high SVR rates.

Several phase 2 clinical trials have been completed, revealing the safety and efficacy of DAA therapy in children as young as 3 years of age. For example, the first pediatric trial showed the safety and efficacy of the combination of ledipasvir (90 mg) and sofosbuvir (400 mg) for treatment of HCV genotype 1 over a 12-week period in children ages 12-17 years. This combination is Food and Drug Administration (FDA) approved for children as young as 3 years of age.

It is important to note that one of the main obstacles is determining an age when a young child is capable of daily compliance with the medications for the recommended 8- to 12-week period. The arrival of DAA therapies in the form of granules is a promising strategy for younger children who cannot swallow whole tablets. These granules can be sprinkled on a spoonful of nonacidic soft food (e.g., pudding or peanut butter). SVR has been achieved in 97% of patients as young as 3 years in phase 2 clinical trials using this formulation of delivery.

Treatment recommendations involve obtaining HCV PCR at baseline (before initiation of DAA therapy), at 12 weeks, and at 24 weeks post initiation of therapy. As long as there was no evidence of long-term damage (e.g., fibrosis, cirrhosis), then patients can have a repeat HCV PCR assessment at 1 year after completion of therapy to affirm SVR.

### Newer Treatments

Pangenotypic agents, capable of being >92% effective at achieving SVR for all genotypes, have now been FDA approved for children ≥3 years. These include the agents sofosbuvir-velpatasvir, given at once-daily

weight-based dosing for 12 weeks, and the combination of glecaprevir-pibrentasvir at three weight-based doses per day for 8 weeks. Thus the need to obtain expensive genotype testing may be unnecessary. With the rapid development of new medications and regimens, frequent review of up-to-date resources, such as [www.hcvguidelines.org](http://www.hcvguidelines.org), will be vital to provide optimal care (Table 406.11).

### Prevention

No vaccine is yet available to prevent HCV, although ongoing research suggests this will be possible in the future. Currently available Ig preparations are not beneficial, likely because preparations produced in the United States do not contain high titers of antibodies to HCV, because blood and plasma donors are screened for anti-HCV and excluded from the donor pool. Broad neutralizing antibodies to HCV were found to be protective and might pave the road for vaccine development.

Once HCV infection is identified, patients should be screened yearly with a liver ultrasound and serum α-fetoprotein for HCC and for any clinical evidence of liver disease. Vaccinating the affected patient against HAV and HBV will prevent superinfection with these viruses and the increased risk of developing severe liver failure. Beginning education to families on DAA therapies and initiating treatment at 3 years of age (or as soon as the child is developmentally ready to complete therapy) are also crucial to prevent the development of fibrosis. However, children with evidence of liver fibrosis should continue to be closely monitored even after eradication of their underlying HCV. Fortunately, adult studies are emerging that reveal mild reversal of fibrosis by DAA treatment. However, for patients with evidence of high-grade fibrosis or cirrhosis, they are still at high risk of developing HCC even after achieving SVR. More histologic data are needed to further support the hypothesis of improved liver scarring post DAA treatment. Children with evidence of fibrosis must be closely followed, given the continued risk of complications such as HCC and portal hypertension.

### Prognosis

DAA therapies have revolutionized treatment for HCV and allow for resolution of the underlying hepatitis in young children and adolescents before development of irreversible chronic liver disease (fibrosis, cirrhosis, HCC). The World Health Organization (WHO) in 2016 set the ambitious goal of eliminating HCV by 2030, and these new DAA therapeutic agents have provided an important step toward achieving this goal.

## HEPATITIS D

### Etiology

HDV, the smallest known animal virus, is considered defective because it cannot produce infection without concurrent HBV infection. The 36-nm-diameter virus is incapable of making its own coat protein; its outer coat is composed of excess HBsAg from HBV. The inner core of the virus is single-stranded circular RNA that expresses the HDV antigen.

### Epidemiology

HDV can cause an infection at the same time as the initial HBV infection (coinfection), or HDV can infect a person who is already infected with HBV (superinfection). Transmission usually occurs by intrafamilial or intimate contact in areas of high prevalence, which are primarily developing countries (see Table 406.1). In areas of low prevalence, such as the United States, the parenteral route is far more common. HDV infections are uncommon in children in the United States but must be considered when ALF occurs. The incubation period for HDV superinfection is approximately 2-8 weeks; with coinfection, the incubation period is similar to that of HBV infection.

### Pathogenesis

Liver pathology in HDV-associated hepatitis has no distinguishing features except that damage is usually severe. In contrast to HBV, HDV causes injury directly by cytopathic mechanisms. The most severe cases of HBV infection appear to result from coinfection of HBV and HDV.

**Table 406.11** Completed Studies with Direct-Acting Antiviral Combinations in Children with Chronic Hepatitis C Virus Infection

THERAPY (DURATION)	HCV GENOTYPE	PARTICIPANT AGE IN YEARS (N)	YEAR	SVR12 (%)
Ledipasvir 90 mg + sofosbuvir 400 mg (12 wk)	1	12-17 (100)	2016	98
Sofosbuvir 400 mg + ribavirin (variable)	2 or 3	12-17 (52)	2017	98
Sofosbuvir 400 mg + ribavirin (variable)	1 or 3	5-18 (35)	2017	97
Ledipasvir 45 mg + sofosbuvir 200 mg (12 wk)	1,4-6	12-17 (144)	2018	99
Ledipasvir 45 mg + sofosbuvir 200 mg (12 wk)	1	6-11 (90)	2018	98
Ledipasvir 90 mg + sofosbuvir 400 mg (12 wk)	4	12-18 (40)	2018	100
Ledipasvir + sofosbuvir ± ribavirin (variable)		7-18 (22)	2018	91
Ledipasvir 22.5 mg + sofosbuvir 100 mg (12 wk)	4	0.5 (1)	2018	100
Ledipasvir 45 mg + sofosbuvir 200 mg (12 wk)	4	6-12 (20)	2018	95
Ledipasvir + sofosbuvir (variable)	1 or 4	6-18 (9)	2019	100
Ledipasvir 90 mg + sofosbuvir 400 mg (12 wk)	4	11-17.5 (51)	2019	100
Ledipasvir 90 mg + sofosbuvir 400 mg (8 wk)	1	12-17 (14)	2019	100
Ledipasvir 90 mg + sofosbuvir 400 mg (12 wk)	4	13, 16 (2)	2019	100
Ledipasvir 180 mg + sofosbuvir 400 mg (12 wk)	not performed	12-18 (46)	2020	98
Ledipasvir 45 mg + sofosbuvir 200 mg (8 or 12 wk)	4	3-6 (22)	2020	100
Ledipasvir 90 mg + sofosbuvir 400 mg (12 wk)	4	9-12 (100)	2020	100
Sofosbuvir 400 mg + ribavirin (variable)	1 or 4	3-11 (54)	2020	98
Ledipasvir + sofosbuvir (variable)	1 or 4	3 to <6 (34)	2020	97
Glecaprevir 300 mg + pibrentasvir 120 mg (8-16 wk)	1-4	12-17 (47)	2020	100
Elbasvir + grazoprevir (12 wk)	1 or 4	3-17 (57)	2020	100
Sofosbuvir + velpatasvir (12 wk)	1-4, 6	3-17 (216)	2020	92
Ledipasvir 45 mg + sofosbuvir 200 mg (8 wk)	4	4-10 (30)	2020	100
Sofosbuvir + velpatasvir (12 wk)	1-6	3-17 (160)	2021	92
Glecaprevir + pibrentasvir (8 wk)	1-6	3-12 (81)	2021	96

### Clinical Manifestations

The symptoms of hepatitis D are similar to, but usually more severe than, those of the other hepatotropic viruses. The clinical outcome for HDV infection depends on the mechanism of infection. In *coinfection*, acute hepatitis, which is much more severe than for HBV alone, is common, but the risk of developing chronic hepatitis is low. In *superinfection*, acute illness is rare and chronic hepatitis is common. The risk of ALF is highest with superinfection. Hepatitis D should be considered in any child who experiences ALF.

### Diagnosis

HDV has not been isolated, and no circulating antigen has been identified. The diagnosis is made by detecting IgM antibody to HDV; the antibodies to HDV develop approximately 2-4 weeks after coinfection and approximately 10 weeks after a superinfection. A test for anti-HDV antibody is commercially available. PCR assays for viral RNA are available as research tools (see Table 406.2).

### Treatment

The treatment is based on supportive measures once an infection is identified. There are no specific HDV-targeted treatments to date. The treatment is mostly based on controlling and treating HBV infection, without which HDV cannot induce hepatitis. Small research studies suggest that IFN is the preferred treatment regimen, but ongoing studies still seek the ideal management strategy, and the regimen should be personalized for each patient.

### Prevention

There is no vaccine for hepatitis D. Because HDV replication cannot occur without hepatitis B coinfection, immunization against HBV also prevents HDV infection. Hepatitis B vaccines and HBIG are used for the same indications as for hepatitis B alone.

### HEPATITIS E

#### Etiology

HEV has been cloned using molecular techniques. This RNA virus has a nonenveloped sphere shape with spikes and is similar in structure to the caliciviruses.

#### Epidemiology

Hepatitis E is the epidemic form of viral hepatitis. Transmission is fecal-oral (often waterborne) and is associated with shedding of 27- to 34-nm particles in the stool (see Table 406.1). The highest prevalence of HEV infection has been reported in the Indian subcontinent, the Middle East, Southeast Asia, and Mexico, especially in areas with poor sanitation. The prevalence, however, appears to be increasing in the United States and other developed countries and has been postulated to be the most common cause of acute hepatitis and jaundice in the world. The mean incubation period is approximately 40 days (range: 15-60 days).

#### Pathogenesis

HEV appears to act as a cytopathic virus. The pathologic findings are similar to those of the other hepatitis viruses.

## Clinical Manifestations

The clinical illness associated with HEV infection is similar to that of HAV but is often more severe. As with HAV, chronic illness does not occur—the sole exception noted to date is chronic hepatitis E occurring in immunosuppressed patients (e.g., post-transplant). In addition to often causing a more severe episode than HAV, HEV tends to affect older patients, with a peak age between 15 and 34 years. HEV is a major pathogen in pregnant women, in whom it causes ALF with a high fatality incidence. HEV could also lead to decompensation of preexisting chronic liver disease.

## Diagnosis

Recombinant DNA technology has resulted in the development of antibodies to HEV particles, and IgM and IgG assays are available to distinguish between acute and resolved infections (see Table 406.3). IgM antibody to viral antigen becomes positive after approximately 1 week of illness. Viral RNA can be detected in stool and serum by PCR.

## Prevention

A recombinant hepatitis E vaccine is highly effective in adults. No evidence suggests that Ig is effective in preventing HEV infections. Ig pooled from patients in endemic areas might prove to be effective.

## Acute Hepatitis of Unknown Etiology

In 2021 and 2022 multiple medical centers in over 35 countries reported cases of acute and often severe hepatitis. Clinical manifestations included jaundice, emesis, diarrhea, and hepatomegaly; fever was not always present. Liver enzyme (ALT, AST) and bilirubin levels were elevated in most; ~77% had hepatic failure requiring liver transplantation. Adenovirus (type 41) was detected by PCR in blood but not consistently in liver biopsy specimens (by immune histopathology, electron microscopy, or PCR). Adeno-associated virus 2 has been recovered in both plasma and liver tissue from most patients. A collaborative registry from 25 centers reported a median age of onset of 41 months (range <1–16 years) with ~27% requiring intensive care unit (ICU)–level care. In that cohort, only 22% had evidence of adenovirus infection. The WHO working case definition is noted in Table 406.12. Treatment is supportive, as indicated for other etiologies of acute hepatitis and hepatic failure. The use of corticosteroids is controversial (especially with adenoviremia); some centers have used cidofovir, an inhibitor of viral (adenovirus) DNA polymerases.

Until further clarification of the etiology, the initial evaluation must include the traditional viral, immune, and toxic etiologies of hepatitis and acute hepatic failure (see Table 406.2).

## APPROACH TO ACUTE OR CHRONIC HEPATITIS

Identifying deterioration of the patient with acute hepatitis and the development of ALF is a major contribution of the primary care provider (Fig. 406.6). If ALF is identified, the clinician should immediately refer the patient to a transplantation center; this can be lifesaving.

**Table 406.12** WHO Working Case Definitions of Severe Acute Hepatitis of Unknown Etiology

- Confirmed case: Not available at present
- Probable case: A person presenting with an acute hepatitis (nonhepatitis A-E<sup>1</sup>) with serum transaminase >500 IU/L (AST or ALT), who is 16 yr and younger, since October 1, 2021
- Epidemiologically linked: A person presenting with an acute hepatitis (nonhepatitis A-E<sup>1</sup>) of any age who is a close contact of a probable case, since October 1, 2021

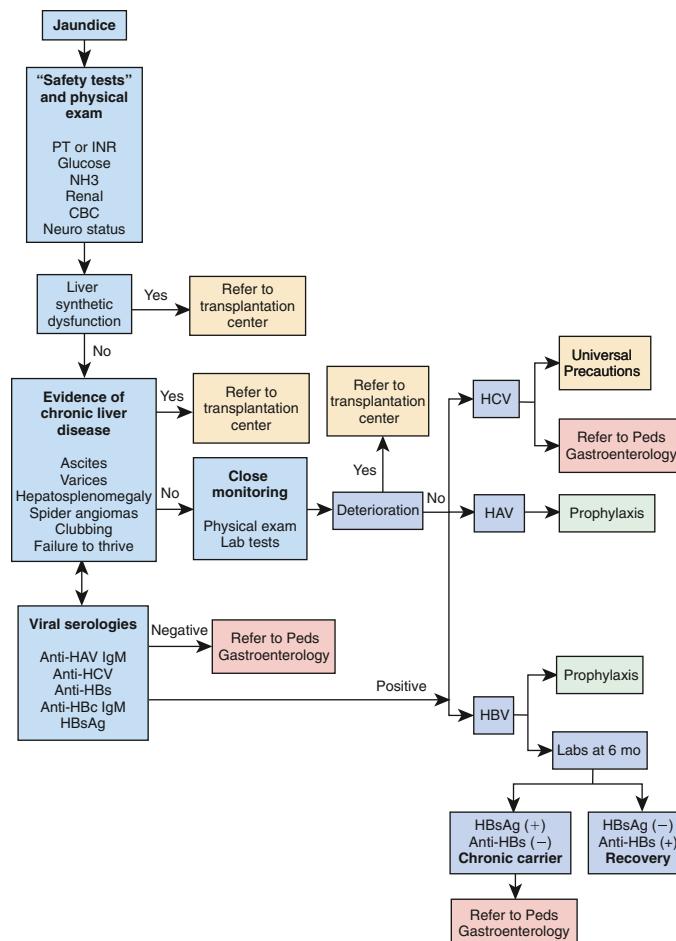
<sup>1</sup>If hepatitis A-E serology results are pending but other criteria are met, these can be reported and will be classified as "pending classification." Cases with other explanations for their clinical presentation are discarded. Delta testing is not required, as it is only undertaken in persons who are HBsAg positive to establish presence of coinfection. From World Health Organization: Disease Outbreak News. Acute hepatitis of unknown aetiology in children – Multi-country. Geneva: World Health Organization, July 12, 2022. Available at <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON400>.

Once chronic infection is identified, close follow-up and referral to a pediatric hepatologist is recommended to enroll the patient in appropriate treatment trials. Treatment of chronic HBV in children should preferably be delivered within, or using data from, pediatric controlled trials, as indications, timing, regimen, and outcomes remain to be defined and cannot be extrapolated from adult data. New DAA therapies have changed the approach to treatment of HCV in children as young as 3 years of age. All patients with chronic viral hepatitis should avoid as much as possible further insult to the liver; HAV and HBV vaccines are recommended. Patients must avoid alcohol consumption and obesity, and they should exercise care when taking new medications, including nonprescription drugs and herbal medications.

International adoption and ease of travel continue to change the epidemiology of hepatitis viruses. In the United States, chronic HBV and HCV have a high prevalence among international adoptee patients; vigilance is required to establish early diagnosis in order to offer appropriate treatment and prophylactic measures to limit viral spread.

Chronic hepatitis can be a stigmatizing disease for children and their families. The pediatrician should offer, with proactive advocacy, appropriate support for them and needed education for their social circle. Scientific data and information about support groups are available for families on the websites for the American Liver Foundation ([www.liverfoundation.org](http://www.liverfoundation.org)) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition ([www.naspgpan.org](http://www.naspgpan.org)) and through pediatric gastroenterology centers.

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**Fig. 406.6** Algorithm showing the clinical approach to viral hepatitis. CBC, Complete blood count with differential; HAV, hepatitis A virus; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IgM, immunoglobulin M; INR, international normalization ratio; NH<sub>3</sub>, ammonia; PT, prothrombin time.

## Chapter 407

# Liver Abscess

Hilary E. Miller-Handley and Joshua K. Schaffzin

Liver abscesses typically have one of two infectious etiologies: pyogenic, meaning involving bacteria, or parasitic, such as with amebiasis, ascariasis, or toxocariasis. Liver abscesses are typically difficult to detect because of their nonspecific presentation, and diagnosis requires a high index of suspicion. Radiographic diagnosis is often contributory, but further confirmation is often indicated to differentiate infectious abscess from hydatid cyst and noninfectious causes, such as malignancy (primary hepatic or metastasis). The differential diagnosis also includes traumatic injury (including procedural, such as a misplaced vascular catheter).

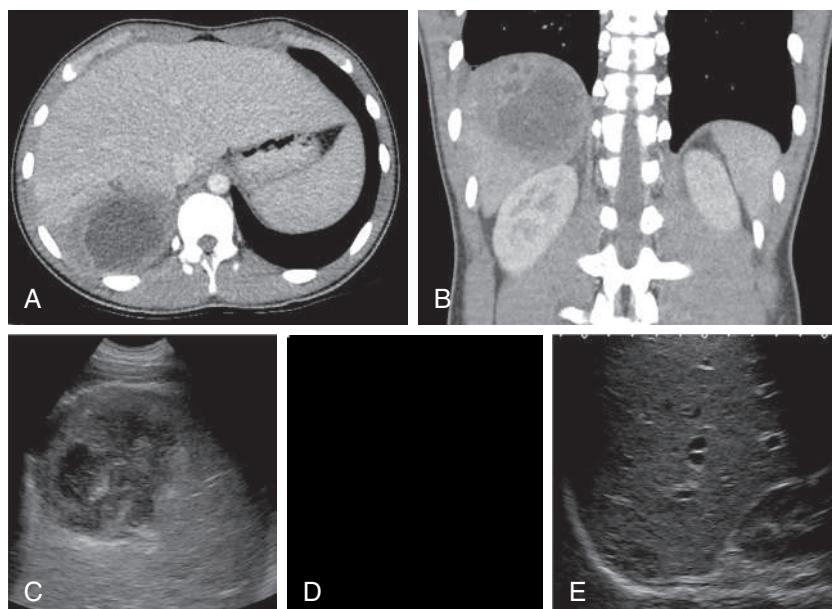
**Pyogenic liver abscesses (PLA)** are uncommon in children but have been reported in all ages. Bacteria can invade the liver through one of four sources: hematogenously through the hepatic artery (e.g., in the presence of bacteremia), through the biliary tract, through the portal vein (portal sepsis), and directly by contiguous infection. In neonates, a portal vein source can include the umbilical vein (e.g., in the presence of omphalitis or injury caused by an umbilical venous catheter). PLA of unknown source are classified as cryptogenic. Children with hepatobiliary malignancy, liver transplantation, primary immune deficiency disorders (i.e., chronic granulomatous disease [CGD] and hyper-IgE syndrome), and gastrointestinal pathology are at increased risk for a liver abscess. Diabetes mellitus is a risk factor associated with PLA in adults; however, it is not as clearly linked in children. PLA are also uncommon in adults, although the annual incidence is higher in Southeast Asia (estimated 17.6/100,000 population) than in the United States or Europe (estimated 2-5/100,000 population). They tend to occur more frequently in males and with older age.

Clinical signs and symptoms of PLA are nonspecific and can include fever, chills, malaise, fatigue, nausea, abdominal pain (with or without right upper quadrant tenderness), and hepatomegaly; jaundice is uncommon. The most common abnormal laboratory

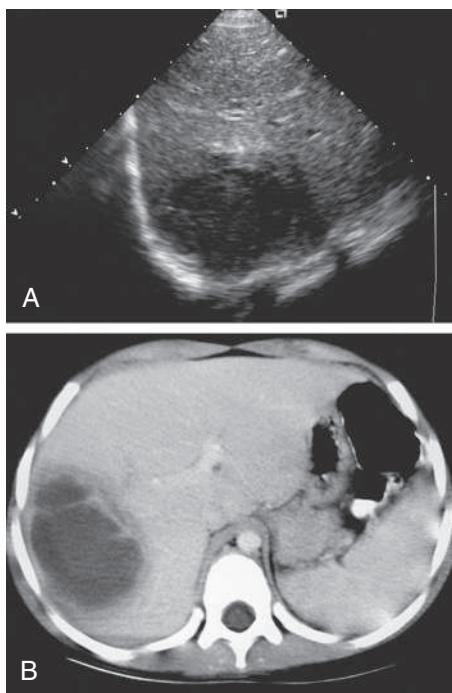
findings are elevated inflammatory markers and hypoalbuminemia. Hepatic function testing can be abnormally elevated, and leukocytosis is common. Radiologic confirmation is often obtained by ultrasound or CT (Fig. 407.1). Chest x-rays may show elevation of the right hemidiaphragm with a right pleural effusion. Solitary lesions of the right hepatic lobe are most common, although solitary abscesses can appear in any hepatic lobe or as multiple disseminated lesions (such as with disseminated candidiasis, bartonellosis, or, rarely, brucellosis).

Cultures of pyogenic liver abscesses are often polymicrobial. In children, *Staphylococcus aureus*, *Streptococcus* spp., enteric gram-negative organisms (*Escherichia coli*, *Klebsiella pneumoniae*), and anaerobic organisms are most common. In immunocompromised children, particularly those with CGD, *Serratia* spp. and *Aspergillus* spp. are also commonly identified. Among adults, *E. coli* and *K. pneumoniae* are the most common organisms, and aerobic gram-positive and anaerobic organisms are less common. Blood cultures are positive in about 25-35% of individuals with a PLA and may be helpful to determine a therapy plan.

Because of the wide range of causative organisms (i.e., aerobic gram-negative, *S. aureus*, and anaerobic organisms) empiric antimicrobial treatment needs to be broad. Potential empiric antimicrobial choices include piperacillin-tazobactam, ampicillin-sulbactam, or metronidazole with a third-generation cephalosporin. Depending on local prevalence and degree of suspicion, vancomycin may be added to cover methicillin-resistant *S. aureus*. Therapy should be modified based on culture susceptibilities. Treatment duration is not standardized and should be based on fever resolution, clinical and inflammatory marker improvement, and serial ultrasound monitoring. Many sources recommend completing 4-6 weeks of therapy, with the first 2 weeks administered parentally. Depending on the size and extent of the lesion(s), percutaneous or surgical drainage may be added to obtain samples for cultures and to shorten illness duration. Percutaneous options include single-pass needle or catheter aspiration, or insertion of a continuously draining catheter. In adults, unless there is evidence of rupture or spread, percutaneous drainage should be attempted first for large lesions ( $\geq 5-7$  cm in diameter). Numerous case series of PLA in premature infants described complete resolution with antibiotic therapy alone, and some advocate for this as an initial approach in smaller lesions. Resolution can be monitored by trending inflammatory markers and/or serial imaging.



**Fig. 407.1** CT (A and B) and ultrasound (C) images of a cryptogenic liver abscess in a 16-yr-old male without known risk factors. The lesion was drained percutaneously, and cultures grew multiple anaerobic organisms (*Fusobacterium nucleatum* and *Parvimonas micra*). He was successfully treated with 2 wk of parenteral followed by 4 wk of oral therapy and was followed with serial ultrasounds 5 days (D) and 34 days (E) after drainage. (Courtesy Dr. Alexander Towbin, Cincinnati Children's Hospital, Cincinnati, Ohio.)



**Fig. 407.2** Amebic abscess. A, Sonogram demonstrates a hypoechoic mass in the right lobe of the liver with a more hypoechoic surrounding rim. B, CT scan demonstrates a low-attenuation mass in the right lobe of the liver with a prominent halo. (From Kuhn JP, Slovis TL, Haller JO. Caffrey's Pediatric Diagnostic Imaging, 10th ed. Philadelphia: Mosby, 2004: p. 1473.)

**Amebic liver abscess** (ALA) is the most common extraintestinal manifestation of *Entamoeba histolytica* infection. Although more common in endemic areas, cases can be diagnosed in the United States among travelers to, and immigrants from, endemic areas. Presentation can be delayed by months to years. ALA is more common among adults aged 18–55 years, and males predominate. Amoebic trophozoites invade colonic mucosa and reach the liver through the portal circulation. Patients may not have an associated colitis. Fever, right upper quadrant pain, anorexia, and weight loss are often present. Laboratory evaluation typically reveals a leukocytosis without eosinophilia and increased alkaline phosphatase. Ultrasonography or CT demonstrates the abscess (Fig. 407.2).

Diagnosis of ALA is often confirmed by serum ELISA. Serology is considered reliable in nonendemic areas but can be prone to false negatives early in the infection and cannot distinguish active infection from previous exposure. Testing for *E. histolytica* presence in stool is specific but not very sensitive, and patients with ALA may not have detectable organisms in their stool. Most sensitive and specific among stool assays is polymerase chain reaction (PCR), followed by stool antigen detection. Least reliable is microscopy because *E. histolytica* cannot easily be distinguished microscopically from its clinically benign relatives *Entamoeba dispar* and *Entamoeba moshkovskii*.

Before effective treatment, ALA-associated mortality was high; it has since decreased significantly. Treatment involves 7–10 days of a nitroimidazole (most commonly metronidazole) to kill trophozoites, followed by 7 days of a luminal agent (such as paromomycin) to kill colonic cysts. Patients with large abscesses ( $\geq 5$ –7 cm in diameter) may benefit from percutaneous aspiration in addition to medical therapy.

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## Chapter 408

# Liver Disease Associated with Systemic Disorders

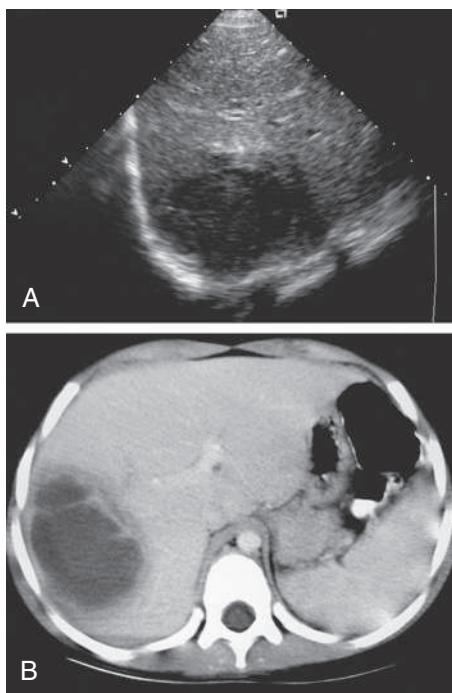
Batul Kaj-Carbaidwala and William F. Balistreri

Liver involvement in systemic illnesses can be the result of the primary pathologic process, secondary to inflammatory or immune responses, or as a complication of therapy.

### INFLAMMATORY BOWEL DISEASE

Hepatobiliary involvement in patients with inflammatory bowel disease (IBD, see Chapter 382) is relatively common; up to 30% of patients will have elevated liver enzymes, and 5% may develop chronic hepatobiliary diseases. Autoimmune diseases (primary sclerosing cholangitis [PSC], autoimmune hepatitis [AIH], PSC-AIH overlap syndrome, and immunoglobulin G4 [IgG4] sclerosing cholangitis) are commonly associated with IBD. Drug-induced liver injury has been associated with both induction and maintenance therapies (thiopurines, methotrexate, 5-ASA, biologics). IBD-related malnutrition can lead to hepatic steatosis and cholelithiasis. Poor intestinal health increases the risk of developing hepatic abscesses secondary to bacterial translocation and systemic infection. Hypercoagulability in IBD can predispose to infarction, Budd-Chiari, and portal venous thrombosis). Figure 408.1 shows a diagnostic approach in IBD patients with abnormal liver tests.

**Primary sclerosing cholangitis** (PSC) is the most common hepatobiliary disease associated with IBD, occurring in 2–8% of adult patients with ulcerative colitis and less often in Crohn disease. Up to 90% of patients with PSC have ulcerative colitis. In children with IBD, PSC typically occurs in the second decade of life, at a median age of 14 years. PSC is characterized by progressive inflammation and fibrosis of intra- and extrahepatic bile ducts, with eventual progression to cirrhosis and end-stage liver disease. Small- and large-duct disease differs in phenotype, with small-duct PSC reported to confer lower mortality and incidence of cholangiocarcinoma and longer transplant-free survival. Concomitant PSC-IBD is a distinct entity with multifactorial pathogenesis, including genetic predisposition, altered intestinal microbiome, and immune-mediated processes. Distinguishing features of PSC-IBD include pancolitis, rectal sparing and backwash ileitis in patients with UC-PSC and extensive colitis in Crohn-PSC. The clinical course is milder but with subclinical persistent intestinal inflammation. Presentation of PSC is typically asymptomatic with elevated liver enzymes (particularly serum alkaline phosphatase and gamma glutamyl transferase) and bilirubin. Ten percent to 15% of adults present with symptoms of anorexia, weight loss, pruritus, fatigue, right upper quadrant pain, and jaundice; intermittent acute cholangitis can also occur. Diagnosis is made with cholangiography demonstrating characteristic multifocal stricturing and dilation of the intra- and extrahepatic bile ducts (referred to as *beading*). Liver biopsy reveals periductal fibrosis and inflammation, fibroobliterative cholangitis, and portal fibrosis. Biopsy is not necessary for diagnosis but can be helpful when imaging findings are not clear (e.g., in small-duct disease) or when overlap syndrome is suspected. There are no approved pharmacologic therapies for PSC. Ursodeoxycholic acid (UDCA), corticosteroids, immunomodulators, and oral antibiotics (such as vancomycin) have been studied, without clear improvement in survival or long-term outcomes. UDCA is widely used in children with PSC; it may improve pruritus and lab parameters; however, it has not been shown to alter the clinical course. Endoscopic intervention (stents, dilatation) for dominant strictures is reserved for patients with symptoms or complications of biliary obstruction. Liver



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## Chapter 408

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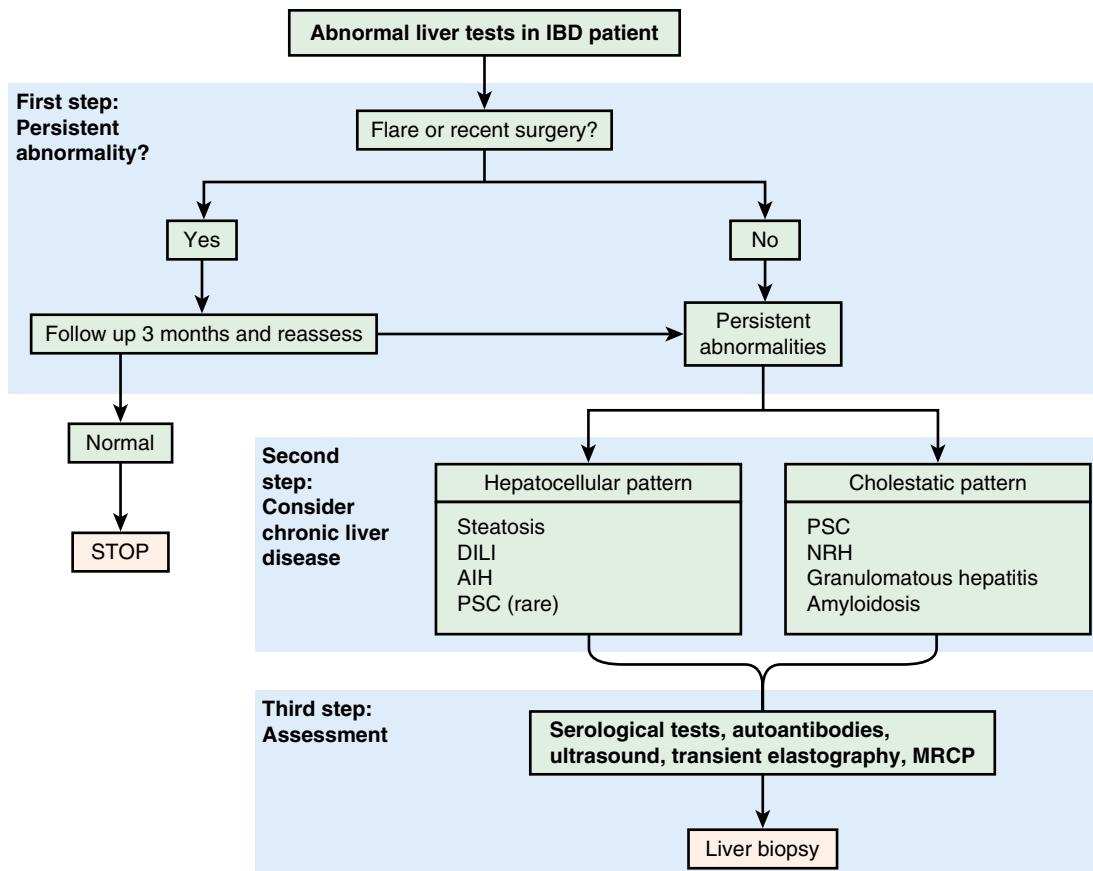
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**Fig. 408.1** Algorithm showing diagnostic approach to elevated liver enzymes in patients with IBD. AIH, Autoimmune hepatitis; DILI, drug induced liver injury; MRCP, magnetic resonance cholangiopancreatography; NRH, nodular regenerative hyperplasia; PSC, primary sclerosing cholangitis. (From Restellini S, Chazouillères O, Frossard JL. Hepatic manifestations of inflammatory bowel diseases. *Liver Int*. 2017;37[4]:475–489. Fig 3)

transplantation remains the only definitive treatment for PSC, with high 5-year survival rates but a relapse rate of ~20% in the allograft. Other management considerations include enteral supplementation to mitigate malnutrition related to chronic liver disease and antibiotic treatment of ascending cholangitis.

PSC is strongly associated with hepatobiliary malignancies (cholangiocarcinoma, hepatocellular carcinoma, gallbladder carcinoma) with a reported incidence varying between 9% and 14% in adults. Concomitant PSC-IBD also confers increased risk of colorectal carcinoma. There are no universal surveillance guidelines for children with PSC-IBD given the rarity of malignancy. In adults, ultrasound or MRCP with or without serum CA 19-9 assessment every 6–12 months are generally recommended.

**PSC-autoimmune hepatitis overlap** is a less common, unique phenotype with clinical and serologic features of AIH, as well as pruritus, cholestasis, histologic bile duct abnormalities, and/or abnormal cholangiography. Prevalence is estimated to be ~2% of children with IBD. Immunosuppressive medication (corticosteroids, azathioprine) is the mainstay of therapy for PSC-AIH overlap syndrome; however, long-term outcomes are not as favorable as in AIH alone. Long-term survival in children with overlap syndrome appears to be similar to those with PSC, with an overall median (50%) survival with native liver of 12.7 years.

### CRITICAL ILLNESS

Mechanisms of liver injury in patients with sepsis/critical illness include hypoxic hepatitis because of ischemia and shock, cholestasis related to altered bile flow, drug-induced hepatocellular damage, and distinct pathologies, such as secondary sclerosing cholangitis. The management of critical illness-associated liver injury involves prompt recognition, early initiation of antimicrobials, and otherwise supportive care.

**Bacterial sepsis** should be excluded in any critically ill patient who develops cholestasis in the absence of markedly elevated serum aminotransferase or alkaline phosphatase (ALP) levels, even when other signs of infection are not evident. Gram-negative bacteremia is most common in these patients, in particular *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Lipopolysaccharides, bacterial endotoxins, and proinflammatory cytokines are thought to produce cholestatic liver injury either by impairing bile formation in hepatocytes or altering bile flow via disruption of canalicular transporters. Liver biopsy shows intrahepatic cholestasis with little or no hepatocyte necrosis. Kupffer cell hyperplasia and an increase in inflammatory cells are also common.

**Secondary sclerosing cholangitis** is a distinct entity in critical illness characterized by inflammation, fibrosis, and destruction of the bile ducts that can quickly progress to cirrhosis. It is thought to occur because of the vulnerability of biliary epithelium to hypoxia, leading to apoptosis or necrosis. Major risk factors include severe systemic hypotension, trauma, acute respiratory distress syndrome, and systemic inflammatory response syndrome.

### CELIAC DISEASE

Celiac disease (see Chapter 384) is an autoimmune condition triggered by ingestion of gluten. Liver involvement in patients with celiac disease presents either as mild to moderate hepatitis with or without prolonged prothrombin time, or secondary to associated autoimmune disorders. In the former, histology demonstrates mild periportal and lobular inflammation. **Celiac hepatitis** refers to liver injury in patients with confirmed celiac disease in whom serum biochemistries and histology normalize after establishment of a gluten-free diet. The exact mechanism remains unclear; it has been proposed that increased intestinal permeability may allow toxins, cytokines, and antigens to reach the liver and produce liver injury through release of proinflammatory

**Table 408.1** Host- and Parenteral Nutrition–Related Factors in Development of Intestinal Failure–Associated Liver Disease

FACTORS IN THE DEVELOPMENT OF INTESTINAL FAILURE–ASSOCIATED LIVER DISEASE		
HOST	TOTAL PARENTERAL NUTRITION	
<ul style="list-style-type: none"> <li>Incompletely expressed enzyme activity</li> <li>Inadequate bile salt uptake and excretion</li> <li>Liver injury from endotoxins, inflammatory cytokines</li> <li>Impaired biliary excretion</li> <li>Prolonged parenteral nutrition (PN) exposure</li> <li>SBBO, dilated bowel, mucosal atrophy → increased bacterial translocation → recurrent sepsis / direct endotoxin mediated liver injury</li> <li>Impaired enterohepatic circulation</li> <li>Decreased cholecystokinin release → biliary stasis</li> <li>Extensive small bowel resection → more severe hepatic fibrosis</li> </ul>	EXCESS MACRONUTRIENTS	<ul style="list-style-type: none"> <li>Glucose → Hyperinsulinism → Steatosis</li> <li>Lipid minimization strategies may require additional dextrose calories</li> </ul>
	AMINO ACID DEFICIENCY	<ul style="list-style-type: none"> <li>Decreased taurine conjugation of bile acids</li> <li>Choline deficiency worsens steatosis</li> </ul>
	LIPIDS	<ul style="list-style-type: none"> <li>Hepatotoxic phytosterols in soy-based lipids</li> <li>Omega-6 LCPUFA is proinflammatory</li> <li>Antioxidant imbalance</li> </ul>
	MINERALS / TRACE ELEMENTS	<ul style="list-style-type: none"> <li>Mg, Cu, Al accumulate in cholestasis causing hepatocellular injury</li> </ul>

SBBO, small bowel bacterial overgrowth; LCPUFA, long-chain polyunsaturated fatty acids; Mg, manganese; Cu, copper; Al, aluminum.

mediators. **Autoimmune liver diseases** (AIH, primary sclerosing cholangitis) have been associated with celiac disease; these are best treated with combination of gluten-free diet and immunosuppressive medications. Children with persistent, unexplained elevation of serum aminotransferase levels should be evaluated for celiac disease, given up to 9% reported incidence of celiac disease in this setting.

### CARDIAC DISEASE

Cardio-hepatic interactions are complex and bidirectional; congestive heart failure (see Chapter 491), congenital cyanotic heart disease (see Chapters 475–480) and acute ischemic shock can all lead to liver injury. There exist distinct cardiac disorders associated with cirrhosis and end-stage liver disease. Various mechanisms are thought to contribute to liver injury in cardiac disease: (1) elevated central venous pressure transmitted to hepatic veins and ultimately hepatocytes results in centrilobular hepatocellular atrophy (congestive hepatopathy); and (2) decreased cardiac output leads to decreased hepatic arterial blood flow, causing centrilobular hepatocellular necrosis due to ischemia. Congenital cyanotic heart disease (hypoplastic left heart syndrome and coarctation of the aorta) are occasionally associated with hepatic necrosis or acute liver failure. Patients with hepatic manifestations of cardiac disease may present with lactic acidosis, elevated aminotransferase levels, cholestasis, prolonged prothrombin time, hyperammonemia, and hypoglycemia because of impaired hepatocellular metabolism. Jaundice, tender hepatomegaly, and, in some cases, ascites and splenomegaly can also occur.

**Acute cardiogenic liver injury** (shock liver or ischemic hepatitis) occurs after circulatory disturbances and can cause a dramatic rise in serum aminotransferase levels to >1,000 units/mL. These rapidly return to normal when perfusion and cardiac function improve, with delayed-onset hyperbilirubinemia that can persist for days to weeks.

**Fontan-associated liver disease** (FALD) is a distinct clinical entity that occurs in patients who have undergone surgical palliation for single ventricle heart disease. Chronically elevated systemic venous pressure after the Fontan procedure causes venous congestion and impaired hepatic blood flow. Patients almost invariably develop progressive hepatic fibrosis, which can lead to cirrhosis, portal hypertension, and hepatocellular carcinoma (HCC). Annual risk of HCC in FALD-cirrhosis is reported as 1.5–5%; cases have been reported of HCC occurring in early adolescence.

The aim of therapy in all causes of cardiac-associated liver disease is to improve cardiac output, reduce systemic venous pressures, and correct hypoxemia. Even mild liver disease may increase mortality after cardiac surgery, with poorer outcomes in patients with progressive liver disease. Combined heart-liver transplant should be considered in Fontan patients with evidence of cirrhosis, especially if decompensated.

### INTESTINAL FAILURE ASSOCIATED LIVER DISEASE

Intestinal failure–associated liver disease (IFALD; previously referred to as parenteral nutrition–associated liver disease) in children is characterized by progressive cholestasis, biliary cirrhosis, and steatohepatitis (see Chapters 385.6 and 386). Advanced IFALD is one of the most important factors contributing to mortality of children on long-term parenteral nutrition (PN) and is a major indication for intestinal and multivisceral transplantation. Host- and PN-related factors contribute to its development (Table 408.1). The pathogenesis of IFALD is multifactorial; sepsis, bacterial translocation, excess caloric intake, high amounts of protein, fat, or carbohydrate, nutrient deficiencies, and toxicities related to components such as manganese, aluminum, and copper can all contribute to hepatic injury. The type (soy-based), volume, and frequency of lipid administered are important risk factors. Prolonged enteral fasting compromises mucosal integrity and increases bacterial mucosal translocation. Fasting also decreases release of cholecystokinin, which leads to biliary stasis, cholestasis, and formation of biliary sludge and gallstones, which can exacerbate hepatic dysfunction. Sepsis, especially gram-negative bacteremia, can also exacerbate liver damage. Clinical manifestations range from mildly elevated serum aminotransferase levels to severe cholestatic liver injury, cirrhosis with portal hypertension and, rarely, hepatocellular carcinoma. Histologic findings include macrovesicular steatosis, canalicular cholestasis, and periportal inflammation.

In addition to cholestasis, biliary complications of intravenous (IV) nutrition include cholelithiasis and the development of biliary sludge, associated with thick, inspissated gallbladder contents. Hepatic steatosis or elevated serum aminotransferase levels can also occur in the absence of cholestasis, particularly in older children. This is generally mild and resolves after total PN (TPN) is discontinued. Serum bilirubin and bile acid levels remain within the normal range. Other causes of liver disease should also be considered, especially if evidence of hepatic dysfunction persists despite weaning from TPN and initiating enteral feeds. If serum ALP or aminotransferase levels remain elevated, liver biopsy may be necessary for accurate diagnosis.

Strategies in the management of IFALD aim to prevent or reverse the disease (Table 408.2). General goals include early initiation of enteral nutrition, minimization of fasting, and advancement of enteral feeds as tolerated. Improved TPN solutions that meet the specific needs of neonates can prevent deficiencies and toxicities. Introducing alternate sources of IV lipid, including fish oil and olive oil to provide more omega-3 fatty acids (and less of the harmful omega-6 fatty acids), have been beneficial. Ursodeoxycholic acid is widely used and may be beneficial in improving bile flow.

### CYSTIC FIBROSIS

Cystic fibrosis (CF; see Chapter 454) is an autosomal recessive genetic disorder characterized by impaired chloride transport

<b>Table 408.2</b> Evidence-Based IFALD Prevention and Treatment Strategies for Children on TPN	
PREVENTION	EXAMPLES
Advancing enteral nutrition	Prokinetic and anti-diarrheal agents to improve enteral tolerance
	Medical induction of intestinal adaptation, i.e., glucagon-like peptide 2 (GLP-2) agonist
	Surgical lengthening procedures; serial transverse enteroplasty (STEP), Bianchi
Modifying lipid emulsions	**Lipid dose reduction
	*Use of combined lipid emulsion (soybean oil, medium chain triglyceride, olive oil, and fish oil)
Cycling TPN	Non-continuous TPN, with time off in a 24-hr period
Microbiome therapies	Addition of various pre- or probiotics
Prevention of central line infections	Antibiotic treatment to prevent bacterial translocation and small bowel bacterial overgrowth
	Use of ethanol locks
Prevention of cholestasis	***Oral choleretic agent: ursodeoxycholic acid
	**Trophic (small volume) feedings
TREATMENT	
Modifying lipid emulsions	Use of combined lipid emulsion (soybean oil, medium chain triglyceride, olive oil, and fish oil)
	**Use of fish oil emulsion
Organ transplantation	Consider isolated intestinal or liver-intestinal transplantation

\*Possibly effective

\*\*Probably effective

\*\*\*Proven effective

Adapted from Lee WS, Chew KS, Ng RT, et al. Intestinal failure-associated liver disease (IFALD): insights into pathogenesis and advances in management. *Hepatol Int.* 2020;14(3):305–316.

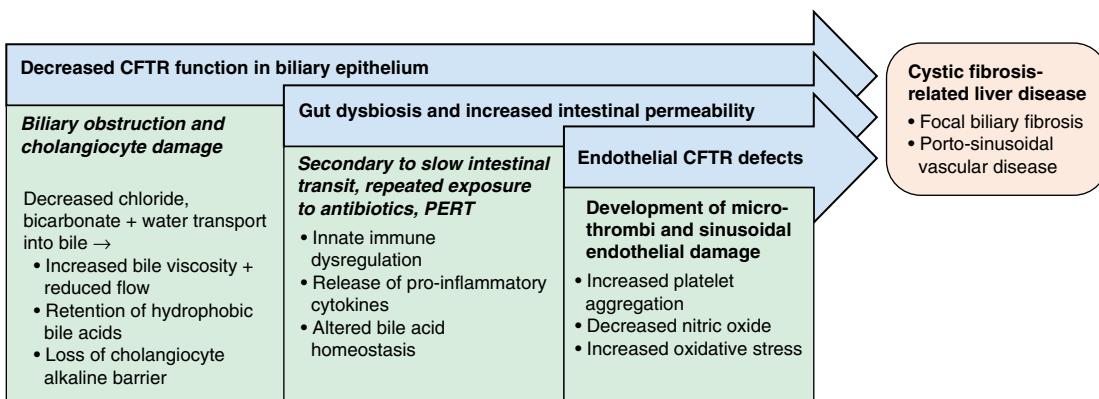
across the apical membranes of epithelial cells in numerous organs. Up to 40% of patients with CF develop some form of hepatobiliary disease, usually in the first 2 decades of life. Hepatobiliary complications account for approximately 2.5% of overall mortality in patients with CF, with development of portal hypertension being a key prognostic factor.

Manifestations range from liver enzyme elevations to cirrhosis with portal hypertension. This can be related to recurrent infections, drug hepatotoxicity, steatosis (because of diabetes, chronic diarrhea, pancreatic insufficiency, malnutrition), cardiopulmonary disease-associated hepatic congestion, biliary disease (neonatal cholestasis, sclerosing cholangitis, micro-gallbladder, gallbladder dysfunction or pigmentary cholelithiasis) and the distinct clinical entity of cystic fibrosis-related liver disease (CFLD); the latter includes two main, sometimes concomitant, entities: primary focal biliary fibrosis and porto-sinusoidal vascular disease. The precise pathogenesis of CFLD remains incompletely understood but is likely multifactorial (Fig. 408.2). Genetic factors associated with increased risk of CFLD include the presence of two abnormal *CFTR* alleles without residual function or presence of *SERPINA1* Z allele. Clinical risk factors include older age, pancreatic insufficiency, male sex, and a history of meconium ileus.

**Focal biliary fibrosis** is the pathognomonic liver lesion in patients with CF, characterized by periductal inflammation, bile duct proliferation, and increased fibrosis within focal portal tracts. Most patients are asymptomatic. Liver stiffness measurements may aid in differentiating focal fibrosis from steatosis. Gradual progression to multi-lobular cirrhosis can occur and result in portal hypertension and end-stage liver disease in 1–8% of patients.

**Porto-sinusoidal vascular disease** occurs more frequently in adults than in children and presents as noncirrhotic portal hypertension. Features that may suggest this diagnosis include evidence of portal hypertension without hepatic parenchymal changes, marked splenomegaly, and development of porto-systemic shunts. A macronodular liver, likely related to regenerative nodular hyperplasia, is a common finding. Liver stiffness measures, however, are typically lower than with cirrhotic portal hypertension, which can aid in differentiation. Typical histologic features include obliterative portal venopathy, nodular regenerative hyperplasia, arterialization, periportal vessels, aberrant portal vessels, irregular portal tracts with centrilobular vein distribution, and sinusoidal dilatation.

Management of CFLD is primarily supportive and targeted at symptoms, including through optimization of nutrition and management of portal hypertensive complications. Treatment with oral UDCA (10–15 mg/kg/day) is widespread, but the survival benefit and effect on



**Fig. 408.2** Proposed mechanisms in the development of cystic fibrosis-related liver disease. PERT, Pancreatic enzyme replacement therapy. (Data from Dana J, Debray D, Beaufrère A, et al. Cystic fibrosis-related liver disease: clinical presentations, diagnostic and monitoring approaches in the era of *CFTR* modulator therapies. *J Hepatol.* 2021;S0168-8278:02115–2.)

clinical course remains controversial. Surgical porto-systemic shunts (distal splenorenal, portacaval) are useful in patients with refractory portal hypertensive complications. Liver transplantation may be offered in severe cases of parenchymal disease with acceptable long-term outcomes with combined liver-lung transplantation being offered at some centers. *CFTR* modulator therapies have shifted the paradigm of pulmonary and nutritional management in CF; however, their role in preventing or reversing CFLD remains unclear. All currently approved modulators may cause elevated liver enzymes; however, small studies have yielded promising results in improving CFLD.

### BONE MARROW TRANSPLANTATION

Liver disease after hematopoietic stem cell transplantation (SCT, see Chapters 177–181) occurs in up to 90% of patients in the first 100 days. Etiologies are listed in Table 408.3. Graft-versus-host disease (GVHD), drug toxicity, and sepsis are the most common causes of liver dysfunction after allogeneic SCT. Diagnosis is often challenging because of the coexistence of multiple risk factors. Clinical course, symptoms and signs, liver biochemistries, and viral serology are helpful in making the correct diagnosis. Percutaneous liver biopsy may be necessary; histology can show extensive bile duct injury in GVHD, viral inclusions in cytomegalovirus disease, or the characteristic endothelial lesion in sinusoidal obstruction syndrome (SOS). Prompt and accurate diagnosis is key because treatment for GVHD with corticosteroids may worsen infectious hepatitis, and delayed treatment in SOS can lead to poorer outcomes. Management of liver disease post-HSCT is mainly supportive. Oral UDCA can decrease the incidence of severe liver disease in patients undergoing SCT and has been shown to reduce the incidence of SOS and transplant-related mortality in adults.

**Graft-versus-host disease** (see Chapter 179) results from donor immunocompetent cells triggering an inflammatory response in recipient organs. Acute GVHD comprises a triad of hepatitis, dermatitis, and enteritis, and usually occurs within 100 days of hematopoietic SCT (HSCT; typically at time of engraftment, 14–21 days after HSCT). Serum aminotransferase and bilirubin levels are markedly elevated. Chronic GVHD occurs later, with liver involvement (slowly progressive cholestasis) in up to 80%. Histologic features of GVHD include loss of intralobular bile ducts, endothelial injury of hepatic and portal venules, and hepatocellular necrosis. Treatment of GVHD varies depending on organ system involved (e.g., skin, intestine) and acute vs chronic presentation. Therapy comprises systemic corticosteroids, optimization of maintenance immunosuppression, and newer agents like ruxolitinib (JAK inhibitor), and it is recommended that management occur in collaboration with the hematopoietic stem cell transplant team. Oral UDCA has also been shown to be beneficial, particularly in chronic GVHD.

**Sinusoidal obstruction syndrome** (SOS; hepatic venoocclusive disease) usually develops in the first 21 days after SCT. The incidence ranges from 5–39% in pediatric patients, with reported mortality rates ranging from 0–47%. Risk factors for SOS are listed in Table 408.4. Pathogenesis is thought to be related to sinusoidal endothelial cell activation and hepatocyte damage from accumulation of toxic metabolites because of conditioning regimens. Patients typically present with jaundice, painful hepatomegaly, rapid weight gain, and ascites. Severe SOS has high morbidity and mortality, with multisystem organ failure. Diagnostic criteria for SOS include presence of hepatomegaly, right upper quadrant pain, ascites, weight gain >5% from baseline, and bilirubin >2 mg/dL before day 21 post HSCT. Exclusion of other causes of liver disease is also necessary. Liver biopsy is generally not needed for diagnosis, and indeed can be contraindicated because of the bleeding risk. However, the classic histologic features of sinusoidal dilatation, erythrocyte extravasation in space of Disse, collagen deposition in sinusoids and small hepatic veins and centrilobular necrosis, are diagnostic.

Treatment of SOS is with defibrotide, a mixture of oligonucleotides that has antithrombotic and thrombolytic properties. There is a survival benefit of defibrotide in both children and adults. Few significant adverse events are noted; bleeding and infection are the most common adverse effects seen in patients with severe SOS.

**Table 408.3** Etiologies of Liver Disease After Hematopoietic Stem Cell Transplantation (HSCT)

Sepsis (viral, bacterial, fungal)
Toxicity (chemotherapy, PN, radiation)
Sinusoidal obstruction syndrome
Acute and chronic GVHD
Hemosiderosis / iron overload
Cholecystitis
Extrahepatic biliary obstruction

PN, Parenteral nutrition; GVHD, graft-versus-host disease.

**Table 408.4** Risk Factors for the Development of Sinusoidal Obstruction Syndrome (SOS) After Hematopoietic Stem Cell Transplantation (HSCT)

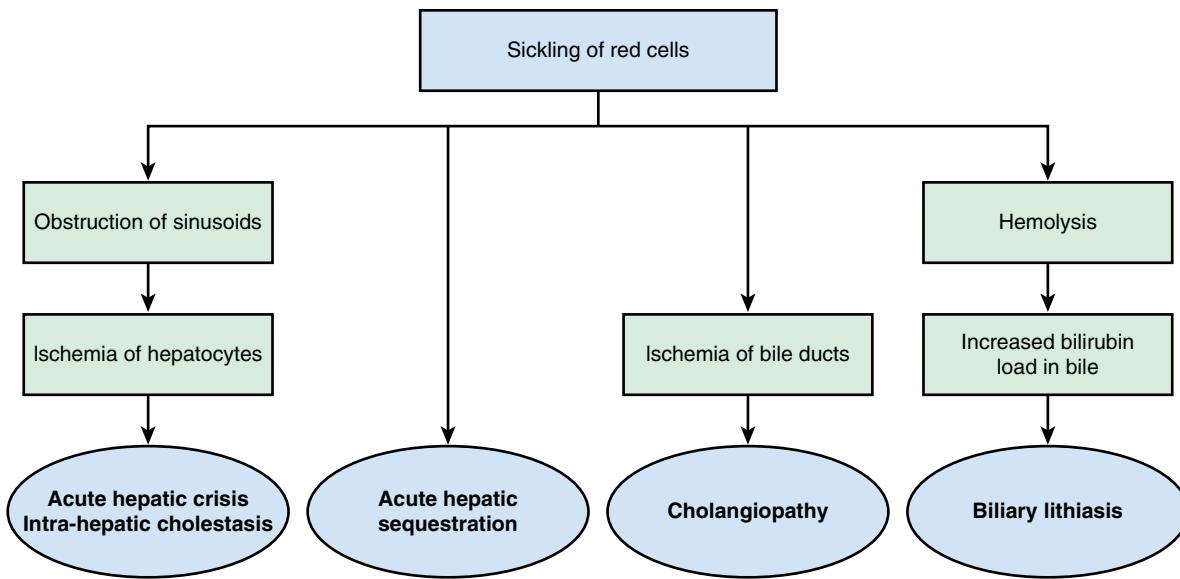
PATIENT-RELATED FACTORS	HSCT-RELATED FACTORS
Younger age	Allogenic transplant
Hematologic malignancy	Bone marrow-derived stem cells
Disease relapse state	Fever during conditioning therapy
Preexisting liver disease	Second transplant
Previous liver radiation therapy	Myeloablative conditioning
Chronic viral hepatitis	Drug hepatotoxicity
Iron overload	

### HEMOGLOBINOPATHIES

Hepatic dysfunction in patients with sickle cell anemia (see Chapter 511.1) or thalassemia (see Chapter 511.10) result from acute or chronic viral hepatitis, chronic iron overload, venous thrombosis, biliary obstruction (cholestasis, cholelithiasis), or acute hepatic crisis (sequestration, ischemic necrosis). Cholelithiasis and chronic iron overload (because of frequent blood transfusions) are common and treatable. Oral chelation therapy (commonly with deferasirox) in iron overload has been demonstrated to reverse or stabilize hepatic fibrosis in patients with thalassemia. Surgical and endoscopic management of gallstones may be necessary, especially in patients with choledocholithiasis.

### Sickle Cell Disease

The pathogenesis of hepatobiliary manifestations in sickle cell disease (SCD) is shown in Figure 408.3. **Hepatic sickle cell crisis** or “sickle hepatopathy” occurs in ~10% of patients, when sickled cells obstruct small vessels and sinusoids. This leads to ischemia, inflammation, endothelial dysfunction, and, when flow is restored, reperfusion injury, manifest as intense RUQ pain and tenderness, fever, leukocytosis, and jaundice. Bilirubin levels may be markedly elevated; serum ALP levels may be only moderately elevated. Prompt diagnosis is key to allow early institution of therapy, although this can be challenging because of overlapping symptoms and signs with other hepatobiliary disorders detailed above. In general, hepatic sickle cell crisis is self-limited and symptoms resolve within 1–3 weeks. However, along the spectrum of sickle crises is the distinct entity of **sickle cell intrahepatic cholestasis** (SCIC), thought to be caused by the trapping of sickle cells in sinusoids causing localized hypoxia, hepatocyte ballooning and intra-canicular cholestasis. This too manifests as hepatomegaly, abdominal pain, hyperbilirubinemia, and coagulopathy but can progress to acute liver failure, multiorgan dysfunction and death. Management of hepatic crises involves exclusion of biliary complications, supportive care, and exchange transfusion if there is evidence of liver synthetic dysfunction or (prolonged prothrombin time) or clinical concern for SCIC. Liver transplantation in SCD (in setting of cirrhosis, end-stage liver disease, and severe SCIC) remains controversial. Although there are some positive experiences reported in adults (with acceptable 5-year survival rates), there remain limited data in children and many clinical challenges. Preoperative optimization in tertiary centers involving



**Fig. 408.3** Pathogenesis of liver disease in sickle cell disease. (From Lacaille F, Allali S, de Montalembert M. The liver in sickle cell disease. *J Pediatr Gastroenterol Nutr.* 2021;72:5–10. Fig 1.)

transplant hepatology and hematology teams is paramount, with attention to transfusion parameters, potential drug toxicity, nephroprotective measures, and intraoperative management to prevent acute crises. Of course, hepatic crises may recur in the allograft, with potential for allograft dysfunction and loss.

## HISTIOCYTIC DISORDERS

**Langerhans cell histiocytosis** (LCH, see Chapter 556.1) is a rare disorder characterized by proliferation and accumulation of Langerhans cells (dendritic antigen-presenting histiocytes). It can affect single or multiple organs, with common sites being bone, skin, pituitary gland, spleen, lungs, and lymph nodes. In the liver, histiocytosis can cause hepatocellular dysfunction and/or a mass lesion. Liver involvement in LCH should be suspected in patients with hepatomegaly, ascites, and/or biochemical evidence of liver injury (elevated liver enzymes, bilirubin, or prothrombin time). Liver biopsy demonstrates Langerhans cell infiltrates (identified with positive immunohistochemical staining for CD1a and S100 antigen). Hepatic LCH carries a high mortality rate (30–50%, compared to <10% in patients without liver involvement). Three-year survival with liver involvement is >96% compared to 52% with liver involvement. In children, LCH is an important cause of secondary sclerosing cholangitis, which can lead to chronic liver disease and need for liver transplantation.

Treatment approaches in LCH vary by clinical severity; those with single-organ involvement and mild disease may be observed or offered immunomodulator monotherapy (oral 6 mercaptourine, methotrexate, and others). Those with hepatic or multiorgan involvement may need to undergo systemic chemotherapy.

**Hemophagocytic lymphohistiocytosis** (HLH) (see Chapter 556.2) is a multiorgan, severe, and potentially fatal inflammatory process from excessive activation of lymphocytes and macrophages. Hepatobiliary manifestations include elevated aminotransferases (50–100%), cholestasis (50%), and hepatomegaly (90%). Acute liver failure may also occur. Liver biopsy shows portal inflammatory infiltrates, hemophagocytosis, and Kupffer cell hyperplasia but is not routinely obtained because of coagulopathy. The mainstay of treatment of HLH involves etoposide-based chemotherapy and bone marrow transplantation.

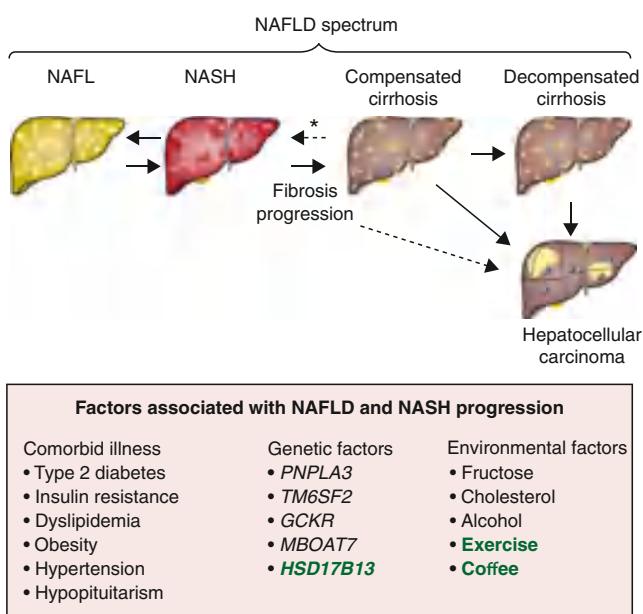
## 408.1 Nonalcoholic Fatty Liver Disease

Sarah H. Orkin and William F. Balistreri

The term **nonalcoholic fatty liver disease** (NAFLD) spans a wide spectrum of histologic liver disease, from nonalcoholic fatty liver (NAFL; steatosis without inflammation) to nonalcoholic steatohepatitis (NASH; steatosis with lobular inflammation); the latter may then progress to fibrosis and end-stage liver disease (ESLD) requiring liver transplantation (Figs. 408.4 and 408.5). In fact, NASH currently is the fastest rising indication for liver transplantation in young adults. The burden of pediatric NAFLD is large; it is the most common cause of chronic liver disease in children and currently affects 1 in 10 youth in the general population, and 1 in 3 youth with obesity. Obesity has contributed to an increased prevalence of NAFLD in children; the severity of obesity is associated with more severe liver disease.

Known risk factors for pediatric NAFLD include male sex, Hispanic ethnicity, genetic predisposition (see Fig. 408.4), obesity, insulin resistance, obstructive sleep apnea, celiac disease, and psychotropic drug use (see Fig. 408.4). There is a lower prevalence of NAFLD in Black children. Autopsy data suggest that 10% of all children, and 38% of children with obesity age 2–19 years old have histologically confirmed NAFLD. Up to 25% of affected children may already have advanced fibrosis at the time of first liver biopsy. There are currently no available clinical, biochemical, or radiographic variables to help predict which children will have severe histologic disease on liver biopsy or who will be at risk of rapid progression. Recommendations in adults are to screen at-risk patients (see Fig. 408.4) with liver function tests as well as additional testing to exclude other diagnoses (chronic hepatitis). If there is evidence of liver disease, hepatic ultrasonography and noninvasive assessment of liver stiffness are indicated (see Fig. 408.5D,E).

Most patients with NAFLD are asymptomatic. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Clinical Practice Guideline recommend assessing the serum alanine aminotransferase (ALT) level as a screening tool for children starting between 9–11 years of age who are either obese (body mass index [BMI]  $\geq 95\text{th}\%$ ) or overweight (BMI  $\geq 85\text{th}\%$  and  $< 95\text{th}\%$  with additional metabolic risk factors). In the United States, sex-specific cut-offs for serum ALT values have been determined to be 22 mg/dL in females and 26 mg/dL in males, and values persistently greater than



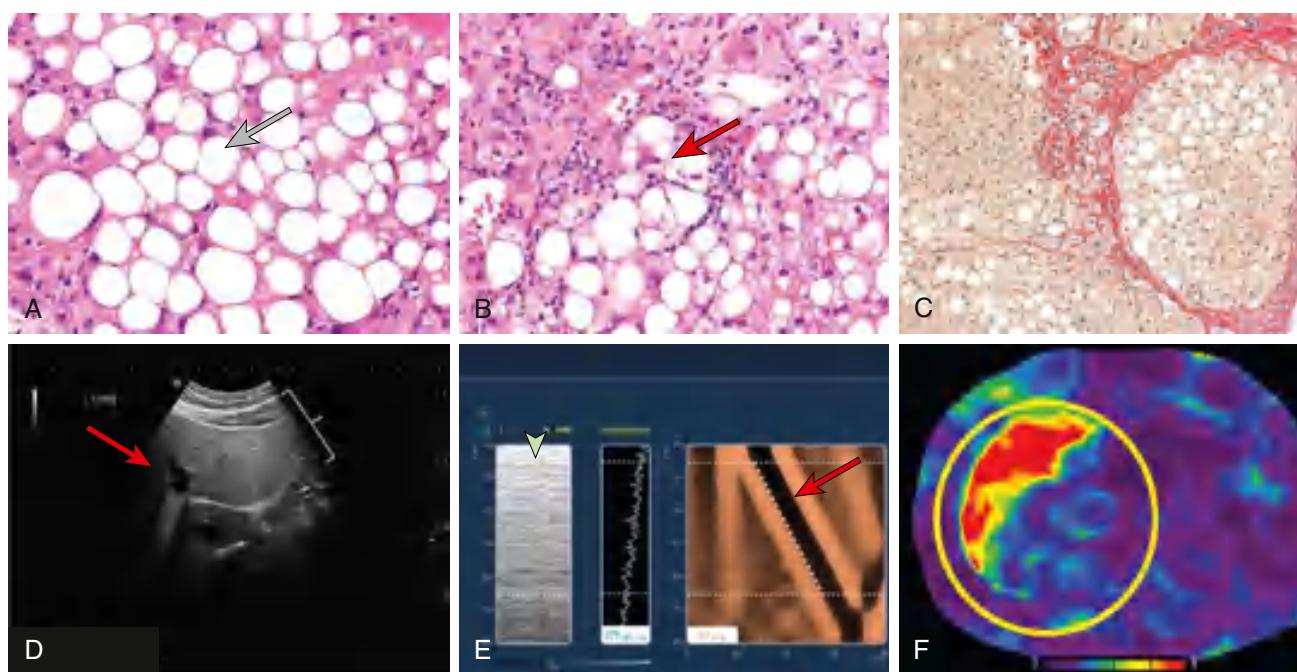
**Fig. 408.4** Spectrum of NAFLD. Factors in black type have an established association with NAFLD and NASH progression (broadly classified into comorbid illness, genetic factors, and environmental factors). **Green type indicates a protective factor.** NAFL, Nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis. \*Fibrosis regression. (From Powell EE, Wong VWS, Rinella M. Non-alcoholic fatty liver disease. Lancet. 2021; 397:2212–2222. Fig. 2.)

two times the sex-specific upper limit of normal, in the absence of any other identified etiology for liver disease is generally regarded as presumed NAFLD. Most children presenting with obesity and elevated liver enzymes and presumed or confirmed NAFLD will have a negative workup for any alternative etiology for liver disease. Although imaging modalities such as ultrasonography or magnetic resonance imaging with proton-density fat fraction and magnetic resonance elastography (MRI-PDFF /MRE) can be used to evaluate the degree of steatosis and fibrosis by using liver stiffness on MRE as a surrogate for fibrosis, the gold standard for diagnosis of NAFLD is liver biopsy examination.

Histologically, NAFLD is diagnosed when steatosis involves >5% of hepatocytes (see Fig. 408.5). Other pertinent histologic characteristics include the presence and severity of lobular inflammation, cellular ballooning, and fibrosis (graded 0-4). The NASH Clinical Research Network has developed a validated tool for histologic assessment. Unlike adults, NASH in children manifest two distinct histologic types: **Type 1 NASH** resembles adult histologic findings with steatosis and balloon degeneration of hepatocytes and/or periportal fibrosis while **Type 2 NASH** includes steatosis and portal inflammation.

During evaluation other causes of steatosis should be kept in mind. **Lysosomal acid lipase deficiency (LAL-D)**, an autosomal recessive disorder due to pathogenic variants in *LIPA* gene, may result in hepatic steatosis. However, in contrast to NAFLD, patients with LAL-D usually demonstrate microvesicular or mixed micro- and macrovesicular steatosis, and not macrovesicular changes alone.

Children diagnosed with NAFLD should be screened for celiac disease plus comorbid conditions, including diabetes, hypertension,



**Fig. 408.5** Histologic and radiologic assessment of nonalcoholic fatty liver disease. A, Nonalcoholic fatty liver is characterized by macrovesicular steatosis with no or little necroinflammation. Large round nonstaining areas represent lipid droplets in hepatocytes (arrow; hematoxylin and eosin stain; magnification  $\times 40$ ). B, Apart from fat accumulation, nonalcoholic steatohepatitis (NASH) is characterized by the presence of lobular inflammation and hepatocyte ballooning. At the center of the image is a ballooned hepatocyte surrounded by inflammatory cells (arrow; hematoxylin and eosin stain; magnification  $\times 40$ ). C, As disease progresses, accumulating liver fibrosis will eventually result in cirrhosis. On the right of this image is a cirrhotic nodule surrounded by thick fibrous tissue. In some cases, steatosis and necroinflammation might reduce or disappear as the disease progresses to cirrhosis, a condition referred to as burned-out NASH (Sirius red; magnification  $\times 10$ ). D, Ultrasonography, the most common method to diagnose fatty liver, characterized by bright liver echotexture (bracket) and blurring of deeper structures (arrow). E, Vibration-controlled transient elastography, a point-of-care measurement of liver stiffness for the estimation of fibrosis that can also estimate hepatic steatosis using the controlled attenuation parameter. The machine is equipped with an M-mode ultrasound for the localization of liver parenchyma (arrowhead). The elastogram (arrow) represents the measurement of liver stiffness. A steeper slope indicates that the shear-wave velocity is higher, and the liver is stiffer. F, Magnetic resonance elastography of a patient with NASH cirrhosis, currently one of the most accurate noninvasive tests of liver fibrosis, with the color scheme reflecting stiffness in different parts of the liver. Red shows areas with greater stiffness (circle). (From Powell EE, Wong VWS, Rinella M. Non-alcoholic fatty liver disease. Lancet. 2021;397:2212–2222. Fig. 1.)

**Table 408.5** Potential Use of Off-Label Therapy for Nonalcoholic Steatohepatitis in Adults

	<b>EFFECTS ON THE LIVER</b>	<b>QUALITY OF EVIDENCE</b>	<b>OTHER BENEFITS</b>	<b>KEY ADVERSE EVENTS</b>	<b>CONTRAINdications AND CAUTIONS</b>
Pioglitazone	Improves hepatic steatosis and necroinflammation and can improve fibrosis	Several small* to moderate† phase 2 randomized controlled trials	Improves insulin sensitivity and diabetic control	Weight gain, fluid retention, bone loss, and might increase bladder cancer	Contraindicated in patients with New York Heart Association (NYHA) class III or IV heart failure; maximum dose 15 mg if used in combination with gemfibrozil or other strong CYP2C8 inhibitors
Vitamin E	Improves hepatic steatosis and necroinflammation; might prevent liver decompensation and mortality in patients with advanced liver fibrosis	Several small* to moderate† randomized controlled trials; data on clinical outcomes based on a retrospective cohort study with propensity score matching	Neutral metabolic effects	A meta-analysis suggests a small increase in overall mortality at high doses; might increase risk of bleeding, prostate cancer, heart failure, and hemorrhagic stroke	Caution in patients with high cardiovascular risk and those at high risk of bleeding
GLP-1 agonists‡	Improves hepatic steatosis and necroinflammation	Several small* to moderate† randomized controlled trials	Improves diabetic control, reduces major adverse cardiovascular events and weight	Nausea, vomiting, dyspepsia, diarrhea, and constipation	Discontinue GLP-1 agonists immediately in case of acute pancreatitis; might cause acute kidney injury rarely; semaglutide might increase diabetic retinopathy complications
SGLT2 inhibitors§	Improves hepatic steatosis, necroinflammation, and liver enzymes	Several small* randomized controlled trials with noninvasive tests; two small* uncontrolled paired liver biopsy studies	Improves diabetic control; modest weight reduction; might have renoprotective benefits; canagliflozin and empagliflozin reduce major adverse cardiovascular events	Genitourinary infection, acute kidney injury, and euglycemic diabetic ketoacidosis; might increase the risk of fractures and limb amputations	Contraindicated if estimated glomerular filtration rate is less than 45 mL/min per 1.73 m <sup>2</sup>

\*Small was defined as less than 50 participants in the active group.

†Moderate was defined as 50–100 participants in the active group.

‡For example, liraglutide and semaglutide.

§For example, canagliflozin, dapagliflozin, and empagliflozin.

From Powell EE, Wong VWS, Rinella M. Non-alcoholic fatty liver disease. *Lancet*. 2021;397:2212–2222.

dyslipidemia, and obstructive sleep apnea, and should be followed clinically at least annually. Counseling against use of alcohol should be provided, as well as minimization of other potentially hepatotoxic drugs, when medically feasible. Prior vaccination against hepatitis A and B should be verified.

There are no approved medical therapies for treatment of pediatric NAFLD. Thus the current management requires lifestyle modification, specifically diet and physical activity changes targeted at weight reduction. A key dietary change includes removal or reduction of sugar sweetened beverages because fructose can be taken up in an insulin-independent fashion and is a prime contributor to hepatic inflammation and steatosis.

Many studies have investigated therapeutic options for treatment of pediatric NAFLD. Vitamin E has been shown to improve balloon degeneration in a subset of children with NASH. Other potential therapeutic options being investigated include thiazolidinediones (pioglitazone), glucagon-like peptide 1 receptor agonists (GLP-1 agonists), and sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors) as well as bariatric surgery for obesity (Table 408.5). Furthermore, emerging data on the role of the gut microbiome in the pathogenesis of NAFLD has positioned the gut flora as a suggested therapeutic target.

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## Chapter 409

# Mitochondrial Hepatopathies

Sindhu Pandurangi and William F. Balistreri

A wide variety of mitochondrial disorders are associated with liver disease. Hepatocytes contain a high density of mitochondria because the liver, with its biosynthetic and detoxifying functions, is highly dependent on adenosine triphosphate. Defects in mitochondrial function can lead to impaired oxidative phosphorylation, increased generation of reactive oxygen species, impairment of other metabolic pathways, and activation of mechanisms of cellular death.

Mitochondrial disorders can be divided into primary, in which the mitochondrial defect is the primary cause of the disorder, and secondary, in which mitochondrial function is affected by exogenous injury or a genetic variant that affects nonmitochondrial proteins (see Chapter 107.4). Primary mitochondrial disorders can be caused by pathogenic variants affecting mitochondrial DNA (mtDNA) or by nuclear genes that encode mitochondrial proteins or cofactors (Table 409.1; see also Chapter 404). Specific patterns may be noted (Table 409.2). Secondary mitochondrial disorders include diseases with an uncertain etiology, such as Reye syndrome; disorders caused by endogenous or exogenous toxins, drugs, or metals; and other

conditions in which mitochondrial oxidative injury may be involved in the pathogenesis of liver injury.

### EPIDEMIOLOGY

Mitochondrial respiratory chain disorders of all types affect 1 in 20,000 children younger than 16 years of age; liver involvement has been reported in 10–20% of patients with respiratory chain defect. Primary mitochondrial disorders, including mtDNA depletion syndromes (MDSs), occur in 1 in 5,000 live births and are a known cause of acute liver failure in children <2 years of age.

More than 200 pathogenic variants, deletions, insertions, and rearrangements that involve mtDNA and nuclear DNA and encode mitochondrial proteins are identified. Mitochondrial genetics are unique because mitochondria can replicate, transcribe, and translate their mitochondrial-derived DNA independently. A typical hepatocyte contains approximately 1,000 copies of mtDNA. Oxidative phosphorylation (the process of adenosine triphosphate production) occurs in the

**Table 409.2** Hepatic Phenotypes of Mitochondrial Cytopathies

- Infantile liver failure
- Neonatal cholestasis
- Pearson syndrome
- Alpers disease
- Chronic liver disease
- Drug-induced mitochondrial toxicity

From Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*, 5th ed. Philadelphia: Elsevier, 2016: Box 71.2, p. 876.

**Table 409.1** Genotypic Classification of Primary Mitochondrial Hepatopathies and Organ Involvement

GENE	RESPIRATORY CHAIN COMPLEX	HEPATIC HISTOLOGY	OTHER ORGANS INVOLVED	CLINICAL FEATURES
Deletion	Multiple (Pearson)	Steatosis, fibrosis	Kidney, heart, CNS, muscle	Sideroblastic anemia, variable thrombocytopenia and neutropenia, persistent diarrhea
MPV17	I, III, IV	Steatosis	CNS, muscle, gastrointestinal tract	Adult-onset multisystemic involvement: myopathy, ophthalmoplegia, severe constipation, parkinsonism
DGUOK	I, III, IV	Steatosis, fibrosis	Kidneys, CNS, muscle	Nystagmus, hypotonia, renal Fanconi syndrome, acidosis
MPV17	I, III, IV	Steatosis, fibrosis	CNS, PNS	Hypotonia
SUCLG1	I, III, IV	Steatosis	Kidneys, CNS, muscle	Myopathy, sensorineural hearing loss, respiratory failure
POLG1	I, III, IV	Steatosis, fibrosis	CNS, muscle	Liver failure preceded by neurologic symptoms, intractable seizures, ataxia, psychomotor regression
C10orf2/Twinkle	I, III, IV	Steatosis	CNS, muscle	Infantile-onset spinocerebellar ataxia, loss of skills
BCS1L	III (GRACILE)		CNS ±, muscle ±, kidneys	Fanconi-type renal tubulopathy
SCO1	IV	Steatosis, fibrosis	Muscle	
TRMU	I, III, IV	Steatosis, fibrosis		Infantile liver failure with subsequent recovery
EFG1	I, III, IV	Steatosis	CNS	Severe, rapidly progressive encephalopathy
EFTu	I, III, IV	Unknown	CNS	Severe lactic acidosis, rapidly fatal encephalopathy

CNS, Central nervous system; GRACILE, growth restriction, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death; PNS, peripheral nervous system.  
From Lee WS, Sokol RJ. Mitochondrial hepatopathies: advances in genetics, therapeutic approaches, and outcomes. *J Pediatr*. 2013;163:942–948. Table 2.

respiratory chain located in the inner mitochondrial membrane and is divided into five multienzyme complexes: reduced nicotinamide adenine dinucleotide coenzyme Q reductase (complex I), succinate-coenzyme Q reductase (complex II), reduced coenzyme Q-cytochrome-c reductase (complex III), cytochrome-c oxidase (complex IV), and adenosine triphosphate synthase (complex V). The respiratory chain peptide components are encoded by both nuclear and mtDNA genes; thus pathogenic variants in either genome can result in disorders of oxidative phosphorylation. Thirteen essential polypeptides are synthesized from the small 16.5-kilobase circular double-stranded mtDNA. mtDNA also encodes the 24 transfer RNAs required for intramitochondrial protein synthesis, whereas nuclear genes encode more than 70 respiratory chain subunits and an array of enzymes and cofactors required to maintain mtDNA, including DNA polymerase- $\gamma$  (POLG), thymidine kinase 2, and deoxyguanosine kinase.

The expression of mitochondrial disorders is complex, and epidemiologic studies are hampered by technical difficulties in collecting and processing the tissue specimens needed to make accurate diagnoses, the variability in clinical presentation, and the fact that most disorders display maternal inheritance with variable penetrance (see Chapter 97). mtDNA undergoes pathogenic variant generation 10 times more often than nuclear DNA because of a lack of introns, protective histones, and an effective repair system in mitochondria. Mitochondrial genetics also displays a threshold effect in that the type and severity of pathogenic variants required for clinical expression varies among people and organ systems; this is explained by the concept of heteroplasmacy, in which cells and tissues harbor both normal and pathologic variant mtDNA in various amounts because of random partitioning during cell division. Pathogenic variants, deletions, or duplications in either mitochondrial or nuclear genes can cause disease, and variants in nuclear genes that control mtDNA replication, transcription, and translation may lead to MDS or to a translational disorder.

## CLINICAL MANIFESTATIONS

Defects in oxidative phosphorylation can affect any tissue to a variable degree, with the most energy-dependent organs being the most vulnerable. One should consider the diagnosis of a mitochondrial disorder in a patient of any age who presents with progressive, multisystem involvement that cannot be explained by a specific diagnosis. Certain mitochondrial disorders have characteristic gastrointestinal presentations, including vomiting, diarrhea, constipation, failure to thrive, and abdominal pain. Pearson marrow-pancreas syndrome manifests with sideroblastic anemia and exocrine pancreatic insufficiency, whereas mitochondrial neurogastrointestinal encephalomyopathy manifests with chronic intestinal pseudoobstruction and cachexia. Hepatic presentations range from chronic cholestasis, hepatomegaly, cirrhosis, and steatosis to fulminant hepatic failure and death. Patients with certain mitochondrial diseases may have normal or minimally elevated lactate levels even in the setting of a metabolic crisis. The lactate-to-pyruvate molar ratio (L:P) has been proposed as a screening test for mitochondrial disorders because it reflects the equilibrium between the product and substrate of the reaction catalyzed by lactate dehydrogenase. An L:P  $\geq 25$  has been considered to be highly suggestive of respiratory chain dysfunction; however, an elevated lactate or an elevated L:P can also represent secondary mitochondrial dysfunction occurring as a result of severe liver disease.

## PRIMARY MITOCHONDRIAL HEPATOPATHIES

### Neonatal Liver Failure

A common presentation of respiratory chain defects is severe liver failure manifested as jaundice, hypoglycemia, coagulopathy, renal dysfunction, and hyperammonemia, with onset within the first few weeks to months of life. Cytochrome-c oxidase (complex IV) is the most common deficiency in these infants, although complexes I and III and MDSs are also implicated (see Tables 409.1 and Chapter 404). The key biochemical features include a markedly elevated plasma lactate concentration, an elevated molar ratio of plasma lactate to pyruvate (L:P) ( $>25$ ), and a raised ratio of  $\beta$ -hydroxybutyrate to acetoacetate ( $>4.0$ ). Symptoms are nonspecific and include lethargy and vomiting. Most

patients additionally have neurologic involvement that manifests as a weak suck, recurrent apnea, or myoclonic epilepsy. Liver biopsy shows predominantly microvesicular steatosis, cholestasis, bile duct proliferation, glycogen depletion, and iron overload. With standard therapy, the prognosis is poor, and most patients die from liver failure or infection in the first few months of life.

### Alpers Syndrome (Alpers-Huttenlocher Syndrome or Alpers Hepatopathic Poliodystrophy)

Diagnostic criteria include refractory mixed-type seizures with a focal component; psychomotor regression that is episodic and triggered by intercurrent infections; and hepatopathy with or without acute liver failure. Alpers syndrome manifests from infancy up to 8 years of age with seizures, hypotonia, feeding difficulties, psychomotor regression, and ataxia. Patients develop hepatomegaly and jaundice and have a slower progression to liver failure than those with cytochrome-c oxidase deficiency. Elevated blood or cerebrospinal fluid lactate and pyruvate levels are supportive of the diagnosis, in addition to characteristic electroencephalographic findings (high-amplitude slow activity with polyspikes), asymmetric abnormal visual evoked responses, and low-density areas or atrophy in the occipital or temporal lobes on computed tomography scanning of the brain. In some patients, complex I deficiency has been found in liver or muscle mitochondria. The disease is inherited in an autosomal recessive fashion; pathogenic variants in the catalytic subunit of the nuclear gene mtDNA POLG have been identified in multiple families with Alpers syndrome, leading to the advent of molecular diagnosis for Alpers syndrome. Patients with POLG pathogenic variants are susceptible to valproate-induced liver dysfunction.

### Mitochondrial DNA Depletion Syndrome

MDS is characterized by a tissue-specific reduction in mtDNA copy number, leading to deficiencies in complexes I, III, and IV. MDS manifests with phenotypic heterogeneity; multisystem and localized disease forms include myopathic, hepatocerebral, and liver-restricted presentations. Infants with the hepatocerebral form present in the neonatal period. The first symptoms are metabolic; these rapidly progress to hepatic failure with hypoglycemia and vomiting. This stage is followed by neurologic involvement affecting the central and peripheral systems. Laboratory studies are characterized by lactic acidosis, hypoglycemia, and markedly elevated  $\alpha$ -fetoprotein in plasma. In some patients, iron overload has been found with elevated transferrin saturation, high ferritin levels, and iron accumulation in hepatocytes and Kupffer cells. Death usually occurs by 1 year of age. Spontaneous recovery has been reported in a patient with liver-restricted disease. Inheritance is autosomal recessive and pathogenic variants in the nuclear deoxyguanosine kinase gene (DGUOK) have been identified in many patients with hepatocerebral MDS. Thymidine kinase 2 has been implicated in the myopathic form; no known genetic defect has been identified in liver-restricted MDS. Multiple other nuclear genes including POLG, MPV17, Twinkle helicase gene, and SUCLG1 have been implicated in hepatocerebral MDS. Greater than 100 affected individuals with MPV17 MDS have been identified, most with early-onset hepatic and neurologic manifestations, although rare late-onset neuromyopathic phenotypes have also been identified.

Liver biopsies of patients with MDS show microvesicular steatosis, cholestasis, focal cytoplasmic biliary necrosis, and cytosiderosis in hepatocytes and sinusoidal cells. Ultrastructural changes are characteristic, with oncotypic transformation of mitochondria, which is characterized by mitochondria with sparse cristae, granular matrix, and dense or vesicular inclusions. If the native DNA-encoded complex II is normal and the activities of the other complexes are decreased, one should investigate mtDNA copy numbers for an MDS. Diagnosis is established by the demonstration of a low ratio of mtDNA (<10%) to nuclear DNA in affected tissues and/or genetic testing. Importantly, the sequence of the mitochondrial genome is normal.

### Navajo Neurohepatopathy

Navajo neurohepatopathy (NNH) is an autosomal recessive sensorimotor neuropathy with progressive liver disease found only in Navajo

people of the southwestern United States. The incidence is 1 in 1,600 live births. Diagnostic criteria include sensory neuropathy, motor neuropathy, corneal anesthesia, and liver disease. Metabolic or infectious complications include failure to thrive, short stature, delayed puberty, or systemic infection. Affected individuals have evidence of central nervous system demyelination on radiographic imaging and peripheral nerves biopsies. An *MPV17* gene variant is implicated in the pathogenesis of NNH. Interestingly, this is the same gene implicated in MDS (see earlier), demonstrating that NNH may be a specific type of MDS found only in Navajos. NNH is divided into three phenotypic variations based on age of presentation and clinical findings.

**Classic NNH** appears in infancy with severe progressive neurologic deterioration manifesting clinically as weakness, hypotonia, loss of sensation with accompanying acral mutilation, corneal ulcerations, and poor growth. Liver disease, present in the majority of patients, is secondary and variable; it includes asymptomatic elevations of liver function tests, Reye syndrome-like episodes, and hepatocellular carcinoma or cirrhosis.  $\gamma$ -Glutamyl transpeptidase levels tend to be higher than in other forms of NNH. Liver biopsy might show chronic portal tract inflammation and cirrhosis but shows less cholestasis, hepatocyte ballooning, and giant cell transformation than in other forms of NNH.

**Infantile NNH** manifests between the ages of 1 and 6 months with jaundice and failure to thrive and progresses to liver failure and death by 2 years of age. Patients have hepatomegaly with moderate elevations in aspartate aminotransferase, alanine aminotransferase, and  $\gamma$ -glutamyl transpeptidase. Liver biopsy demonstrates pseudoacinar formation, multinucleate giant cells, portal and lobular inflammation, canalicular cholestasis, and microvesicular steatosis. Progressive neurologic symptoms are not usually noticed at presentation but develop later.

**Childhood NNH** manifests from age 1-5 years with the acute onset of fulminant hepatic failure leading to death within months. Most patients also have evidence of neuropathy at presentation. Liver biopsies are similar to those in infantile NNH, except for significant hepatocyte ballooning and necrosis, bile duct proliferation, and cirrhosis, which are also seen.

There is no effective treatment for any of the forms of NNH, and neurologic symptoms often preclude liver transplantation. The identical *MPV17* pathogenic variant is seen in patients with both the infantile and classic forms of NNH, highlighting the clinical heterogeneity of NNH.

### Pearson Syndrome

Pearson marrow-pancreas syndrome has a neonatal-onset with severe macrocytic anemia, variable neutropenia and thrombocytopenia, and ringed sideroblasts in the bone marrow. Diarrhea and fat malabsorption develop in early childhood secondary to extensive pancreatic fibrosis, acinar atrophy, and partial villous atrophy of the small intestine. The liver involvement includes hepatomegaly, steatosis, and cirrhosis. Liver failure and death have been reported before the age of 4 years. Other features of the syndrome include renal tubular disease, photosensitivity, diabetes mellitus, hydrops fetalis, and the late development of visual impairment, tremor, ataxia, proximal muscle weakness, external ophthalmoplegia, and a pigmentary retinopathy. Methylglutaconic aciduria is a useful diagnostic marker. Large deletions of mtDNA are reported in most patients, resulting in deficiency of complexes I and III. mtDNA deletions can be detected in patients' cultured fibroblasts as well as in peripheral blood lymphocytes.

### Villous Atrophy Syndrome

Children with this disease present with severe anorexia, vomiting, chronic diarrhea, and villous atrophy in the first year of life. Hepatic involvement includes mild elevation of aminotransferase levels, hepatomegaly, and steatosis. Lactic acidosis is worsened with high-dextrose intravenous infusions or enteral nutrition. Diarrhea improves by 5 years of age in association with the normalization of intestinal biopsies. Subsequently, patients develop retinitis pigmentosa, cerebellar ataxia, sensorineural deafness, and proximal muscle weakness, with eventual death late in the first decade of life. The disease is attributed to a

mtDNA rearrangement defect. A complex III deficiency was found in the muscle of affected patients.

### GRACILE Syndrome

The acronym GRACILE summarizes the most important clinical features, namely fetal growth restriction (birthweight about -4 SD), aminoaciduria (caused by Fanconi-type tubulopathy), cholestasis (with steatosis and cirrhosis), iron overload, severe lactic acidosis, and early death. The syndrome is associated with pathogenic variants of the complex III assembly factor *BCS1L*. The liver histology shows microvesicular steatosis and cholestasis with abundant iron accumulation in hepatocytes and Kupffer cells. The liver iron content decreases slightly with age, concomitantly with increasing fibrosis and cirrhosis. Abnormal aminotransferase levels and coagulation are noted, but the cause of death seems to be related more to energy depletion than to liver failure. About half of these patients die within the first 2 weeks of life.

### Pathogenic Variants in Nuclear Translation and Elongation Factor Genes

Pathogenic variants in nuclear translation factor genes (*TRMU*) of the respiratory chain enzyme complexes have been identified as the etiology of acute liver failure manifesting at ages 1 day to 6 months. The respiratory chain deficit was similar to that seen in MDS, where the activity of the native DNA-encoded complex II was normal whereas complexes I, III, and IV were decreased. The elongation factor *EFG1* (gene *GFM1*) variant was associated with fetal growth restriction, lactic acidosis, and liver dysfunction that progresses into liver failure and death. The variant in the elongation factor *EFTu* manifests as severe lactic acidosis and lethal encephalopathy with mild hepatic involvement.

### Secondary Mitochondrial Hepatopathies

Secondary mitochondrial hepatopathies are caused by exposure to a hepatotoxic metal, drug, toxin, or endogenous metabolite. In the past, the most common secondary mitochondrial hepatopathy was *Reye syndrome*, the prevalence of which peaked in the 1970s and had a mortality rate of >40%. Although mortality has not changed, the prevalence has decreased from >500 cases in 1980 to fewer than four cases annually since 1994. The decline in the reported incidence of Reye syndrome may be partially related to more accurate modern diagnosis of infectious, genetic, metabolic, or toxic disease, thus reducing the percentage of idiopathic or true cases of Reye syndrome. Reye syndrome is precipitated in a genetically susceptible person by the interaction of a viral infection (influenza, varicella) and salicylate and/or antiemetic use. Clinically it is characterized by a preceding viral illness that appears to be resolving and the acute onset of vomiting and encephalopathy (Table 409.3). Neurologic symptoms can rapidly progress to seizures, coma, and death. Liver dysfunction is invariably present when vomiting develops, with coagulopathy and elevated serum levels of aspartate aminotransferase, alanine aminotransferase, and ammonia. Importantly, patients remain anicteric and serum bilirubin levels are normal. Liver biopsies show microvesicular steatosis without evidence of liver inflammation or necrosis. Death is usually secondary to increased intracranial pressure and cerebral herniation. Patients who survive

**Table 409.3** Clinical Staging of Reye Syndrome and Reye-Like Diseases

Symptoms at the time of admission:

- I. Usually quiet, **lethargic**, and sleepy, vomiting, laboratory evidence of liver dysfunction
- II. Deep lethargy, **confusion**, delirium, combativeness, hyperventilation, hyperreflexia
- III. Obtunded, **light coma** ± seizures, decorticate rigidity, intact pupillary light reaction
- IV. Seizures, deepening coma, **decerebrate rigidity**, loss of oculocephalic reflexes, fixed pupils
- V. Coma, loss of deep tendon reflexes, respiratory arrest, fixed dilated pupils, **flaccidity/decerebration** (intermittent); isoelectric electroencephalogram

**Table 409.4**

## Diseases That Present a Clinical or Pathologic Picture Resembling Reye Syndrome

- Metabolic disease
  - Organic aciduria
  - Disorders of oxidative phosphorylation
  - Urea cycle defects (carbamoyl phosphate synthetase, ornithine transcarbamylase)
  - Defects in fatty acid oxidation metabolism
  - Acyl-coenzyme A dehydrogenase deficiencies
  - Systemic carnitine deficiency
  - Hepatic carnitine palmitoyltransferase deficiency
  - 3-OH, 3-methylglutaryl-coenzyme A lyase deficiency
  - Fructosemia
  - Infantile liver failure syndrome 1. Caused by leucyl-tRNA synthetase (LARS) gene variants
- Central nervous system infections or intoxications (meningitis), encephalitis, toxic encephalopathy
- Hemorrhagic shock with encephalopathy
- Drug or toxin ingestion (salicylate, valproate)

have full recovery of liver function but should be carefully screened for fatty-acid oxidation and fatty-acid transport defects (**Table 409.4**).

Acquired abnormalities of mitochondrial function can be caused by several drugs and toxins, including valproic acid, cyanide, amiodarone, chloramphenicol, iron, the emetic toxin of *Bacillus cereus*, and nucleoside analogs. Valproic acid is a branched fatty acid that can be metabolized into the mitochondrial toxin 4-envalproic acid. Children with underlying respiratory chain defects appear more sensitive to the toxic effects of this drug, and valproic acid is reported to precipitate liver failure in patients with **Alpers syndrome** and **cytochrome-c oxidase deficiency**. Nucleoside analogs directly inhibit mitochondrial respiratory chain complexes. The reverse transcriptase inhibitors zidovudine, didanosine, stavudine, and zalcitabine—used to treat patients infected with HIV— inhibit DNA POLG of mitochondria and can block elongation of mtDNA, leading to mtDNA depletion. Other conditions that can lead to mitochondrial oxidative stress include cholestasis, non-alcoholic steatohepatitis,  $\alpha_1$ -antitrypsin deficiency, and Wilson disease.

### DIAGNOSTIC EVALUATION

Screening tests include common biochemical tests (comprehensive metabolic profile, INR,  $\alpha$ -fetoprotein, CPK, phosphorus, complete blood cell count, ammonia, lactate, pyruvate, serum ketone bodies; both quantitative 3-hydroxybutyrate and quantitative acetoacetate, total free fatty acids, serum acylcarnitine profile; serum-free and total carnitines, urine organic acids, and serum amino acids) (**Table 409.5**). These results will guide subsequent confirmatory testing to establish a molecular diagnosis. Genotyping, including single gene or panel screening for common mitochondrial disease, is used in clinical practice. Whole exome or genome sequencing is also helpful and is replacing single gene or gene panel testing. However, the identification of multiple gene variants of uncertain significance will require detailed clinical and biochemical confirmation for interpretation. Tissue (liver biopsy, skin fibroblast, and muscle biopsy) may be needed to make a specific biochemical diagnosis.

### TREATMENT OF MITOCHONDRIAL HEPATOPATHIES

There is no effective therapy for most patients with mitochondrial hepatopathies; neurologic involvement often precludes orthotopic liver transplantation. Patients with mitochondrial disorders remain at risk for transplant-related worsening of their underlying metabolic disease, especially patients with POLG-related disease. Children who receive

**Table 409.5**

## Tiered Investigations in Suspected Mitochondrial Liver Disease

**TIER 1**

- Pre-/postprandial plasma lactate, glucose, FFA, and 3-OH
- Plasma carnitine, acylcarnitines
- Plasma amino acids, creatine kinase, thymidine
- Urinary organic acids, amino acids, tubular resorption phosphate, albumin/creatinine ratio CSF lactate/protein (if feasible)
- Electrocardiography and echocardiography
- Electroencephalography and visual-evoked potentials
- Pathogenic variants in *POLG*, *DGUOK*, *MPV17*, and *TRMU*

**TIER 2**

- Tissue analysis
- Liver biopsy:** (if feasible). Tissue for light microscopy, electron microscopy, and Oil Red O stain
- Frozen tissue for respiratory chain enzyme activity analysis and mtDNA copy number
- Muscle biopsy:** Tissue for light microscopy, electron microscopy, Oil Red O stain, and histochemistry for respiratory chain complexes
- Frozen tissue for respiratory chain enzyme activity analysis and mtDNA copy number
- Skin biopsy:** Set up for fibroblast culture

**TIER 3**

- Cranial MRI/MRS

**TIER 4**

- Extended molecular screening. This will be guided by the clinical phenotype, results of the tissue analysis, and local facilities.

Currently suggested genes should include *SUCLG1*, *BCS1L*, *SOC1*, *TFSM*, *TWINKLE*, *ACAD9*, *EARS2*, *GFM1*, *RRM2B*, *TK2*, and *SUCLA2*.

FFA, Free fatty acid; CSF, cerebrospinal fluid; MRS, magnetic resonance spectroscopy. From Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*, 5th ed. Philadelphia: Elsevier, 2016: Box 71-3, p. 876.

liver transplants for *DGUOK* MDS have decreased rates of survival post-transplant than those who are transplanted for other diseases. Liver transplantation for *MPV17*-related mtDNA depletion syndrome is associated with poor post-transplant outcomes because of multiorgan failure and sepsis. Several therapeutic drug combinations—including antioxidants, vitamins, cofactors, and electron acceptors—have been proposed, but no randomized controlled trials have been completed to evaluate them.

Treatment strategies are supportive and include the infusion of sodium bicarbonate for acute metabolic acidosis, transfusions for anemia and thrombocytopenia, and exogenous pancreatic enzymes for pancreatic insufficiency. It is important to discontinue or avoid medications that may exacerbate hepatopathy, including sodium valproate, tetracycline, and macrolide antibiotics, azathioprine, chloramphenicol, quinolones, and linezolid. Ringer lactate should be avoided because patients with liver dysfunction may not be able to metabolize lactate. Propofol should be avoided during anesthesia because of potential interference with mitochondrial function. In patients with lactic acidosis, lactate levels should be monitored during procedures. It is important to maintain anabolism using a balanced intake of fat and carbohydrates while avoiding unbalanced intakes (e.g., glucose only at a high intravenous rate) or fasting for >12 hours.

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## Chapter 410

# Autoimmune Hepatitis

Amy G. Feldman and Frederick J. Suchy

Autoimmune hepatitis (AIH) is an immune-mediated liver disease manifested by elevated serum aminotransaminase concentrations, liver-associated serum autoantibodies, and/or hypergammaglobulinemia. The serologic autoantibody profile defines two main types of autoimmune hepatitis: **AIH type 1**, with positivity for antinuclear antibodies (ANA) and/or anti-smooth muscle antibody (SMA) and **AIH type 2**, with positivity for anti-liver kidney microsomal type 1 antibody (anti-LKM-1). The targets of the inflammatory process can include hepatocytes and, to a lesser extent, bile duct epithelium. Autoimmune hepatitis typically refers to a primarily hepatocyte-specific process, whereas **autoimmune cholangiolopathy** and **sclerosing cholangitis** predominately involve intrahepatic and extrahepatic bile duct injury. **Overlap** of the process involving both hepatocyte and bile duct-directed injury may be more common in children. Chronicity is determined either by duration of liver disease (typically >3–6 months), by evidence of chronic hepatic decompensation (hypoalbuminemia, thrombocytopenia) or physical stigmata of chronic liver disease (clubbing, spider telangiectasia, splenomegaly, ascites). The severity is variable; the affected child might have only biochemical evidence of liver dysfunction, might have stigmata of chronic liver disease, or can present in hepatic failure. De novo hepatitis can be seen in a subset of liver transplant recipients whose initial disease was not autoimmune.

### Etiology

Autoimmune hepatitis arises in a genetically predisposed host after an unknown trigger leads to a T cell-mediated immune response targeting liver autoantigens. A dense portal mononuclear cell infiltrate invades the surrounding parenchyma and comprises T and B lymphocytes, macrophages, and plasma cells. The immunopathogenic mechanisms underlying autoimmune hepatitis are unsettled. Triggering factors can include molecular mimicry, infections, drugs, and the environment (toxins) in a genetically susceptible host. Several human leukocyte antigen class II molecules—particularly DR3, DR4, and DR7 isoforms—confer susceptibility to autoimmune hepatitis. Self-antigenic peptides are processed by populations of antigen-presenting cells and presented to CD4 and CD8 effector T cells. CD4<sup>+</sup> T lymphocytes recognizing a self-antigenic liver peptide orchestrate liver injury. Cell-mediated injury by cytokines released by CD8<sup>+</sup> cytotoxic T cells and/or antibody-mediated cytotoxicity can be operative. There is also evidence that regulatory T cells from patients with autoimmune hepatitis are impaired in their ability to control the proliferation of CD4 and CD8 effector cells. Cytochrome P450 2D6 is the main autoantigen in type 2 autoimmune hepatitis.

Antibody-coated hepatocytes may be lysed by complement or Fc-bearing natural killer lymphocytes. Heterozygous pathogenic variants in the autoimmune regulator gene (*AIRE*), which encodes a transcription factor controlling the negative selection of autoreactive thymocytes, can be found in some children with autoimmune hepatitis types 1 and 2. *AIRE* variants also cause **autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy** (also called *autoimmune polyendocrinopathy syndrome*), in which autoimmune hepatitis occurs in approximately 20% of patients.

### Pathology

The histologic features common to untreated cases include inflammatory infiltrates, consisting of lymphocytes and plasma cells that

expand portal areas and often penetrate the lobule (interface hepatitis); moderate to severe piecemeal necrosis of hepatocytes extending outward from the limiting plate; variable necrosis, fibrosis, and zones of parenchymal collapse spanning neighboring portal triads or between a portal triad and central vein (bridging necrosis); and variable degrees of bile duct epithelial injury. Distortion of hepatic architecture can be severe; cirrhosis may be present in over a third of children at the time of diagnosis. Histologic features in acute liver failure may be obscured by massive necrosis and multilobular collapse. Other histologic features may suggest an alternative diagnosis; characteristic periodic acid-Schiff-positive, diastase-resistant granules are seen in  $\alpha_1$ -antitrypsin deficiency, and macrovesicular and microvesicular steatosis is found in nonalcoholic steatohepatitis and often in Wilson disease. Bile duct injury can suggest an autoimmune cholangiolopathy or an overlap syndrome. Ultrastructural analysis might suggest distinct types of storage disorders.

### Clinical Manifestations

The clinical features and course of autoimmune hepatitis are extremely variable. Signs and symptoms at the time of presentation comprise a wide spectrum of disease including a substantial number of asymptomatic patients and some who have an acute, even fulminant, onset. In 25–30% of patients with autoimmune hepatitis, particularly children, the illness mimics acute viral hepatitis. *In most, the onset is insidious*. Patients can be asymptomatic or have fatigue, malaise, behavioral changes, anorexia, and amenorrhea, sometimes for many months before jaundice or stigmata of chronic liver disease are recognized. **Extrahepatic manifestations** can include arthritis, vasculitis, nephritis, thyroiditis, Coombs-positive anemia, and rash (vitiligo, Sweet syndrome, pyoderma gangrenosum, erythema nodosum). Some patients' initial clinical features reflect cirrhosis (ascites, hypersplenism, bleeding esophageal varices, or hepatic encephalopathy). There may be mild to moderate jaundice in severe cases. Spider telangiectasias and palmar erythema may be present. The liver may be tender and slightly enlarged but might not be felt in patients with cirrhosis. The spleen is commonly enlarged. Edema and ascites may be present in advanced cases.

### Laboratory Findings

The findings are related to the severity of presentation. In many asymptomatic cases, serum aminotransferase ranges between 100 and 300 IU/L, whereas levels in excess of 1,000 IU/L can be seen in young symptomatic patients. Serum bilirubin concentrations may be normal in mild cases but are commonly 2–10 mg/dL in more severe cases. Serum alkaline phosphatase and  $\gamma$ -glutamyl transpeptidase activities are normal to slightly increased but may be more significantly elevated in autoimmune cholangiolopathy or in the setting of overlap with sclerosing cholangitis. Serum  $\gamma$ -globulin levels can show marked polyclonal elevations. Hypoalbuminemia is common. The prothrombin time or international normalized ratio (INR) is prolonged, most often as a result of vitamin K deficiency but also as a reflection of impaired hepatocellular function. A normochromic normocytic anemia, leukopenia, and thrombocytopenia are present and become more severe with the development of portal hypertension and hypersplenism.

Most patients with autoimmune hepatitis have hypergammaglobulinemia. Serum immunoglobulin G levels usually exceed 16 g/L. Characteristic patterns of serum autoantibodies define distinct subgroups of autoimmune hepatitis (Table 410.1). The most common pattern (type 1) is associated with the formation of non-organ-specific antibodies, such as antiactin (smooth muscle) and ANA. Approximately 50% of these patients are 10–20 years of age. High titers of a liver-kidney microsomal antibody are detected in another form (type 2) that usually affects children 2–14 years of age. A subgroup of primarily young females might demonstrate autoantibodies against a soluble liver antigen but not against nuclear or microsomal proteins. Antineutrophil cytoplasmic antibodies may

**Table 410.1** Classification of Autoimmune Hepatitis

VARIABLE	TYPE 1 AUTOIMMUNE HEPATITIS	TYPE 2 AUTOIMMUNE HEPATITIS
Characteristic autoantibodies	Antinuclear antibody* Smooth-muscle antibody* Antiactin antibody Autoantibodies against soluble liver antigen and liver-pancreas antigen† Atypical perinuclear antineutrophil cytoplasmic antibody	Antibody against liver-kidney microsome type 1* Antibody against liver cytosol type 1* Antibody against liver-kidney microsome type 3
Geographic variation	Worldwide	Worldwide; rare in North America
Age at presentation	Any age	Predominantly early childhood
Sex of patients	Female in ~75% of cases	Female in ~95% of cases
Association with other autoimmune diseases	Common	Common§
Clinical severity	Broad range, variable	Generally severe
Histopathologic features at presentation	Broad range, mild disease to cirrhosis	Generally advanced
Treatment failure	Infrequent	Frequent
Relapse after drug withdrawal	Variable	Common
Need for long-term maintenance	Variable	~100%

\*The conventional method of detection is immunofluorescence.

†This antibody is detected by enzyme-linked immunosorbent assay.

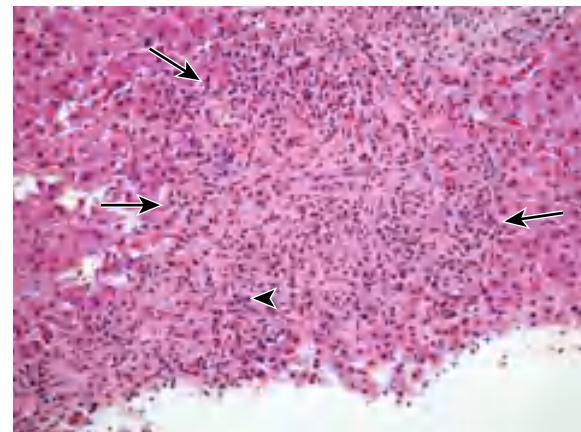
§Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy is seen only in patients with type 2 disease.

Modified from Krawitt EL. Autoimmune hepatitis. *N Engl J Med*. 2006;354:54–66.

be seen more commonly in autoimmune cholangiopathy. Autoantibodies are rare in healthy children, so that titers as low as 1:40 may be significant, although nonspecific elevation in autoantibodies can be observed in a variety of liver diseases. Up to 20% of patients with apparent autoimmune hepatitis might not have autoantibodies at presentation but have histologic features and clinical course consistent with the disorder. Other, less common autoantibodies include rheumatoid factor, antiparietal cell antibodies, atypical p-ANCA, antithyroid antibodies, and anti-liver cytosol type 1 antibody (anti-LC-1).

## DIAGNOSIS

The diagnosis of autoimmune hepatitis is based on clinical, biochemical, immunologic, and histologic features and the exclusion of other known causes of liver disease. Diagnostic criteria with scoring systems have been developed for adults and modified slightly for children, although these scoring systems were developed as research rather than diagnostic tools and lack validation by prospective studies and lack accuracy in the setting of concurrent sclerosing cholangitis, nonalcoholic fatty liver disease, or fulminant liver failure. Autoimmune hepatitis should be considered in all children presenting with elevated liver function tests and/or signs of chronic liver disease, including children who are asymptomatic, in liver failure, or who have autoantibody-negative hepatitis. Important positive features include primary elevation in transaminases and not alkaline phosphatase (or GGT), elevated γ-globulin levels, the presence of autoantibodies (most commonly antinuclear, smooth muscle, or liver-kidney microsome), and characteristic histologic findings (Fig. 410.1). Other causes of acute hepatitis and chronic liver disease must be excluded including infection (Epstein-Barr virus [EBV], hepatitis A [Hep A], B, C, D), drug or toxin exposure, α<sub>1</sub>-antitrypsin deficiency (see Chapter 405) and Wilson disease (see Chapter 405.2) (Table 410.2). To exclude these processes viral



**Fig. 410.1** Autoimmune hepatitis. Liver biopsy showing fibrous expansion of the portal tracts with moderate portal lymphocytic infiltrates rich in plasma cells (arrowhead). There is extensive interface hepatitis (arrows). Original magnification  $\times 20$ . (Courtesy Dr Margret Magid, Mount Sinai School of Medicine.)

titers (Hep A IgM, Hep B surface Ag, Hep C Ab), α<sub>1</sub>-antitrypsin level/phenotype and serum ceruloplasmin should be obtained. Magnetic resonance (MR) cholangiography may be very useful for screening for evidence of sclerosing cholangitis. An **overlap syndrome** with features of primary sclerosing cholangitis and autoimmune hepatitis is being increasingly recognized with wider application of MR cholangiography. Ultimately, liver biopsy is necessary to confirm compatible histologic features as well as to look for features of small duct primary sclerosing cholangitis.

**Table 410.2** Disorders Producing Chronic Hepatitis

- Chronic viral hepatitis
  - Hepatitis B
  - Hepatitis C
  - Hepatitis D
- Autoimmune hepatitis
  - Anti-actin antibody-positive
  - Anti-nuclear antibody
  - Anti-liver-kidney microsomal antibody-positive
  - Anti-soluble liver antigen antibody-positive
  - Others (includes antibodies to liver-specific lipoproteins or asialoglycoprotein)
  - Overlap syndrome with sclerosing cholangitis and autoantibodies
  - Systemic lupus erythematosus
  - Celiac disease
- Drug-induced hepatitis
- Metabolic disorders associated with chronic liver disease
  - Wilson disease
  - Nonalcoholic steatohepatitis
  - $\alpha_1$ -Antitrypsin deficiency
  - Tyrosinemia
  - Niemann-Pick disease type 2
  - Glycogen storage disease type IV
  - Cystic fibrosis
  - Galactosemia
  - Bile acid biosynthetic abnormalities

## TREATMENT

Prednisone, with or without azathioprine, improves the clinical, biochemical, and histologic features in most patients with autoimmune hepatitis and prolongs survival in most patients with severe disease. The goal is to suppress or eliminate hepatic inflammation with minimal side effects. Prednisone at an initial dose of 1-2 mg/kg/24 hr is continued until aminotransferase values return to normal. Budesonide (9 mg/daily) can be used instead of prednisone for children who do not have cirrhosis or severe acute autoimmune hepatitis. In some centers, azathioprine (1.5-2.0 mg/kg/24 hr, up to 100 mg/24 hr) is started at the same time as glucocorticoids, whereas other centers prefer to wait ~2 weeks before starting azathioprine to confirm steroid responsiveness and allow improvement in liver function. Measurement of thiopurine methyltransferase activity should be performed at some point in the beginning of therapy as patients with low activity (10% prevalence) or absent activity (prevalence 0.3%) are at risk for developing severe drug-induced myelotoxicity from accumulation of the unmetabolized drug. Once liver function tests normalize and biochemical remission is achieved the prednisone or budesonide dose should then be lowered (in 5-mg decrements for prednisone and 3-mg decrements for budesonide) over several months. Liver function tests should be monitored every 1-2 weeks while tapering steroids to ensure the child stays in biochemical remission. Once tapered off steroids, liver function tests should be monitored every 3-4 months to ensure the child stays in biochemical remission. Cyclosporine, tacrolimus, and mycophenolate mofetil can be trialed as *second-line agents* for cases refractory

to standard therapy. Use of these agents should be reserved for practitioners with extensive experience in their administration because the agents have a more restricted therapeutic to toxic ratio.

If the child has sustained normal serum levels of aminotransferases, negative autoantibodies and normal IgG levels for at least 2 years after steroids have been withdrawn, a follow-up liver biopsy can be performed and if there is no evidence of ongoing inflammation, then gradual withdrawal of azathioprine can be attempted. However, there is a high rate of relapse after discontinuation of therapy and many children with autoimmune hepatitis require lifelong azathioprine.

Patients with primary sclerosing cholangitis/autoimmune hepatitis overlap syndrome respond similarly to immunosuppressive therapy. Prednisone, azathioprine and ursodeoxycholic acid (UDCA) (10 mg/kg/dose BID) are recommended for children with overlap syndrome.

## PROGNOSIS

The initial response to therapy in autoimmune hepatitis is generally prompt, with a >75% rate of remission. Transaminases and bilirubin fall to near-normal levels, often in the first 1-3 months. When present, abnormalities in serum albumin and prothrombin time respond over a longer period (3-9 months). In patients meeting the criteria for tapering and then withdrawal of treatment (25-40% of children), 50% are weaned from all medication. However, long-term biochemical remission has been possible in only 20% of children with type 1 autoimmune hepatitis and rarely in children with type 2 autoimmune hepatitis. Relapse usually responds to retreatment. Many children will not meet the criteria for an attempt at discontinuation of immunosuppression and should be maintained on the smallest dose of prednisone or azathioprine that minimizes biochemical activity of the disease. A careful balance of the risks of continued immunosuppression and ongoing hepatitis must be continually evaluated. This requires frequent screening for complications of medical therapy (monitoring of linear growth velocity, ophthalmologic examination, bone density measurement, blood pressure monitoring). Intermittent flares of hepatitis can occur and can necessitate recycling of prednisone therapy.

Some children have a relatively steroid-resistant form of hepatitis. More extensive evaluations of the etiology of their hepatitis should be undertaken, directed particularly at reassessing for the presence of either sclerosing cholangitis or Wilson disease. Nonadherence to medical therapy is one of the most common causes of "resistance" to medical therapy. Progression to cirrhosis can occur in autoimmune hepatitis despite a good response to drug therapy and prolongation of life. Corticosteroid therapy in fulminant autoimmune disease may be useful, although it should be administered with caution, given the predisposition of these patients to systemic bacterial and fungal infections.

Liver transplantation has been successful in patients with end-stage or fulminant liver disease associated with autoimmune hepatitis (see Chapter 416). Disease recurs after transplantation in approximately 30% of patients and is associated with increased concentrations of serum autoantibodies and interface hepatitis on liver biopsy. Patients generally respond well to an increase in immunosuppression, particularly to the addition of azathioprine.

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## Chapter 411

# Drug- and Toxin-Induced Liver Injury

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The liver is the main site of drug metabolism and is particularly susceptible to structural and functional injury after the ingestion, parenteral administration, or inhalation of chemical agents, drugs, plant derivatives (home remedies), herbal or nutritional supplements, or environmental toxins. The possibility of drug use or toxin exposure at home or in the parents' workplace should be explored for every child with liver dysfunction. Host factors related to hepatotoxicity include age, genetic predisposition, nutritional status, concomitant medications, and underlying diseases. The clinical spectrum of illness can vary from asymptomatic biochemical abnormalities of liver function to fulminant failure (Table 411.1). Liver injury may be the only clinical feature of an adverse drug reaction or may be accompanied by systemic manifestations and damage to other organs. In hospitalized patients, clinical and laboratory findings may be confused with the underlying illness. After acetaminophen, antimicrobials, supplements, and central nervous system agents are the most commonly implicated drug classes causing liver injury in children.

There is growing concern about environmental hepatotoxins that are insidious in their effects. Many environmental toxins—including the plasticizers, biphenyl A, and the phthalates—are ligands for nuclear receptors that transcriptionally activate the promoters of many genes involved in xenobiotic and lipid metabolism and may contribute to obesity and **nonalcoholic fatty liver disease**. Some herbal, weight loss, and body building supplements have been associated with hepatic injury or even liver failure (Table 411.2) related to their intrinsic toxicity or because of contamination with fungal toxins, pesticides, or heavy metals.

Hepatic metabolism of drugs and toxins is mediated by a sequence of enzymatic reactions that in large part transform hydrophobic, less-soluble molecules into more nontoxic, hydrophilic compounds that can be readily excreted in urine or bile (see Chapter 94). Relative liver size, liver blood flow, and extent of protein binding also influence drug metabolism. Phase 1 of the process involves enzymatic activation of the substrate to reactive intermediates containing a carboxyl, phenol, epoxide, or hydroxyl group. Mixed-function monooxygenase, cytochrome-c reductase, various hydrolases, and the cytochrome P450 (CYP) system are involved in this process. Nonspecific induction of these enzymatic pathways, which can occur during intercurrent viral infection, with starvation, and with the administration of certain drugs such as anticonvulsants, can alter drug metabolism and increase the potential for hepatotoxicity. A single agent can be metabolized by more than one biochemical reaction. The reactive intermediates that are potentially damaging to the cell are enzymatically conjugated in phase 2 reactions with glucuronic acid, sulfate, acetate, glycine, or glutathione. Some drugs may be directly metabolized by these conjugating reactions without first undergoing phase 1 activation. Phase 3 is the energy-dependent excretion of drug metabolites and their conjugates by an array of membrane transporters in the liver and kidney such as the multidrug resistant protein 1.

Pathways for **biotransformation** are expressed early in the fetus and infant, but many phase 1 and phase 2 enzymes are immature, particularly in the first year of life. CYP3A4 is the primary hepatic CYP expressed postnatally and metabolizes more than 75 commonly used therapeutic drugs and several environmental pollutants and procarcinogens. Hepatic CYP3A4 activity is poorly expressed in the fetus but increases after birth to reach 30% of adult values by 1 month and 50% of adult values between 6 and 12 months of age. CYP3A4 can be

induced by a number of drugs, including phenytoin, phenobarbital, and rifampin. Enhanced production of toxic metabolites can overwhelm the capacity of phase 2 reactions. Conversely, numerous inhibitors of CYP3A4 from several different drug classes, such as erythromycin and cimetidine, can lead to toxic accumulations of CYP3A4 substrates. By contrast, although CYP2D6 is also developmentally regulated (maturation by 10 years of age), its activity depends more on genetic polymorphisms than on sensitivity to inducers and inhibitors because more than 70 allelic variants of CYP2D6 significantly influence the metabolism of many drugs. Uridine diphosphate glucuronosyltransferase 1A6, a phase 2 enzyme that glucuronidates acetaminophen, is also absent in the human fetus, increases slightly in the neonate, but does not reach adult levels until sometime after 10 years of age. Mechanisms for the uptake and excretion of organic ions can also be deficient early in life. Impaired drug metabolism via phase 1 and phase 2 reactions present in the first few months of life is followed by a period of enhanced metabolism of many drugs in children through 10 years of age compared with adults.

Genetic polymorphisms in genes encoding enzymes and transporters mediating phases 1, 2, and 3 reactions can also be associated with impaired drug metabolism and an increased risk of hepatotoxicity. Some cases of **idiosyncratic hepatotoxicity** can occur as a result of aberrations (polymorphisms) in phase 1 drug metabolism, producing intermediates of unusual hepatotoxic potential combined with developmental, acquired, or relative inefficiency of phase 2 conjugating reactions. Genome-wide association studies have identified HLA associations in certain cases of **drug- and toxin-induced liver injury (DILI)**. Children may be less susceptible than adults to hepatotoxic reactions; liver injury after the use of the anesthetic halothane is rare in children, and acetaminophen toxicity is less common in infants than in adolescents, whereas most cases of fatal hepatotoxicity associated with sodium valproate use have been reported in children. Excessive or prolonged therapeutic administration of acetaminophen combined with reductions in caloric or protein intake can produce hepatotoxicity in children. In this setting, acetaminophen metabolism may be impaired by reduced synthesis of sulfated and glucuronated metabolites and reduced stores of glutathione. Immaturity of hepatic drug metabolic pathways can prevent degradation of a toxic agent; under other circumstances, the same immaturity might limit the formation of toxic metabolites. Severe sodium valproate hepatotoxicity is often associated with an underlying inherited mitochondrial disorder (**Alpers syndrome**).

Chemical hepatotoxicity can be predictable or idiosyncratic. Predictable hepatotoxicity implies a high incidence of hepatic injury in exposed persons depending on dose. It is understandable that only a few drugs in clinical use fall into this category. These agents might damage the hepatocyte directly through alteration of membrane lipids (peroxidation) or through denaturation of proteins; such agents include carbon tetrachloride and trichloroethylene. Indirect injury can occur through interference with metabolic pathways essential for cell integrity or through distortion of cellular constituents by covalent binding of a reactive metabolite; examples include the liver injury produced by acetaminophen or by antimetabolites such as methotrexate or 6-mercaptopurine.

**Idiosyncratic hepatotoxicity** is unpredictable and accounts for the majority of adverse reactions. Higher doses of drugs metabolized in the liver pose a greater risk for hepatotoxicity. Idiosyncratic drug reactions in certain patients can reflect aberrant pathways for drug metabolism, possibly related to genetic polymorphisms, with production of toxic intermediates (isoniazid and sodium valproate can cause liver damage through this mechanism). Duration of drug use before liver injury varies (weeks to  $\geq 1$  year) and the response to reexposure may be delayed.

An idiosyncratic reaction can also be immunologically mediated as a result of prior sensitization (**hypersensitivity**); extrahepatic manifestations of hypersensitivity can include fever, rash, arthralgia, and eosinophilia. Duration of exposure before reaction is generally 1-4 weeks, with prompt recurrence of injury on reexposure. Studies indicate that arene oxides, generated through oxidative (CYP) metabolism of aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine),

**Table 411.1** Most Common or Well-Described Drug-Induced Liver Injury Agents and the Patterns of Their Liver Injury

	LATENCY*	TYPICAL PATTERN OF INJURY/IDENTIFYING FEATURES
<b>ANTIBIOTICS</b>		
Amoxicillin/clavulanate	Short to moderate	Cholestatic injury but can be hepatocellular; drug-induced liver injury onset is frequently detected after drug cessation
Isoniazid	Moderate to long	Acute hepatocellular injury similar to acute viral hepatitis
Trimethoprim/sulfamethoxazole	Short to moderate	Cholestatic injury but can be hepatocellular; often with immunoallergic features (e.g., fever, rash, and eosinophilia)
Fluoroquinolones	Short	Variable—hepatocellular, cholestatic, or mixed in relatively similar proportions
Macrolides	Short	Hepatocellular but can be cholestatic
Nitrofurantoin		Hepatocellular
Acute form (rare)	Short	Typically hepatocellular; often resembles idiopathic autoimmune hepatitis
Chronic form	Moderate to long (months-years)	Hepatocellular
Minocycline	Moderate to long	Hepatocellular and often resembles autoimmune hepatitis
<b>ANTIEPILEPTICS</b>		
Phenytoin	Short to moderate	Hepatocellular, mixed, or cholestatic often with immune-allergic features (e.g., fever, rash, and eosinophilia) (anticonvulsant hypersensitivity syndrome)
Carbamazepine	Moderate	Hepatocellular, mixed, or cholestatic often with immune-allergic features (anticonvulsant hypersensitivity syndrome)
Lamotrigine	Moderate	Hepatocellular often with immune-allergic features (anticonvulsant hypersensitivity syndrome)
Valproate		
Hyperammonemia	Moderate to long	Elevated blood ammonia and encephalopathy
Hepatocellular	Moderate to long	Hepatocellular
Reye-like syndrome	Moderate	Hepatocellular, acidosis; microvesicular steatosis on biopsy
<b>ANALGESICS</b>		
Nonsteroidal antiinflammatory agents	Moderate to long	Hepatocellular injury
Diclofenac		Hepatocellular injury with autoimmune features
<b>IMMUNE MODULATORS</b>		
Interferon-beta	Moderate to long	Hepatocellular
Interferon-alpha	Moderate	Hepatocellular, autoimmune hepatitis-like
Anti-TNF agents	Moderate to long	Hepatocellular. Can have autoimmune hepatitis features
Azathioprine	Moderate to long	Cholestatic or hepatocellular but can present with portal hypertension (veno-occlusive disease and nodular regenerative hyperplasia)
<b>IMMUNE-CHECKPOINT INHIBITORS</b>		
Ipilimumab (CTLA-4 inhibitor) Nivolumab, pembrolizumab, and cemiplimab (PD-1 inhibitors) Atezolizumab, avelumab, and durvalumab (PDL-1 inhibitors)	Under 12 wk	Initially mixed pattern but evolves primarily into hepatocellular pattern, without significant autoantibodies
<b>MISCELLANEOUS</b>		
Methotrexate (oral)	Long	Fatty liver, fibrosis
Allopurinol	Short to moderate	Hepatocellular or mixed. Often with immune-allergic features. Granulomas often present on biopsy
Amiodarone (oral)	Moderate to long	Hepatocellular, mixed, or cholestatic. Macrovesicular steatosis and steatohepatitis on biopsy
Androgen-containing steroids	Moderate to long	Cholestatic. Can present with peliosis hepatis, nodular regenerative hyperplasia, or hepatocellular carcinoma
Inhaled anesthetics	Short	Hepatocellular. May have immune-allergic features ± fever
Sulfasalazine	Short to moderate	Mixed, hepatocellular, or cholestatic. Often with immunoallergic features
Proton pump inhibitors	Short	Hepatocellular; very rare

\*Short = 3-30 days; moderate = 30-90 days; long >90 days.

CTLA-4, Cytotoxic T-lymphocyte antigen-4; PD-1, programmed cell death receptor-1; PDL-1, programmed cell death receptor-ligand 1; TNF, tumor necrosis factor.

From Chalasani NP, Maddur H, Russo MW, et al. ACG clinical guideline: diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol*. 2021;116(5):878-898. Table 6.

REMEDY	POPULAR USES	SOURCE	HEPATOTOXIC COMPONENT	TYPE OF LIVER INJURY
Ayurvedic herbal medicine	Multiple	Multiple	Uncertain (may contain heavy metal contaminants)	Hepatitis
Barakol	Anxiolytic	<i>Cassia siamea</i>	Uncertain	Reversible hepatitis or cholestasis
Black cohosh	Menopausal symptoms	<i>Cimicifuga racemosa</i>	Uncertain	Hepatitis (causality uncertain)
"Bush tea"	Fever	<i>Senecio</i> , <i>Heliotropium</i> , <i>Crotalaria</i> spp.	Pyrrolizidine alkaloids	SOS
Cascara	Laxative	<i>Cascara sagrada</i>	Anthracene glycoside	Cholestatic hepatitis
Chaparral leaf (greasewood, creosote bush)	"Liver tonic," burn salve, weight loss	<i>Larrea tridentata</i>	Nordihydroguaiaretic acid	Acute and chronic hepatitis, FHF
Chaso/onshido	Weight loss	—	N-nitro-fenfluramine	Acute hepatitis, FHF
Chinese medicines (traditional)				
Jin bu huan	Sleep aid, analgesic	<i>Lycopodium serratum</i>	Levo-tetrahydropalmatine	Acute or chronic hepatitis or cholestasis, steatosis
Ma huang	Weight loss	<i>Ephedra</i> spp.	Ephedrine	Severe hepatitis, FHF
Shou-wu-pian	Antiaging, neuroprotection, laxative	<i>Polygonum multiflorum</i> Thunb. (fleeceflower root)	Anthraquinone	Acute hepatitis or cholestasis
Syo-saiko-to	Multiple	<i>Scutellaria</i> root	Diterpenoids	Hepatocellular necrosis, cholestasis, steatosis, granulomas
Comfrey	Herbal tea	<i>Symphytum</i> spp.	Pyrrolizidine alkaloid	Acute SOS, cirrhosis
Germaneder	Weight loss, fever	<i>Teucrium chamaedrys</i> , <i>T. capitatum</i> , <i>T. polium</i>	Diterpenoids, epoxides	Acute and chronic hepatitis, FHF, autoimmune injury
Greater celandine	Gallstones, IBS	<i>Chelidonium majus</i>	Isoquinoline alkaloids	Cholestatic hepatitis, fibrosis
Green tea leaf extract	Multiple	<i>Camellia sinensis</i>	Catechins	Hepatitis (causality questioned)
Herbalife	Nutritional supplement, weight loss	—	Various; ephedra	Severe hepatitis, FHF
Hydroxycut	Weight loss	<i>Camellia sinensis</i> , among other constituents	Uncertain	Acute hepatitis, FHF
Impila	Multiple	<i>Callilepis laureola</i>	Potassium atractylate	Hepatic necrosis
Kava	Anxiolytic	<i>Piper methysticum</i>	Kava lactone, pipermethystine	Acute hepatitis, cholestasis, FHF
Kombucha	Weight loss	Lichen alkaloid	Usnic acid	Acute hepatitis
Limbrel (Flavocoxid)	Osteoarthritis	Plant bioflavonoids	Baicalin, epicatechin	Acute mixed hepatocellular-cholestatic injury
Lipokinetix	Weight loss	Lichen alkaloid	Usnic acid	Acute hepatitis, jaundice, FHF
Mistletoe	Asthma, infertility	<i>Viscum album</i>	Uncertain	Hepatitis (in combination with skullcap)
Oil of cloves	Dental pain	Various foods, oils	Eugenol	Zonal necrosis
Pennyroyal (squawmint oil)	Abortifacient	<i>Hedeoma pulegioides</i> , <i>Mentha pulegium</i>	Pulegone, monoterpenes	Severe hepatocellular necrosis
Prostata	Prostatism	Multiple	Uncertain	Chronic cholestasis
Sassafras	Herbal tea	<i>Sassafras albidum</i>	Safrole	HCC (in animals)
Senna	Laxative	<i>Cassia angustifolia</i>	Sennoside alkaloids; anthrone	Acute hepatitis
Skullcap	Anxiolytic	<i>Scutellaria</i>	Diterpenoids	Hepatitis
Valerian	Sedative	<i>Valeriana officinalis</i>	Uncertain	Elevated liver enzymes

FHF, Fulminant hepatic failure; HCC, hepatocellular carcinoma; SOS, sinusoidal obstruction syndrome.

From Lewis JH. Liver disease caused by anesthetics, chemicals, toxins, and herbal preparations. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 10th ed. Philadelphia: Elsevier; 2016: Table 89.6.

can initiate the pathogenesis of some hypersensitivity reactions. Arene oxides, formed in vivo, can bind to cellular macromolecules, thus perturbing cell function and possibly initiating immunologic mechanisms of liver injury.

The pathogenesis of hepatotoxicity is most likely multifactorial, particularly the role played by the host immune system. Activation of liver nonparenchymal Kupffer cells and infiltration by neutrophils perpetuate toxic injury by many drugs by release of reactive oxygen and nitrogen species as well as cytokines. Stellate cells can also be activated, potentially leading to hepatic fibrosis and cirrhosis.

The pathologic spectrum of drug-induced liver disease is extremely wide, is rarely specific, and can mimic other liver diseases (Table 411.3; see also Table 411.1). Predictable hepatotoxins, such as acetaminophen, produce centrilobular necrosis of hepatocytes. **Steatosis** is an important feature of tetracycline (microvesicular) and ethanol (macrovesicular) toxicities. A cholestatic hepatitis can be observed, with injury caused by erythromycin estolate and chlorpromazine. **Cholestasis** without inflammation may be a toxic effect of estrogens and anabolic steroids. Use of oral contraceptives and androgens has also been associated with benign and malignant liver tumors. Some idiosyncratic drug reactions can produce mixed patterns of injury, with diffuse cholestasis and cell necrosis. Chronic hepatitis has been associated with the use of methyldopa and nitrofurantoin.

Clinical manifestations can be mild and nonspecific, such as fever and malaise. Fever, rash, and arthralgia may be prominent in cases of hypersensitivity. In ill hospitalized patients, the signs and symptoms of

hepatic drug toxicity may be difficult to separate from the underlying illness. The differential diagnosis should include acute and chronic viral hepatitis, biliary tract disease, septicemia, ischemic and hypoxic liver injury, malignant infiltration, and inherited metabolic liver disease.

The laboratory features of drug- or toxin-related liver disease are extremely variable. Hepatocyte damage can lead to elevations of serum aminotransferase activities and serum bilirubin levels and to impaired synthetic function as evidenced by decreased serum coagulation factors and albumin. Hyperammonemia can occur with liver failure or with selective inhibition of the urea cycle (sodium valproate). Toxicologic screening of blood and urine specimens can aid in detecting drug or toxin exposure. Percutaneous liver biopsy may be necessary to distinguish drug injury from complications of an underlying disorder or from intercurrent infection. Vanishing bile duct syndrome can be seen in a small portion of patients with idiosyncratic DILI.

Slight elevation of serum aminotransferase activities (generally <2–3 times normal) can occur during therapy with drugs, particularly anticonvulsants, capable of inducing microsomal pathways for drug metabolism. Liver biopsy reveals proliferation of smooth endoplasmic reticulum but no significant liver injury. Liver test abnormalities often resolve with continued drug therapy.

## TREATMENT

Treatment of drug- or toxin-related liver injury is mainly supportive. Contact with the offending agent should be avoided. Corticosteroids might have a role in immune-mediated disease. Treatment with *n*-acetylcysteine, by stimulating glutathione synthesis, is effective in preventing or attenuating hepatotoxicity when administered within 16 hours after an acute overdose of acetaminophen and appears to improve survival in patients with severe liver injury even up to 36 hours after ingestion. Intravenous L-carnitine may be of value in treating valproic acid-induced hepatotoxicity. Orthotopic liver transplantation may be required for treatment of drug- or toxin-induced hepatic failure.

## PROGNOSIS

The prognosis of DILI depends on its type and severity. Injury is usually completely reversible when the hepatotoxic factor is withdrawn. The mortality of submassive hepatic necrosis with fulminant liver failure can, however, exceed 50%. Hyperbilirubinemia, coagulopathy, and elevated serum creatinine are associated with an increased risk of death or need for liver transplantation. With continued use of certain drugs, such as methotrexate, effects of hepatotoxicity can proceed insidiously to cirrhosis, even with normal or near normal liver tests. Neoplasia can follow long-term androgen therapy. Rechallenge with a drug suspected of having caused previous liver injury is rarely justified and can result in fatal hepatic necrosis.

## PREVENTION

The prevention of drug-induced liver injury remains a challenge. Monitoring of liver biochemical tests may be useful in some cases, but it can prove difficult to sustain for agents used for many years. Children who take medications with potential for hepatotoxicity, such as some anticonvulsants and antineoplastic drugs, require frequent monitoring for evidence of liver injury. Such testing may be particularly important in patients with preexisting liver disease. For drugs with hepatotoxic potential, even if episodes are infrequent in children, such as with the use of isoniazid, patients should be advised to immediately stop the medication with onset of nausea, vomiting, abdominal pain, and fatigue until liver damage is excluded. Obvious symptoms of liver disease, such as jaundice and dark urine, can lag behind severe hepatocellular injury. Monitoring for toxic metabolites and genotyping can be effective in preventing severe toxicity with the use of azathioprine. Advances in pharmacogenomics, such as the use of gene chips to detect variants in some of the CYP enzymes, hold promise of a personalized approach to prevent hepatotoxicity.

**Table 411.3** Patterns of Hepatic Drug Injury

DISEASE	DRUG
Centrilobular necrosis	Acetaminophen Carbon tetrachloride Cocaine Ecstasy Iron Halothane
Microvesicular steatosis	Valproic acid Tetracycline Toluene Methotrexate
Acute hepatitis	Isoniazid Anti-tumor necrosis factor agents Valproic acid
General hypersensitivity	Sulfonamides Phenytoin Minocycline
Fibrosis	Methotrexate
Cholestasis	Chlorpromazine Aniline Erythromycin Paraquat Estrogens Sertraline
Sinusoidal obstruction syndrome (venoocclusive disease)	Irradiation plus busulfan Arsenic Cyclophosphamide
Portal and hepatic vein thrombosis	Estrogens Androgens
Biliary sludge	Ceftriaxone
Hepatic adenoma or hepatocellular carcinoma	Oral contraceptives Anabolic steroids

## Chapter 412

## Acute Hepatic Failure

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Acute liver failure is a clinical syndrome associated with significant morbidity and mortality resulting from massive necrosis of hepatocytes or from severe functional impairment of hepatocytes. The synthetic, excretory, and detoxifying functions of the liver are all severely impaired. In adults, hepatic **encephalopathy** has been an essential diagnostic feature. However, in pediatrics, this narrow definition may be problematic because early hepatic encephalopathy can be difficult to detect in infants and children, and some children in acute liver failure may not develop encephalopathy (Table 412.1). The accepted definition in children includes biochemical evidence of acute liver injury (usually <8 weeks duration); no evidence of chronic liver disease; and hepatic-based coagulopathy defined as a prothrombin time (PT) >15 seconds or international normalized ratio (INR) >1.5 not corrected by vitamin K in the *presence* of clinical hepatic encephalopathy, or a PT >20 seconds or INR >2 *regardless* of the presence of clinical hepatic encephalopathy.

Liver failure in the perinatal period can be associated with prenatal liver injury and even cirrhosis. Examples include **gestational allo-immune liver disease** (GALD), tyrosinemia, familial **hemophagocytic lymphohistiocytosis** (HLH), and some cases of congenital viral (herpes simplex virus [HSV]) infection. Liver disease may be noticed at birth or after several days of apparent well-being. Fulminant **Wilson disease** and fulminant **autoimmune hepatitis** also occurs in older children who were previously asymptomatic but, by definition, have preexisting liver disease (Table 412.2). Other forms of acute-on-chronic liver failure can occur when a patient with an underlying liver disease such as biliary atresia develops hepatic decompensation after viral or **drug-induced hepatic injury**. In some cases of liver failure, particularly in the idiopathic form of acute hepatic failure, the onset of encephalopathy occurs later, from 8 to 28 weeks after the onset of jaundice.

## ETIOLOGY

## Infection

Acute hepatic failure can be a complication of **viral hepatitis** (A, B, D, and, rarely, E), Epstein-Barr virus (EBV), HSV, adenovirus, adeno-associated virus, enterovirus, influenza A, cytomegalovirus, parvovirus B19, human herpesvirus (HHV)-6, varicella zoster infection, parechovirus, coronavirus-2 (SARS-CoV-2) and other respiratory illnesses (see Table 412.2; see also Chapter 406). An unusually high rate of fulminant hepatic failure occurs in young people who have combined infections with the hepatitis B virus (HBV) and hepatitis D. Pathogenic gene variants in the precore and/or promoter region of HBV DNA are associated with fulminant and severe hepatitis. HBV is also responsible for some cases of fulminant liver failure in the absence of serologic markers of HBV infection but with HBV DNA found in the liver. Hepatitis E virus is an uncommon cause of fulminant hepatic failure in the United States but can occur in pregnant women, in whom mortality rates rise dramatically to up to 25%. Patients with chronic hepatitis C are at risk if they have superinfection with hepatitis A virus.

## Autoimmune Hepatitis

Acute hepatic failure is caused by **autoimmune hepatitis** in approximately 5–28% of cases (see Chapter 410). Patients have a positive autoimmune marker (e.g., antinuclear antibody, anti-smooth muscle antibody, liver-kidney microsomal antibody, or soluble liver antigen) and possibly an elevated serum immunoglobulin G level. If a biopsy can be performed, liver histology often demonstrates interface hepatitis and a plasma cell infiltrate.

## Metabolic Diseases

Metabolic disorders account for 28–36% of cases of pediatric acute liver failure and include galactosemia, tyrosinemia, hereditary fructose intolerance, Niemann-Pick type C, mitochondrial hepatopathies (in particular, mitochondrial DNA depletion disorders), urea cycle defects, defects in β-oxidation of fatty acids, and disorders of bile acid synthesis in infants and young children and **Wilson disease** and acute fatty liver of pregnancy in older children (see Table 412.2; see also Chapters 405.1 and 405.5). Family history of consanguinity, recurrent pregnancy loss, stillbirths, or death of children before the age of 1 and/or patient history of diarrhea, vomiting, failure to thrive, or developmental delay should alert one to the possibility of metabolic disease. Patients with Wilson disease who present in acute

**Table 412.1** Hepatic Encephalopathy in Pediatric Acute Liver Failure

STAGE		CLINICAL	REFLEXES	NEUROLOGIC SIGNS	EEG CHANGES
0		None	Normal	None	Normal
I	Infant/child	Inconsolable, crying, inattention to task, parents describe child as "not acting like self"	Normal or hyperreflexia	Difficult or impossible to assess	Normal or diffuse slowing to theta rhythm, triphasic waves
	Adolescent/young adult	Confused, mood changes, altered sleep habits, forgetful	Normal	Tremor, apraxia, impaired handwriting	
II	Infant/child	Inconsolable, crying, inattention to task, parents describe child as "not acting like self"	Normal or hyperreflexia	Difficult or impossible to assess	Abnormal, generalized slowing, triphasic waves
	Adolescent/young adult	Drowsy, inappropriate behavior, decreased inhibitions	Hyperreflexia	Dysarthria, ataxia	
III	Infant/child	Somnolence, stupor, combativeness	Hyperreflexia	Difficult or impossible to assess	Abnormal, generalized slowing, triphasic waves
	Adolescent/young adult	Stuporous, obeys simple commands	Hyperreflexia, (+) Babinski	Rigidity	
IV	Infant/child	Comatose, arouses with painful stimuli (IVa) or no response (IVb)	Absent	Decerebrate or decorticate	Abnormal, very slow, delta activity
	Adolescent/young adult	Comatose, arouses with painful stimuli (IVa) or no response	Absent	Decerebrate or decorticate	

EEG, Electroencephalography.

Modified from Squires RH Jr. Acute liver failure in children. *Semin Liver Dis.* 2008;28(2):157–166. Table 1.

**Table 412.2** Etiologies of Acute Liver Failure**DRUG-INDUCED LIVER INJURY**

Acetaminophen

Antibiotics: amoxicillin-clavulanate, ciprofloxacin, nitrofurantoin, minocycline, dapsoe, doxycycline, trimethoprim-sulfamethoxazole, efavirenz, didanosine, abacavir, ketoconazole

Antiepileptics: valproic acid, phenytoin, carbamazepine

Antituberculosis drugs: isoniazid, rifampin-isoniazid, pyrazinamide

Antihypertensives: methyldopa, hydralazine, labetalol, nicotinic acid (slow release)

NSAIDs: diclofenac, ibuprofen, indomethacin, naproxen

Herbs and supplements: ma huang, kava kava, Herbalife, green tea extract, ginseng, black cohosh, anabolic steroids

Anesthetics: halothane

Miscellaneous: propylthiouracil, amitriptyline, statins, amiodarone, methotrexate

**VIRAL HEPATITIS**Hepatitis A, B ( $\pm$ D), C, and E

Adenovirus, adeno-associated virus, CMV, EBV, herpes virus, parvovirus, varicella zoster virus

**PREGNANCY-RELATED LIVER DISEASE**

Acute fatty liver of pregnancy

HELLP syndrome

Preeclampsia-associated liver disease

Acute hepatic rupture

**ISCHEMIC HEPATITIS**

Systemic hypotension

Budd-Chiari syndrome

Hepatic artery thrombosis

Congestive hepatopathy

**REVERSIBLE ETIOLOGIES**

Autoimmune hepatitis

Leptospirosis, hepatic amoebiasis, malaria, rickettsial disease

**GENETIC**

Wilson disease

Galactosemia

Urea cycle defects

Hereditary fructose intolerance

Hemochromatosis

Mitochondrial disorders

 $\alpha_1$ -Antitrypsin deficiency

Tyrosinemia

Pathogenic variants in NBAS, DLD, CPT1A, FAH, LARS1, MPV17, NPC1, POLG, SUCLG1, TWINK, DGUOK, RINT1, SCYL1, ITCH

**MISCELLANEOUS**

Malignancy

Mushroom poisoning

Heat injury

Reye syndrome

Hemophagocytic lymphohistiocytosis

Gestational alloimmune liver disease

Idiopathic

NSAID, Nonsteroidal antiinflammatory drug; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HELLP, hemolysis, elevated liver enzymes, low platelet count.

Modified from Montrif T, Koyfman A, Long B. Acute liver failure: a review for emergency physicians. Am J Emerg Med. 2019;37:329–337. Table 3.

Liver failure often have high bilirubin levels, low alkaline phosphatase levels, low uric acid levels, aspartate aminotransferase levels that are higher than alanine aminotransferase levels, and a Coombs-negative hemolytic anemia.

**Neoplasm**

Acute liver failure can occur with malignancies, including leukemia, lymphoma, and **familial HLH**. Acute liver failure is a common feature of HLH caused by several gene defects, infections by mostly viruses of the herpes group, and a variety of other conditions, including organ transplantation and malignancies. Impaired function of natural killer cells and cytotoxic T-lymphocyte cells with uncontrolled

hemophagocytosis and cytokine overproduction is characteristic for genetic and acquired forms of HLH. Patients with HLH present with a combination of fever, splenomegaly, cytopenias, high triglyceride levels, very high ferritin levels, low natural killer cell activity, and high soluble CD25 levels; they may also have hemophagocytosis on bone marrow or liver biopsy (see Chapter 556).

**Gestational Alloimmune Liver Disease**

GALD is the most common cause of acute liver failure in the neonate (see Chapter 405.4). In this alloimmune process, maternal immunoglobulin (Ig) G antibodies bind to fetal liver antigens and activate the terminal complement cascade, resulting in hepatocyte injury and death. Infants with GALD present at birth or within the first few days of life with low/normal aminotransferases that are out of proportion to their degree of liver failure. They may have significant hypoglycemia, jaundice, coagulopathy, and hypoalbuminemia. Alpha fetoprotein levels are typically high, as are serum ferritin levels. Extrahepatic iron deposition can be observed on MRI or buccal biopsy.

**Drug-Induced Liver Injury**

Various hepatotoxic drugs and chemicals can also cause drug-induced liver injury and acute hepatic failure (see Table 412.2; see also Chapter 411). Predictable liver injury can occur after exposure to carbon tetrachloride or *Amanita phalloides* mushrooms or after acetaminophen overdose. Acetaminophen is the most common identifiable etiology of acute hepatic failure in children and adolescents in the United States and England. In addition to the acute intentional ingestion of a massive dose, a therapeutic misadventure leading to severe liver injury can also occur in ill children given doses of acetaminophen exceeding weight-based recommendations for many days. Such patients can have reduced stores of glutathione after a prolonged illness and a period of poor nutrition. Idiosyncratic damage can follow the use of drugs such as halothane, isoniazid, ecstasy, or sodium valproate. Herbal and weight loss supplements are additional causes of hepatic failure (see Chapter 411). The website Liver Tox (<https://www.ncbi.nlm.nih.gov/books/NBK547852/>) is available to provide up-to-date information about liver injury attributable to medications, herbs, and dietary supplements.

**Vascular**

Ischemia and hypoxia resulting from hepatic vascular occlusion, severe heart failure, cyanotic congenital heart disease, or circulatory shock can produce liver failure. Venoocclusive disease (VOD) is a clinical process characterized by weight gain, painful hepatomegaly, ascites, and hyperbilirubinemia resulting from hepatic sinusoidal obstruction, most commonly after hematopoietic stem cell transplant. Liver failure is uncommon with VOD but can occur.

**Idiopathic Acute Liver Failure**

Idiopathic acute liver failure accounts for 40–50% of acute hepatic failure cases in children. The disease occurs sporadically and usually without the risk factors for common causes of viral hepatitis. It is likely that the etiology of these cases is heterogeneous, including unidentified or variant viruses, excessive immune activation, and undiagnosed genetic or metabolic disorders. There is increasing recognition of some children presenting with indeterminate acute hepatitis or acute liver failure who have evidence of immune activation, including markedly elevated soluble interleukin 2 receptor (sIL-2R) levels but never fulfilling diagnostic criteria for HLH.

**Other**

There is a growing category of autosomal recessive disorders including pathogenic variants in the neuroblastoma amplified sequence gene NBAS, LARS, SCYL1, and RINT1 that can result in recurrent episodes of pediatric acute liver failure, sometimes associated with concurrent fevers (see Table 412.2). Patients with NBAS variants may also have short stature, skeletal abnormalities, intellectual disability, ophthalmic and facial abnormalities, cardiac abnormalities, and low serum

immunoglobulins. Patients with *SCYL1* variants may have low gamma-glutamyl transpeptidase (GGT), cholestasis, and a variable neurologic phenotype. Patients with *RINT1* variants may have persistently abnormal liver function tests (LFTs) between acute liver failure episodes. Most patients recovered with restoration of normal liver function after control of fever and maintenance of energy balance with the infusion of intravenous glucose.

### PATHOLOGY

Liver biopsy usually reveals patchy or confluent massive necrosis of hepatocytes. Multilobular or bridging necrosis can be associated with collapse of the reticulin framework of the liver. There may be little or no regeneration of hepatocytes. A zonal pattern of necrosis may be observed with certain insults. Centrilobular damage is associated with acetaminophen hepatotoxicity or with circulatory shock. Evidence of severe hepatocyte dysfunction rather than cell necrosis is occasionally the predominant histologic finding (microvesicular fatty infiltrate of hepatocytes is observed in Reye syndrome,  $\beta$ -oxidation defects, and tetracycline toxicity).

### PATHOGENESIS

It is unknown why only approximately 1–2% of patients with viral hepatitis experience liver failure. Massive destruction of hepatocytes might represent both a direct cytotoxic effect of the virus and an immune response to the viral antigens. Of patients with HBV-induced liver failure, 30–50% become negative for serum hepatitis B surface antigen within a few days of presentation and often have no detectable HBV antigen or HBV DNA in serum. These findings suggest a hyperimmune response to the virus that underlies the massive liver necrosis. Formation of hepatotoxic metabolites that bind covalently to macromolecular cell constituents is involved in the liver injury produced by drugs such as acetaminophen and isoniazid; acute hepatic failure can follow depletion of intracellular substrates involved in detoxification, particularly glutathione. Whatever the initial cause of hepatocyte injury, various factors can contribute to the pathogenesis of liver failure, including impaired hepatocyte regeneration, altered parenchymal perfusion, endotoxemia, and decreased hepatic reticuloendothelial function.

### CLINICAL MANIFESTATIONS

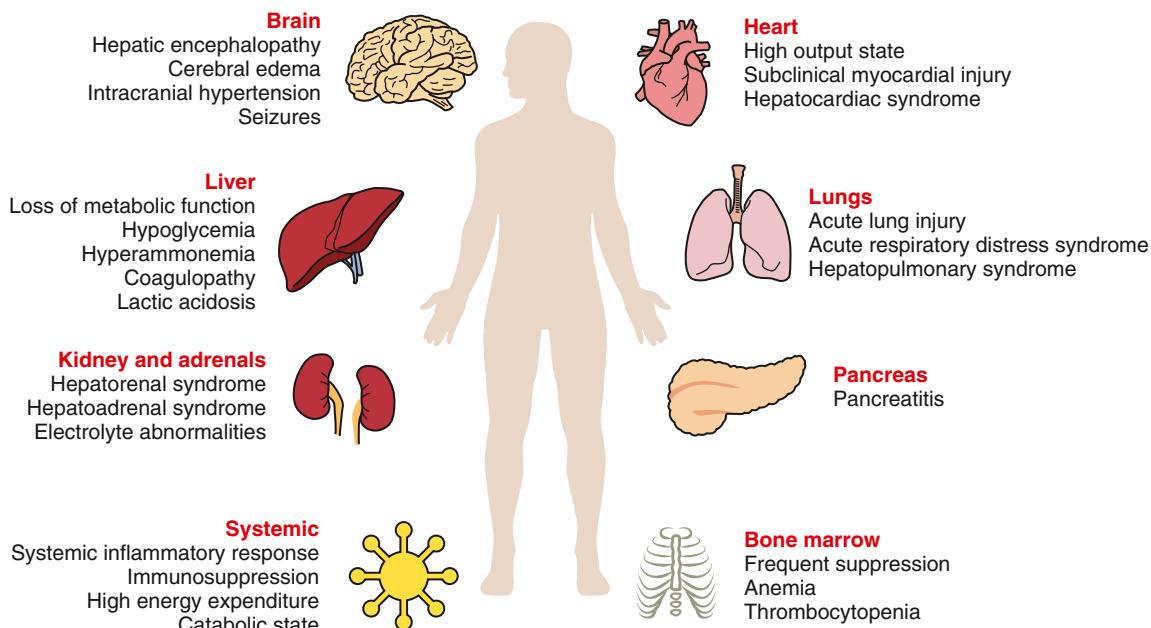
Acute hepatic failure can be the presenting feature of liver disease, or it can complicate previously known liver disease (**acute-on-chronic liver failure**). Progressive jaundice, fetor hepaticus, fever, anorexia, vomiting, and abdominal pain are common. A rapid decrease in liver size without clinical improvement is an ominous sign. A hemorrhagic diathesis and ascites can develop. In addition, acute liver failure is a multisystem disorder (Fig. 412.1).

Patients should be closely observed for hepatic encephalopathy, which is initially characterized by minor disturbances of consciousness or motor function. Irritability, poor feeding, and a change in sleep rhythm may be the only findings in infants; asterixis may be demonstrable in older children. Patients are often somnolent, confused, or combative on arousal and can eventually become responsive only to painful stimuli. Patients can rapidly progress to deeper stages of coma in which extensor responses and decerebrate and decorticate posturing appear. Respirations are usually increased early, but respiratory failure can occur in stage IV coma (see Table 412.1). The pathogenesis of hepatic encephalopathy is likely related to increased serum levels of ammonia, false neurotransmitters, amines, increased  $\gamma$ -aminobutyric acid receptor activity, or increased circulating levels of endogenous benzodiazepine-like compounds. Decreased hepatic clearance of these substances can produce marked central nervous system dysfunction. The mechanisms responsible for cerebral edema and intracranial hypertension in acute liver failure suggest both cytotoxic and vasogenic injury (Fig. 412.2). There is increasing evidence for an inflammatory response (synthesis and release of inflammatory factors from activated microglia and endothelial cells), which acts in synergy with hyperammonemia to cause severe astrocyte swelling/brain edema.

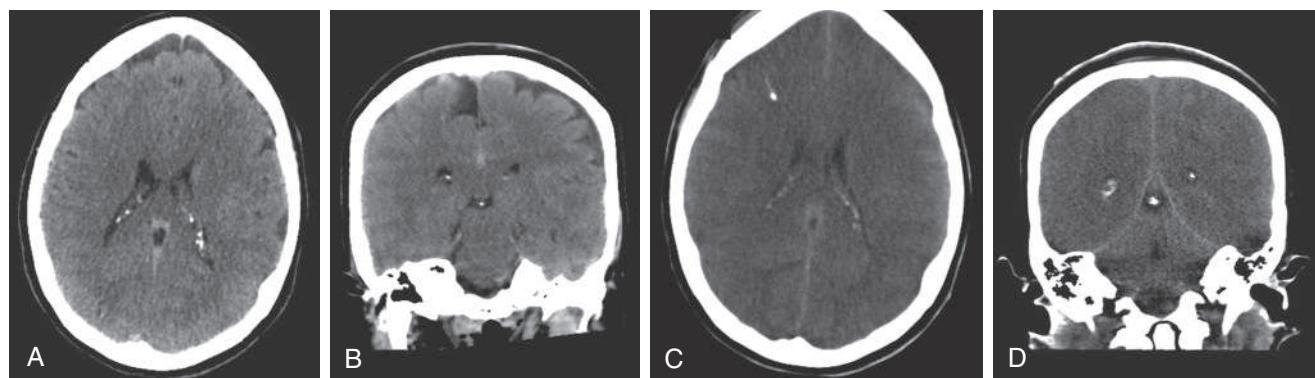
### LABORATORY FINDINGS

Serum direct and indirect bilirubin levels and serum aminotransferase activities may be markedly elevated. Serum aminotransferase activities do not correlate well with the severity of the illness and can decrease as a patient deteriorates. The blood ammonia concentration is usually increased, but hepatic coma can occur in patients with a normal blood ammonia level. PT and the INR are prolonged and do not improve after parenteral administration of vitamin K. Hypoglycemia can occur,

### Clinical manifestations of acute liver failure



**Fig. 412.1** Clinical manifestations of acute liver. (From Montrif T, Koyfman A, Long B. Acute liver failure: a review for emergency physicians. Am J Emerg Med. 2019;37:329–337. Fig. 1.)



**Fig. 412.2** CT of the head in a patient with acute liver failure (ALF) who developed cerebral edema. **A**, Axial scan before the development of cerebral edema. **B**, Coronal scan before the development of cerebral edema. **C**, Axial scan after the development of cerebral edema. **D**, Coronal scan after development of cerebral edema. All in a dying patient with brainstem herniation because of acetaminophen-induced ALF. **C** and **D** show the loss of gray-white demarcation and effacement of sulci. (From Stravitz RT, Lee WM. Acute liver failure. *Lancet*. 2019;394:869–880. Fig. 3.)

<b>Table 412.3</b> Investigations in Acute Liver Failure	
SERUM CHEMISTRIES	VIRAL HEPATITIS SEROLOGIES
Basic metabolic panel: sodium, potassium, bicarbonate, calcium, magnesium, phosphate, glucose, blood urea nitrogen, creatinine	Anti-HAV IgM
Amylase, lipase	Hep B surface Ag, anti-hep B core Ab IgM
Serum lactate	Hep D Ab, hep D RNA
HEPATIC PANEL	Anti-HCV, ±hepatitis C RNA
AST, ALT, albumin, total bilirubin, alkaline phosphatase	PCR
ARTERIAL BLOOD	±Anti-HEV IgM
Blood gas	Anti-VZV IgM
Serum ammonia	Anti-HSV IgM
TOXICOLOGIC	AUTOIMMUNE MARKERS
Blood alcohol level	Antinuclear antibody
Acetaminophen level	Anti-smooth muscle antibody
Urine toxicology screen	Serum IgG levels
Serum salicylate level	URINE
HEMATOLOGIC	Pregnancy test
Complete blood count	Urinalysis and urine culture
Blood type and screen	Toxicology
Coagulation studies: PT/INR, fibrinogen, PTT, TEG, D-dimer	MISCELLANEOUS
	Serum ceruloplasmin
	Blood cultures
	Electrocardiogram
	Exome sequencing
	Mitochondrial DNA
	Specific gene panels
	IMAGING
	CT brain scan without contrast
	Abdominal US
	Chest x-ray
	Echocardiogram
	Transcranial Doppler

PT, Prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time; TEG, thromboelastography.

Modified from Montrif T, Koyfman A, Long B. Acute liver failure: a review for emergency physicians. *Am J Emerg Med*. 2019;37:329–337. Table 4.

particularly in infants. Hypokalemia, hyponatremia, metabolic acidosis, or respiratory alkalosis can also develop. Laboratory studies are important to monitor the course of liver failure, to detect complications, and to better define the etiology (Table 412.3).

### TREATMENT

Specific therapies for identifiable causes of acute liver failure include *N*-acetylcysteine (acetaminophen), acyclovir (HSV), penicillin (*Amanita* mushrooms), nucleos(t)ide analogs such as entecavir (HBV), and prednisone (autoimmune hepatitis) (Table 412.4). Immunosuppression

<b>Table 412.4</b> Potential Disease-Directed Therapies in Pediatric Acute Liver Failure	
	<b>THERAPY</b>
Acetaminophen toxicity	<i>N</i> -acetylcysteine
Drug-induced liver injury	Cessation of offending agent; consider steroids
Neonatal acute liver failure secondary to gestational alloimmune disease	Exchange transfusion and immunoglobulin
Autoimmune liver disease	Steroids
Vascular etiologies (e.g., Budd-Chiari syndrome and sinusoidal obstruction syndrome)	Anticoagulation and hepatic decompression (usually with a transhepatic portosystemic shunt)
Wilson disease	Copper chelation
Herpes simplex virus	Acyclovir
Adenovirus	Cidofovir
Hepatitis A	No specific treatment
Hepatitis B	Lamivudine, entecavir, tenofovir
Hepatitis E	Ribavirin, $\alpha$ -interferon
Galactosemia	Lactose-free diet
Hereditary fructose intolerance	Fructose-free, sucrose-free, and sorbitol-free diet
Tyrosinemia	2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione in addition to a diet restricted in tyrosine and phenylalanine
Urea cycle defects	Protein restriction, ammonia scavengers; renal replacement therapy might be required

Modified from Deep A, Alexander EC, Bulut Y, et al. Advances in medical management of acute liver failure in children: promoting native liver survival. *Lancet Child Adolesc*. 2022;6:725–737.

with corticosteroids should also be considered in children with the indeterminate form of fulminant hepatic failure with immune activation to avoid progression to liver transplantation or death. However, controlled trials have shown a worse outcome in patients treated with corticosteroids in patients without an immune basis for liver injury. Treatment of GALD involves intravenous immunoglobulin (IVIG)

(1 g/kg) followed by a combination of double-volume exchange transfusion to remove existing reactive antibody and a second dose of IVIG (1 g/kg) to block antibody-induced complement activation.

Management of other types of acute hepatic failure is supportive. No therapy is known to reverse hepatocyte injury or to promote hepatic regeneration (Fig. 412.3). Continuous kidney replacement therapy and extracorporeal liver support have been used as potential bridging therapies pending native liver recovery or liver transplantation.

An infant or child with acute hepatic failure should be cared for in an institution able to perform a liver transplantation if necessary and managed in an intensive care unit (ICU) with continuous monitoring of vital functions. Endotracheal intubation may be required to prevent aspiration, to reduce cerebral edema by hyperventilation, and to facilitate pulmonary toilet. Mechanical ventilation and supplemental oxygen are often necessary in advanced coma. Sedatives should be avoided unless needed in the intubated patient because these agents can aggravate or precipitate encephalopathy. Opiates may be better tolerated than benzodiazepines. Prophylactic use of proton pump inhibitors should be considered because of the high risk of gastrointestinal bleeding.

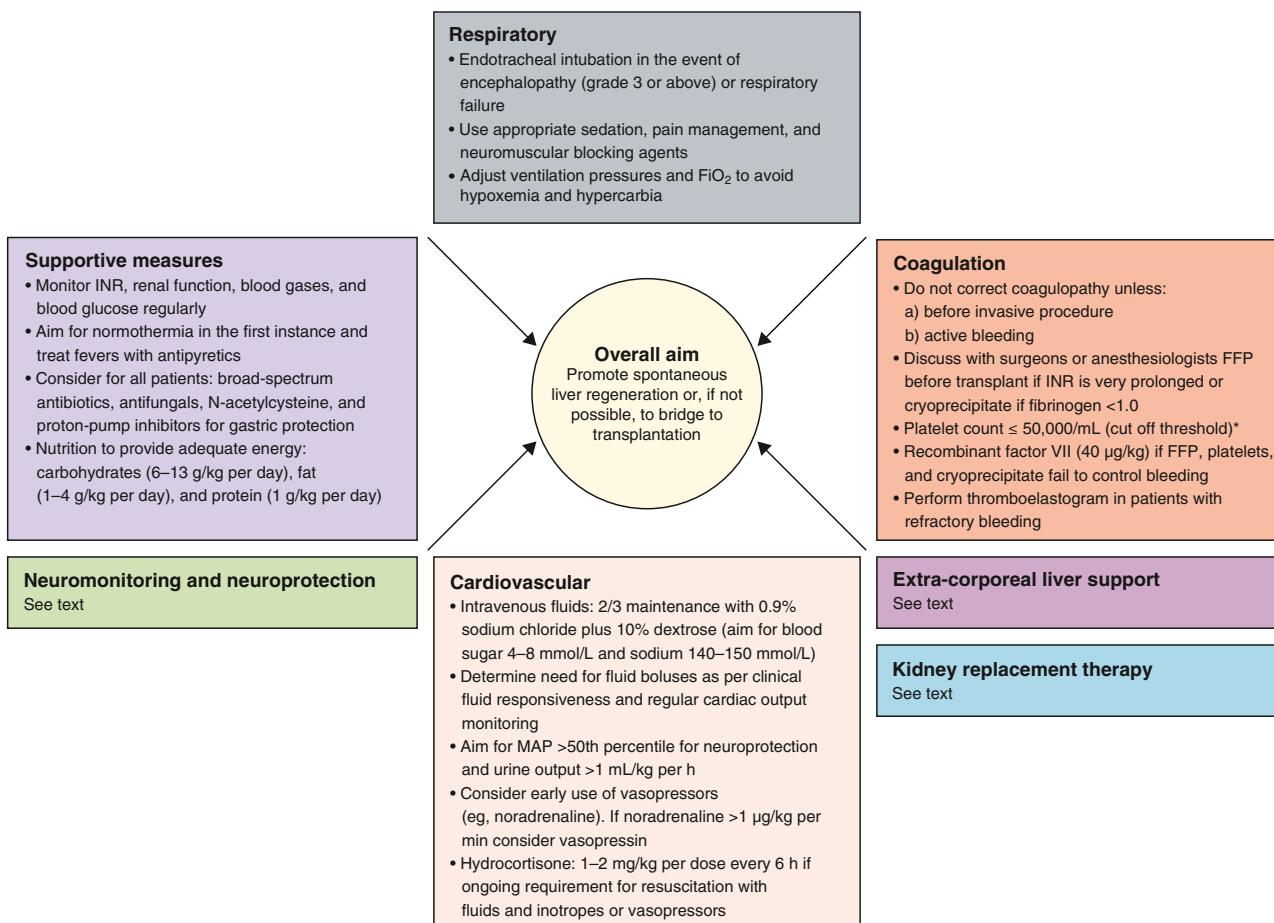
Hypovolemia should be avoided and treated with cautious infusions of *isotonic* fluids and blood products. Renal dysfunction can result from dehydration, acute kidney injury, or functional renal failure (**hepatorenal syndrome**). Electrolyte and glucose solutions should be administered intravenously to maintain urine output, to correct or prevent hypoglycemia, and to maintain normal serum potassium concentrations. In a cardiovascularly stable patient, fluids should be kept around 90% of maintenance. Hyponatremia is common and should be avoided; it is usually dilutional and not a result of sodium depletion.

Parenteral supplementation with calcium, phosphorus, and magnesium may be required. Hypophosphatemia, probably a reflection of liver regeneration, and early phosphorus administration are associated with a better prognosis in acute liver failure, whereas hyperphosphatemia predicts a failure of spontaneous recovery. Coagulopathy should be treated with parenteral administration of vitamin K. Fresh-frozen plasma, cryoprecipitate, platelets, activated factor VII, or prothrombin complex concentrates can be used to treat clinically significant bleeding or can be given if an invasive procedure such as placement of a central line or an intracranial monitor needs to be performed. Plasmapheresis can permit temporary correction of the bleeding diathesis without resulting in volume overload. Continuous hemofiltration is useful for managing fluid overload, acute renal failure, and hyperammonemia.

Patients should be monitored closely for infection, including sepsis, pneumonia, peritonitis, and urinary tract infections. At least 50% of patients experience serious infection. Gram-positive organisms (*Staphylococcus aureus*, *Staphylococcus epidermidis*) are the most common pathogens, but gram-negative and fungal infections are also observed.

Gastrointestinal hemorrhage, infection, constipation, sedatives, electrolyte imbalance, and hypovolemia can precipitate encephalopathy and should be identified and corrected. Protein intake should be restricted to 1 g/kg, depending on the degree of encephalopathy. If encephalopathy or hyperammonemia develops, lactulose or rifaximin can be administered. N-acetylcysteine is not effective in improving the outcome of patients with acute liver failure not associated with acetaminophen.

Cerebral edema is an extremely serious complication of hepatic encephalopathy that responds poorly to measures such as corticosteroid



**Fig. 412.3** Nontransplant management for pediatric acute liver failure. FFP, Fresh-frozen plasma;  $\text{FiO}_2$ , fractional concentration of oxygen in inspired air; INR, international normalized ratio; MAP, mean arterial pressure. \*Platelet counts of  $\leq 50,000$  is controversial. (Modified from Deep A, Alexander EC, Bulut Y, et al. Non-transplant management for paediatric acute liver failure. Advances in medical management of acute liver failure in children: promoting native liver survival. Lancet Child Adolesc. 2022;6:725–737. Fig. 2.)

administration and osmotic diuresis. Monitoring intracranial pressure can be useful in preventing severe cerebral edema, maintaining cerebral perfusion pressure, and establishing the suitability of a patient for liver transplantation.

Temporary liver support continues to be evaluated as a bridge for the patient with liver failure to liver transplantation or regeneration. Non-biologic systems, essentially a form of liver dialysis with an albumin-containing dialysate, and biologic liver support devices that involve perfusion of the patient's blood through a cartridge containing liver cell lines or porcine hepatocytes can remove some toxins, improve serum biochemical abnormalities, and, in some cases, improve neurologic function, but there has been little evidence of improved survival, and few children have been treated.

Orthotopic liver transplantation can be lifesaving in patients who reach advanced stages (III, IV) of hepatic coma. Various predictive tests suggest a poor prognosis and need for liver transplantation (Table 412.5). Reduced-size allografts and living donor transplantation have been important advances in the treatment of infants with hepatic failure. Partial auxiliary orthotopic or heterotopic liver transplantation is successful in a small number of children, and, in some cases, it has allowed regeneration of the native liver and eventual withdrawal of immunosuppression. Orthotopic liver transplantation should not be done in patients with liver failure and neuromuscular dysfunction secondary to a mitochondrial disorder because progressive neurologic deterioration is likely to continue after transplantation.

## PROGNOSIS

Children with acute hepatic failure fare better than adults. Improved survival can be attributed to careful intensive care and if necessary, liver transplantation. In the largest prospective study from the Pediatric Acute Liver Failure Study Group, 709 children were assessed at 21 days: 50.3% of patients survived with supportive care alone, 36.2% survived after liver transplantation, and 13.4% died. Prognosis varies considerably with the cause of liver failure and stage of hepatic

encephalopathy. Survival rates with supportive care may be as high as 90% in acetaminophen overdose and with fulminant hepatitis A. By contrast, spontaneous recovery can be expected in only approximately 40% of patients with liver failure caused by the idiopathic (indeterminate) form of acute liver failure or an acute onset of Wilson disease. Prognosis is also poor for spontaneous recovery in patients with mitochondrial deficits, hemophagocytic syndromes, herpes simplex disease, and idiosyncratic drug reactions. In patients who progress to stage IV coma (see Table 412.1), the prognosis is extremely poor. Brain stem herniation is the most common cause of death. Major complications such as sepsis, severe hemorrhage, or renal failure increase the mortality. The prognosis is particularly poor in patients with liver necrosis and multiorgan failure. Age <1 year, stage IV encephalopathy, an INR >4, PT >90 seconds, low factor V levels, and the need for dialysis before transplantation are associated with increased mortality. Pre-transplantation serum bilirubin concentration or the height of hepatic enzymes is *not* predictive of posttransplantation survival. A plasma ammonia concentration >200 μmol/L is associated with a fivefold increased risk of death. Children with acute hepatic failure are more likely to die while on the waiting list compared with children with other liver transplant-requiring diagnoses. Because of the severity of their illness, the 6-month post-liver transplantation survival of approximately 75% for acute liver failure is significantly lower than the 90% achieved in children with chronic liver disease. Patients who recover from fulminant hepatic failure with only supportive care do not usually develop cirrhosis or chronic liver disease. Aplastic anemia occurs in approximately 10% of children with the idiopathic form of fulminant hepatic failure and is often fatal without bone marrow transplantation. Long-term survivors demonstrate average IQ and visual spatial ability but greater than expected impairments in motor skills, attention, executive function, and health-related quality of life.

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**Table 412.5** Tests and Indices for Predicting Mortality and Need for Liver Transplantation in Patients with Acute Liver Failure

CAUSE OF ACUTE LIVER FAILURE		THRESHOLD FOR POOR PROGNOSIS OR NEED FOR LIVER TRANSPLANTATION
King's College Criteria	Acetominophen	Arterial pH <7.30 or all of the following: prothrombin time >100 s (international normalized ratio >6.5), creatinine >3.4 mg/dL, and grade 3 or 4 encephalopathy
King's College Criteria	Non-acetaminophen	Prothrombin time >100 s (international normalized ratio >6.5) or any three of the following: non-A, non-B viral hepatitis, or drug or halothane cause; jaundice to encephalopathy >7 days; age between 10 and 40 years; prothrombin time >50 s; bilirubin >17.4 mg/dL
Factor V (Clichy criteria)	Viral	Age <30 years with clotting factor V <20% or any age with clotting factor V <30% and grade 3 or 4 encephalopathy
Liver biopsy	Mixed causes	Hepatocyte necrosis >70%
Arterial phosphate	Acetominophen	>1.2 mmol/L
Serum lactate	Acetominophen	>3.5 mmol/L
APACHE II score	Acetominophen	Score >15
MELD score	Acetominophen	Score >33
BiLE score	Mixed causes	Score >6.9
Volumetric CT	Non-acetaminophen	Liver volume <1000 cm <sup>3</sup>
ALFSG Prognostic Index*	Mixed causes	Continuous

\*The ALFSG Prognostic Index, in contrast to the other indices listed, is designed to predict transplant-free survival rather than death or need for liver transplantation.

MELD, Model for end-stage liver disease; BiLE, bilirubin, lactate, and etiology score; ALFSG, Acute Liver Failure Study Group.

From Stratitz RT, Lee WM. Acute liver failure. *Lancet*. 2019;394:869–880. Table 2.

## Chapter 413

# Cystic Diseases of the Biliary Tract and Liver

Frederick J. Suchy and Amy G. Feldman

Cystic lesions of liver may be initially recognized during infancy and childhood. Hepatic fibrosis can also occur as part of an associated developmental defect (Table 413.1). Cystic renal disease is usually associated and often determines the clinical presentation and prognosis. Virtually all proteins encoded by genes mutated in combined cystic diseases of the liver and kidney are at least partially localized to primary cilia in renal tubular cells and cholangiocytes.

A solitary, congenital liver cyst (nonparasitic) can occur in childhood and has been identified in some cases on prenatal ultrasound. Abdominal distention and pain may be present, and a poorly defined right-upper-quadrant mass may be palpable. These benign lesions are

**Table 413.1** Syndromes Associated with Congenital Hepatic Fibrosis

DISORDER	ASSOCIATED FEATURES
Autosomal recessive polycystic kidney disease	Ductal plate malformation, Caroli syndrome
Autosomal dominant polycystic kidney disease	Ductal plate malformation, Caroli syndrome
Autosomal dominant polycystic liver disease	Rarely, congestive heart failure
Jeune syndrome	Asphyxiating thoracic dystrophy, with cystic renal tubular dysplasia, Caroli syndrome
Joubert syndrome	Central nervous system defects, cardiac malformations
COACH syndrome	Cerebellar vermis hypoplasia, oligophrenia, congenital ataxia, ocular coloboma, hepatic fibrosis
Meckel-Gruber syndrome	Cystic renal dysplasia, abnormal bile duct development with fibrosis, posterior encephalocele, polydactyly
Carbohydrate-deficient glycoprotein syndrome type 1b	Phosphomannose isomerase 1 deficiency chronic diarrhea, protein-losing enteropathy
Ivemark syndrome type 2	Autosomal-recessive renal-hepatic-pancreatic dysplasia
Nephronophthisis type 3	Tapetoretinal degeneration
Bardet-Biedl syndrome	Retinal degeneration, obesity, limb deformities, hypogonadism
Oral-facial-digital syndrome type 1	Oral clefts, hamartomas or cysts of the tongue, digital anomalies pancreatic cysts
Miscellaneous syndromes	Intestinal lymphangiectasia, enterocolitis, cystic short rib (Beemer-Langer) syndrome, osteochondrodysplasia

Adapted from Suchy FJ, Sokol RJ, Balistreri WF, eds. *Liver Disease in Children*, 3rd ed. New York: Cambridge University Press; 2014: p. 713.

best left undisturbed unless they compress adjacent structures or a complication occurs, such as hemorrhage into the cyst. Operative management is generally reserved for symptomatic patients and enlarging cysts.

## CHOLEDOCHAL MALFORMATIONS

Choledochal malformations (previously known as **choledochal cysts**) are congenital dilatations of the common bile duct that can cause progressive biliary obstruction and biliary cirrhosis. Cylindrical (fusiform) and spherical (saccular) dilatations of the extrahepatic ducts are the most common types (see Table 413.1). Choledochal malformations are classified according to the Todani method (see Fig. 404.5). **Type I** choledochal malformations, the most common variant, involve a saccular or fusiform dilation of the common bile duct. **Type II** malformations are congenital diverticula protruding from the common bile duct. **Type III** malformations, or choledochoceles, involve a herniation of the intraduodenal segment of the common bile duct into the duodenum. **Type IVa** malformations, or **Caroli disease**, involve multiple intrahepatic and extrahepatic cysts. **Type IVb** malformations involve only the extrahepatic duct. Solitary liver cysts (**type V**) are very rare.

The pathogenesis of choledochal malformations remains uncertain. Some reports suggest that junction of the common bile duct and the pancreatic duct before their entry into the sphincter of Oddi might allow reflux of pancreatic enzymes into the common bile duct, causing inflammation, localized weakness, and dilation of the duct. It has also been proposed that a distal congenital stenotic segment of the biliary tree leads to increased intraluminal pressure and proximal biliary dilation.

Approximately 75% of cases appear during childhood. The infant typically presents with cholestatic jaundice; severe liver dysfunction including ascites and coagulopathy can rapidly evolve if biliary obstruction is not relieved. An abdominal mass is rarely palpable. In an older child, the classic triad of abdominal pain, jaundice, and mass occurs in <33% of patients.

Features of acute cholangitis (fever, right-upper-quadrant tenderness, jaundice, and leukocytosis) may be present. The diagnosis is made by ultrasonography; choledochal malformations have been identified prenatally using this technique. Magnetic resonance cholangiography is useful in the preoperative assessment of choledochal malformations anatomy.

Because of bile stasis and inflammation, choledochal malformations have the potential to develop into cholangiocarcinoma; therefore the treatment of choice is primary excision of the abnormal biliary segment and a Roux-en-Y choledochojejunostomy. The postoperative course can be complicated by recurrent cholangitis or stricture at the anastomotic site. Long-term follow-up is necessary to ensure that no malignancy develops.

## Autosomal Recessive Polycystic Kidney Disease

Autosomal recessive polycystic kidney disease (ARPKD) manifests predominantly in childhood (see Chapter 563.2). Bilateral enlargement of the kidneys is caused by a generalized dilation of the collecting tubules. The disorder is invariably associated with **congenital hepatic fibrosis** and various degrees of biliary ductal ectasia, discussed in detail later. Approximately 40% of patients have nonobstructive intrahepatic ductal dilatation (**Caroli disease**).

The polycystic kidney and hepatic disease 1 (*PKHD1*) gene, altered in ARPKD, encodes a protein that is called fibrocystin, which is localized to cilia on the apical domain of renal collecting cells and cholangiocytes. The primary defect in ARPKD may be ciliary dysfunction related to the abnormality in this protein. Fibrocystin appears to have a role in the regulation of cellular adhesion, repulsion, and proliferation and/or the regulation and maintenance of renal collecting tubules and bile ducts, but its exact role in normal and cystic epithelia remains unknown.

Kidney and liver disease are independent and variable in severity; they are not readily explainable by the type of *PKHD1* pathogenic variants. Approximately 750 *PKHD1* pathogenic variants have been identified, of which approximately half are missense changes. Phenotypic variability among affected siblings suggests the importance of modifier genes as well as possibly environmental influences.

In ARPKD, the cysts arise as ectatic expansions of the collecting tubules and bile ducts, which remain in continuity with their structures of origin. ARPKD normally presents in early life, often shortly after birth, and is generally more severe than autosomal dominant polycystic kidney disease (ADPKD). Fetal ultrasound may visualize large echogenic kidneys, also described as bright, with low or absent amniotic fluid (oligohydramnios). However, in many instances, the features of ARPKD are not visualized on sonography until the third trimester or after birth.

Patients with ARPKD can die in the perinatal period from renal failure or lung dysgenesis. The kidneys in these patients are usually markedly enlarged and dysfunctional. Respiratory failure can result from compression of the chest by grossly enlarged kidneys, from fluid retention, or from concomitant pulmonary hypoplasia. The clinical pathologic findings within a family tend to breed true, although there has been some variability in the severity of the disease and the time for presentation within the same family. In patients surviving infancy because of a milder renal phenotype, liver disease may be a prominent part of the disorder. The liver disease in ARPKD is related to congenital malformation of the liver with varying degrees of periportal fibrosis, bile ductular hyperplasia, ectasia, and dysgenesis. Initial symptoms are liver related in approximately 26% of patients. This can manifest clinically as variable cystic dilation of the intrahepatic biliary tree with congenital hepatic fibrosis. Congenital hepatic fibrosis and Caroli disease likely result from an abnormality in remodeling of the embryonic ductal plate of the liver. **Ductal plate malformation** refers to the persistence of excess embryonic bile duct structures in the portal tracts. The synthetic function of the liver remained largely intact even in patients with advanced portal hypertension. ARPKD patients with recurrent cholangitis or complications of portal hypertension may require combined liver-kidney transplant.

### Cystic Dilation of the Intrahepatic Bile Ducts (Caroli Disease/Caroli Syndrome)

In Caroli disease, there is isolated ectasia or nonobstructing segmental dilatation of the larger intrahepatic ducts. Caroli syndrome is the more common variant, in which malformations of small bile ducts are associated with congenital hepatic fibrosis. Congenital saccular dilation can affect several segments of the intrahepatic bile ducts; the dilated ducts are lined by cuboidal epithelium and are in continuity with the main duct system, which is usually normal. Choledochal malformations have also been associated with Caroli disease. Bile duct dilation leads to stagnation of bile and formation of biliary sludge and intraductal lithiasis. There is a marked predisposition to ascending cholangitis, which may be exacerbated by calculus formation within the abnormal bile ducts.

Affected patients usually experience symptoms of acute cholangitis as children or young adults. Fever, abdominal pain, mild jaundice, and pruritus occur, and a slightly enlarged, tender liver is palpable. Elevated alkaline phosphatase activity, direct-reacting bilirubin levels, and leukocytosis may be observed during episodes of acute infection. In patients with Caroli disease, clinical features may be the result of a combination of recurring episodes of cholangitis, reflecting the intrahepatic ductal abnormalities and portal hypertensive bleeding resulting from hepatic fibrosis. Ultrasonography shows the dilated intrahepatic ducts, but definitive diagnosis and extent of disease must be determined by percutaneous transhepatic, endoscopic, or magnetic resonance cholangiography.

Cholangitis and sepsis should be treated with appropriate antibiotics. Calculi can require surgery. Partial hepatectomy may be curative in rare cases in which cystic disease is confined to a single lobe. The prognosis is otherwise guarded, largely because of difficulties in controlling cholangitis and biliary lithiasis and because of a significant risk for developing cholangiocarcinoma.

### Congenital Hepatic Fibrosis

Congenital hepatic fibrosis is usually associated with ARPKD and is characterized pathologically by diffuse periportal and perilobular fibrosis in broad bands that contain distorted bile duct-like structures

and that often compress or incorporate central or sublobular veins (see Table 413.1). Irregularly shaped islands of liver parenchyma contain normal-appearing hepatocytes. Caroli disease and choledochal malformations may be associated. Most patients have renal disease, mostly ARPKD and rarely nephronophthisis. Congenital hepatic fibrosis also occurs as part of the **COACH syndrome** (cerebellar vermis hypoplasia, oligophrenia, congenital ataxia, coloboma, and hepatic fibrosis). Congenital hepatic fibrosis has been described in children with a congenital disorder of glycosylation caused by mutations in the gene encoding phosphomannose isomerase (see Chapter 107.7).

Several different forms of congenital hepatic fibrosis have been defined clinically: portal hypertensive (most common) cholangitic, mixed, and latent. The disorder usually has its onset in childhood, with hepatosplenomegaly or with bleeding secondary to portal hypertension. In a recent study, splenomegaly, as a marker for portal hypertension, developed early in life and was present in 60% of children younger than 5 years of age.

Cholangitis can occur in these patients because they have abnormal biliary tracts even without Caroli disease. Hepatocellular function is usually well preserved. Serum aminotransferase activities and bilirubin levels are usually normal in the absence of cholangitis and choledocholithiasis; serum alkaline phosphatase activity may be slightly elevated. The serum albumin level and prothrombin time are normal. Liver biopsy is rarely required for diagnosis, particularly in patients with obvious renal disease.

Treatment of this disorder should focus on control of bleeding from esophageal varices and aggressive antibiotic treatment of cholangitis. Infrequent mild bleeding episodes may be managed by endoscopic sclerotherapy or band ligation of the varices. After more severe hemorrhage, portacaval anastomosis can relieve portal hypertension. The prognosis may be greatly improved by a shunting procedure, but survival in some patients may be limited by renal failure.

### AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

ADPKD (see Chapter 563.3), the most commonly inherited cystic kidney disease, affects 1 in 1,000 live births. It is characterized by progressive renal cyst development and cyst enlargement and an array of extrarenal manifestations. There is a high degree of intrafamilial and interfamilial variability in the clinical expression of the disease. The prevalence of hepatic cysts in children with ADPKD is <5%, with no reports of severe cases. However, hepatic cysts increase in number and size with age with prevalence in patients ages 15–24 years on MRI close to 60%.

ADPKD is caused by pathogenic variants in one of two genes, *PKD1* or *PKD2*, which account for 85–90% and 10–15% of cases, respectively. The proteins encoded by these genes, polycystin-1 and polycystin-2, are expressed in renal tubule cells and in cholangiocytes. Polycystin-1 functions as a mechanosensor in cilia, detecting the movement of fluid through tubules and transmitting the signal through polycystin-2, which acts as a calcium channel.

Dilated noncommunicating cysts are most commonly observed. Other hepatic lesions are rarely associated with ADPKD, including the **ductal plate malformation**, **congenital hepatic fibrosis**, and **biliary microhamartomas** (the von Meyenburg complexes). Approximately 50% of patients with renal failure have demonstrable hepatic cysts that are derived from the biliary tract but not in continuity with it. The hepatic cysts increase with age. In one study, the prevalence of hepatic cysts was 58% in patients 15–24 years old. Hepatic cystogenesis appears to be influenced by estrogens. Although the frequency of cysts is similar in males and females, the development of large hepatic cysts is mainly a complication in females. Hepatic cysts are often asymptomatic but can cause pain and are occasionally complicated by hemorrhage, infection, jaundice from bile duct compression, portal hypertension with variceal bleeding, or hepatic venous outflow obstruction from mechanical compression of hepatic veins, resulting in tender hepatomegaly and exudative ascites. Cholangiocarcinoma can occur. Subarachnoid hemorrhage can result from the associated cerebral arterial aneurysms.

Selected patients with severe symptomatic polycystic liver disease and favorable anatomy benefit from liver resection or fenestration. Combined liver-kidney transplantation may be required. There is considerable evidence for a role of cyclic adenosine monophosphate in epithelial proliferation and fluid secretion in experimental renal and hepatic cystic disease. Several clinical trials in adults have shown that somatostatin analogs can blunt hepatic cyst expansion by blocking secretin-induced cyclic adenosine monophosphate generation and fluid secretion by cholangiocytes. Surgical or pharmacologic therapies for hepatic cysts are not likely to be required in childhood.

### AUTOSOMAL DOMINANT POLYCYSTIC LIVER DISEASE

Autosomal dominant polycystic liver disease is a distinct clinical and genetic entity in which multiple cysts develop and are unassociated with cystic kidney disease. Liver cysts arise from but are not in continuity with the biliary tract. Females are more commonly affected than males, and the cysts often enlarge during pregnancy. Cysts are rarely identified in children. Cyst complications are related to effects of local compression, infection, hemorrhage, or rupture. The genes associated with autosomal dominant polycystic liver disease are *PRKCSH* and *SEC63*, which encode hepatocystin and Sec63, respectively. Hepatocystin is a protein kinase C substrate adK-H, which is involved in the proper folding and maturation of glycoproteins. It has been localized to the endoplasmic reticulum. *SEC63* encodes the protein SEC63P, which is a component of the protein translocation machinery in the endoplasmic reticulum.

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## Chapter 414

# Diseases of the Gallbladder

Frederick J. Suchy and Amy G. Feldman

The incidence of gallbladder disease, particularly cholelithiasis and biliary dyskinesia, has been increasing in children and has been associated with a rise in the number of cholecystectomies.

### ANOMALIES

The gallbladder is congenitally absent in approximately 0.1% of the population. Hypoplasia or absence of the gallbladder can be associated with extrahepatic biliary atresia or cystic fibrosis. Duplication of the gallbladder occurs rarely. Gallbladder ectopia may occur with a transverse, intrahepatic, left-sided, or retroplaced location. Multiseptate gallbladder, characterized by the presence of multiple septa dividing the gallbladder lumen, is another rare congenital anomaly of the gallbladder.

### ACUTE HYDROPS

Table 414.1 lists the conditions associated with hydrops of the gallbladder.

Acute noncalculous, noninflammatory distention of the gallbladder can occur in infants and children. It is defined by the absence of calculi, bacterial infection, or congenital anomalies of the biliary system. The disorder may complicate acute infections and Kawasaki disease, but the cause is often not identified. Hydrops of the gallbladder may also develop in patients receiving long-term parenteral nutrition,

**Table 414.1** Conditions Associated with Hydrops of the Gallbladder

Cholelithiasis
Cholecystitis
Kawasaki disease
Streptococcal pharyngitis
Staphylococcal infection
Leptospirosis
Ascariasis
Threadworm
Sickle cell crisis
Typhoid fever
Thalassemia
Total parenteral nutrition
Prolonged fasting
Viral hepatitis
Sepsis
IgA vasculitis (Henoch-Schönlein purpura)
Mesenteric adenitis
Necrotizing enterocolitis

presumably because of gallbladder stasis during the period of enteral fasting. Hydrops is distinguished from acalculous cholecystitis by the absence of a significant inflammatory process and is a generally benign prognosis.

Affected patients usually have right upper quadrant pain with a palpable mass. Fever, vomiting, and jaundice may be present and are usually associated with a systemic illness such as streptococcal infection. Ultrasonography shows a markedly distended echo-free gallbladder, without dilation of the biliary tree. Acute hydrops is usually treated conservatively with a focus on supportive care and managing the intercurrent illness; cholecystostomy and drainage are rarely needed. Spontaneous resolution and return of normal gallbladder function usually occur over a period of several weeks. If a laparotomy is required, a large edematous gallbladder is found to contain white, yellow, or green bile. Obstruction of the cystic duct by mesenteric adenopathy is occasionally observed. Cholecystectomy is required if the gallbladder is gangrenous. Pathologic examination of the gallbladder wall shows edema and mild inflammation. Cultures of bile are usually sterile.

### CHOLECYSTITIS AND CHOLELITHIASIS

Acute acalculous cholecystitis is uncommon in children and is usually caused by infection. Pathogens include streptococci (groups A and B), gram-negative organisms—particularly *Salmonella* and *Leptospira interrogans*—and a number of viral infections (hepatitis A, Epstein-Barr [EB] virus, and cytomegalovirus). Parasitic infestation with *Ascaris* or *Giardia lamblia* may be found. Acalculous cholecystitis may be associated with abdominal trauma or burn injury or with a severe systemic illness such as leukemia, end-stage liver disease, and systemic vasculitis.

Clinical features include right upper quadrant or epigastric pain, nausea, vomiting, fever, and jaundice. Right upper quadrant guarding and tenderness are present. Ultrasonography discloses an enlarged, thick-walled gallbladder without calculi. Serum alkaline phosphatase activity and direct-reacting bilirubin levels are elevated. Leukocytosis is usual.

Patients may recover with treatment of systemic and biliary infection. Because the gallbladder can become gangrenous, daily ultrasonography is useful in monitoring gallbladder distention and wall thickness. Cholecystectomy is required in patients who fail to improve with conservative management. Cholecystostomy drainage is an alternative approach in a critically ill patient.

**Cholelithiasis** is relatively rare in otherwise healthy children, occurring more commonly in patients with various predisposing disorders (Table 414.2). Gallstones are rarely detected by ultrasonography in the fetus but generally remain asymptomatic and resolve spontaneously during the first year of life. In an ultrasonographic survey of

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**Table 414.2** Conditions Associated with Cholelithiasis

Chronic hemolytic disease (sickle cell anemia, spherocytosis, thalassemia, others)
Ileal resection or disease
Cystic fibrosis
Cirrhosis
Cholestasis
Crohn disease
Obesity
Insulin resistance
Prolonged parenteral nutrition
Prematurity with complicated medical or surgical course
Prolonged fasting or rapid weight reduction
Treatment of childhood cancer
Abdominal surgery
Pregnancy
Sepsis
Genetic (ABCB4, ABCG5/G8) progressive familial intrahepatic cholestasis
Gilbert disease
Cephalosporins

1570 children (ages 6–19 years) the overall prevalence of gallstone disease was 0.13% (0.27% in female subjects). Older reports consistently found that >70% of gallstones were the pigment type, 15–20% were cholesterol stones, and the remainder were composed of a mixture of cholesterol, organic matrix, and calcium bilirubinate. Black pigment gallstones, composed mostly of calcium bilirubinate and glycoprotein matrix, are a frequent complication of chronic hemolytic anemias. However, because of obesity, cholesterol gallstones now predominate in children, while the number of patients with hemolytic anemia-associated gallstones have remained stable.

Brown pigment stones form mostly in infants as a result of biliary tract infection. Unconjugated bilirubin is the predominant component, formed by the high  $\beta$ -glucuronidase activity of infected bile. Cholesterol gallstones are composed purely of cholesterol or contain >50% cholesterol along with a mucin glycoprotein matrix and calcium bilirubinate. Calcium carbonate stones have also been described in children.

Patients with hemolytic disease (including sickle cell anemia, the thalassemias, and red blood cell enzymopathies) and Wilson disease are at increased risk for black pigment cholelithiasis. In sickle cell disease, pigment gallstones can develop before age 4 years and have been reported in 17–33% of patients 2–18 years of age. Genetic variation in the promoter of uridine diphosphate-glucuronosyltransferase 1A1 (the [TA]7/[TA]7 and [TA]7/[TA]8 genotypes) underlies Gilbert syndrome, a relatively common, chronic form of unconjugated hyperbilirubinemia, and is a risk factor for pigment gallstone formation in sickle cell disease.

Cirrhosis and chronic cholestasis also increase the risk for pigment gallstones. Sick premature infants may also have gallstones; their treatment is often complicated by such factors as bowel resection, necrotizing enterocolitis, prolonged parenteral nutrition without enteral feeding, cholestasis, frequent blood transfusions, and use of diuretics. Cholelithiasis in premature infants is often asymptomatic and may resolve spontaneously. Brown pigment stones are found in infants with obstructive jaundice and infected intra- and extrahepatic bile ducts. These stones are usually radiolucent, owing to a lower content of calcium phosphate and carbonate and a higher amount of cholesterol than in black pigment stones. MDR3 deficiency caused by ABCB4 pathologic gene variant is a cholestatic syndrome related to impaired biliary phospholipid excretion. It is associated with symptomatic and recurring cholelithiasis. Patients may show intrahepatic lithiasis, sludge, or microlithiasis along the biliary tree.

Obesity has assumed an increasingly important role as a risk factor for cholesterol cholelithiasis in children, particularly in adolescent females. Cholesterol gallstones are also found in children with

disturbances of the enterohepatic circulation of bile acids, including patients with ileal disease and bile acid malabsorption, such as those with ileal resection, ileal Crohn disease, and cystic fibrosis. Pigment stones can also occur in these patients.

Cholesterol gallstone formation results from an excess of cholesterol in relation to the cholesterol-carrying capacity of micelles in bile. Supersaturation of bile with cholesterol, leading to crystal and stone formation, could result from decreased bile acid or from an increased cholesterol concentration in bile. Other initiating factors that may be important in stone formation include gallbladder stasis or the presence in bile of abnormal mucoproteins or bile pigments that may serve as a nidus for cholesterol crystallization.

Prolonged use of high-dose ceftriaxone, a third-generation cephalosporin, has been associated with the formation of calcium-ceftriaxone salt precipitates (*biliary pseudolithiasis*) in the gallbladder. Biliary sludge or cholelithiasis can be detected in >40% of children who are treated with ceftriaxone for at least 10 days. In rare cases, children become jaundiced and develop abdominal pain; precipitates usually resolve spontaneously within several months after discontinuation of the drug.

Acute or chronic cholecystitis is often associated with gallstones. The acute form may be precipitated by impaction of a stone in the cystic duct. Proliferation of bacteria within the obstructed gallbladder lumen can contribute to the process and lead to biliary sepsis. Chronic calculous cholecystitis is more common. It can develop insidiously or follow several attacks of acute cholecystitis. The gallbladder epithelium commonly becomes ulcerated and scarred.

More than 50% of patients with gallstones have symptoms, and 18% present with a complication as the first indication of cholelithiasis, such as pancreatitis, choledocholithiasis or acute calculous cholecystitis. The most important clinical feature of cholelithiasis is recurrent abdominal pain, which is often colicky and localized to the right upper quadrant. An older child may have intolerance for fatty foods. Acute cholecystitis is characterized by fever, pain in the right upper quadrant, and often a palpable mass. Jaundice occurs more commonly in children than adults. Pain may radiate to an area just below the right scapula. A plain x-ray of the abdomen may reveal opaque calculi, but radiolucent (cholesterol) stones are not visualized. Accordingly, ultrasonography is the method of choice for gallstone detection. Hepatobiliary scintigraphy is a valuable adjunct in that failure to visualize the gallbladder provides evidence of cholecystitis. Laboratory evaluation may reveal elevated aminotransferase levels, leukocytosis, and mild hyperbilirubinemia. Marked elevations of the direct bilirubin, alkaline phosphatase, or gamma-glutamyl transpeptidase (GGT) levels should prompt evaluation for choledocholithiasis.

Patients with cholecystitis and persistent fever or concern for obstruction should be hospitalized and started on antibiotics. Cholecystectomy is curative. Laparoscopic cholecystectomy is routinely performed in symptomatic infants and children with cholelithiasis. Common bile duct stones are unusual in children, occurring in 2–6% of cases with cholelithiasis, often in association with obstructive jaundice and pancreatitis. Rarely a common bile duct stone may appear after a successful cholecystectomy. Operative cholangiography should be done at the time of surgery, however, to detect unsuspected common duct calculi. Endoscopic retrograde cholangiography with extraction of common duct stones is an option before laparoscopic cholecystectomy in older children and adolescents.

Asymptomatic patients with cholelithiasis pose a more difficult management problem. Studies in adults indicate a lag time of more than a decade between initial formation of a gallstone and development of symptoms. Spontaneous resolution of cholelithiasis has been reported in infants and children. However, if surgery is deferred for any patient, parents should be counseled about signs and symptoms consistent with cholecystitis or obstruction of the common bile duct by a gallstone. In patients with chronic hemolysis or ileal disease, cholecystectomy can be carried out at the same time as another surgical procedure. Because laparoscopic surgery can safely be performed in children with sickle cell disease, elective cholecystectomy is being

done more frequently at the time of gallstone diagnosis before symptoms or complications develop. In cases associated with liver disease, severe obesity, or cystic fibrosis, the surgical risk of cholecystectomy may be substantial so that the risks and benefits of the operation need to be carefully considered.

### BILIARY DYSKINESIA

Biliary dyskinesia is a motility disorder of the biliary tract that may cause biliary colic in children, often in association with nausea and fatty food intolerance, but symptoms may overlap with functional abdominal pain. There are no gallstones on imaging. Sphincter of Oddi dysfunction may be a variant that can present with chronic abdominal pain and recurrent pancreatitis. The diagnosis is based on a cholecystokinin-di-isopropyl iminodiacetic acid scan or an ultrasound done with a fatty meal demonstrating a gallbladder ejection fraction of <35%. Reproduction of pain on cholecystokinin administration may also be seen, as well as the absence of gallbladder filling on an otherwise normal ultrasound examination. Although laparoscopic cholecystectomy is performed for many patients with this disorder, short-term and long-term symptomatic improvement is highly variable.

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**Table 415.1** Causes of Portal Hypertension

#### EXTRAHEPATIC PORTAL HYPERTENSION

Portal vein agenesis, atresia, stenosis  
Portal vein thrombosis or cavernous transformation  
Splenic vein thrombosis  
Increased portal flow  
Arteriovenous fistula

#### INTRAHEPATIC PORTAL HYPERTENSION

Hepatocellular disease  
Acute and chronic viral hepatitis  
Cirrhosis  
Congenital hepatic fibrosis  
Wilson disease  
 $\alpha_1$ -Antitrypsin deficiency  
Glycogen storage disease type IV  
Hepatotoxicity  
Methotrexate  
Parenteral nutrition  
Biliary tract disease  
Biliary atresia  
Cystic fibrosis  
Choledochal cyst  
Sclerosing cholangitis  
Intrahepatic bile duct paucity  
Idiopathic portal hypertension  
Postsinusoidal obstruction  
Budd-Chiari syndrome  
Venoocclusive disease

## Chapter 415

# Portal Hypertension and Varices

Amy G. Feldman and Frederick J. Suchy

Portal hypertension, defined as an elevation of portal pressure >10–12 mm Hg or a hepatic venous pressure gradient >4 mm Hg, is a major cause of morbidity and mortality in children with liver disease. Portal hypertension occurs when there is increased portal resistance or increased blood flow through the portal system. When portal hypertension occurs, children can develop varices, splenomegaly, ascites, and gastrointestinal bleeding.

### ETIOLOGY

Portal hypertension can result from obstruction to portal blood flow anywhere along the course of the portal venous system (prehepatic, intrahepatic, or posthepatic). Table 415.1 outlines the various disorders associated with portal hypertension.

**Portal vein thrombosis** is the most common cause of extrahepatic portal hypertension. The obstruction can occur at any level of the portal vein. In neonates, portal vein thrombosis can occur from umbilical infection (omphalitis) with or without a history of catheterization of the umbilical vein, dehydration, and/or sepsis. Rare developmental anomalies producing extrahepatic portal hypertension include agenesis, atresia, stenosis, or a web of the portal vein. In older children, portal vein thrombosis can occur with intraabdominal infection (appendicitis, peritonitis, pancreatitis), inflammatory bowel disease, celiac disease, primary sclerosing cholangitis, or biliary infection. Portal vein thrombosis is also associated with hypercoagulable states, such as deficiencies of factor V Leiden, protein C, or protein S. The portal vein can be replaced by a fibrous remnant or contain an organized thrombus. At least half of reported cases have no defined cause. Uncommonly, presinusoidal hypertension can be caused by increased flow through the portal system as a result of a congenital or acquired arteriovenous fistula.



**Fig. 415.1** Coronal CT image of the abdomen in a patient with cirrhosis. The liver is shrunken (green cross), shows nodularity (white arrowhead), and is surrounded by ascites (green arrowheads). The spleen is enlarged (star). Gastro-esophageal varices are seen (white arrow). There is a splenorenal shunt between a tributary of the splenic vein (green arrow) and the left renal vein (red arrow). The left renal vein is seen entering the inferior vena cava (green curved arrow). (From Ginés P, Krag A, Abraldes JG, et al. Liver cirrhosis. Lancet. 2021;398:1359–1374. Fig. 1.)

The intrahepatic causes of portal hypertension are numerous. The most common cause of portal hypertension in children is **cirrhosis** (Fig. 415.1). The numerous causes of cirrhosis include recognized disorders such as biliary atresia, autoimmune hepatitis, chronic viral

hepatitis, and metabolic liver disease such as  $\alpha_1$ -antitrypsin deficiency, Wilson disease, glycogen storage disease type IV, hereditary fructose intolerance, and cystic fibrosis.

Portal infiltration with malignant cells or granulomas can also contribute. An idiopathic form of portal hypertension characterized by splenomegaly, hypersplenism, and portal hypertension without occlusion of portal or splenic veins and with no obvious disease in the liver has been described. In some patients, noncirrhotic portal fibrosis has been observed.

Postsinusoidal causes of portal hypertension are also observed in childhood. **Budd-Chiari syndrome** occurs with obstruction to hepatic veins anywhere between the efferent hepatic veins and the entry of the inferior vena cava into the right atrium. In most cases, no specific cause can be found, but thrombosis can occur from inherited and acquired hypercoagulable states (antithrombin III deficiency, protein C or S deficiency, factor V Leiden or prothrombin gene variants, paroxysmal nocturnal hemoglobinuria, antiphospholipid syndrome, pregnancy, oral contraceptives) and can complicate hepatic or metastatic neoplasms, collagen vascular disease, infection, and trauma. Additional causes of the Budd-Chiari syndrome include Behcet syndrome, inflammatory bowel disease, celiac disease, sarcoidosis, pancreatitis, aspergillosis, dacarbazine therapy, autoinflammatory-recurrent fever syndromes, and inferior vena cava webs.

**Sinusoidal obstruction syndrome** (venoocclusive disease) is the most common cause of hepatic vein obstruction in children. In this disorder, occlusion of the centrilobular venules or sublobular hepatic veins occurs. The disorder most frequently occurs in bone marrow transplant recipients after total body irradiation with or without cytotoxic drug therapy, but it can also be seen in patients on azathioprine, mercaptopurine, thioguanine, and those taking herbal remedies that contain pyrrolizidine alkaloids.

## PATOPHYSIOLOGY

The primary hemodynamic abnormality in portal hypertension is increased resistance to portal blood flow. This is the case whether the resistance to portal flow has an intrahepatic cause such as cirrhosis or is because of portal vein obstruction. Portosystemic shunting should decompress the portal system and thus significantly lower portal pressures. However, despite the development of significant collaterals deviating portal blood into systemic veins, portal hypertension is maintained by an overall increase in portal venous flow and thus maintenance of portal hypertension. A hyperdynamic circulation is achieved by tachycardia, an increase in cardiac output, decreased systemic vascular resistance, and increased splanchnic dilation. Overall, the increase in portal flow likely contributes to an increase in variceal transmural pressure. The increase in portal blood flow is related to the contribution of hepatic and collateral flow; the actual portal blood flow reaching the liver is reduced. It is also likely that hepatocellular dysfunction and portosystemic shunting lead to the generation of various humoral factors that cause vasodilation and an increase in plasma volume.

Many complications of portal hypertension can be accounted for by the development of a remarkable collateral circulation. Collateral vessels can form prominently in areas in which absorptive epithelium joins stratified epithelium, particularly in the esophagus or anorectal region. The superficial submucosal collaterals, especially those in the esophagus and stomach, and, to a lesser extent, those in the duodenum, colon, or rectum, are prone to rupture and bleeding under increased pressure. In portal hypertension, the vascularity of the stomach is also abnormal and demonstrates prominent submucosal arteriovenous communications between the muscularis mucosa and dilated precapillaries and veins. The resulting lesion, a vascular ectasia, has been called *congestive gastropathy* and contributes to a significant risk of bleeding from the stomach.

## CLINICAL MANIFESTATIONS

**Bleeding** is the most common presentation of portal hypertension in children. In large series of children with portal hypertension, two thirds

presented with hematemesis or melena, most commonly from rupture of an esophageal varix (see Fig. 415.1). Less commonly, patients bleed from portal gastropathy, gastric antral ectasia, or stomal, intestinal, or anorectal varices. The risk of a first bleed in children with cirrhosis is 22% but rises to 38% in children with known varices over a 5-year period. In children with biliary atresia, 15–25% have bleeding on long-term follow-up. The age of first bleed is dependent on the underlying etiology of portal hypertension. Hemorrhage, particularly in children with portal vein obstruction, can be precipitated by a minor febrile, intercurrent illness. The mechanism is often unclear; aspirin or other nonsteroidal antiinflammatory drugs may be a contributing factor by damaging the integrity of a congested gastric mucosa or interfering with platelet function. Coughing during a respiratory illness can also increase intravariceal pressure.

**Splenomegaly** is the second most common finding in children with portal hypertension and may be initially recognized on routine physical examination (see Fig. 415.1). Because more than half of patients with portal vein obstruction do not experience bleeding until after 6 years of age, underlying liver disease should be considered in any child with splenomegaly, especially if there is concurrent cytopenia. Most children with splenomegaly are asymptomatic.

**Ascites** is the presenting sign of portal hypertension in 7–21% of children. Ascites can develop at any time with cirrhosis or if there is new onset portal vein obstruction. Children with portal hypertension can also suffer from growth impairment, minimal hepatic encephalopathy, and impaired quality of life. Some develop **portal hypertensive biliopathy**, where portal vein obstruction occurs as a result of external compression of the bile ducts by cavernous transformation of the portal vein.

Children with portal hypertension may also develop pulmonary complications, including **hepatopulmonary syndrome** (HPS) and **portopulmonary hypertension** (PP-HTN). HPS is defined as an arterial oxygenation defect induced by intrapulmonary microvascular dilation, resulting from release of a number of endogenous vasoactive molecules, including endothelin-1 and nitric oxide into the venous circulation. HPS develops in ≥10% of patients with portal hypertension. Patients with HPS may present with dyspnea, cyanosis, clubbing, and spider nevi. PP-HTN is defined by a pulmonary arterial pressure greater than 25 mm Hg at rest or a left-ventricular end-diastolic pressure of less than 15 mm Hg. Patients with PP-HTN most commonly present with exertional dyspnea. Histologically, these patients have pulmonary arteriopathy with laminar intimal fibrosis.

## DIAGNOSIS

In patients with established chronic liver disease or in those in whom portal vein obstruction is suspected, an experienced ultrasonographer should be able to demonstrate the patency of the portal vein, and Doppler flow ultrasonography can demonstrate the direction of flow within the portal system. The pattern of flow correlates with the severity of cirrhosis and encephalopathy. Reversal of portal vein blood flow (hepatofugal flow) is more likely to be associated with variceal bleeding. Ultrasonography is also effective in detecting the presence of esophageal varices. Another important feature of extrahepatic portal vein obstruction is cavernous transformation of the portal vein, in which an extensive complex of small collateral vessels forms in the parahepatic and epipancreatic venous system to bypass the obstruction. Other imaging techniques also contribute to further definition of the portal vein anatomy but are required less often; contrast-enhanced CT and magnetic resonance angiography provide information similar to ultrasonography. Selective arteriography of the celiac axis, superior mesenteric artery, and splenic vein may be useful in precise mapping of the extrahepatic vascular anatomy. This is not required to establish a diagnosis but can prove valuable in planning surgical decompression of portal hypertension. The platelet count, spleen length measured by ultrasonography, and serum albumin are the best noninvasive predictors of portal hypertension in children.

In a patient with hypoxia (HPS), intrapulmonary microvascular dilation is demonstrated with contrast-enhanced bubble echocardiography that shows delayed appearance in the left heart of microbubbles from a saline bolus injected into a peripheral vein.

Endoscopy is the most reliable method for detecting esophageal varices and for identifying the source of gastrointestinal bleeding. Although bleeding from esophageal or gastric varices is most common in children with portal hypertension, up to one third of patients, particularly those with cirrhosis, have bleeding from some other source, such as portal hypertensive gastropathy or gastric or duodenal ulcerations. There is a strong correlation between variceal size as assessed endoscopically and the probability of hemorrhage. Red spots apparent over varices at the time of endoscopy are a strong predictor of imminent hemorrhage.

## TREATMENT

The therapy of portal hypertension can be divided into emergency treatment of potentially life-threatening hemorrhage and prophylaxis directed at prevention of initial or subsequent bleeding.

Treatment of patients with acute variceal hemorrhage must focus on stabilization of the patient. Fluid resuscitation should be administered, initially in the form of crystalloid infusion, followed by the replacement of red blood cells. Care should be taken to avoid over transfusing children with portal hypertension-induced bleeding because this can result in overfilling the intravascular space and increasing portal pressure. A reasonable goal hemoglobin level after variceal bleed is between 7 and 9 g/dL. Correction of coagulopathy by administration of vitamin K and/or infusion of platelets or fresh-frozen plasma may be required. A nasogastric tube should be placed to document the presence of blood within the stomach and to monitor for ongoing bleeding. An H<sub>2</sub>-receptor blocker or proton pump inhibitor should be given intravenously to reduce the risk of bleeding from gastric erosions. Intravenous antibiotics should be considered because there is high risk of infectious complications during variceal bleeding.

Pharmacologic therapy to decrease portal pressure should be initiated in patients with continued bleeding. Vasopressin or one of its analogs is commonly used and is thought to act by increasing splanchnic vascular tone and thus decreasing portal blood flow. Vasopressin is administered initially with a bolus of 0.33 units/kg over 20 min, followed by a continued infusion of the same dose on an hourly basis or a continuous infusion of 0.2 units/1.73 m<sup>2</sup>/min. The drug has a half-life of approximately 30 minutes. Its use may be limited by the side effects of vasoconstriction, which can impair cardiac function and perfusion to the heart, bowel, and kidneys and can also, as a result, exacerbate fluid retention. More commonly, the somatostatin analog, octreotide, is used because it decreases splanchnic blood flow with few side effects. Octreotide is initially administered with a bolus of 1 µg/kg followed by a continuous intravenous infusion of 1.0–5.0 µg/kg/hr. A total of 15% of children with a portal hypertensive bleed will have persistent hemorrhage despite initiation of some form of splanchnic vasoconstriction.

After an episode of variceal hemorrhage or in patients in whom bleeding cannot be controlled with pharmacologic therapy, endoscopy with variceal band ligation or variceal sclerotherapy should be performed. Endoscopic band ligation is preferred because it has been shown in adults to be more effective and has fewer side effects. For smaller children in whom the banding device cannot be used, sclerosants can be injected either intra- or paravariceal until bleeding has stopped. Sclerotherapy treatments may be associated with bleeding, bacteremia, esophageal ulceration, and stricture formation. After band ligation or sclerosis, repeat endoscopy should be performed until varices are obliterated.

In patients who continue to bleed despite pharmacologic and endoscopic methods to control hemorrhage, a Sengstaken-Blakemore tube may be emergently placed to stop hemorrhage by mechanically

compressing esophageal and gastric varices. The device is rarely used now, but it may be the only option to control life-threatening hemorrhage until a more definitive procedure can be performed. It carries a significant rate of complications and a high rate of bleeding when the device is removed, and it poses a particularly high risk for pulmonary aspiration. The tube is not well tolerated in children without significant sedation and intubation.

Various surgical procedures have been devised to divert portal blood flow and to decrease portal pressure. A portacaval shunt diverts nearly all of the portal blood flow into the subhepatic inferior right vena cava. Although portal pressure is significantly reduced, because of the significant diversion of blood from the liver, patients with parenchymal liver disease have a marked risk for hepatic encephalopathy. Even mild hepatic encephalopathy can impair cognitive function, including school performance. More selective shunting procedures, such as mesocaval or distal splenorenal shunt (see Fig. 415.1), can effectively decompress the portal system while allowing a greater amount of portal blood flow to the liver. The small size of the vessels makes these operations technically challenging in infants and small children, and there is a significant risk of failure as a result of shunt thrombosis. A shunt may be a good option for a child with relatively well-preserved liver function, as sometimes occurs in patients with biliary atresia, congenital hepatic fibrosis, or cystic fibrosis. For children with an extrahepatic portal vein thrombosis, a Meso-Rex shunt (superior mesenteric vein to left portal vein bypass) may successfully restore physiologic portal blood flow and inflow of hepatotrophic factors. In one large single-center experience, 84% of children with idiopathic extrahepatic portal vein thrombosis were successfully treated with a Meso-Rex shunt. Growth and cognitive function improve after this procedure.

A transjugular intrahepatic portosystemic shunt (TIPS), in which a stent is placed by an interventional radiologist between the right hepatic vein and the right or left branch of the portal vein, can aid in the management of portal hypertension in children, especially in those needing temporary relief before liver transplantation. The transjugular intrahepatic portosystemic shunt procedure can precipitate hepatic encephalopathy and is prone to thrombosis.

Orthotopic liver transplantation represents a much better therapy for portal hypertension resulting from intrahepatic disease and cirrhosis. A prior portosystemic shunting operation does not preclude a successful liver transplantation but makes the operation technically more difficult.

Long-term treatment with nonspecific β blockers, such as propranolol, has been used extensively in adults with portal hypertension. These agents might act by lowering cardiac output and inducing splanchnic vasoconstriction. Evidence in adult patients shows that β blockers can reduce the incidence of variceal hemorrhage and improve long-term survival. A therapeutic effect is thought to result when the pulse rate is reduced by ≥25%. There is limited published experience with the use of this therapy in children.

## PROGNOSIS

Portal hypertension secondary to intrahepatic disease has a poor prognosis. Portal hypertension is usually progressive in these patients and is often associated with deteriorating liver function. Efforts should be directed toward prompt treatment of acute bleeding and prevention of recurrent hemorrhage with available methods. Patients with progressive liver disease and significant esophageal varices ultimately require orthotopic liver transplantation. Liver transplantation is the only effective therapy for HPS and should also be considered for patients with portal hypertension secondary to hepatic vein obstruction or resulting from severe venoocclusive disease.

## Chapter 416

# Liver Transplantation

Jorge D. Reyes and Evelyn K. Hsu

Survival rates for pediatric liver transplantation are >90% in the United States, in large part thanks to refinements made in the critical care management of children with liver failure and advances in perioperative care and immunosuppression management. Protocols for immune suppression withdrawal in the setting of allograft tolerance have introduced the possibility of transplantation for children without the need for long-term immunosuppression. In the United States, a national allocation system matches donor organs with waitlist candidates (the Organ Procurement and Transplantation Network and the United Network for Organ Sharing [UNOS]); this organization has been given the responsibility of allocating scarce organs to the neediest patients and has undergone continuous revisions with this goal in mind—the most significant in 2002, with the adoption of the Pediatric End-Stage Liver Disease (PELD) and Medical End-Stage Liver Disease (MELD; for adolescents) illness severity scoring system.

### INDICATIONS

The diseases for which liver transplantation is indicated can be categorized into the following groups:

- *Obstructive biliary tract disease:* biliary atresia, sclerosing cholangitis, and traumatic or postsurgical injury
- *Metabolic disorders with liver parenchymal disease:*  $\alpha_1$ -antitrypsin deficiency, tyrosinemia type I, glycogen storage disease type IV, Wilson disease, gestational alloimmune liver disease (GALD, previously known as *neonatal hemochromatosis*), and cystic fibrosis
- *Metabolic disorders without liver parenchymal disease:* Crigler-Najjar type I, familial hypercholesterolemia, primary oxalosis (with kidney), organic acidemia, and urea cycle defects
- *Acute hepatitis:* fulminant hepatic failure, viral, toxin, or drug-induced
- *Chronic hepatitis with cirrhosis:* hepatitis B or C, autoimmune
- *Intrahepatic cholestasis:* idiopathic neonatal hepatitis, Alagille syndrome, progressive familial intrahepatic cholestasis, and bile acid synthetic disorders
- *Primary liver tumors:* benign tumors (hamartomas, hemangioendothelioma), unresectable hepatoblastoma, and hepatocellular carcinoma
- *Miscellaneous:* cryptogenic cirrhosis, congenital hepatic fibrosis, Caroli disease, polycystic kidney and liver disease, and cirrhosis induced by total parenteral nutrition
- *Emerging indications:* graft-versus-host disease (a complication of bone marrow transplantation), hemophilia, and portosystemic shunts

**Biliary atresia** is the most common indication for liver transplantation in children, accounting for about half of all pediatric liver transplants performed in the United States, followed by metabolic liver disease and inborn errors of metabolism, autoimmune and familial cholestatic disorders, and acute hepatic necrosis. Biliary atresia may present in two clinical patterns: an acquired form for which there may be nonrandom clustering of potential etiologies (80% of cases) and a syndromic/embryonic form that includes other anomalies, such as polysplenia preduodenal portal vein, intestinal malrotation, situs anomalies, and absence of the retrohepatic vena cava. Hepatopancreaticostomy benefits survival if performed within the first 60 days of life; however, some patients with successful drainage later develop cirrhosis with portal hypertension (variceal bleeding and ascites). Children with biliary atresia (or any other obstructive biliary disorder) who do not achieve successful drainage will experience continued decline and end-stage liver disease, usually requiring liver transplantation within the first year of life.

**Inborn errors of metabolism** result from a single enzyme deficiency that results in alteration of synthesis, breakdown, transport, or function of carbohydrate, fat, or protein. These disorders can be grouped into those diseases that cause liver parenchymal disease and eventual cirrhosis with end-stage liver disease, as well as liver cancer (i.e.,  $\alpha_1$ -antitrypsin deficiency, Wilson disease, cystic fibrosis, progressive familial intrahepatic cholestasis), and those inborn errors that manifest principally by their hepatic enzyme deficiency with no hepatocellular injury; complications occur in “satellite” systems such as the brain (hyperammonemic conditions), the kidney (hyperoxaluria type 1), or heart (familial hypercholesterolemia). Some metabolic disorders place patients at risk for decompensation throughout their entire lives, and others manifest principally after adolescence. Liver transplantation is a form of enzyme replacement; the value and risk: benefit of doing so in the absence of cirrhosis has prompted the pursuit of gene therapy and hepatocyte transplantation as possible alternatives, but the therapeutic benefit of these modalities of treatment is as yet equivocal.

Although a proportion of children with **acute hepatic failure** will survive without transplant, it accounts for approximately 10% of pediatric liver transplantation and requires the most intense concentration of multimodal management/support yet devised. This diagnosis lacks clear etiology in the majority of cases, and posttransplantation survival varies but is worse than the general population, likely because of multifactorial issues related to comorbidities and listing/transplantation graft option availability.

**Primary hepatic malignancies** in children are rare (<2% of all pediatric malignancies) and account for about 7% of pediatric transplants. Hepatoblastoma accounts for the majority of cases (75% of primary liver tumors in childhood) and usually presents in an advanced stage; adjuvant chemotherapy and total hepatectomy with transplantation provide cure and long-term survival for the majority of these children. Survival of >85% has been reported by the International Society of Pediatric Oncology and several American centers.

The impact of chronic liver disease and its impact on growth, development, and quality of life of children can be devastating. Liver transplantation is a valid therapy and cure. The allocation of deceased donor livers in the United States follows guidelines based on the severity of liver disease as reflected in the PELD/MELD scoring system implemented in 2002, which is calculated from the measurable values of bilirubin, albumin, or creatinine (depending on age) and international normalization ratio. The PELD scoring system was initially modeled from a cohort of 884 children on the pediatric liver transplant wait list and is intended to predict death, decompensation, or transplantation within 3 months. Since 2002, the number of liver transplants performed in children in the United States has remained relatively stable, whereas the number of liver transplants performed in adults has steadily increased by approximately 10% per year. A change (2020) to the allocation algorithm that prioritized local adults over critically ill children nationally has in the short term led to increased rates of transplantation in adolescent patients. This and other issues highlight the importance of advocacy on behalf of children in this growing field.

**Contraindications to liver transplantation** include uncontrolled infection of extrahepatic origin, extrahepatic malignancies, and severely disabling and uncorrectable disease in other organ systems, principally the brain, heart, and lungs. Although combined liver and heart or lung transplantation has been performed in adults and children, such cases require special consideration and centers dedicated to the complexities of posttransplantation management.

### TECHNICAL INNOVATIONS

There are no limitations on age or weight for liver transplantation. To enhance the availability of liver grafts to children and optimize the timing of transplantation, techniques allowing the use of reduced-size or segmental grafts (a right or left lobe of liver, or the left lateral segment of the left lobe) were developed; this allows a liver from a larger donor to be implanted into a child, overcoming the barrier of size mismatch. In the same era, techniques were developed for the use of segments from living donors (usually the left lateral segment for small pediatric recipients), and then split-liver grafts from deceased donors where the

left lateral segment is transplanted into a child and the remaining segments of right lobe and medial segment of left lobe are transplanted into an adult, allowing increased utilization of deceased donor grafts without affecting adult waitlist mortality. Reduction of a liver graft is performed *ex vivo* (i.e., outside of the body); split-liver procurement surgery can be performed either *ex vivo* or *in situ* (in the hemodynamically stable brain-dead donor). Donors suitable for aforementioned graft variants should ideally be young (younger than 45 years of age), healthy, and nonobese; however, variations are guided by the severity of illness and urgency for transplantation of the recipient. Not all centers have the degree of surgical expertise required to perform these more complex surgeries; thus options may be limited for children at centers that accept only size-matched organs. This has implications for their waitlist survival.

The implantation of a liver (either whole organ or segment) involves removal of the native liver and encompasses four anastomoses: the suprahepatic vena cava, the portal vein, the hepatic artery, and the bile duct. Modifications of the procedure generally involve retaining (or not) of the retrohepatic vena cava, the performance (or not) of a temporary portacaval shunt to decompress the splanchnic venous system during the anhepatic phase, and the use of vascular homografts of donor iliac vein or artery to replace the native inflow (guided by the presence of recipient anomalies or thrombosis of native vessels). The donor bile duct may be connected to a loop of recipient intestine (Roux-en-Y limb) or the native bile duct. UNOS reported outcomes analyzing graft types, and outcomes have shown improved graft survival in children younger than 3 years of age for live donor grafts when compared with deceased donor whole, split, and reduced grafts. After the first year, however, patient and allograft survivals were similar, independent of graft type.

### IMMUNOSUPPRESSION

The long-term goal of effective clinical immunosuppression after solid-organ transplantation is to inhibit antigen-induced T-lymphocyte activation and cytokine production and to interrupt alloimmune-major histocompatibility complex recognition. To prevent weakening the host response to infection, this goal should be achieved while preserving host immunocompetence. A major emphasis is on the prevention of acute and chronic rejection and preserving the ability to reverse refractory acute rejection. These efforts have been successful; the challenge for the future of pediatric liver transplantation is achieving long-term survival and improved quality of life. This inherently involves strategies to minimize the long-term toxicity of immunosuppressive drug therapy, which can include renal failure, cardiovascular complications, and infections. Strategies of drug minimization, steroid-free therapy, and complete withdrawal of drugs have been accomplished in select patients and under careful medical supervision.

Immediately peri- or posttransplantation induction immunosuppressive therapy can involve antilymphocyte antibody induction with depleting antibodies (monoclonal or polyclonal), such as antithymocyte globulin antibody or the use of a chimeric mouse–human antibody that blocks the interleukin-2 receptor of the T cell, thus preventing activation and replication of antigen-selected T cells. Corticosteroids act through the suppression of antibody production and cytokine synthesis (interleukin-2, and interferon- $\gamma$ ), decreasing proliferation of T cells (helper, suppressor, and cytotoxic), B cells, and neutrophils. Maintenance immunosuppression is achieved by using calcineurin phosphatase inhibitor (cyclosporine or tacrolimus); these drugs interfere with the production and release of interleukin-2, a critical factor in the cytotoxic T-cell response. Calcineurin phosphatase inhibitors are most effectively directed toward inhibiting T-cell-mediated acute cellular rejection. Tacrolimus is the mainstay of most immunosuppressive regimens, and its ability to progress or initiate maintenance immunosuppression in the absence of corticosteroids is of particular benefit in children. Adjuvant immunosuppression, such as azathioprine or mycophenolate mofetil, which inhibits the synthesis of purine nucleosides and subsequently the proliferation of T and B lymphocytes as well as antibody formation, may be added to

enhance the antirejection profile, allow for decrease in the calcineurin dosage, or manage chronic rejection. Rapamycin, a macrolide that binds its molecular target of mammalian target of rapamycin receptor, decreases interleukin-2 production and, in turn, T- and B-cell activation and proliferation.

### COMPLICATIONS

Posttransplantation complications can be related to the pretransplantation condition of the recipient and the donor match and type, immunologic responses to the graft and the need for enhanced immunosuppressive drug therapy, and toxicity effects of these drugs or infections from over-immunosuppression. Post-transplant complications can occur at varying specific frequencies over a fairly well-defined time course (early, late, remote).

The most anticipated early complications involve those inherent to the transplantation operation: primary nonfunction of the graft, hepatic artery thrombosis, portal/hepatic venous strictures or occlusions, and biliary strictures. Primary nonfunction of the graft is rare in pediatric recipients given the selection criteria of potential donors. Hepatic artery thrombosis is the most frequent and early vascular complication; it occurs in 5–10% of recipients and can have devastating consequences on the graft (acute necrosis and gangrene, biliary leaks/stricture/bilomas) and may require urgent retransplantation. Portal vein or hepatic vein strictures/occlusions are rare and generally occur later posttransplantation. Biliary strictures are the most frequent surgical complication (10–30%) after liver transplantation and should be included in the differential diagnosis of any posttransplantation liver allograft dysfunction. Management of these complications varies and may include interventional radiologic procedures, reoperation, or retransplantation. Advancements in interventional radiology technique have allowed for a less invasive and equally efficacious approach to resolving these complications.

Rejection usually occurs after the first 2 weeks after transplantation, with the highest incidence (30–60%) within the first 90 days. Diagnosis of rejection is suspected based on abnormal liver function studies; rarely are there systemic signs such as fever, abdominal pain, new-onset ascites, or hydrothorax. Diagnosing rejection requires biopsy confirmation; treatment algorithms include high doses of corticosteroids and antilymphocyte antibodies. Chronic rejection is less frequent (5–10%) and is characterized by progressive damage and loss of bile ductules with consequent cholestasis; treatment involves long-term enhancement of maintenance immunosuppression with corticosteroids and other agents.

The need to treat rejection can place the patient at a higher risk of drug toxicity or infection. The most common transplantation-related infections are cytomegalovirus and Epstein-Barr virus infections, for which there are well-developed algorithms of prophylaxis and screening. Epstein-Barr virus-induced **posttransplant lymphoproliferative disease** (PTLD) represents a unique complication of over-immunosuppression and infection occurring in approximately 10% of patients. It is managed primarily by withdrawal of immunosuppression and antiviral therapy; some patients require chemotherapy.

### OUTCOMES

UNOS data reveal a 1-year patient and graft survival for biliary atresia of 95% and 87%, respectively. Examination of 461 5-year survivors of pediatric liver transplantation in a North American registry found a first graft survival of 88%, with 12% requiring a second graft and 2% requiring a third transplant. The same investigators published a study of 167 10-year survivors and found that only 30% of the group had an “ideal outcome” of normal liver-associated enzymes, no retransplant, and no evidence of PTLD, chronic rejection, hypertension, or renal disease. Longer-term survival is inherently dependent on adequacy of long-term immunosuppression management, adherence to care protocols, and prevention of infection/toxicities/chronic rejection.

## Section 7

# Peritoneum

## Chapter 417

### Peritoneal Malformations

Jamie F. Merves and Chris A. Liacouras

Numerous anomalies can occur during peritoneal development. Many are rarely of clinical importance, but peritoneal bands and cysts can result in manifestations such as abdominal pain and obstruction. Additionally, peritoneal encapsulation can occur because of an accessory peritoneal sac. Absence or duplication of the omentum occurs rarely.

**Congenital peritoneal bands** represent anatomically unabsorbed portions of omentum and mesentery and most commonly occur in the regions of the duodenum, duodenjejunal flexure, ileocecal junction, and ascending colon. Although usually benign, they may be responsible for symptoms ranging from nonspecific chronic abdominal pain to intestinal obstruction, malrotation, volvulus, and internal herniation with potential for resulting associated necrosis. Evaluation includes abdominal radiography, fluoroscopy, and, less commonly, CT and angiography. Even when discovered incidentally, surgical management generally remains the standard of care to prevent complications.

**Omental cysts** arise from obstructed or ectopic lymphatic channels within the omentum. They may be congenital or can result from trauma. They are usually asymptomatic, but abdominal pain or partial small bowel obstruction can result from compression or torsion of the small bowel from traction on the omentum. **Mesenteric cysts** are also rare and may coexist with omental cysts. They most commonly arise from the small bowel mesentery but can also occur in the large bowel mesentery or retroperitoneum. They too arise from lymphatic anomalies, and the cysts can be single or multiple and are often large. Presentation varies but most frequently involves abdominal pain, distention, and appreciation of an abdominal mass and/or suspected ascites on examination. Gastrointestinal symptoms may also include nausea, emesis, constipation, or loose stools. Mesenteric cysts are mostly benign lesions but may act as lead points for torsion and intussusception and can develop hemorrhage, infection, and, rarely, malignant transformation. Cysts are usually well defined and identified on imaging via ultrasound or CT scan. Treatment is typically simple excision, which can be performed laparoscopically in most cases, with excellent results and generally good prognosis.

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## Chapter 418

### Ascites

Jessica W. Wen and Chris A. Liacouras

Ascites is the pathologic accumulation of fluid within the peritoneal cavity. Multiple causes of ascites have been described in different age-groups (Tables 418.1-418.3). In children, hepatic and renal disease are the most common causes, but ascites can also be caused by cardiac disease, trauma, infection, or neoplasia.

**Table 418.1** Causes of Fetal Ascites

#### Gastrointestinal disorders

- Meconium peritonitis
- Intestinal malrotation
- Small intestinal or colonic atresia
- Intussusception
- Volvulus

#### Hepatobiliary disorders

- Gestational alloimmune liver disease
- Cystic fibrosis
- Biliary atresia
- Portal venous malformations

#### Infection

- Parvovirus
- Syphilis
- Cytomegalovirus
- Toxoplasmosis
- Acute maternal hepatitis

#### Genitourinary disorders

- Hydronephrosis
- Polycystic kidney disease
- Urinary obstruction
- Ovarian cyst
- Persistent cloaca

#### Chylous ascites

- Lymphangiectasia
- Lymphatic malformations

#### Cardiac disorders

- Arrhythmia
- Heart failure

#### Chromosomal abnormalities

- Trisomy
- Turner syndrome

#### Neoplasm

- Neuroblastoma
- Leukemia

#### Hematologic

- Hemolytic anemias

#### Metabolic disease

- Niemann-Pick type C
- Congenital disorders of glycosylation
- Lysosomal storage diseases

#### Other

- Maternal/fetal injury
- Congenital lupus erythematosus
- Idiopathic

Modified from Giefer MJ, Murray KF, Colletti RB. Pathophysiology, diagnosis, and management of pediatric ascites. *J Pediatr Gastroenterol Nutr*. 2011;52(5):503-513. Table 1.

The clinical hallmark of ascites is abdominal distention. Early satiety and dyspnea can occur with a moderate amount of ascites. Considerable intraperitoneal fluid can accumulate before ascites is detectable by the classic physical signs: bulging flanks, dullness to percussion, shifting dullness, a fluid wave, and the *puddle sign* (percussion of a supine person's abdomen over the umbilicus becomes dull as the patient is moved to a prone position and ascitic fluid puddles in dependent regions). Umbilical herniation can be associated with tense ascites. Ultrasound examination is useful for detecting small amounts of ascites.

Abdominal paracentesis can provide symptomatic relief and may be diagnostic of the cause of the ascites. Determining the serum-ascites albumin gradient can help determine the cause of ascites. A gradient greater than 1.1 g/dL (high-gradient ascites) is consistent with ascites caused by portal hypertension, whereas a gradient <1.1 g/dL (low-gradient ascites) indicates ascites of non-portal-hypertensive etiology.

The course, prognosis, and treatment of ascites depend entirely on the cause. For most patients, treatment consists of dietary sodium restriction and diuretic therapy with spironolactone, with the addition of furosemide in more severe cases. Supplemental albumin can also aid in ascitic fluid mobilization. Refractory cases may require large volume paracentesis or transjugular intrahepatic portosystemic shunting. Patients with any type of ascites are at increased risk for spontaneous bacterial peritonitis.

## Section 7

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## Chapter 417

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- Toxoplasmosis
- Acute maternal hepatitis

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- Ovarian cyst
- Persistent cloaca

#### Chylous ascites

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- Lymphatic malformations

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#### Other

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**Table 418.2** Causes of Neonatal Ascites

<b>Hepatobiliary disorders</b>
Cirrhosis
α <sub>1</sub> -Antitrypsin deficiency
Congenital hepatic fibrosis
Viral hepatitis
Budd-Chiari syndrome
Gestational alloimmune liver disease
Biliary atresia
Bile duct perforation
Portal venous malformation
Ruptured mesenchymal hamartoma
<b>Gastrointestinal disorders</b>
Intestinal malrotation
Intestinal perforation
Acute appendicitis
Intestinal atresia
Pancreatitis
<b>Chylous ascites</b>
Intestinal lymphangiectasia
Lymphatic duct obstruction
Lymphatic duct trauma
<b>Parenteral nutrition extravasation</b>
<b>Metabolic disease (see Table 418.1)</b>
<b>Genitourinary disorders</b>
Obstructive uropathy
Posterior urethral valves
Ureterocele
Lower ureteral stenosis
Ureteral atresia
Imperforate hymen
Bladder rupture
Bladder injury from umbilical artery catheterization
Nephrotic syndrome
Ruptured corpus luteum cyst
<b>Cardiac</b>
Arrhythmia
Heart failure
<b>Other</b>
Cutis marmorata telangiectatica congenita
Intravenous vitamin E
Pseudo-ascites
Small bowel duplication
Abdominal trauma
Idiopathic

From Giefer MJ, Murray KF, Colletti RB. Pathophysiology, diagnosis, and management of pediatric ascites. *J Pediatr Gastroenterol Nutr.* 2011;52(5):503–513. Table 2.

## 418.1 Chylous Ascites

Jessica W. Wen and Chris A. Liacouras

Chylous ascites refers to peritoneal fluid that contains lymphatic drainage with a characteristic milky appearance that is rich in triglycerides. Chylous ascites can result from congenital anomaly, injury, or obstruction of the intraabdominal portion of the thoracic duct. Although uncommon, it can occur at any age. In the pediatric population, the most common cause is lymphatic malformation (lymphangiectasia). Other causes include surgical injury to the lymphatics, trauma, cirrhosis, peritoneal bands, generalized lymphangiomatosis, chronic inflammatory processes of the bowel, and mycobacterial infection. Malignancy is a common cause in the adult population but uncommon in pediatrics. Congenital anomalies of the lymphatic system can be associated with Turner, Noonan, yellow nail, and Klippel-Trenaunay-Weber syndromes. Other etiologies include nephrotic syndrome, familial visceral myopathy, sarcoidosis, intestinal malrotation and volvulus, pancreatitis, constrictive pericarditis, and Behçet disease. Postsurgical chylous ascites has been associated with a variety of abdominal surgical procedures, including Nissen fundoplication, appendectomy, liver and kidney transplant, and others. It can occur early, within a week post operation, or weeks to months later due to adhesions and extrinsic compression of lymphatic vessels.

The most common presentation is painless abdominal distention, and it may be accompanied by poor weight gain and loose stools. Peripheral edema is common. Massive chylous ascites can result in scrotal edema, inguinal and umbilical herniation, and respiratory difficulties.

Diagnosis of chylous ascites depends on the demonstration of milky ascitic fluid obtained via paracentesis after a fat-containing feeding. Ascites

**Table 418.3** Causes of Ascites in Infants and Children

<b>Hepatobiliary disorders</b>
Cirrhosis
Congenital hepatic fibrosis
Acute hepatitis
Budd-Chiari syndrome
Bile duct perforation
Liver transplantation
<b>Gastrointestinal disorders</b>
Acute appendicitis
Intestinal atresia
Pancreatitis
Pyloric duplication
<b>Serositis</b>
Crohn disease
Eosinophilic enteropathy
IgA vasculitis (Henoch-Schönlein purpura)
<b>Chylous ascites</b>
Intestinal lymphangiectasia
Lymphatic duct obstruction
Lymphatic duct trauma
<b>Parenteral nutrition extravasation</b>
<b>Infectious</b>
Tuberculosis
Abscess
Schistosomiasis
<b>Neoplasm</b>
Lymphoma
Wilms tumor
Clear cell renal sarcoma
Glioma
Germ cell tumor
Ovarian tumor
Mesothelioma
Neuroblastoma
<b>Metabolic disease</b>
<b>Genitourinary disorders</b>
Nephrotic syndrome
Peritoneal dialysis
<b>Cardiac</b>
Heart failure
<b>Pseudo-ascites</b>
Celiac disease
Cystic mesothelioma
Omental cyst
Ovarian cyst
<b>Other</b>
Systemic lupus erythematosus
Ventriculoperitoneal shunt
Vitamin A toxicity
Chronic granulomatous disease
Nonaccidental trauma
Protein losing enteropathy
Idiopathic

Modified from Giefer MJ, Murray KF, Colletti RB. Pathophysiology, diagnosis, and management of pediatric ascites. *J Pediatr Gastroenterol Nutr.* 2011;52(5):503–513. Table 3.

fluid analysis reveals high protein content, elevated triglycerides, and lymphocytosis. If the patient has had nothing by mouth, the fluid may appear serous. Hypoalbuminemia, hypogammaglobulinemia, and lymphopenia are common in these patients. MR lymphangiography will identify lymphatic malformations.

Treatment includes a high-protein, low-fat diet supplemented with medium-chain triglycerides that are absorbed directly into the portal circulation and decrease lymph production. Parenteral alimentation may be necessary if nutrition remains impaired on oral feedings; this may also significantly decrease lymph flow and facilitate sealing at the point of lymph leakage. Octreotide, a somatostatin analog, has been used subcutaneously in chylous ascites. The mechanism is not clearly understood; however, it decreases intestinal blood flow, leading to decreased portal pressure, and it also inhibits lymphatic secretion through somatostatin receptors in the intestinal wall. Paracentesis should be repeated only if abdominal distention causes respiratory distress. Lymphangiography with adjunctive embolization may be very successful in treating chylous ascites with identified site of leakage or a malformation. Laparotomy may be indicated if conservative management has been unsuccessful for potential surgical ligation of lymphatics.

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## Chapter 419

# Peritonitis

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Inflammation of the peritoneal lining of the abdominal cavity can result from infectious, autoimmune, neoplastic, and chemical processes. Infectious peritonitis is usually defined as primary (spontaneous) or secondary. In primary peritonitis, the source of infection originates outside the abdomen and seeds the peritoneal cavity via hematogenous, lymphatic, or transmural spread. Secondary peritonitis arises from the abdominal cavity itself through extension from or rupture of an intraabdominal viscus or an abscess within an organ. Tertiary peritonitis refers to recurrent diffuse or localized disease and is associated with poorer outcomes than secondary peritonitis.

Clinically, patients have abdominal pain, abdominal tenderness, and rigidity on exam. Peritonitis can result from rupture of a hollow viscus, such as the appendix or a Meckel diverticulum; disruption of the peritoneum from trauma or peritoneal dialysis catheter; chemical peritonitis from other bodily fluid, including bile and urine; and infection. Meconium peritonitis is described in Chapter 135. Peritonitis is considered a surgical emergency and requires exploration and lavage of the abdomen, except in spontaneous bacterial peritonitis.

## 419.1 Acute Primary Peritonitis

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### ETIOLOGY AND EPIDEMIOLOGY

Primary peritonitis usually refers to bacterial infection of the peritoneal cavity without a demonstrable intraabdominal source. Most cases occur in children with ascites resulting from cirrhosis or nephrotic syndrome. Infection can result from translocation of gut bacteria as well as immune dysfunction. Rarely, primary peritonitis occurs in previously healthy children. Pneumococci (most common), group A streptococci, enterococci, staphylococci, and gram-negative enteric bacteria, especially *Escherichia coli* and *Klebsiella pneumoniae*, are most commonly found. *Mycobacterium tuberculosis*, *Neisseria meningitidis*, and *Mycobacterium bovis* are rare causes. A small percentage are polymicrobial or culture negative.

### CLINICAL MANIFESTATIONS

Onset may be insidious or rapid and is characterized by fever, abdominal pain, and a toxic appearance. Vomiting and diarrhea may be present. Hypotension and tachycardia are common, along with shallow, rapid respirations because of discomfort associated with breathing. Abdominal palpation might demonstrate rebound tenderness and rigidity. Bowel sounds are hypoactive or absent. However, signs and symptoms may be subtle at times, and increased vigilance is needed in cirrhotic patients who have ascites and present with unexplained leukocytosis, azotemia, or metabolic acidosis.

### DIAGNOSIS AND TREATMENT

Peripheral leukocytosis with a marked predominance of polymorphonuclear cells is common, although the white blood cell (WBC) count can be affected by preexisting hypersplenism in patients with cirrhosis. Patients with nephrotic syndrome generally have proteinuria, and low serum albumin in these patients is associated with an increased risk of peritonitis. X-ray examination of the abdomen reveals dilation of the large and small intestines, with increased separation of loops secondary to bowel wall thickening. Distinguishing primary peritonitis from appendicitis may be difficult in patients without a history of nephrotic syndrome or cirrhosis; accordingly, the diagnosis of primary peritonitis is made by CT scan, laparoscopy, or laparotomy. In a child with known renal or hepatic disease and ascites, the presence of peritoneal signs should prompt diagnostic paracentesis. Infected fluid usually reveals a WBC count of  $\geq 250$  cells/mm $^3$ , with  $>50\%$  polymorphonuclear cells.

Primary peritonitis is usually *monomicrobial*. The presence of mixed bacterial flora on ascitic fluid examination or free air on abdominal roentgenogram in children with presumed peritonitis mandates further evaluation to localize a perforation as a likely *intraabdominal* source of the infection. Inoculation of ascitic fluid obtained at paracentesis directly into blood culture bottles increases the yield of positive cultures. Parenteral antibiotic therapy with broad-spectrum coverage, such as cefotaxime, should be started promptly, with subsequent changes dependent on sensitivity testing (vancomycin for resistant pneumococci). Patients with risk factor for multidrug resistant organisms such as nosocomial infection, recent exposure to antibiotics, or with sepsis or septic shock should receive broad-spectrum coverage with piperacillin/tazobactam with consideration for addition of vancomycin if prior infection or positive surveillance swab for methicillin-resistant *Staphylococcus aureus*. Therapy should be continued for 5–10 days.

**Culture-negative neutrocytic ascites** is a variant of primary peritonitis with an ascitic fluid WBC count of  $>500$  cells/mm $^3$ , a negative culture, no intraabdominal source of infection, and no prior treatment with antibiotics. It should be treated in a similar way to primary peritonitis.

## 419.2 Acute Secondary Peritonitis

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Acute secondary peritonitis most often results from entry of enteric bacteria into the peritoneal cavity through a necrotic defect in the wall of the intestines or other viscus as a result of obstruction or infarction or after rupture of an intraabdominal visceral abscess. It most commonly follows perforation of the appendix. Other causes include incarcerated hernias, rupture of a Meckel diverticulum, midgut volvulus, intussusception, hemolytic uremic syndrome, peptic ulceration, inflammatory bowel disease, necrotizing cholecystitis, necrotizing enterocolitis, typhlitis, and traumatic perforation.

Peritonitis in the neonatal period most often occurs as a complication of necrotizing enterocolitis but may be associated with meconium ileus or spontaneous (or indomethacin-induced) rupture of the stomach or intestines. In postpubertal females, bacteria from the genital tract (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*) can gain access to the peritoneal cavity via the fallopian tubes, causing secondary peritonitis. The presence of a foreign body, such as a ventriculoperitoneal catheter or peritoneal dialysis catheter, can predispose to peritonitis, with skin microorganisms, such as *Staphylococcus epidermidis*, *S. aureus*, and *Candida albicans*, contaminating the shunt. Secondary peritonitis results from direct toxic effects of bacteria as well as local and systemic release of inflammatory mediators in response to organisms and their products (lipopolysaccharide endotoxin). The development of sepsis depends on various host and disease factors, as well as the promptness of antimicrobial and surgical intervention.

### CLINICAL MANIFESTATIONS

Similar to primary peritonitis, characteristic symptoms include fever, diffuse abdominal pain, nausea, and vomiting. Physical findings of peritoneal inflammation include rebound tenderness, abdominal wall rigidity, a paucity of body motion (lying still), and decreased or absent bowel sounds from paralytic ileus. Massive exudation of fluid into the peritoneal cavity, along with the systemic release of vasodilatory substances, can lead to the rapid development of shock. A toxic appearance, irritability, and restlessness are common. Basilar atelectasis, as well as intrapulmonary shunting, can develop, with progression to acute respiratory distress syndrome.

Laboratory studies reveal a peripheral WBC count  $>12,000$  cells/mm $^3$ , with a marked predominance of polymorphonuclear forms. X-rays of the abdomen can reveal free air in the peritoneal cavity, evidence of ileus or obstruction, peritoneal fluid, and obliteration of the psoas shadow. Other peritoneal fluid findings suggestive of secondary peritonitis include elevated total protein ( $>1$  g/dL), and low glucose ( $<50$  mg/dL).

### TREATMENT

Aggressive fluid resuscitation and support of cardiovascular function should begin immediately. Stabilization of the patient before surgical intervention is mandatory. Antibiotic therapy must provide coverage for organisms that predominate at the site of presumed origin of the infection. Initial empiric antibiotics for spontaneous bacterial peritonitis has included cefotaxime or ceftriaxone. In contrast to primary peritonitis, secondary peritonitis is typically *polymicrobial*. For perforation of the lower gastrointestinal tract, a regimen of ampicillin, gentamicin, and clindamycin or metronidazole will adequately address infection by *E. coli*, *Klebsiella*, and *Bacteroides* spp. and enterococci. Alternative therapy could include piperacillin/tazobactam or a carbapenem. Surgery to repair a perforated viscus should proceed after the patient is stabilized and antibiotic therapy is initiated. Intraoperative peritoneal fluid cultures will indicate whether a change in the antibiotic regimen is warranted. Empirical treatment for peritoneal dialysis catheter-related peritonitis may include intraperitoneal vancomycin or a first-generation cephalosporin (such as cefazolin) for gram-positive organism coverage, and third- or fourth-generation cephalosporin (such as cefepime or ceftazidime), aminoglycoside, carbapenem or aztreonam (for patients allergic to cephalosporins) for gram-negative organism coverage. Serious infection from peritoneal dialysis catheters can generally be prevented with good catheter hygiene and prompt removal and replacement with signs of progressive infection.

### 419.3 Acute Secondary Localized Peritonitis (Peritoneal Abscess)

Jessica W. Wen and Chris A. Liacouras

#### ETIOLOGY

Intraabdominal abscesses occur less commonly in children and infants than in adults, but they can develop in visceral intraabdominal organs (hepatic, splenic, renal, pancreatic, tubo-ovarian abscesses) or in the inter-intestinal, periappendiceal, subdiaphragmatic, subhepatic, pelvic, or retro-peritoneal spaces. Most commonly, periappendiceal and pelvic abscesses arise from a perforation of the appendix. Transmural inflammation with fistula formation can result in intraabdominal abscess formation in children with inflammatory bowel disease.

#### CLINICAL MANIFESTATIONS

Prolonged fever, anorexia, vomiting, and lassitude suggest the development of an intraabdominal abscess. The peripheral WBC count is elevated, as is the erythrocyte sedimentation rate. With an appendiceal abscess, there is localized tenderness and a palpable mass in the right lower quadrant. A pelvic abscess is suggested by abdominal distention, rectal tenesmus with or without the passage of small-volume mucous stools, and bladder irritability. Rectal examination might reveal a tender mass anteriorly. Subphrenic gas collection, basal atelectasis, elevated hemidiaphragm, and pleural effusion may be present with a subdiaphragmatic abscess. Psoas abscess can develop from extension of infection from a retroperitoneal appendicitis, Crohn disease, or perirenal or intrarenal abscess. Abdominal findings may be minimal, and presentation can include a limp, hip pain, and fever. Ultrasound examination, CT scanning, and MRI may be used to localize intraabdominal abscesses; MRI gives the best resolution of disease involvement.

#### TREATMENT

An abscess should be drained, and appropriate antibiotic therapy provided. Drainage can be performed under radiologic control (ultrasonogram or CT guidance) and an indwelling drainage catheter left in place, or surgically depending on location of abscess. Initial broad-spectrum antibiotic coverage such as a combination of ampicillin, gentamicin, and clindamycin or ciprofloxacin and metronidazole should be started and can be modified, depending on the results of sensitivity testing. The treatment of appendiceal rupture complicated by abscess formation may be problematic because intestinal phlegmon formation can make surgical resection more difficult. Intensive antibiotic therapy for 4–6 weeks followed by an interval appendectomy is often the treatment course followed.

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## Chapter 420

### Epigastric Hernia

John J. Aiken

Epigastric hernias in children are ventral hernias in the midline of the abdominal wall between the xiphoid process of the sternum and the umbilicus. Epigastric hernias are more likely to be congenital than acquired. The defect typically contains only preperitoneal fat without a peritoneal sac or abdominal viscera. Because most epigastric hernias are small and asymptomatic, the true incidence is unknown, but the reported incidence in childhood varies from <1% to as high as 5%. The etiology of epigastric hernia is unknown. The two main hypotheses are the vascular lacunae hypothesis and the tendinous fiber decussation hypothesis; the former proposes that the protrusion is through small spaces created where the vascular lacunae penetrate the linea alba, and the latter proposes that epigastric hernia occurs exclusively at sites where affected patients do not have triple lines of decussation. In addition, undiagnosed collagen disorders, increased

intraabdominal pressure, and, in older patients, previous midline incision may play a role in the development of epigastric hernia. Epigastric hernias may be single or multiple and are 2–3 times more common in males than females. Through the small midline defect there is often herniation of preperitoneal fat into the superficial abdominal wall, although as the defect becomes progressively larger, the rare possibility exists of herniation of intraabdominal contents. Epigastric (incisional) hernias can occur in a previous incision site or be associated with ventricular-peritoneal shunts.

#### CLINICAL PRESENTATION

Epigastric hernias typically appear in young children as a visible or palpable mass in the midline, between the umbilicus and the xiphoid process of the sternum, noted by the parents or primary care practitioner. The mass is almost always small (<1 cm), asymptomatic, and typically reported as always present, but most apparent at times of irritability or straining. Occasionally the mass is intermittent, and the child relates pain localized to the site. Physical examination demonstrates a firm mass, directly in the midline, anywhere between the umbilicus and the xiphoid process. The mass may be intermittent if the fat reduces with relaxation of the abdominal muscles. Epigastric hernias typically contain only preperitoneal fat, and most are not reducible because of the small size of the fascial defect. Rarely, a fascial defect is noted without a palpable mass. Herniation of intestines or abdominal viscera in an epigastric hernia would be exceptionally rare if the defect enlarges over time. The mass may be tender to examination, but strangulation of the hernia contents is uncommon. Physical examination is almost always diagnostic, and imaging studies are generally unnecessary. If the diagnosis is unclear, imaging may be useful. Ultrasound typically shows a small mass that is isoechoic to the adjacent subcutaneous fat and possibly connection through a small fascial defect with the preperitoneal fat. MRI imaging might be helpful in diagnosis but is not routinely used.

The natural history of epigastric hernia is for gradual enlargement over time as intermittently more preperitoneal fat is extruded through the defect at times of straining or increased intraabdominal pressure. Left untreated, the defect can enlarge and allow herniation of intraabdominal viscera within a peritoneal sac, mostly seen in adults. Epigastric hernias do not resolve spontaneously, and therefore operative repair is the recommended treatment. The site should be carefully marked preoperatively because the mass and defect can be difficult to localize in a relaxed abdominal wall after induction of anesthesia. A limited transverse incision is made over the mass, and dissection is performed to delineate the edges of the fascial defect. If herniated fat is present, it is dissected free of the subcutaneous tissues and can be reduced or ligated and excised. The defect is closed using absorbable suture. The skin is closed with an absorbable subcuticular suture. Post-operative complications are rare, and the recurrence rate is low.

### 420.1 Incisional Hernia

John J. Aiken

Hernia formation in the site of a previous laparotomy is uncommon in childhood. Incisional hernias can also occur at the incision sites for the laparoscopic ports used in minimally invasive surgery. Factors associated with an increased risk of incisional hernia include increased intraabdominal pressure, wound infection, and midline incision. The laparoscopic port sites pose a technical challenge to visualize the fascia in a small incision. Transverse abdominal incisions are favored because of their increased strength and blood supply, which reduces the likelihood of wound infection and incisional hernia. Although most incisional hernias require repair, operation should be deferred until the child is in optimal medical condition. Some incisional hernias resolve, especially those occurring in infants. Some recommend elastic bandaging to discourage enlargement of the hernia and to promote spontaneous healing. Initial management should be conservative, with repair deferred until around 1 year of age. Incarceration is very uncommon in incisional hernias but is an indication for prompt repair. Newborns with abdominal wall defects represent the largest group of children with incisional hernias.

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