Fifth Edition

First Principles of Gastroenterology

The Basis of Disease and an Approach to Management

JANSSEN-ORTHO

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Manifestations of Gastrointestinal Disease in the Child

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1. FUNCTIONAL GASTROINTESTINAL DISORDERS WITH ABDOMINAL PAIN / M. Robertson

1.1 Definitions and Introduction

Complaints of recurrent or chronic abdominal pain are very common in the pediatric population. Studies report that in a three-month period 10-35% of school-aged children have at least three episodes of abdominal pain severe enough to interfere with activity. Although chronic abdominal pain may be part of the presentation of numerous conditions, including peptic ulcer disease, celiac disease and Crohn's disease, the majority of children with recurrent or chronic abdominal pain have a functional gastrointestinal disorder. Functional disorders are defined as conditions in which symptoms are present in the absence of any readily identifiable structural or biochemical abnormality. Diagnostic criteria have been proposed for functional gastrointestinal disorders in childhood. Those functional disorders associated with abdominal pain in children appear to fit mainly into three groups. 1) Functional dyspepsia refers to pain or discomfort which is centered in the upper abdomen. The pain may be associated with nausea and feelings of early satiety. 2) In irritable bowel syndrome (IBS), abdominal pain is associated with defecation or change in bowel habit. 3) The third and probably most common group of children does not fit the criteria for IBS or functional dyspepsia and is diagnosed with functional abdominal pain or functional abdominal pain syndrome.

1.2 Pathophysiology

Researchers now believe functional abdominal pain arises when there is a

communication disorder between the central nervous system and enteric nervous system (the "brain-gut axis"). The enteric nervous system, which has been called the "mini-brain," communicates with the central nervous system but also acts autonomously. It has three categories of neurons: sensory neurons, interneurons and motor neurons, and a library of programs that determine patterns of gut behavior. The sympathetic and parasympathetic nervous systems transmit signals between the central nervous system and the gut. Afferent signals from the viscera will normally result in sensations such as hunger and satiety but will sometimes result in feelings of pain or nausea. High-amplitude contractions, luminal distention and inflammation can all produce painful sensations. It is currently hypothesized that functional abdominal pain, particularly in IBS may result from visceral hypersensitivity with increased afferent signals from the gut. Possible triggers for this increase in afferent signals include preceding infection, trauma and allergy. Developmental and genetic factors are also likely involved. The central response to these afferent signals may also be magnified. In this situation even physiologic sensory input from the gut may be interpreted as discomfort. Stress, anxiety and depression modify the physiologic state which in turn can alter not only the perception of pain but also intestinal motor and secretory function.

The morbidity resulting from functional abdominal pain syndrome often relates more to the individual, family and school responses to the symptoms, rather than the severity of the symptoms themselves. Because of the potentially complex interactions between biological, psychological and social factors, children with functional abdominal pain are best assessed and managed using a bio-psycho-social model of disease.

1.3 Clinical Evaluation

The history and physical examination are important, not only in evaluation, but also in the successful management of children with functional gastrointestinal disorders. A diagnosis of functional abdominal pain can be strongly considered if a history has been elicited that is typical of functional pain, with no symptoms suggestive of organic disease, and the physical examination is normal. Education of the family about the nature of this condition can therefore often begin at the first visit.

The characteristic pattern of functional abdominal pain includes:

1. Pain is localized in the umbilical to mid-epigastric region, but sometimes poorly localized and felt all over the abdomen.
2. Pain does not radiate.
3. Pain may vary from mild to so severe that the patient may be pale and diaphoretic.

4. Children will often have difficulty describing the nature of the pain or they may provide extremely colorful analogies.
5. Episodes may occur once daily or several times a day and may often cluster. The clusters may last weeks to months.
6. There is usually no consistent relationship to meals, defecation or exercise.
7. Some children may have more episodes in the mornings or evenings. They may have difficulty falling asleep but are rarely woken from sleep by the pain.

These children are more likely to have irritable bowel syndrome and migraine headaches in their family history. Psychological or emotional disturbance will be a primary diagnosis in only a very small number of children presenting with functional abdominal pain. It is, however, useful to use the bio-psycho-social model for diagnostic evaluation, as social or psychological stressors may be influencing the child's physiologic state. Alterations in physiologic state may alter pain perception and possibly gastrointestinal function. In addition, reviewing the impact of the pain episodes on the child's life as well as the family's and school's responses to episodes of pain is necessary to identify any possible secondary gain to the child.

The physical examination of children with functional gastrointestinal disorders associated with abdominal pain should be entirely normal. Plots of the previous and currently measured heights and weights will demonstrate a normal growth velocity, and importantly, there will be no physical signs of disease.

1.4 Differential Diagnosis and Approach to Investigation

The differential diagnosis of chronic or recurrent abdominal pain in childhood is extensive. Nevertheless, a complete history and physical examination with limited laboratory investigations will usually be sufficient for the physician to make a positive diagnosis of functional abdominal pain. The approach to diagnosis should not be one of extensive investigation to exclude organic disease. In the majority of cases, history and physical examination might be supported by a complete blood count, sedimentation rate, serum albumin, urinalysis and possibly stool occult blood. Comprehensive lists of organic causes of chronic abdominal pain are available but need be referred to only when features of the history and physical examination or investigations suggest an organic problem that is not readily apparent. Specific aspects of the history that should signal concern on the part of the physician include significant recurrent pain in a child under the age of 3; consistent localization of pain away from the umbilicus; frequently being woken from sleep by pain; repetitive or bilious emesis; and any constellation of symptoms and signs that are typical of a specific organic etiology.

Genitourinary and gastrointestinal disorders are the most common organic causes of chronic abdominal pain. Recurrent urinary tract infection and hydronephrosis or obstructive uropathy can present with abdominal pain. Usually features in the history atypical for functional pain and/or abnormal urinalysis would suggest the diagnosis.

Constipation is a common disorder and patients may experience crampy abdominal discomfort in association with the urge to defecate. A suggestive history and the demonstration on physical examination of bulky stool retained in the rectum should initiate a trial of appropriate treatment.

A history of abdominal pain, bloating, flatus and watery diarrhea that occurs with heavy ingestion of "sugarless" gums or confections suggests the possibility of malabsorption of nonabsorbable carbohydrates. The same history occurring with milk intake in individuals whose ethnic background might predispose to lactase deficiency (oriental, black or peri-Mediterranean) suggests lactose malabsorption.

A history of frequent vomiting or bilious vomiting in the presence of abdominal pain should be a "red flag" suggesting the possibility of intestinal obstruction. Malrotation or incomplete rotation of the mid-gut is a disorder that may present as a bowel obstruction and also predisposes to intestinal volvulus. Whenever malrotation is suspected an upper gastrointestinal series should be performed to determine the position of the duodenojejunal flexure, and a barium enema may be required to ensure proper location of the cecum in the lower right quadrant.

Primary peptic ulcer disease is much less common in children than in adults and frequently lacks the typical meal-related characteristics that are common with the adult presentation. A family history of peptic ulcer disease, vomiting, nighttime awakening with pain, hematemesis or melena, or unexplained anemia should suggest the diagnosis.

1.5 Management

To successfully manage the child, it is crucial the history and physical examination are conducted with care and thoroughness. Such caution demonstrates the physician has seriously evaluated the complaint. Once a diagnosis of functional abdominal pain has been made, it is important to cease investigations and to educate and reassure the patient and parents.

It must be made clear that the discomfort of the recurrent abdominal pain is genuine, not imagined or manufactured for gain or manipulation. It is important to point out that this is a common complaint. Identify for the parent those criteria upon which you based the diagnosis of the functional gastrointestinal disorder, for example with functional abdominal pain syndrome: the periumbilical location of the discomfort, the absence of any constellation of historical or objective physical findings that suggest under-

lying organic disease, continued normal growth and development (show the parents the growth chart), continued general well-being between episodes, and a family history of similar functional complaints, if that exists. In those cases where they can be identified note the positive association of the pain with stressful situations or events and any characteristics of the child's personality that might serve to exaggerate the stress. Try to elicit and allay any specific concerns on the part of the child or parents (e.g., "Does my child have appendicitis?").

Encourage the parents to discuss potential stressful contributing events with the child, and recommend a positive approach to coping that includes a return to all normal activities. Insist on attendance at school. Discuss the prognosis of this condition with the parents and provide reassurance by offering to reassess the child should there be any change in the symptoms.

Such an approach is generally very effective in relieving the parents' anxiety. Drugs, and specifically analgesics or sedatives, are not considered effective or appropriate. However, a significant decrease in recurrent abdominal pain may occur in children given additional dietary fiber.

1.6 Prognosis

Many children and their parents experience considerable immediate relief at having organic disease excluded. In the long term one-third of patients managed in this fashion are completely free of pain as adults, one-third experience continuing abdominal pain, and one-third develop alternative symptomatology such as headaches. Almost all lead unrestricted lives. The goal of management should be to develop, through education, the increased understanding and constructive coping mechanisms that will prevent symptoms from generating dysfunctional behavior.

2. VOMITING AND REGURGITATION / M. Robertson

2.1 The Vomiting Child

2.1.1 DEFINITIONS AND INTRODUCTION

Vomiting is a complex, coordinated reflex mechanism that may occur in response to a variety of stimuli and results in forceful expulsion of gastric contents. Gastroesophageal reflux is the apparently effortless passage of gastric contents into the esophagus due to impairment of the antireflux mechanism at the gastroesophageal junction.

The approach to the vomiting child is one of the most difficult problems in pediatrics, as the differential diagnosis is not limited to the gastrointestinal tract and includes conditions that are pediatric emergencies. In addition, persistent vomiting can lead to complications such as dehydration, electrolyte

abnormalities, Mallory-Weiss tears and aspiration of gastric contents. It is important to develop an approach to the child who presents with chronic vomiting that allows for rapid diagnosis and assessment of the degree of sickness with minimal investigation.

2.1.2 PATHOPHYSIOLOGY

The response of vomiting is mediated by neural efferents in the vagal, phrenic and spinal nerves. The complex neurohumoral brain-gut interactions are coordinated in the medulla. The process involves retrograde peristalsis, coordinated abdominal wall and respiratory movements with resulting forceful expulsion of the contents of the stomach through the mouth. This is a protective reflex since it promotes rapid expulsion of ingested toxins or relieves pressure in hollow organs distended by distal obstruction. The vomiting reflex may cause nausea, gastric atony, and signs and symptoms of autonomic excitation such as increased salivation, sweating, pupil dilatation, changed heart rate and respiratory rhythm.

2.1.3 CLINICAL EVALUATION

Vomiting is a nonspecific sign. It is a prominent feature of many disorders of other systems including, renal, neurologic, metabolic, endocrine and infectious disorders. Although it is a diagnostic challenge, the etiology of most vomiting can be determined by history and physical examination.

A number of features are particularly helpful in reaching a diagnosis:
These include:

1. Age of the patient
2. Associated signs and symptoms
3. Temporal pattern of vomiting

2.1.3.1 Age

Vomiting in the neonatal and early infant period may frequently be due to congenital obstructive gastrointestinal malformations such as atresias or webs of the esophagus or intestines, meconium ileus, or Hirschsprung's disease. Inborn errors of metabolism and endocrine disorders such as adrenal insufficiency often present with prominent vomiting in the neonate (Table 1). Some conditions will occur in specific age ranges: pyloric stenosis at two to eight weeks of age; intussusception at three to 18 months. Appendicitis is rare before the age of 12 months.

2.1.3.2 Associated symptoms and signs

Associated symptoms often provide important diagnostic clues (Table 2). For example bile-stained vomitus suggests intestinal obstruction distal to the

TABLE 1. Causes of vomiting according to age of presentation

Neonate/infancy	
Gastrointestinal disorders	*Nongastrointestinal disorders*
Common	Common
Gastroenteritis	Upper respiratory tract infection
Gastroesophageal reflux	Septicemia/meningitis
Pyloric stenosis	Pneumonia
Intussusception	Urinary tract infection
Anatomic obstruction	
Atresia – esophagus, small intestine	
Malrotation and volvulus	
Hirschsprung's disease	
Rare	Rare
Meconium ileus	Inborn error of metabolism
	Raised intracranial pressure – tumor/hydrocephalus
	Endocrine deficiency – adrenal, thyroid
	Renal tubular acidosis
	Genetic syndromes (trisomy 21, 13, 18)
Child/adolescent	
Gastrointestinal disorders	*Nongastrointestinal disorders*
Common	Common
Gastroenteritis	Infection – URTI, OM, UTI
Appendicitis	Toxin/drug ingestion
Intussusception	Bulemia
Pancreatitis	Pregnancy
Celiac disease	
Inflammatory bowel disease	
Rare	Rare
Hepatitis	Cyclic vomiting syndrome/migraine
Intestinal obstruction	Brain tumor
Peptic ulcer	Testicular torsion
Achalasia	Ovarian cyst/salpingitis
Reye's syndrome	

second part of the duodenum, while hematemesis suggests esophageal, gastric or duodenal mucosal disease. Furthermore, symptoms will often point to the organ system which is involved. For example, seizures in a neonate may suggest a metabolic or neurological cause for the vomiting.

2.1.3.3 Temporal pattern of vomiting

Recurrent vomiting may be approached by looking at the temporal pattern of vomiting and classifying as either the chronic continuous pattern or a cyclic sporadic pattern. The chronic continuous pattern includes about two-thirds of

TABLE 2. Differential diagnosis of vomiting by associated symptoms and signs

Symptom	*Features of Symptom*	*Condition*
Vomiting	Undigested food	Achalasia
	Bile	Post-ampullary obstruction
	Blood or "coffee grounds"	Gastritis, ulcers, esophagitis, varices
	Initially without blood and then with blood	Mallory Weiss tear
	Projectile	Pyloric stenosis, and other gastric obstruction Occasionally gastroesophageal reflux
Diarrhea		Infectious enteritis, partial luminal obstruction, toxins Sometimes non-intestinal conditions such as UTI
"Red Current Jelly" stool		Intussusception
Abdominal Pain	Central, colicky	Obstruction, gastroenteritis
	Right iliac fossa	Appendicitis
	Epigastric/central, radiating to back	Pancreatitis
	Right upper quadrant	Biliary obstruction, hepatitis
Bowel Sounds	Active, high-pitched	Obstruction
	Quiet, absent	Ileus
Jaundice		Hepatitis, hepatobiliary obstruction
	Neonate	Urinary tract infection or bowel obstruction
Neurological Symptoms and signs	Abnormal tone, seizures Fundoscopic or fontanelle evidence of raised ICP Headache, confusion Loss of developmental skills	Metabolic, toxic and central nervous system diseases

children with recurrent vomiting. These children vomit nearly every day with one to three emeses per day. The diagnostic focus for this group will be on disorders within the upper gastrointestinal tract and exclusion of extra-intestinal disorders. This can be done primarily on history and physical examination. The remaining third of children who present with recurrent vomiting have a

cyclic pattern. The bursts of vomiting may be cyclic and predictable or sporadic and unpredictable. Typically they will have an intense cluster of vomiting during a discrete episode and then a symptom-free period. Significant gastrointestinal problems presenting with a cyclic pattern include malrotation, intermittent volvulus, duplication cysts and others. The cause for vomiting in the group of children with a cyclic pattern is frequently not gastrointestinal. Laboratory screening for metabolic and endocrine disorders is optimally performed during the acute episode before any therapeutic intervention, for example, with intravenous glucose solutions.

2.1.4 INVESTIGATIONS

Investigation of the vomiting child is dependent on the history and results of physical examination. Consideration of age, signs and symptoms and temporal pattern of vomiting will serve to develop a focused differential diagnosis to guide the choice of investigations.

2.1.4.1 Blood tests

A complete blood count may show an elevated white cell count with infection or inflammation, but is relatively nonspecific. Anemia may be present and be secondary to an acute bleed, or be of a long-term nature in the presence of chronic disease (normochromic) or ongoing blood loss (hypochromic, microcytic). Electrolytes, urea, creatinine and anion gap provide information regarding fluid balance and metabolic status. Generally, frequent vomiting results in hypochloremic, hypokalemic alkalosis; however, acidosis may occur if dehydration is severe or secondary to an underlying metabolic disorder. Abnormalities of urea are found in dehydration (high) and in urea cycle disorders (low). Hypo- or hypernatremia may occur if inappropriate fluid replacement is given.

2.1.4.2 Radiology

Any child with symptoms that suggest a surgical problem such as intestinal obstruction requires an urgent radiograph of the abdomen with both supine and erect films. Intestinal obstruction is suggested by dilated loops of bowel with air-fluid levels, although a similar appearance can occur with an ileus accompanying gastroenteritis. The history and examination usually allow differentiation. Other conditions have more specific appearances, such as the right upper quadrant mass in intussusception, the double-bubble appearance of duodenal atresia and a distended loop of bowel with volvulus. An abdominal ultrasound may be of help in the diagnosis of pyloric stenosis (hypertrophic mass at outlet of stomach), liver disease (gallstones and thickened gallbladder wall in cholecystitis, liver enlargement in hepatitis), pancreatitis (swollen, edematous pancreas), renal disease (hydronephrosis or small

kidneys). A child who presents with persistent bile-stained emesis requires an upper GI contrast study to exclude anatomical causes of obstruction including intestinal malrotation, webs, rings and strictures. The contrast study may include a follow-through of the small intestine to identify more distal problems such as terminal Crohn's disease.

2.1.4.3 Microbiology

Urinalysis is important to exclude urinary pathology such as infection. Stool examinations for bacterial culture, ova and parasites, and viruses are indicated if diarrhea is present, and for Clostridium difficile toxin if there is a recent history of antibiotic use. In the severely ill and/or febrile child with emesis and suspected sepsis or meningitis, cultures of the blood and cerebrospinal fluid are required.

2.1.4.4 Endoscopy

Upper gastrointestinal endoscopy may be employed to exclude mucosal disease in the esophagus (esophagitis), stomach (H. pylori gastritis, ulceration) or duodenum (ulceration, Crohn's disease, celiac disease).

2.1.5 CYCLIC VOMITING SYNDROME

A group of children present with recurrent severe discrete episodes of vomiting in which investigations reveal no organic cause. These children are diagnosed with cyclic vomiting syndrome (CVS). Given the broad differential diagnosis of this type of vomiting, including many surgical and metabolic entities, CVS is considered to be a diagnosis of exclusion.

This entity is characterized by:

1. Recurrent severe discrete episodes of vomiting
2. Varying intervals of normal health in between episodes
3. Duration of vomiting episodes lasting from hours to days
4. No apparent cause of vomiting (negative laboratory, radiographic, endoscopic testing)

The episodes tend to be stereotypical and self-limited. Events are usually of rapid onset, often starting during sleep or in the early morning. The episodes may persist for hours to days and may be separated by symptom-free intervals. Associated symptoms may include lethargy, nausea, abdominal pain, headache, and, less frequently, motion sickness and photophobia. Children may be pale and, with less frequency, may have other signs including diarrhea and fever. They may have severe abdominal pain that can mimic an acute abdomen. Various triggering events have been described including psychological stress, infections, dietary and hormonal (menses).

2.1.6 MANAGEMENT

Management of the vomiting child centers on establishing an accurate diagnosis and stabilizing the patient's condition with regard to fluid and electrolyte abnormalities. Treatment is specific to the underlying cause of vomiting. Therapy for cyclic vomiting syndrome is empiric. The high rate of dehydration necessitates support with intravenous dextrose-containing solutions and antiemetics. Often sedative-induced sleep is helpful to relieve the persistent nausea. A proportion of the patients will respond to antimigraine treatment. Triggers of the episodes should be thoroughly investigated, as some might be avoided.

2.2 Gastroesophageal Reflux Disease (GERD)

2.2.1 INTRODUCTION AND DEFINITIONS

Gastroesophageal reflux (GER) is the apparently effortless passage of gastric contents into the esophagus. This occurs throughout the day in healthy infants, children and adults. Regurgitation refers to the passage of refluxed material into the mouth. During infancy, GER is most often manifest with vomiting (expulsion of the regurgitated material through the mouth) and is a normal physiological phenomenon. It is noted in more than 50% of healthy infants in the first six months of life. The frequency of regurgitation peaks at about four months of age, with most infants outgrowing this by seven months, and almost all by one year.

Physiological reflux is also common in older children who eat in excess. Functional reflux refers to daily regurgitation or vomiting without other symptoms or clinical signs suggestive of disease. Pathological reflux (or GERD) is defined as when reflux is secondary to another disorder or when there are symptoms or complications of gastroesophageal reflux. These include esophagitis, growth failure and respiratory disease. A small minority (approximately 6-7%) of infants will have GERD, necessitating investigation and treatment. In preschool-aged children, GER may present with recurrent vomiting, but the older child usually presents with complaints similar to those seen in adults. About 50% of children aged three to 16 years diagnosed with GERD will continue to require therapy one to eight years later.

2.2.2 PATHOPHYSIOLOGY

Reflux of gastric contents into the esophagus is prevented by the antireflux mechanism at the gastroesophageal junction, which consists primarily of the diaphragmatic crura and the lower esophageal sphincter (LES). The LES is a physiologically defined region of the lower esophagus that is maintained in a partial contractile condition to create a high-pressure zone, but relaxes as part of the swallowing reflex to allow food passage into the stomach. The primary cause of reflux is transient relaxation of the LES unrelated to swallowing,

rather than a consistently low pressure of the sphincter. Although gastric volume and composition of gastric contents are important influences, the mechanism of this transient relaxation is not understood. Other factors important in the prevention of complications of reflux include esophageal peristalsis, which clears refluxed contents from the esophagus; salivary secretions, which assist in neutralizing refluxed gastric acid; esophageal mucosal resistance; and the protective pulmonary reflexes that prevent reflux into the respiratory tree.

2.2.3 CLINICAL EVALUATION

Reflux is usually diagnosed based on the history, examination and observation of the patient. It is important to establish, if possible, whether the child is refluxing or vomiting. Gastroesophageal reflux is often effortless while vomiting is more forceful, although overlap occurs. The approach to the evaluation and management of infants and children with GERD will depend upon the presenting symptoms and signs. The initial approach to the infant and child with regurgitation should therefore be similar to the previously outlined approach to recurrent vomiting. Many of the entities that need to be considered in the differential diagnosis are critical and may be lethal if undiagnosed, for example CNS tumor, intestinal obstruction, and inborn errors of metabolism.

2.2.3.1 Infant with recurrent vomiting

An accurate diagnosis and effective treatment of an infant who presents with recurrent vomiting should be based on a complete medical and feeding history and physical examination. Feeds of inappropriately large volume are more likely to be refluxed. The frequency and volume of the reflux episodes should be established and any signs or symptoms of complicated reflux sought. Indications that an infant may have a more significant problem include poor growth, feeding problems, respiratory problems, excessive irritability, hematemesis or signs and symptoms suggesting a disease of another system. Infants with uncomplicated regurgitation do not require further testing. These infants can be managed with parental reassurance and education, and some conservative measures. Parents should be counseled that the aim of these measures is to decrease the frequency of regurgitation, not elimination of the problem. Symptoms should largely resolve by 12 to 18 months of age.

Conservative Measures include:

1. Keep infant upright at least 30 minutes after a meal
2. Elevate head of crib and changing table to 30 degrees
3. Do not place infant in car seat in the home
4. Avoid over-feeding child
5. Thickening of formula may be tried

Rarely, infants may have a cow's milk or soy protein allergy and trial of a hypoallergenic diet may be indicated.

2.2.3.2 Infant with recurrent vomiting and poor weight gain and/or excessive irritability

When the infant presents with recurrent vomiting and poor weight gain or excessive irritability further investigation is essential before attributing the symptoms to GERD. The caloric intake should be calculated and feeding skills evaluated. When caloric intake is adequate then other causes for weight loss and vomiting should be considered and the appropriate diagnostic work-up done. An anatomical abnormality should be excluded, likely by an upper gastrointestinal study as well as testing for inborn errors of metabolism and other systemic diseases. Excessive irritability may also result from a number of systemic diseases, which will need to be excluded on the basis of history, examination and appropriate investigations. If it is likely that these symptoms result from GER, the following diagnostic and treatment strategies may be useful: 1. Empiric treatment with either a sequential or a simultaneous two-week trial of a hypoallergenic formula and acid suppression may be initiated. 2. If this is not successful, then the infant should likely be referred to a pediatric gastroenterologist for either a 24-hour pH probe or endoscopy and biopsy looking for esophagitis. An algorithm, outlining this approach, which is part of the clinical practice guidelines for investigation and management of pediatric gastroesophageal reflux, can be found on the web-site of the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition: www.naspghan.org, or www.cdhnf.org.

2.2.4 COMPLICATIONS OF GASTROESOPHAGEAL REFLUX (TABLE 3)

2.2.4.1 Failure to thrive

Failure to thrive occurs in association with gastroesophageal reflux when caloric intake is insufficient as a result of the loss of milk through reflux, or when children with esophagitis limit intake due to pain or dysphagia associated with feeding.

2.2.4.2 Esophagitis

Esophagitis may be indicated by dysphagia, hematemesis, anemia, hypoalbuminemia and thrombocytosis. While dysphagia may occur secondary to esophageal ulceration or strictures, it may also be secondary to the impaired motility that is associated with esophagitis and often presents as food sticking.

2.2.4.3 Respiratory complications

Aspiration of gastric contents causing pneumonia is relatively common in the

TABLE 3. Complications of GER

Systemic
Failure to thrive
Esophageal
Pain
Esophagitis
Hematemesis
Anemia
Hypoproteinemia
Dysphagia secondary to stricture or dysmotility
Sandifer's syndrome – an unusual posturing of head and upper body in infants with reflux esophagitis
Respiratory
Apnea
Bronchospasm
Laryngospasm
Aspiration pneumonia

neurologically impaired child, but aspiration of food during its ingestion may also occur as a result of incoordinate swallowing. Some children with asthma, especially nocturnal asthma, may have symptoms secondary to reflux. Gastroesophageal reflux is a less common cause of apnea in premature infants, most apnea in this age group being of central origin. Gastroesophageal reflux is not responsible for SIDS.

2.2.5 INVESTIGATIONS

Infants and children whose reflux is persistent, severe or associated with symptoms or signs of an underlying disorder require further evaluation and may require referral to a pediatric gastroenterologist for specialized investigations.

2.2.5.1 Upper Gastrointestinal Study (UGI)

This should be performed when history, signs or symptoms suggest that it is important to exclude predisposing anatomic abnormalities such as malrotation or strictures. This is not a sensitive, nor a specific, test for the diagnosis of GERD.

2.2.5.2 Esophageal pH monitoring

Esophageal pH monitoring is useful to establish the presence of abnormal amounts of reflux as well as the temporal association of frequently occurring symptoms and reflux episodes. It may be performed to assess the adequacy of therapy when there is no apparent response of symptoms to acid suppression. It is less useful when the concerns are respiratory in nature, such as cough or

apnea, or are very intermittent, as in these circumstances the symptoms may be caused by reflux even in the presence of a normal pH probe.

2.2.5.3 Endoscopy and biopsy

Endoscopy with biopsy can assess the presence and severity of esophagitis as well as exclude other disorders such as Crohn's disease or eosinophilic esophagitis. Biopsy is necessary to detect microscopic esophagitis as well as to exclude these other entities.

2.2.6 MANAGEMENT

Management of most children with gastroesophageal reflux often requires no more than an explanation to parents that reflux is a normal phenomenon in infants. Conservative measures may be helpful. These include positioning the infant and smaller, more frequent thickened feedings; rarely, continuous drip feedings may be necessary. Positioning the child in a head-elevated position after feeds can be useful, but the use of infant seats has been shown to make reflux worse. Thickening of feeds (usually with rice formula) decreases the number of emeses and time spent crying, but has not been shown to decrease the time spent refluxing, as shown by esophageal pH monitoring.

For those children with complicated or severe reflux unresponsive to conservative management, drug therapy may be necessary. Acid suppression is helpful in those patients with esophagitis or reflux-associated pain. Proton pump inhibitors are the most effective acid suppressants and are superior to histamine 2- receptor antagonists in relieving symptoms and healing esophagitis.

Surgery may be necessary in patients with gastroesophageal reflux who fail medical therapy or who have life-threatening reflux-associated apnea. Nissen fundoplication, where the fundus of the stomach is wrapped 360° around the lower esophagus to produce an esophageal high-pressure zone, is the operation of choice. Fundoplication is effective, and a successful clinical outcome is seen in almost 90% of patients at five years, but major complications such as postoperative adhesions, wound infection and pneumonia occur in approximately 10–20% of patients. Fundoplication is less successful in controlling reflux in neurologically impaired children, where clinical success rates are of the order of 50–60% and complication rates are higher.

3. CHRONIC CONSTIPATION / M. Robertson

3.1 Introduction and Definitions

Constipation is a symptom indicative of an abnormality in stool or its elimination: the stool is too large or too hard; passage is too infrequent, painful or incomplete. It is a common and frustrating problem, estimated to occur in

5-10% of school-aged children. Many parents worry that there is a serious disease causing symptoms. However more than 95% of children have no organic cause for their symptoms but have a diagnosis of functional constipation. A functional gastrointestinal disorder is one in which there are troublesome symptoms in the absence of evidence of mucosal or anatomic disease. Symptom-based criteria for functional defecation disorders in childhood have been developed by the Rome II working group.

Disorders described include:

1. Functional Constipation (FC): This refers to the situation where there has been at least two weeks of hard stools (scybalous or pebble-like) for the majority of stools, or firm stools two or less times a week and no evidence of structural, endocrine or metabolic disease.
2. Functional Fecal Retention (FFR): From infancy to 16 years of age, passage of large diameter stools at infrequent intervals (< 2 per week) with associated retentive posturing. Retentive posturing refers to the attempts a child will make to avoid defecation. This includes contracting pelvic muscles and squeezing the gluteal muscles together. This posturing may be misinterpreted by parents as straining unsuccessfully to stool. FFR is the entity most commonly associated with encopresis (soiling).

Constipation in this section will refer generally to both functional constipation and functional fecal retention with and without encopresis.

3.2 Pathophysiology

There is a wide variation in what should be considered normal defecation frequency in childhood. The normal frequency of bowel movements will depend on whether the infant is breast or formula fed. Healthy breast-fed infants may have intervals of seven to 10 days between bowel movements, while formula-fed infants may have several per day. Greater than 90% of healthy infants pass their first bowel movement within the first 24 hours after birth, although this may be delayed in premature infants. (Approximately 90% of infants with Hirschsprung's disease will not pass meconium in the first 24 hours of life). Infants pass a mean of four stools per day in the first week of life and the frequency declines to about two per day at two years of age and 1.2 per day at four years of age. The daily number of high amplitude propagated contractions (HAPC), (powerful peristaltic waves propelling stools to the rectum), is related inversely to age. Intestinal transit time, which is inversely related to frequency of defecation, increases with age (Table 4).

Fibre-rich diets favor the retention of water and result in increased stool weight and volume, shorter transit time and increased stool frequency.

TABLE 4. Intestinal transit time as a function of age

Age	*Intestinal Transit Time (hours)*
1 month	8
2 years	16
3-13 years	26
adult	48

Precipitants of constipation include:
1. Decreased fluid intake or increased fluid losses
2. Diet low in fibre
3. Chronic voluntary inhibition of defecation

There are three periods when a child is particularly vulnerable to developing constipation:
1. The introduction of solid food in the diet of an infant
2. Toilet training
3. The start of school

Any event such as an illness which might lead to prolonged fecal stasis in the colon with continued reabsorption of fluids will result in an increase in the size of the stool as well as drier consistency, which can cause painful defecation. The passage of large hard stools may then result in the child making efforts to withhold stool when they next experience an urge to defecate. Children will tighten their anal sphincter and contract their pelvic muscles in an attempt to withhold stool. They may be seen to stiffen their buttocks and legs, wriggle and grimace and often hide. Parents observing these contortions may not recognize that these are efforts to retain stool and believe that the child is straining in an attempt to defecate. The rectum will habituate to the presence of stool and the urge will subside. Over time the rectal wall stretches and becomes less sensitive. Furthermore, when the rectum is distended with a stool mass there is loss of the rectal-anorectal angle and the continence function of the puborectalis sling. Whenever there is a mass movement (HPAC) the only residual continence mechanism in these children is the external voluntary anal sphincter, which rapidly fatigues. This leads to involuntary soiling (encopresis).

3.3 Clinical Evaluation

By far the majority of children with elimination problems have a functional defecation disorder. Some of the organic causes of constipation are listed in

TABLE 5. Organic causes of constipation in childhood

	Examples
Anatomic malformations	Imperforate anus Anterior anus Strictures
Central nervous system/ Neuroenteric disorders	Hirschsprung's disease Neurointestinal dysplasia Spinal cord abnormalities Neurofibromatosis Cerebral Palsy Hypotonia
Metabolic/endocrine disorders	Hypothyroidism Hypercalcemia Hypokalemia Multiple Endocrine Neoplasia IIB Porphyria Cystic fibrosis Diabetes mellitus Diabetes insipidus Renal acidosis
Gastrointestinal disorders	Celiac disease Cows' milk allergy
Drugs	Opiates Anticholinergics Diuretics Iron Antidepressants
Systemic/genetic disorders	Ehlers-Danlos, Scleroderma
Others	Lead intoxication Botulism

Table 5. A thorough history and careful, focused physical examination is all that is usually necessary to make a diagnosis of a functional defecation disorder and exclude organic causes. There are a number of features of history and/or physical examination which would suggest the possibility of an organic cause for constipation ("red flags") (Table 6).

One of the most frequently considered organic problems in the differential diagnosis of infants presenting with constipation is Hirschsprung's disease. This is a rare disease (approximately 1:5,000 live births), which is characterized by a lack of ganglion cells in the myenteric and sub mucous plexuses of the distal colon. This results in sustained contraction of this aganglionic segment.

TABLE 6. "Red Flags" on history and examination suggesting possible organic cause for constipation

Onset less than 6 months
Delayed passage of meconium
No history of withholding behaviour
No soiling
Growth failure
Polyuria/polydypsia
Empty rectal ampulla
Bladder disease
Neurological abnormalities of lower limbs
Sacral dimple or hair tuft
Pigmentary abnormalities
Heme-positive stools
Extra intestinal symptoms
No response to conventional treatment

The bowel proximal to the ganglion segment becomes dilated due to the distal obstruction. Hirschsprung's disease can often be distinguished from functional constipation by differences in history and examination which are detailed in Table 7.

3.4 Management

If an organic cause of constipation is suspected, it should be investigated and treated. However, the majority of children with constipation have functional constipation or functional fecal retention (often with encopresis). The North American Society for Pediatric Gastroenterology and Nutrition has developed algorithms to assist in the diagnosis and management of infants and children with constipation (www.naspghan.org).

The goal of treatment is to promote daily soft bowel movements. In time this will extinguish the fear of defecation, which has lead to withholding behavior, and allow the muscles and nerves of the rectum to recover strength and sensitivity. The most successful approach to a child with functional constipation includes:

1. Education
2. Behavioral modifications
3. Medical therapy
4. Diet and exercise modifications

3.4.1. EDUCATION

Education is an important component of the treatment plan. Demystifying the

TABLE 7. Differentiating features of functional constipation and aganglionic megacolon (Hirschsprung's disease)

	Functional constipation	*Hirschsprung's disease*
Age of onset	Acquired sometime after birth	Present from birth
Growth	Normal	Poor
History	Coercive bowel training Colicky abdominal pain Rarely abdominal distention Periodic voluminous stools Soiling	Lack of coercive bowel training Rarely abdominal pain Abdomen distended Pellet-like or ribbon-like stools No soiling
Past history	No episodes of intestinal obstruction	Frequent episodes of intestinal obstruction
Physical exam	Well child Feces-packed, capacious rectum	Nutritional status poor Empty rectum
Barium enema	Absence of transition zone and a distended distal colon	Presence of transition zone
Manometry	Rectoanal inhibitory reflex intact	Absent rectoanal inhibitory reflex
Biopsy	Normal	Absence of ganglia in myenteric plexus and hypertrophy of nerve trunks
Course	Negligible mortality Variable morbidity	High mortality, depending on promptness of diagnosis, and variable morbidity, depending on type and outcome of surgical management

condition and reassuring the family that this is a benign, common behavioral disorder will often alleviate much of their anxiety and frustration. Understanding that the soiling is not "willful" may improve family relationships and promote a more productive, positive approach to the treatment recommendations. Understanding how the therapy works within the context of the pathophysiology of defecation/constipation lays the ground work for increased compliance. It is important that the family understand that in severe functional fecal retention, the therapy must be aggressive and may be required for three to six months, or longer. Prognosis is good, provided there is compliance with the treatment plan. Close follow-up is essential.

3.4.2. DISIMPACTION

Disimpaction is indicated when there is a large fecal mass which is unlikely to be passed painlessly. Management of milder constipation, however, may begin with maintenance therapy. Disimpaction may be accomplished by oral medications or enemas and should be as rapid and free of discomfort and danger to the child as possible. Phosphate soda enemas are frequently used and are effective. These should be used according to instructions, at the appropriate dose and should not be repeated immediately if the initial enema is retained. The use of soap suds, tap water and magnesium enemas is not recommended because of their potential toxicity. High dose oral medication has also been used successfully.

3.4.3 MAINTENANCE THERAPY

The treatment focuses on maintenance therapy once the impaction has been removed. The aim of maintenance therapy is to assure that bowel movements occur at normal intervals with full painless evacuation of the rectum.

Maintenance therapy consists of:

3.4.3.1 Dietary intervention

It is generally recommended that the child increase intake of fluids and absorbable and nonabsorbable fibre.

3.4.3.2 Behavioral modification to establish a regular toileting regimen

Establishment of a regular bowel habit and a prompt response to the urge to defecate are necessary. Positive reinforcement for appropriate toileting behavior including calendars and sticker charts may be helpful.

3.4.3.3 Laxative therapy

It is often necessary to use medication to help children with constipation achieve regular bowel motions (Table 8). Mineral oil, magnesium hydroxide, lactulose or sorbitol (or a combination) is recommended. The chronic use of stimulant laxatives should be avoided. A stimulant laxative may be necessary intermittently to avoid recurrence of impaction. Referral to a specialist may become necessary when the child fails therapy, when there is a concern that an organic disease exists, or when management is very complex.

4. GROWTH FAILURE AND MALNUTRITION / M. Robertson, S.A. Zamora and H.G. Parsons

4.1 Introduction and Definitions

Protein-energy malnutrition accounts for 1-5% of tertiary hospital admissions for infants and is reported in about 10% of low-income preschool children

TABLE 8. Medications for use in the treatment of constipation
(adapted from Table 7 in Constipation in Infants and Children: Evaluation and Treatment, Baker SS, Liptak GS et al, JPGN 29: 612-626,1999)

Mechanism	*Laxatives*	*Dose*	*Side Effect*	*Comments*
Osmotic	Lactulose	1-3 mL/kg in divided doses	Flatulence, abdominal cramps	Synthetic, non-digested disaccharide
	Sorbitol	1-3 mL/kg /day in divided doses	As per lactulose	
	Barley malt extract			Unpleasant odour
	Magnesium hydroxide		Infants are susceptible to magnesium poisoning	
Osmotic enema	Phosphate enemas	< 2 years not recommended	Risk of trauma to rectal wall Abdominal distension, vomiting May cause severe episodes of hyperphosphatemia, hypocalcaemia with tetany	
Lubricant	Mineral oil	< 1 year old not recommended Not recommended if any concern about air-way protection Maintenance: 1-3 mL/kg /day	Lipoid pneumonia if aspirated	Softens stool and decreases water absorption More palatable if given cold
Stimulants	Bisacodyl	> 2 years old	Abdominal pain Diarrhea and hypokalemia Abnormal rectal mucosa	
Glycerine suppositories			No side effects	

seen in community-based settings. Failure to thrive is a widely used term to describe a spectrum of pathologic states resulting from childhood undernutrition. Growth occurs so quickly in early childhood that it is a very vulnerable time for protein-energy malnutrition to occur. Prompt recognition of the infant or child with inadequate growth and timely intervention are important for preventing malnutrition and the developmental sequelae.

Inadequate growth can be diagnosed by observation of growth over time using a standard growth chart. (Growth charts can be found at www.cdc.gov). Accurate equipment and measurement techniques are essential because the resulting measurements are used to make fundamental decisions about the child. In general, values between the 5th and 95th percentiles are considered within the normal range, as long as the pattern of growth is similar to the shape of the growth curve. Values outside of this range, or significant changes in the pattern of growth warrant further investigation, including a thorough dietary history and physical examination. It is generally agreed that there may be reason for concern if the child's weight-for-age falls below the 5th percentile of an appropriate growth chart or crosses two percentiles from a previously established growth channel (or the loss of 10% of an infant's body weight). However a prudent clinician may want to start an investigation and basic nutritional and behavioral intervention well before this.

4.2 Normal Pediatric Growth and Feeding

A child's growth rate and size are affected by gestational age at birth, birth weight, type of feeding (breast or formula), parental stature, adequate nutrition, chronic disease and any special health needs.

In general, term infants will lose 5-10% of their birth weight initially and then regain birth weight by the end of the second week of life. During the first three months of life the infant should gain 25-30 g per day, 12 g per day between six and 12 months, and 8 g per day between 12 to 18 months. The growth rate for infants who have been breast fed for more than three months is slower than that of formula-fed infants. This slower growth rate of otherwise healthy and thriving breast-fed infants compared to reference data should not lead to unnecessary monitoring and investigation as there is no evidence this is of any health-related significance. The discrepancy is gone by 12 months.

Although crossing weight percentiles may be a cause for concern, many normal healthy infants may change 25 percentile points during the first two years of life. Up to 50% of infants will grow to catch up to their genetic potential in the first three months. Infants born larger than their genetic potential will often shift curves downwards between three and 18 months of age. The distinction between normal and abnormal growth may be difficult to make at times. Constitutional growth delay and familial short stature are the two most common variants of normal growth.

4.2.1 CONSTITUTIONAL GROWTH DELAY

These children present with marked deceleration of growth in the first three years of life and then follow a lower growth curve into adolescence when a late pubertal growth spurt occurs and they catch up to their original growth percentile. The deceleration begins in the first six months of life and will be greatest in the first two years of life. These children will have a two- to four-year delay in skeletal maturation and will enter puberty late. There is frequently a family history of this type of delayed growth and pubertal development.

4.2.2 FAMILIAL (GENETIC) SHORT STATURE

Familial short stature is genetically determined, and these children are short throughout life. The final height is determined by mid-parental height, and a readjustment with drop in percentiles may take place in the first two years of age. After this deceleration phase, these children grow normally at constant rates and enter puberty at an appropriate age. Weight in these children is usually proportional to length, and they have no bone age delay. The diagnosis of familial short stature is confirmed on the basis of a normal history and physical examination and if, during follow-up, the child maintains the new growth channel appropriate to his or her genetic potential.

4.2.3 SMALL FOR GESTATIONAL AGE AND PREMATURE INFANTS

Infants small for their gestational age are a heterogeneous group that fails to grow in utero (intrauterine growth retardation, or IUGR) as a result of environmental, maternal, placental or fetal factors. Asymmetric IUGR (birth weight disproportionally more depressed than length or head circumference) frequently results from placental insufficiency. These newborns have a good prognosis for catch-up growth if they are provided with enhanced postnatal nutrition. Symmetric IUGR may result from intrauterine infections, chromosomal abnormalities or prenatal exposure to toxins such as alcohol, drugs or anticonvulsants. Infants who are symmetrically growth retarded at birth have a poor prognosis for later growth. Because of the initial small size, the weight gain and growth progression of these patients may give the false impression of growth failure; however, the patient should double the birth weight by 4 months of age and triple it by 1 year of age.

In premature infants corrected age should be used in growth monitoring or they will be inappropriately labeled as having growth failure. The age at measurement should be corrected for the number of weeks the child was premature (the difference between 40 weeks and gestational age). Corrected age should be used to 18 months for head circumference, 24 months for weight and 40 months for height. Premature infants without serious medical problems may show catch-up growth in the first year of life, whereas more severely affected premature infants may not show catch-up growth but should at least parallel reference curves.

4.3 Infant Feeding

Exclusive breast feeding is recommended until six months of age with breast feeding continued at least another six to 12 months or longer. Fruit juice should be limited so as not to interfere with the intake of breast milk (or iron-fortified formula). Whole cow's milk should preferably not be introduced until 12 months of age. It is recommended that solids be started at six months if the child is neurologically and gastrointestinally mature enough to support their intake. Signs of readiness include: disappearance of the extrusion reflex, hand-to-mouth movements and ability to sit with support. Iron-fortified cereals are currently recommended as the first foods since iron stores may be depleted by this time. At one year of age children should be eating 70% liquids and 30% solids for their total caloric intake.

In the second year of life children should be offered small frequent nutritious and energy-dense feedings of a variety of foods from the different food groups. By age one to two years, the rate of weight gain slows and the toddler often begins to appear leaner. It is important that these normal patterns of growth are recognized so that conflicts about meals and eating and consequent poor-eating behaviors do not develop. Parents and caregivers should be encouraged to recognize and respond appropriately to their toddler's individual verbal and non-verbal hunger cues as well as to satiety cues.

4.4 Pathophysiology

Delayed or abnormal growth usually results from an imbalance between nutrient availability and requirements. Less commonly, in some children with adequate nutrient availability there may be impaired utilization of calories. Children with various metabolic, endocrine and genetic conditions will have abnormal growth because of the inability to utilize nutrients for growth at the cellular level.

4.5 Clinical Evaluation

The key to diagnosing whether a child has inadequate growth is to accurately measure and plot weight, height and head circumference and then assess the trend. One approach to the differential diagnosis of inadequate growth is based on the pattern of deviance of weight, height and head circumference on the growth charts (Table 9).

Type I

Head circumference is normal and weight is reduced disproportionately to height. This pattern results when there is undernutrition (an imbalance between caloric requirements and availability) (Figure 1).

Type II

Head circumference is normal or enlarged and weight is reduced in proportion

TABLE 9. Differential diagnosis of growth failure based on anthropometric criteria

Type I – HC normal, W reduction >>> H reduction	
Inadequate caloric intake	
Psychosocial factors*	Genitourinary diseases (e.g., UTI)
Neurologic and neuromuscular diseases	Malignancy
Chronic infection	Cardiovascular disorders
Increased losses	
Gastroesophageal reflux or vomiting	
Diarrhea	
Malabsorption	
Cystic fibrosis	Parasitic infestation
Milk protein enteropathy	Immunodeficiency
Celiac disease	Inflammatory bowel disease
Shwachman syndrome	Hepatobiliary disorders
Short gut	Intermittent midgut volvulus
Impaired caloric utilization	
Glycogen storage disease	Chronic infection
Galactosemia	Renal disease
Fructose intolerance	Malignancy
Phenylketonuria	Anemia
Increased metabolic requirements	
Hyperthyroidism	Hyperkinesia (attention deficit disorders, athetoid cerebral palsy)
Diencephalic syndrome	
Type II – HC normal or enlarged, W reduction = or > H reduction	
a. Bone age delay = height age delay	
Constitutional growth delay	Metabolic disease
Celiac disease	Chronic diseases
b. Bone age not delayed; height age delayed	
Familial short stature	
c. Bone age delay >>> height age delay	
Endocrine disorder (growth hormone deficiency, hypothyroidism, hypopituitarism)	Maternal deprivation syndrome (deprivation dwarfism)
Type III – HC subnormal, W reduction = H reduction	
Dysmorphic	
Chromosomal abnormalities	Birth asphyxia
Congenital infections	CNS abnormalities
Toxic intrauterine exposure (alcohol, drugs, anticonvulsants)	Familial

HC = head circumference; W = weight; H = height or length
*Environmental causes are the most common source of problems.
SOURCE: Adapted from Roy CC, Silverman A, Alagille D (eds.). Pediatric clinical gastroenterology. 4th ed. St. Louis: Mosby-Year Book, 1995:3–10.

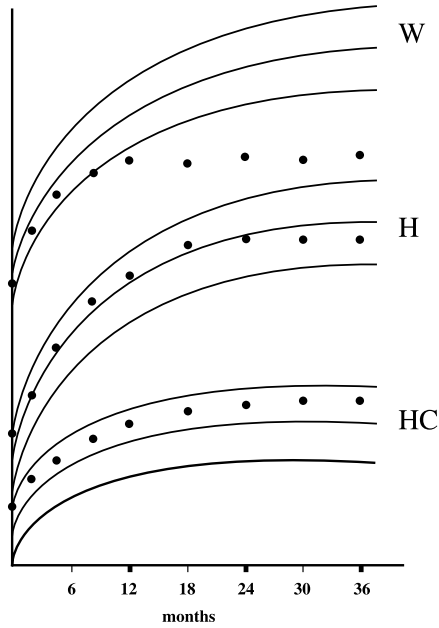

FIGURE 1. Type I failure to thrive. *W* refers to weight, *H* to height or length, *HC* to head circumference.

to (or only slightly more) than the reduction in height velocity (Figure 2). This pattern is representative of children with normal variant growth patterns such as constitutional growth delay and familial short stature. It may also be seen in endocrinopathies as well as when there is chronic undernutrition and/or chronic disease such as celiac disease or Crohn's disease.

Type III

Head circumference, weight and height are all proportionally subnormal (Figure 3). Patients in this category may have chromosomal abnormalities, intrauterine or perinatal insults, or CNS abnormalities.

When it has been determined that the growth pattern is of concern and is not a physiological variant, evaluation should focus on a careful history and physical examination. Where the growth pattern is consistent with undernutrition (Type I) the aim should be to identify factors which are contributing to the imbalance between caloric intake and requirements. Many times the etiology is multifactorial and includes both medical and psychosocial/behavioral

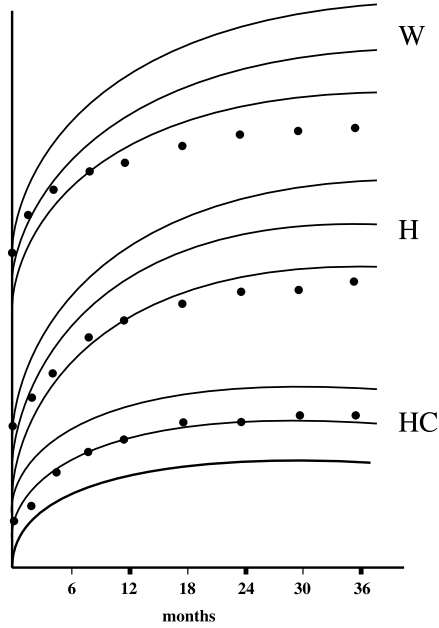

FIGURE 2. Type II failure to thrive. *W* refers to weight, *H* to height or length, *HC* to head circumference.

factors. It is essential to begin nutritional rehabilitation as soon as possible and not delay while waiting for the results of any indicated tests.

History should include a dietary and feeding history as well as past and current medical history. The dietary history should be as specific as possible, including quantities. For formula-fed infants it is possible to quantify the caloric intake. It is important to determine that formula is being prepared correctly. Points to cover in the feeding history include specifically, where, how and for how long the meals take place. Questions should be asked about whether the infant coughs or chokes with feeds and whether they seem to tire when feeding. Social and family history are essential, not only because they may have primary etiological significance, but also in order to prescribe and institute successful interventions.

The goals of physical examination include:

1. Assessment of the severity of malnutrition and signs of possible micronutrient deficiencies
2. Identification of features suggesting a genetic cause for growth failure

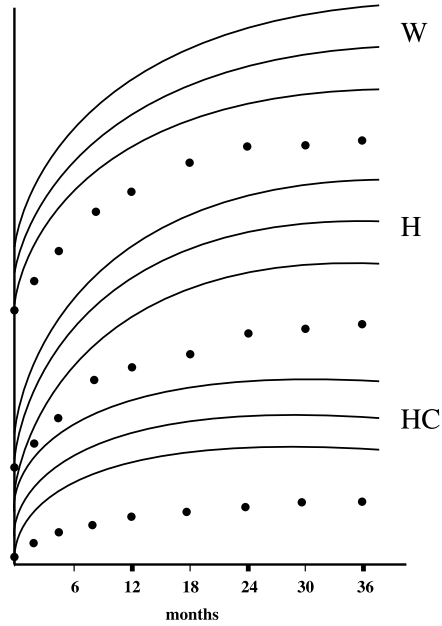

FIGURE 3. Type III failure to thrive. *W* refers to weight, *H* to height or length, *HC* to head circumference.

3. Detection of any chronic disease which may be contributing to impaired growth
4. Assessment for signs of possible child abuse
5. Developmental assessment

Observing the interaction between parent and child during a feeding session may provide valuable insight into their relationship. This session should occur when the child is hungry and particular attention should be paid to the child's ability to cue to the parent, the warmth of the interaction, and the parent's ability to read the child's cues of hunger and satiety.

4.6 Investigations

The large majority of infants will require no immediate investigations unless the history and physical examination have suggested the likelihood of a medical cause such as malabsorption. If children do not respond to adequate calories for nutritional rehabilitation then possible malabsorption should be investigated. Tests might include stool for fat and reducing substances, a sweat test for cystic fibrosis and possibly a celiac antibody profile.

4.7 Management

Management begins with identifying the underlying factors contributing to undernutrition and correcting them if possible. In more complex cases it is very helpful to have a multidisciplinary approach with physician and nurses, dietitian, social worker and, if indicated, a behavioral psychologist or feeding specialist. The goal of nutritional management is to promote compensatory catch-up growth. Children diagnosed with growth failure secondary to protein calorie malnutrition may need to receive up to 150% of the recommended daily caloric intake for their expected, (not actual) weight for age. This is usually achieved by attempting to provide nutrient-dense food. For infants, the caloric density of formula can be increased and, in toddlers, nutrient density is increased by enriching preferred food with butter, peanut butter, oil, cheese or carbohydrate additives. Fruit juice may contribute to poor growth and should be limited to 240-480 mL/day. Small, frequent feedings should be offered. In cases of moderate and severe malnutrition, a multivitamin supplement should be offered. Severe malnutrition should be managed in-hospital, with close monitoring of electrolytes and fluid balance to prevent refeeding syndrome.

5. ACUTE DIARRHEA IN CHILDREN / J.D. Butzner

5.1 Introduction

A North American child will develop between 6 and 12 episodes of acute diarrhea before the age of 5. This contributes to approximately 12% of childhood hospitalizations and approximately 300 deaths per year. Worldwide, acute diarrheal disease is the leading cause of childhood morbidity and mortality, accounting for three million deaths each year. Most deaths are caused by failure to treat acute dehydration properly and to correct electrolyte imbalances. Studies from both the developing and developed world demonstrate that hospitalization can be avoided and morbidity and mortality can be drastically reduced by the prompt introduction of two simple treatments: oral rehydration therapy and early refeeding. In spite of recommendations to use oral rehydration therapy and to continue or resume feeding early in mild to moderate diarrheal illnesses, the use of unsuitable treatments persists. These include unnecessary intravenous therapy, inappropriate oral fluids (unbalanced sugar-electrolyte solutions), prolonged starvation with a slow introduction of limited feeds, and the inappropriate use of antibiotics as well as antimotility and antidiarrheal agents.

5.2 Pathophysiology of Acute Diarrheal Disease

An understanding of the physiology of intestinal fluid, electrolyte and nutrient transport provides a basis for understanding the mechanisms of acute diarrheal disease and successful oral rehydration therapy. Water absorption occurs

primarily in the small intestine, driven by osmotic gradients that depend on the transport of the electrolytes sodium and chloride, as well as nutrients such as glucose and amino acids. Sodium, glucose and several amino acids are transported through the apical membranes of intestinal epithelial cells by sodium-dependent nutrient cotransporters. Sodium is then transported from the cell across the basolateral membrane to the extracellular space by the enzyme Na^+/K^+-ATPase. This enzyme utilizes energy to reduce the intracellular sodium concentration, which produces a negative extracellular electrical charge. The resultant electrochemical gradient facilitates sodium absorption by the epithelial cell, which drives the sodium-dependent nutrient cotransporters. The anion chloride is absorbed to maintain electrical neutrality across the epithelium, and water is passively absorbed in response to the transport of these electrolytes and nutrients. Successful oral rehydration therapy with balanced sugar-salt solutions depends upon these simple physiologic principles.

Diarrhea associated with small intestinal injury in infants and children is caused by four major mechanisms. These include (1) increased osmotic fluid losses, (2) inappropriate secretion, (3) inflammation associated with exudative fluid and protein losses and finally, (4) altered intestinal motility. The most frequent cause of osmotic diarrhea and acute infectious diarrhea worldwide is viral enteritis due to the rotavirus. This virus stimulates the shedding of mature absorptive epithelial cells from the small intestinal villi. These cells are replaced by immature cells with inadequately developed transporters, including the sodium-dependent glucose cotransporter and Na^+/K^+-ATPase. When unbalanced sugar-electrolyte solutions such as fruit juice, soda pop and broth are provided as treatments, the intestine's immature transport capacity is overwhelmed. The osmotic forces created by nonabsorbed nutrients that remain in the lumen stimulate watery diarrheal fluid losses. Children with intestinal injury caused by an acute enteritis may also develop secondary disaccharidase deficiencies, which contribute to osmotic diarrhea by the malabsorption of the disaccharides lactose and sucrose. Interestingly, the frequency of this complication has been markedly decreased in children with mild to moderate dehydration by the prompt implementation of treatment protocols that stress oral rehydration and early refeeding. Osmotic diarrhea is also caused by infections due to Giardia lamblia, Cryptosporidium, Salmonella and enteroadherent E. coli. Medications that contain nonabsorbable sugars such as sorbitol, lactulose and mannitol and poorly absorbable ions such as magnesium, sulfate, phosphate and citrate may also provoke osmotic diarrhea. Healthy children who ingest excessive quantities of fruit juice, soda pop or sugar-free products such as sorbitol-containing gum or mints may develop osmotic diarrhea due to the malabsorption of the fructose and sorbitol found in these products. This is a major cause of chronic nonspecific diarrhea of childhood.

The second major mechanism of diarrheal disease results from the active secretion of the anions chloride and bicarbonate, followed by passive water secretion. Luminal secretagogues include bacterial enterotoxins produced by V. cholerae, heat-labile and heat-stable E. coli, staphylococcal enterotoxins, Clostridium perfringens and Bacillus cereus, as well as hydroxy fatty acids from malabsorbed dietary lipids and nonabsorbed bile acids. Investigators have described rotavirus-induced intestinal secretion. Endogenous secretagogues include hormones secreted by intestinal tumors and inflammatory mediators released in response to food allergy, inflammatory bowel disease and systemic infections. These mediators include histamine, eicosanoids, platelet-activating factor, serotonin and IL-1. They are released after direct activation of inflammatory cells or through stimulation of these cells by the enteric nervous system. Cholera toxin was the first described and remains the classic cause of secretory diarrhea. The B subunit of this toxin binds to the luminal surface of the microvillus membrane of the enterocyte. The A subunit is then internalized and irreversibly activates adenylate cyclase, which stimulates the formation of cyclic adenosine monophosphate (cAMP). This activates protein phosphorylation, which triggers chloride secretion and impairs Na^+Cl^- absorption. In secretory diarrhea no morphologic epithelial injury is present and the sodium-dependent glucose transporter and the enzyme Na^+/K^+-ATPase function normally. This permits successful oral rehydration therapy in the face of ongoing intestinal secretion.

The third mechanism causing diarrhea results from exudation of fluid and protein secondary to inflammation and ulceration of intestinal or colonic mucosa. This results in bloody diarrhea or dysentery caused by the bacteria Shigella, Campylobacter jejuni, Salmonella, Yersinia enterocolitica, enteroinvasive and enterohemorrhagic E. coli, as well as the protozoa Entamoeba histolytica. This type of diarrhea is also seen in inflammatory bowel disease, particularly ulcerative colitis. The diarrheal stools contain mucus, exudate and blood. As mentioned above, the release of inflammatory mediators also stimulates fluid secretion.

Finally, both hyper- and hypomotility result in diarrheal fluid losses. Hypermotility occurs in intestinal infections, hyperthyroidism, functioning tumors and irritative-type laxative abuse. Hypomotility is observed in the intestinal pseudo-obstructive syndromes and with partial anatomic obstruction that results in the intestinal blind loop syndrome. With decreased motility, bacterial contamination develops with resultant malabsorption of nutrients and stimulation of secretory diarrheal fluid losses.

5.3 Clinical Assessment

The infant or child with an acute watery diarrheal illness has most likely contacted a viral enteritis. However, these symptoms can be presenting features

of other gastrointestinal and nongastrointestinal illnesses, including otitis media, urinary tract infection, bacterial sepsis, meningitis, pneumonia, allergy and toxic ingestion. Children who develop loose, watery stools in conjunction with infections such as those involving the middle ear or urinary tract usually do not become dehydrated. A careful history and physical examination play a crucial role in differentiating an acute gastroenteritis from the other causes of acute diarrhea. In addition, accurate assessment of the degree of dehydration, ongoing fluid losses and the ability to drink are required to ensure adequate fluid replacement and maintenance of intake.

5.3.1 HISTORY

Specific questions about the frequency, volume and duration of vomiting and diarrhea are required to determine the severity of fluid deficit and electrolyte imbalance. Significant dehydration can also be manifested by a decreased activity level, reduced urine volume and weight loss. A summary of the assessment of dehydration appears in Table 10. Information about the consistency of stool as well as the presence and quantity of blood aids in establishing a diagnosis and in determining appropriate investigation. In infants suspected of having a gastrointestinal infection, a history of illness among contacts, including playmates, siblings and day-care attendees, as well as exposure to visiting travelers may provide clues to the source of infection. Mild upper respiratory infections in parents or older children may result in acute vomiting and diarrhea in the infant or toddler. In addition to person-to-person contact, exposure to animals and contaminated drinking water and food may lead to enteric infections. Foods cause acute vomiting and diarrhea by multiple mechanisms. These include immunologic reactions resulting in food allergies as well as metabolic, pharmacologic and toxin-induced reactions to food and its contaminants. Lactose intolerance due to adult-onset lactase deficiency; “Chinese restaurant syndrome” due to monosodium glutamate ingestion; and staphylococcal food poisoning occurring one to six hours after the ingestion of preformed toxins are examples of the nonimmunologic causes of food poisoning. Infants who suffer an acute diarrheal illness in the first few weeks of life are more likely to have a congenital anatomic abnormality of the GI tract or an inherited metabolic disease such as abetalipoproteinemia, cystic fibrosis or one of the rare intestinal transporter deficiencies.

5.3.2 PHYSICAL EXAMINATION

The inaccurate assessment of fluid deficits and ongoing fluid losses is the most important cause of the morbidity and mortality associated with acute vomiting and diarrhea in children. Infants are particularly susceptible to the development of dehydration for they sustain greater fluid losses because of an increased intestinal surface area per kilogram of body weight compared to

TABLE 10. Dehydration assessment and management

Degree of dehydration; % deficit	*General*	*Thirst*	*Eyes; tears*	*Mouth*	*Skin*	*Urine*	*Rehydration therapy within 4 hrs.*	*Replacement of fluid losses*
None; < 2%	Well, alert	Drinks normally	Normal; tears present	Moist	Normal	Normal	Not required; proceed with maintenance and replacement of ongoing losses	10 mL/hr or $^1/_2$–1 cup of ORS for each diarrheal stool; 2–5 mL/kg for each emesis
Mild; 3–5%	Well	Drinks eagerly	Normal; decreased tears	Decreased moisture	Normal	Decreased	ORS 50 mL/kg	As above
Moderate; 6–9%	Restless, irritable	Drinks eagerly	Sunken; absent	Dry	Pallor; delayed capillary refill; tenting < 2 sec.	Absent	ORS 100 mL/kg	As above
Severe; ≥ 10%	Lethargy, floppy, decreased consciousness, rapid weak pulse, rapid breathing	Drinks poorly or not able to drink	Very sunken and dry; absent	Very dry	Pallor; delayed capillary refill; tenting > 2 sec.	Absent	IV fluids (normal saline, Ringer's lactate) 20 mL/kg/hr until pulse and mental status return to normal; then ORS 50–100 mL/kg	As above

SOURCE: Modified from Butzner JD. Acute vomiting and diarrhea. In: Walker-Smith JA, Walker WA, Hamilton JR (eds.), Practical pediatric gastroenterology. 2d ed. Toronto: BC Decker, 1996:51–69.

adults. An immature renal concentrating ability, increased metabolic rate and dependence on others to provide fluids also contribute to the rapid development of severe fluid deficits in the pediatric patient. An immediate pre-illness weight provides the most sensitive mechanism of determining severity of dehydration. Unfortunately, this is rarely available. A weight should be obtained at the time of initiation of treatment in order to judge ongoing losses and gauge successful therapy. As outlined in Table 10, the severity of dehydration used to gauge the level of rehydration therapy can be assessed rapidly with history and physical examination. Watery diarrhea sometimes is mistaken for urine in the diaper. This may result in an underestimation of fluid losses. Evidence of particulant matter or a positive dipstick for sugar or protein suggests watery stool. Rapid, deep breathing may suggest an uncomplicated metabolic acidosis. In the child with a distended abdomen, auscultation of bowel sounds should be performed to rule out a paralytic ileus, and a rectal exam should be performed to determine if fluid is being third-spaced in the gut lumen. Examination of the stool for blood, white blood cells, reducing substances, pH, fat and fatty acid crystals may provide valuable clues about the etiology of a diarrheal illness.

5.3.3 INVESTIGATIONS

The majority of episodes of acute watery diarrhea in previously healthy children are self-limited and associated with only mild dehydration. In this situation, the performance of biochemical or microbiologic examination is rarely required. When an advanced stage of dehydration is suspected, assessment of serum electrolytes, urea nitrogen, and acid/base chemistry will aid in tailoring ongoing rehydration therapy. Virologic and microbiologic examination should be performed only when results will be utilized to alter patient management or treat patient contacts, or for the protection of other hospitalized patients. Examples that require further investigation include an outbreak of diarrheal disease in a day-care center or hospital, diarrhea in a patient with a recent history of travel to an area of endemic diarrheal disease, and evaluation of the immunocompromised patient or of the patient where initial therapeutic measures are unsuccessful. In the infant or child with bloody diarrhea, stool cultures and antibiotic sensitivities should be performed to guide appropriate antibiotic therapy, if treatment is indicated. In areas where enterohemorrhagic E. coli causes bloody diarrhea, additional laboratory investigations including a CBC with a platelet count, blood smear for evidence of intravascular hemolysis, serum electrolytes, serum creatinine and serial urinalyses are warranted to aid in the diagnosis and management of hemolytic-uremic syndrome, the leading cause of acute renal failure in children under the age of six.

5.4 Management – Oral Rehydration Therapy

5.4.1 ORAL REHYDRATION

In children with acute diarrhea associated with mild to moderate dehydration, the administration of a balanced oral rehydration solution (ORS) should be immediately instituted as described in Table 10. Parents should be instructed in the proper administration of oral rehydration therapy as part of preventive health care. An oral rehydration solution with a carbohydrate-to-sodium ratio of less than 2:1 and an osmolality that is similar to or slightly less than plasma is recommended. In North America, most oral rehydration solutions have a sodium content of 45–75 mmol/L because stool sodium losses (approximately 35–45 mmol/L) in viral enteritis are much less than those in secretory diarrheas such as cholera (90–140 mmol/L). For children with continued high purging rates (> 10 mL/kg/hr), solutions with a higher sodium content may be required. When solutions with a sodium content of > 60 mmol/L are used for maintenance, low-sodium fluids such as breast milk, infant formula, diluted juice or water must be provided simultaneously to prevent the development of hypernatremia. In North America, intravenous electrolyte solutions are used to manage children with severe dehydration because of their wide availability and high degree of success. In the developing world, children suffering from severe dehydration can usually be successfully rehydrated with oral solutions. More than 90% of vomiting infants can be successfully rehydrated and maintained with oral hydration providing 5–10 mL every 2 to 3 minutes and gradually increasing the amount administered.

About 5–10% of children fail initial oral rehydration therapy as a result of either persistent vomiting or a persistently high stooling rate of > 10 mL/kg/hr. Parents should be instructed to seek further care if the child develops (1) irritability or lethargy that inhibits drinking, (2) intractable vomiting, (3) worsening fluid deficits associated with persistent diarrhea, (4) bloody diarrhea, or (5) decreased urinary output. These children require re-evaluation and intravenous rehydration similar to that provided for the severely dehydrated child. Their hydration status should be monitored, and when rehydration is complete, maintenance therapy to replace ongoing losses can be commenced. If dehydration persists, the fluid deficit should be recalculated and rehydration therapy continued for an additional 2 to 4 hours with ongoing assessment of fluid losses.

There are only a few contraindications to the use of oral rehydration therapy for the initial management of acute diarrheal disease. These include (1) severe (> 10%) dehydration associated with hemodynamic instability, (2) refusal to drink due to extreme irritability, lethargy, stupor or coma, and (3) intestinal ileus. These children should be managed initially with intravenous fluids and switched to oral rehydration therapy when they can safely

drink. Homemade oral rehydration solutions are not recommended because electrolyte abnormalities caused by inappropriate mixing are a well-recognized complication.

5.4.2 EARLY REFEEDING

Recommendations for the dietary management of acute diarrheal disease stress the importance of continued breastfeeding throughout the illness and early refeeding of the formula-fed infant and older child. Continued feeding throughout a diarrheal illness improves nutritional status, stimulates intestinal repair, and diminishes the severity as well as the duration of illness. Breastfed infants should be allowed to nurse as often and as long as they want throughout a diarrheal illness. The refeeding of the non-breastfed infant remains somewhat controversial. Recent evidence suggests that the infant with mild to moderate dehydration should receive the full-strength infant formula that was fed prior to illness. There is no need to routinely switch to a lactose-free milk or to refeed with dilute formula. Treatment failure rates of 10–15% when refeeding is carried out in this manner are no higher than with more cautious approaches. Infants with severe dehydration, pre-existing intestinal injury and severe malnutrition, and those who have failed initial refeeding, should receive a lactose-free formula; they occasionally require a more predigested formula during refeeding.

The older child, who is established on a wider variety of foods, should receive a well-balanced, energy-rich, and easily digestible diet. Complex carbohydrates including rice, noodles, potatoes, toast, crackers and bananas should be offered initially, with the rapid addition of vegetables and cooked meats. Foods to avoid include those high in simple sugars such as soft drinks, undiluted fruit juice, caffeinated beverages, presweetened gelatins and sugar-coated cereals. Foods high in fat may be poorly tolerated because of delayed gastric emptying that results in increased vomiting. In some children watery stools will persist for longer than 10 days, but not to the extent where they cause recurrent dehydration. In these cases infection should be excluded and stools examined for reducing substances suggesting ongoing carbohydrate malabsorption.

5.4.3 USE OF MEDICATIONS

The prescription of antiemetic, antimotility and antidiarrheal agents for the treatment of acute diarrhea seldom benefits the child and may be associated with serious complications. In children with acute diarrheal disease, these agents do not reduce stool volume or duration of illness. They often have anorexic or sedating effects, which prevent successful oral rehydration therapy. Their use results in a third spacing of fluid, which leads to an under-estimation of ongoing losses. This results in inadequate fluid replacement therapy.

Antibiotics should be used in the treatment of diarrheal disease only when specifically indicated. Antibiotics are not effective for the treatment of viral enteritis. Giardiasis should be treated when the diarrheal illness persists and when cysts or trophozoites are identified in the stool. There is no benefit to treating asymptomatic carriers of Giardia lamblia. Antibiotic therapy for the bacterial diarrheas remains controversial because most infections are self-limiting and antibiotic therapy does not shorten the duration of illness. Antibiotic therapy is indicated (1) when a treatable pathogen has been identified, (2) in the immunocompromised host, (3) as an adjunctive therapy in the treatment of cholera and (4) in infants less than 3 months of age with positive stool cultures. Infants at this age are at increased risk to develop septicemia. Infants and children with diarrhea who display signs of septicemia should be treated with parenteral antibiotics.

6. CYSTIC FIBROSIS / H. Machida

Cystic fibrosis (CF) is an autosomal recessive disease that causes chronic morbidity and decreases the life-span of most affected individuals. Because of a defect at a single gene locus that encodes a protein, the cystic fibrosis transmembrane regulator (CFTR), individuals with cystic fibrosis have defective cyclic adenosine monophosphate–regulated chloride transport in epithelial cells of exocrine organs. Although the exact pathophysiology remains to be clarified for each involved organ, there is an accumulation of viscous secretions associated with progressive obstruction and subsequent destruction of excretory ducts.

Chronic pulmonary disease is the major cause of morbidity in the majority of patients. These individuals have progressive bronchiectasis and associated bacterial endobronchial infections, commonly secondary to Pseudomonas species.

Although the pulmonary disease is most prominent, the GI manifestations of cystic fibrosis are extensive and contribute to significant morbidity and even mortality. This section will review the clinical problems related to the gastrointestinal tract, particularly the pancreatic insufficiency and hepatic disease in cystic fibrosis.

6.1 Pancreatic Insufficiency

Approximately 80% of patients with cystic fibrosis are born with pancreatic insufficiency, and another 5–10% develop pancreatic insufficiency in subsequent years. These patients have marked impairment of pancreatic exocrine function, including decreased secretion of water, bicarbonate, lipase, amylase and proteinases from the pancreas into the duodenum. In the very young, the endocrine function of the pancreas is usually normal, but many gradually develop evidence of glucose intolerance; a small number develop clinical

diabetes requiring insulin therapy. Infants and children with cystic fibrosis and pancreatic insufficiency can present with any of the following clinical entities with or without pulmonary disease.

6.1.1 MECONIUM ILEUS

Meconium ileus is partial or complete obstruction of the intestine, commonly the ileum, with thick inspissated meconium. This occurs in approximately 15% of infants with cystic fibrosis. Any infant with meconium ileus must have cystic fibrosis excluded. These infants may present with delayed passage of meconium, abdominal distention, vomiting or other signs of obstruction. Meconium ileus may be complicated by antenatal or postnatal volvulus, atresia, perforation of the bowel and meconium peritonitis. In cases with complications, infants may require surgery shortly after birth. Extensive bowel resection may leave them with the short bowel syndrome.

Initially, these infants are investigated with a plain abdominal x-ray for evidence of obstruction or perforation. If the bowel perforates in utero the perforation often seals, and the x-ray may show calcifications from the meconium in the peritoneum. If meconium ileus is a possibility, surgery should be considered immediately. As long as the x-ray shows no evidence of free air (implying a perforation), most infants are given a gentle water-soluble contrast enema to attempt to relieve the obstruction or at least outline the obstruction for the surgeon. These hypertonic enemas can cause significant fluid shifts in small neonates, therefore an IV must be running during the procedure. If the procedure is unsuccessful, surgery is required. The majority of infants with meconium ileus also have pancreatic insufficiency, but this condition can rarely occur in pancreatic-sufficient patients as well.

6.1.2 CHRONIC DIARRHEA

After the neonatal period, chronic diarrhea with or without failure to thrive is common. These infants have loose stools essentially from birth, and one may obtain a history of delay in the passage of meconium. The parents may describe the diarrheal stools as being pale, foul smelling, fatty and/or soupy. The diarrhea is primarily secondary to fat malabsorption because of the pancreatic insufficiency. However, infants who have had a small bowel resection such as for bowel atresia secondary to meconium ileus may develop mucosal disease secondary to bacterial overgrowth. This will contribute significantly to the diarrhea and may cause it to become more watery. Initially, if they do not have respiratory problems, infants with cystic fibrosis tend to have a relatively good appetite and can in some cases compensate for the extreme loss of nutrients by increasing their intake. However, with a pulmonary exacerbation or as the child develops more significant lung disease, their appetite tends to decrease.

6.1.3 FAILURE TO THRIVE

In cystic fibrosis, growth failure is usually a result of a combination of decreased intake, loss of fat in the stools and increased metabolic requirements. The requirements of the average cystic fibrosis patient have been reported to be 120% of normal. Nevertheless, some patients have essentially normal caloric requirements, and others may have requirements in excess of 150% of normal.

Infants with growth failure after pancreatic enzymes are introduced, and whose status is not improving on oral feeds, may require nasogastric tube supplementation either by bolus or continuous nocturnal feeds. Often these are infants who have significant pulmonary difficulties, and/or have had bowel surgery. In most cases the nasogastric feeds would be required only for weeks or months. Breast milk is encouraged but many infants and toddlers are given supplementary high-calorie formulas until they have demonstrated appropriate catch-up growth and are taking milk and solid foods well.

In the early childhood years, most maintain their nutritional status well with appropriate pancreatic enzyme supplementation and good nutrition. Unfortunately, the increased caloric requirements of puberty coupled with deteriorating lung function often make it impossible for the more severely affected patients to maintain adequate caloric intake for normal growth. In addition, CF patients may develop anorexia during chronic disease or have difficulty eating due to chronic cough. They present with a gradual decrease in growth percentiles, first of the weight and subsequently of the height. Puberty may be delayed or arrested in the early stages. At this time, nutritional supplementation becomes extremely important. Pancreatic enzyme supplementation must be maximized and nutritional supplementation given either orally or by enteral tube feeding. Total parenteral nutrition is rarely required. If enteral feeds are needed, nasogastric tube feeding can be successfully initiated in most patients. (Significant nasal polyps can be a contraindication.) Patients as young as four years of age can be taught to put the tube down nightly. In most cases, once they have increased their weight the tube feedings can be done five to six nights a week for eight to 10 hours. The supplement chosen for these enteral feeds should be a complete high-calorie, age-appropriate formula. Pancreatic enzymes can be given orally prior to the tube feeding. Supplemental enteral feeding of the older child or adolescent may only be required for one to two years while they are advancing through puberty but more commonly there will be a long term requirement. For many patients a gastrostomy tube would be indicated, particularly in the presence of very poor lung function. Such decisions should be made with input from the patient and parents, as well as the multidisciplinary cystic fibrosis clinic team.

6.1.4 FAT-SOLUBLE VITAMIN DEFICIENCY

Patients may present with overt evidence of bruising or bleeding due to vitamin K deficiency resulting from significant malabsorption prior to treatment. While biochemical deficiencies of vitamins A, D and E are often found, the clinical effects are not often evident if the patients are started on fat-soluble vitamin supplementation at the time of diagnosis.

6.1.5 HYPOALBUMINEMIA AND EDEMA

In spite of their pancreatic insufficiency, most infants with cystic fibrosis do not present with hypoalbuminemia secondary to protein malabsorption. Protein malabsorption, however, is a problem in infants who are fed a soy protein formula, and sometimes in those who are breastfed. These infants may present with significant hypoalbuminemia, edema and usually a history of diarrhea. Feeding with soy formula must be discontinued, but often those who are receiving breast milk may have their albumin corrected with pancreatic enzyme supplementation. Infants and children, who have persistent hypoalbuminemia after adequate pancreatic enzyme therapy, should be further investigated for causes of protein-losing enteropathy such as celiac disease, bacterial overgrowth, Crohn's disease and milk protein allergy. Older patients with severe malnutrition or cor pulmonale may also develop hypoalbuminemia.

6.1.6 RECTAL PROLAPSE

An infant with untreated pancreatic insufficiency becomes increasingly malnourished and continues to pass numerous stools, and thus may begin to have regular rectal prolapse. Rectal prolapse may be the presenting problem for some infants with cystic fibrosis. In these cases, the primary diagnosis must be made quickly and the child renourished. The tendency to prolapse will resolve with appropriate nutrition and pancreatic enzyme supplementation to decrease the stooling. The rectal prolapse usually reduces spontaneously. If it does not, it must be gently reduced manually.

6.1.7 DISTAL INTESTINAL OBSTRUCTION SYNDROME

The distal intestinal obstruction syndrome (DIOS), also known as meconium ileus equivalent, is partial or complete obstruction of the bowel resulting from fecal masses, usually in the cecum. This can occur in any age of child with cystic fibrosis, but more commonly in the older child. Younger children with DIOS present with decreased appetite, decreased stooling, distention and often vomiting. Older patients complain of grumbling or crampy abdominal pain and a gradual decrease in stooling. If there is right lower quadrant tenderness, appendicitis must be considered. In these cases an ultrasound and lab work may be helpful. However, most cases are diagnosed by the clinical

history with a plain film of the abdomen, if necessary. When the diagnosis is made early, most can be treated with N-acetylcysteine given orally. A loading dose is given in cola, and three subsequent doses (one dose every six hours over 24 hours). Fluids must be encouraged during this time. If there is evidence of marked obstruction, patients are admitted to hospital and given polyethylene glycol-salt solution (GoLYTELY™) orally or by nasogastric tube. This completely clears the obstructive fecal masses. It is essential to ensure that patients who have an episode of DIOS are being adequately supplemented with pancreatic enzymes, as the syndrome seems to occur most often in those who are taking insufficient enzymes.

6.1.8 PANCREATITIS

Five to 10% of patients with cystic fibrosis will remain pancreatic-sufficient throughout their life. Unfortunately, some pancreatic-sufficient patients develop pancreatitis, which may present with vomiting and acute pain that radiates to the back, or with recurrent low-grade abdominal pain and perhaps a change in appetite. Those who present with acute pancreatitis should be treated as any other patient with pancreatitis. The bowel is rested until the lipase normalizes and the patient is asymptomatic. In patients with mild abdominal pain and only a slight increase in the serum lipase, management is less definitive. However, as in other patients with chronic pancreatitis, the administration of exogenous enzymes with meals can be helpful to manage pain.

6.2 Hepatobiliary Disease

Hepatobiliary disease in cystic fibrosis is well documented. Fortunately, although a significant number of patients have subtle manifestations of hepatobiliary abnormalities, only five to 15% develop severe liver disease. The following briefly outlines the clinical features of some of the hepatobiliary problems associated with cystic fibrosis.

6.2.1 NEONATAL JAUNDICE

Prolonged conjugated hyperbilirubinemia is reported to occur in neonates with cystic fibrosis. In some cases, the conjugated hyperbilirubinemia may be secondary to a problem unrelated to cystic fibrosis; nevertheless, any neonate with conjugated hyperbilirubinemia of unknown origin should be investigated for cystic fibrosis.

6.2.2 ELEVATED LIVER ENZYMES

A significant portion of patients with cystic fibrosis have mildly elevated liver enzymes, including alkaline phosphatase, γ-glutamyl transferase (GGT),

aspartate aminotransferase (AST) and alanine aminotransferase (ALT). This is not uncommon in patients who had a meconium ileus as a neonate and are pancreatic-insufficient. In most of these patients, the enzymes either normalize or remain slightly elevated throughout their life. A small proportion develop serious liver disease.

6.2.3 HEPATOSPLENOMEGALY

Children with cystic fibrosis can have mild hepatomegaly, probably secondary to fatty infiltration because of poor nutritional status. In these patients, the liver is smooth and soft. Approximately five to 15% of patients with cystic fibrosis go on to develop more serious liver disease with focal nodular cirrhosis. The pathogenesis appears to be the result of decreased or absent chloride secretion in the bile ducts. This causes increased viscosity and decreased flow of bile. Subsequently there is focal biliary obstruction, which can cause hepatocyte injury and focal biliary fibrosis and eventually multinodular cirrhosis. The disease tends to progress slowly and is more common in males and patients who have had a meconium ileus as an infant. Because it is initially a disease involving the bile ducts, there can be remarkably advanced liver disease with normal liver enzymes and liver function studies. Recent literature suggests that abdominal ultrasounds may be useful in detecting CF liver disease prior to biochemical changes. By the time there are changes in the liver texture on clinical exam the disease is very advanced.

Initially clinical problems are usually the result of hypersplenism and then of portal hypertension. Splenomegaly is usually not detected until the patient is aged six or older. On histologic examination of the liver, these patients have multinodular or biliary cirrhosis. It can be years before there are changes in the albumin, coagulation tests, or an elevation of the bilirubin. With the significant portal hypertension, the patients are at risk for bleeding from esophageal or small bowel varices. As the life-span of patients with cystic fibrosis increases, one would expect to see increasing morbidity and mortality from liver failure.

In recent years, ursodeoxycholic acid has been used to try to improve the liver disease in cystic fibrosis. Short-term studies report that patients treated with ursodeoxycholic acid show improvement in their liver enzymes and, in some cases, in liver function studies. It has yet to be determined whether long-term treatment will actually prevent progression of the liver disease and perhaps protect some children from developing cirrhosis.

6.3 Management of Pancreatic Insufficiency

As there are numerous gastrointestinal problems in cystic fibrosis and their interrelationship can be quite complex, it is beyond the scope of this section to discuss the management in detail. In the majority of cases, the problem

must be identified, assessed and managed as in patients without cystic fibrosis. Nevertheless, because pancreatic insufficiency causes most of the gastrointestinal problems, an approach to its management is outlined.

There are several indirect methods that assess pancreatic insufficiency, but the only direct measurement of pancreatic function is a pancreatic stimulation test. Unfortunately, this test requires intubation of the duodenum, is invasive and uncomfortable for the patient, and generally will not contribute significantly to the patient's management. Therefore, this test is usually reserved for complicated cases. Most patients have a 72-hour fecal fat collection, which measures the percentage of fat lost in the stool from the dietary intake of fat in one day. In infants and children a five-day dietary record is kept to obtain an average daily fat intake. If possible, this test is obtained at diagnosis prior to the initiation of exogenous pancreatic enzymes.

The aim of treatment is to control the fat malabsorption to ensure normal growth and nutritional status. The enzymes are given in capsule form and contain enteric-coated spheres of lipase, amylase, and proteases. These enteric-coated spheres are released in the alkaline environment of the duodenum. In infants and toddlers who are unable to swallow pills, the capsules are opened and given in a small spoon of food. The strength of these preparations varies and usually the dosage is expressed in lipase units. Children under four years of age require 1,000-2,500 units of lipase/kg/meal. Over the age of four years, 500-2,500 units/kg/meal is appropriate. The dose should be individualized for each patient and they must be given an appropriate amount for snacks as well as meals. Obviously the fat content of the meal is important and fat should never be restricted. If a dietary record is obtained infants should receive 450-900 units/g of fat and children over one year of age usually 500-4,000 units/g of fat. Because of the risk of fibrosing colonopathy, higher doses of exogenous pancreatic enzymes should be avoided.

If there is still evidence clinically of malabsorption when the recommended dose of exogenous enzymes is being taken, the cause may be the lack of secretion of bicarbonate from the pancreas causing suboptimal enzyme activity. An H_2 antagonist such as ranitidine may improve the efficacy of the enzymes and therefore nutrient digestion and absorption in these patients.

Fat malabsorption will also affect absorption of the fat soluble vitamins. These vitamins will need to be supplemented using water miscible forms. In Canada, the vitamin supplement used is ADEK, a multivitamin preparation designed for use in the presence of fat malabsorption.

6.4 Summary

The gastrointestinal effects of cystic fibrosis are extensive. The major gastrointestinal problems are secondary to pancreatic insufficiency. Once this is

TABLE 11. Factors contributing to physiological jaundice in the neonate

Absence of placental bilirubin metabolism
Reduced hepatic blood flow via ductus venosus shunting
Decreased red blood cell survival
Increased red blood cell mass
Reduced enteric bacterial flora
Presence of intestinal β-glucuronidase
Immature liver function
Delayed oral feeding

treated adequately with supplemental pancreatic enzymes, vitamins and appropriate nutrition, many problems will resolve. Severe liver disease, while less common, can be devastating. It must be screened-for in young infants and children. At present the only pharmacologic treatment is ursodeoxycholic acid and whether it can prevent the development of multi-nodular cirrhosis in cystic fibrosis is unknown. Because both failure to thrive and liver disease tend to have insidious presentations, it is essential to monitor children with cystic fibrosis with regular documentation of height and weight, a complete physical examination, lab work and screening abdominal ultrasounds.

7. APPROACH TO THE JAUNDICED NEONATE / M. Robertson and S.R. Martin

7.1 Definitions and Introduction

Neonatal jaundice refers to yellowish discoloration of the skin and/or sclerae of the infant resulting when an elevated serum bilirubin causes deposition of pigment in the tissues. Bilirubin is a product of heme catabolism and is produced during the breakdown of hemoglobin and other heme-containing proteins. There are four distinct stages in liver metabolism of bilirubin including: uptake from the circulation, intracellular storage, conjugation with glucuronic acid and biliary excretion (Chapter 13).

Jaundice is very common, occurring in up to 60% of term infants and 80% of preterm neonates. It is usually a physiological phenomenon but it is essential to differentiate the more infrequent occurrence of cholestasis from the common unconjugated hyperbilirubinemia of physiological jaundice. Physiological jaundice refers to a mild unconjugated bilirubinemia which affects nearly all newborns but which usually resolves within the first two weeks after birth. Any jaundice after two weeks of age in a term newborn should be considered prolonged and needs to be explained.

7.2 Physiological Jaundice

A mild hyperbilirubinemia is seen in nearly all newborns but resolves usually within the first two weeks after birth. This is always unconjugated and the rate of rise of bilirubin should be no greater than 85 micromolar per day. Peak levels of bilirubin rarely exceed 150 micromolar in term infants. Several mechanisms contributing to development of physiological jaundice are outlined in Table 11.

The shorter half life of the neonate's red blood cells and a more rapid turnover, along with the relatively high hematocrit, result in an increased production of bilirubin. There is also a decreased clearance of bilirubin because of lower activity of the uridine glucuronyl transferase (UGT), the enzyme which is involved in conjugation. Meconium has high levels of bilirubin and there are decreased enteric bacteria which usually transform the conjugated bilirubin to urobilinogen. The presence of intestinal ß-glucuronidase results in greater transformation of conjugated back to unconjugated bilirubin. This form of bilirubin may be then reabsorbed back into the circulation via the enterohepatic circulation.

Genetic variations lead to increased susceptibility to jaundice in various ethnic groups.

7.3 Pathological Jaundice

Potentially life-threatening illnesses may present with jaundice in the neonatal period so it is very important to distinguish between physiological and pathological jaundice. The following features would suggest pathological jaundice which would need to be investigated:

1. Jaundice appearing in the first 24 hours
2. Rate of rise of bilirubin of greater than 85 micromoles/litre/day (3.54 micromoles /litre/hour)
3. Serum total bilirubin greater than the hour-specific 95th percentile
4. Conjugated bilirubin of greater than 34 micromolar or > 15% of total bilirubin
5. Persistence of jaundice beyond two weeks of age

The first step in evaluating a jaundiced infant is to determine the total and conjugated bilirubin concentrations.

7.3.1 UNCONJUGATED HYPERBILIRUBINEMIA

Jaundice is caused by either an increased production or decreased clearance of bilirubin by the liver. The causes of pathological unconjugated bilirubinemia are outlined in Table 12. The most common cause of increased bilirubin production is the increased red blood cell breakdown seen in hemolytic disease

TABLE 12. Causes of unconjugated hyperbilirubinemia in the neonate

Increased bilirubin production
Hemolytic disease
Blood group incompatibility (Rh, ABO, minor groups)
Membrane defects (spherocytosis, elliptocytosis, infantile pyknocytosis)
Enzyme deficits (G6-PD, hexokinase, pyruvate kinase)
Drugs (oxytocin, vitamin K)
Increased breakdown
Infection
Hematoma, swallowed maternal blood
Increased RBC mass
Polycythemia (maternal diabetes, delayed cord clamp, small for gestational age, altitude)
Decreased bilirubin metabolism
Reduced uptake
Portacaval shunt, hypoxia, sepsis, acidosis, congenital heart disease
Decreased conjugation
Crigler-Najjar type I, II
Gilbert's syndrome
Lucey-Driscoll syndrome
Hypothyroidism
Panhypopituitarism
Altered enterohepatic circulation
Breastfeeding
Free fatty acids, steroids, breast milk β-glucuronidase
Intestinal hypomotility
Retained meconium
Reduced intestinal flora
Newborn, antibiotic use

caused by immune-mediated or inherited red cell membrane defects, and less frequently hemoglobinopathies.

Unconjugated bilirubin concentration will be affected by any condition which reduces the clearance of bilirubin from the liver. These are primarily inherited conditions resulting in defects in uridine glucuronyl transferase (UGT) the enzyme which conjugates bilirubin. These conditions include Crigler-Najjar syndrome types I and II and Gilbert Syndrome which are discussed in more detail in Chapter 13. The Lucey-Driscoll syndrome is a transient form of acquired reduction in UGT which is likely caused by an unidentified maternal serum factor.

Congenital hypothyroidism and panhypopituitarism may also result in an unconjugated hyperbilirubinemia by unknown mechanisms.

TABLE 13. Causes of conjugated hyperbilirubinemia in the neonate

Infection
Bacterial urinary tract infection/sepsis
Cytomegalovirus
Rubella
Herpes viruses: simplex; type 6
Toxoplasmosis
Syphilis
Other viruses: adenovirus, Coxsackie virus, echovirus, parvovirus B19
Metabolic
Galactosemia
Fructosemia
Tyrosinemia
Peroxisomal disorders
Bile acid synthesis disorders
α_1-antitrypsin deficiency
Cystic fibrosis
Niemann-Pick disease
Endocrine disorders: hypopituitarism, hypothyroidism
Neonatal hemochromatosis
Progressive familial intrahepatic cholestasis
Bile duct disorders
Extrahepatic
Biliary atresia
Bile duct perforation, stenosis
Neonatal sclerosing cholangitis
Choledochal cyst
Cholelithiasis
Intra/extrahepatic masses
Inspissated bile/bile plug
Intrahepatic
Alagille's syndrome
Byler's disease (familial progressive cholestasis)
Nonsyndromic bile duct paucity
Miscellaneous
Parenteral nutrition
Intestinal obstruction
Shock
Trisomy 21

7.3.1.1 Breastfeeding failure jaundice

This phenomenon which occurs early in the neonatal period probably results from an exaggeration of the mechanisms of physiological jaundice because of decreased feeding. In the fasting infant there will be an increased enterohepatic circulation of bilirubin.

7.3.1.2 Breast milk jaundice

This relatively common entity usually begins after three to five days, peaking at about two weeks. Bilirubin levels are usually restored by three to 12 weeks. A number of factors in breast milk have been implicated and the mechanism appears to be related to enhanced absorption of bilirubin resulting in increased enterohepatic circulation. It is important in breast-fed babies who remain jaundiced to check the conjugated bilirubin level at two weeks of age or, if the baby is feeding and growing well with a normal examination, to check the level at three weeks.

7.3.1.3 Intestinal obstruction

An ileus or mechanical gastrointestinal obstruction can increase the level of circulating bilirubin.

7.3.1.4 Management

Unconjugated bilirubin that is not bound to albumin can enter the brain and is a potential neurotoxin. It may result in an acute encephalopathy, with lethargy and poor feeding or it may cause chronic neurodevelopmental sequelae, (kernicterus). With very high total serum bilirubin concentration the increased free bilirubin may overwhelm the albumin-binding capacity. Acidosis and some antibiotics may increase toxicity by decreasing albumin binding of bilirubin.

Total serum bilirubin concentrations should be compared to an age-in-hours-specific percentile-based nomogram. Infants at risk require close monitoring and follow-up. Management usually involves phototherapy to expose the infant's skin to light, which detoxifies bilirubin.

Exchange transfusion to remove bilirubin from the circulation is performed if intensive light therapy fails in severe hyperbilirubinemia.

7.3.2 CONJUGATED HYPERBILIRUBINEMIA IN THE NEONATE

7.3.2.1 Definitions and introduction

Conjugated hyperbilirubinemia in the new born period is a sign of cholestasis and always needs to be investigated. Cholestasis results when there is decreased excretion of bilirubin at any level from the hepatocyte, through biliary canaliculae, and bile ducts to the duodenum. Direct (conjugated) hyperbilirubinemia is always pathological. Conjugated bilirubin should not be

greater than 17 micromolar if the total bilirubin is less than 85 micromolar and should be no more than 20% of the total bilirubin when it is greater than 85 micromolar.

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recommends measuring total and direct (conjugated) serum bilirubin in any infant jaundiced at two weeks of age. Healthy breast-fed infants with a normal history (no dark urine or pale stool) could be asked to return at three weeks of age for the blood test.

Cholestastic jaundice is uncommon, occurring in one in 2,500 infants. The more common causes of neonatal cholestasis are outlined in Table 13.

The most common causes of neonatal cholestasis are biliary atresia and the multifactorial cholestasis seen in premature infants. However, there is such a wide differential diagnosis, a structured approach to investigation is essential. It is imperative to first recognize conditions needing immediate treatment and any other treatable causes of cholestasis. Early detection and accurate diagnosis of biliary atresia are also very important because infants who have biliary drainage surgery performed by 45-60 days of age have the best outcome.

7.3.2.2 Biliary atresia

This condition occurs with a frequency variously reported to be between 1:8,000 and 1:21,000 live births. It is the most common cause for children requiring liver transplantation. In biliary atresia, all or part of the extrahepatic biliary ducts is obliterated leading to complete obstruction of bile flow. The etiology of biliary atresia is unknown and it is likely that it is a condition with multiple etiologies. Typically, jaundice is noticed between three to six weeks of age in an otherwise healthy baby. Light-colored stools may have been evident from birth and on examination hepatomegaly is evident. Approximately 10-15% of babies have other congenital abnormalities which include polysplenia, malrotation, preduodenal portal vein and a number of cardiovascular abnormalities.

The diagnosis involves the exclusion of other known causes of neonatal cholestasis. Hepatobiliary scanning shows no excretion of the isotope into the intestine. Although this test has 100% sensitivity for biliary atresia it has only 60% specificity. The isotope is also not excreted in many babies with severe intrahepatic cholestasis, particularly in those conditions where there is a paucity of intrahepatic bile ducts.

The liver biopsy findings are classically those of extrahepatic biliary obstruction with bile duct proliferation, bile duct plugs and expansion of the portal tracts. When the biopsy findings are consistent with biliary atresia the diagnosis is confirmed at laparotomy and with intraoperative cholangiogram.

When biliary atresia is confirmed by the intraoperative cholangiogram, it should be followed by a surgical biliary drainage procedure or so-called hepatoportoenterostomy operation (also known as a Kasai procedure). The atretic extrahepatic segment is dissected and a loop of bowel surgically attached to the area of the liver with the newly exposed biliary ductules. The age of the infant at surgery is one of the critical factors predicting successful drainage after surgery. After 60-80 days of age the likelihood of success falls with time. Where the surgery is successful, with bile drainage and clearance of jaundice, there is long-term benefit although most children may eventually require liver transplantation.

One of the major complications of biliary atresia after the Kasai operation is cholangitis (infection of the biliary tree). This may present with increasing jaundice and elevated liver enzymes and should be treated aggressively with intravenous antibiotics.

7.3.2.3 Alpha-1-antitrypsin deficiency

This is the most common inherited cause of neonatal cholestasis and can be associated with progressive liver disease. The homozygous deficiency state or Pi ZZ phenotype occurs in 1:2,000 live births. These patients have markedly reduced levels of alpha-1-antitrypsin, which is the principal serum inhibitor of proteolytic enzymes. Only 10-20% of all newborns with the ZZ mutation will develop neonatal cholestasis and the pathophysiology of the hepatic manifestations of this disorder is not fully understood.

The presentation of alpha-1-antitrypsin deficiency can be very similar to the presentation of biliary atresia. Hepatomegaly and acholic stools may be present and the liver biopsy may show proliferation of bile ducts. Intralobular bile duct paucity may be found at a later time. The accumulation of alpha-1-antitrypsin protein in the characteristic granules may not be evident in the early biopsy. The outcome of this form of neonatal cholestasis is quite variable. Some infants will develop early cirrhosis but in the majority of patients the jaundice clears within the first four months of life.

7.3.2.4 Alagille's syndrome

This is a form of familial intrahepatic cholestasis occurring in 1:100,000 live births. It results from mutations in the Jagged 1 gene which codes for a ligand for the notch intracellular signaling pathway. This pathway is involved in the regulation of cell differentiation and proliferation. Cholestasis results because of the progressive loss of bile ducts causing bile duct paucity. In the neonatal period the infant may have acholic stools, but unlike biliary atresia, liver size is usually normal or only slightly enlarged. This is a multisystem disorder and the infant with chronic cholestasis may have a number of other characteristic

clinical findings. These include abnormal facies, (but the characteristic features are often less apparent in the neonate than the older child or adult), as well as congenital heart disease (the most common being peripheral pulmonary artery stenosis). Other abnormalities may be present including skeletal (butterfly vertebra), renal and ocular manifestations. The prognosis of infants with Alagilles syndrome is related to severe sometimes progressive cholestasis causing metabolic bone disease, xanthomata and pruritus, as well as the congenital heart disease and the risk of intracranial bleeding.

7.3.2.5 Progressive Familial Intrahepatic Cholestasis (PFIC)

These inherited forms of intrahepatic cholestasis often present in the neonatal period. These infants have normal intrahepatic and extrahepatic bile ducts but have mutations causing the abnormal function of transporter proteins important in the formation of bile. Two of these entities PFIC 1 and PFIC 2 are characterized by low serum levels of the enzyme gamma-glutamyl transferase (GGT) which is usually very high in other conditions causing neonatal cholestasis, especially biliary atresia. These conditions, which are all autosomal recessive in inheritance, can progress to cirrhosis.

7.4 Clinical Evaluation

When conjugated hyperbilirubinemia has been established, then history and physical examination and initial investigations should focus on determining the severity of liver dysfunction, detecting readily treatable disorders and making a timely diagnosis of biliary atresia. Guidelines for cholestatic jaundice in infants have been published by NASPGHAN with an algorithm outlining the recommended steps for assessment of the jaundiced infant aged two to eight weeks old. As well this document tabulates history and physical findings to consider for the differential diagnosis of infants with conjugated hyperbilirubinemia.

7.4.1 HISTORY AND PHYSICAL EXAMINATION

A history of maternal illness with rash and fever antenatally may point to infectious causes of neonatal cholestasis. The likelihood of metabolic disorders such as tyrosinemia and Niemann-Pick disease or genetic disorders such as cystic fibrosis and alpha-1-antitrypsin deficiency is increased if there is consanguinity. There may be a family history consistent with familial or inherited conditions including Alagilles or PFIC. Important information to obtain also includes birth weight, growth and feeding history as well as formula type. Exposure to galactose or sucrose or fructose may point to galactosemia or fructosemia. Enquiries should be made about urine and stool color. Although having acholic stools is a sensitive indicator of liver disease in the neonate it can be seen in both extrahepatic and intrahepatic causes of cholestasis.

TABLE 14. Laboratory evaluation of conjugated hyperbilirubinemia

Total and direct serum bilirubin
Alkaline phosphatase, aminotransferases, γ-glutamyl transpeptidase
Prothrombin time or INR, serum albumin (factor V levels, if available)
Complete blood cell count, differential
Urine culture (blood/cerebrospinal fluid, if indicated)
Serology for cytomegalovirus, rubella, herpes simplex, herpes type 6, toxoplasmosis, syphilis (adenovirus, Coxsackie virus, reovirus III, parvovirus B19, if available)
Urine for reducing substances, serum galactose-1-phosphate uridyltransferase, serum/urine amino acids and organic acids
Sweat chloride
α_1-antitrypsin level and Pi phenotype
Urine for bile acid metabolites
Serum ferritin
TSH
T4, glucose, cortisol

On physical examination the general health of the infant should be assessed. The infant with lethargy or poor feeding and vomiting is more likely to be septic or have a metabolic cause of cholestasis. Infants with biliary atresia may appear well with normal growth and increasing jaundice as well as an enlarged, firm nodular liver. The murmur of peripheral pulmonary artery stenosis may be apparent on chest auscultation in the infant with Alagilles syndrome.

7.4.2 INVESTIGATIONS

All infants with conjugated hyperbilirubinemia that is not related to a readily identifiable surgical cause such as a choledochal cyst or cholelithiasis should be referred to a pediatric gastroenterologist. The main diagnostic concern is to differentiate hepatocellular from obstructive cholestasis and identify treatable causes early. It is important to evaluate or repeat the newborn screen for galactosemia and hypothyroidism, as these are treatable conditions requiring urgent management to prevent serious sequelae. Timely recognition and accurate diagnosis results in optimal outcomes for the surgical management of infants with choledochal cysts and biliary atresia.

7.4.2.1 Laboratory investigations

Blood tests useful for the evaluation of the cholestatic infant are outlined in Table 14.

Serum bilirubin is used to determine the severity of the cholestasis. The degree of liver dysfunction is estimated by the INR and prothrombin time (after correction of any Vitamin K deficiency) as well as serum albumin. In the appropriate clinical settings urgent investigations should be conducted to exclude

possible bacterial infection and metabolic or endocrine disorders where prompt therapy will reverse the cholestasis and improve the outcome of the neonate. Tests for galactosemia include urine for reducing substances (while the infant is ingesting lactose containing milk) and/or serum galactose 1-phosphate uridyl transferase. Tests for hypothyroidism and/or panhypopituitarism should also be done to exclude these treatable conditions where clinically indicated. A very high alkaline phosphatase (ALP) and GGT is suggestive of biliary obstruction.

7.4.2.2 Radiology

Abdominal ultrasonography is non-invasive, easily available and can identify structural abnormalities of the hepatobiliary tract. This investigation will define cystic or obstructive dilatation of the biliary tree. The common bile duct is not dilated in biliary atresia. Features suggestive of polysplenia syndrome (multiple splenules, abnormalities of the inferior vena cava, preduodenal portal vein and situs inversus) may be identified suggesting the likelihood that biliary atresia is the cause of the cholestasis.

Radiographs of the vertebral column, long bones and skull may be helpful in the diagnosis of Alagille's syndrome or congenital infection.

Hepatobiliary scintigraphy, examining excretion of a tracer into the bile and intestine can be performed. In the presence of biliary atresia there will be rapid uptake of tracer into the liver but no excretion in 24 hours. Although this test is believed to have a high sensitivity in the diagnosis of biliary atresia, the specificity of the test is low. Severe intrahepatic cholestasis may also result in no excretion of tracer into the intestine. Scintigraphy therefore adds little to the evaluation of the cholestatic infant but may be of some value in demonstrating patency of the common bile duct and excluding biliary atresia.

7.4.2.3 Percutaneous liver biopsy

This is the single most important test in diagnostic evaluation of the cholestatic infant and when biliary atresia is high on the list of differential diagnoses a liver biopsy should be performed. The NASPGHAN guideline recommends that most infants with undiagnosed etiology of cholestasis should have a percutaneous liver biopsy. Biliary atresia has been variously reported to be correctly diagnosed by biopsy 50-99% of the time and incorrectly suspected from the biopsy in 0-46%. If the biopsy is done in an infant less than six weeks old it may be equivocal and need to be repeated.

7.5 Management

For the infant with a non-treatable cause of cholestasis, management is largely supportive. The aim is to promote growth and development and to minimize discomfort. Steatorrhea is common in infants with significant cholestasis because

decreased bile excretion leads to inadequate digestion and absorption of lipids. Medium chain triglycerides do not require solubilization by bile salts so may be absorbed more readily. They can be administered orally in one of several specialized infant formulas or as a supplement. To provide nutrition adequate for growth, a high calorie diet is usually necessary, providing up to 125-150% of recommended calories for ideal body weight. Adequate protein should be provided as well as adequate administration of oral supplements of the fat-soluble vitamins.

Pruritus is a complication of bile acid retention which can cause considerable morbidity. This can be seen by the time the infant is three months of age. Treatment can include ursodeoxycholic acid, which is a hydrophilic bile acid which can stimulate bile flow and displace toxic bile acids from the liver. This medication may cause increased toxicity in patients with poor bile flow. Biliary diversion procedures have been performed when intractable pruritus or hypercholesterolemia and xanthomata result from intrahepatic cholestasis.

SUGGESTED READING and / or References

Comprehensive information on all sections may be found in the textbook:

Walker WA, Goulet OJ, Kleinman RE, et al. (eds.). Pediatric gastrointestinal disease. 4th ed. Hamilton: BC Decker, 2004.

Section 1: Functional Gastrointestinal Disorders with Abdominal Pain

1. Hyman PE, Rasquin-Weber A, Fleisher DR, et al. Childhood functional gastrointestinal disorders. In: Drossman DA (ed.), The functional gastrointestinal disorders. 2d ed. Lawrence: Allen Press, 2000:533–575.

Section 2: Vomiting and Regurgitation

1. Brown JB, Li B. Recurrent vomiting in children. Clin Perspectives in Gastroenterol 2002; 5:35–39.
2. Rudolph CD, Mazur LJ, Liptak GS, et al. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr 2001; 32:(Suppl 2):1–31.

Section 3: Chronic Constipation

1. Baker SS, Liptak GS, Colletti RB, et al. Constipation in infants and children: evaluation and treatment. J Pediatr Gastroenterol Nutr 1999; 29:612–626.
2. Hyman PE, Rasquin-Weber A, Fleisher DR, et al. Childhood functional gastrointestinal disorders. In: Drossman DA (ed.), The functional gastrointestinal disorders. 2d ed. Lawrence: Allen Press, 2000:533–575.

Section 4: Growth Failure and Malnutrition

1. Dietitians of Canada and Canadian Paediatric Society. A health professional's guide to using growth charts. Paediatr Child Health 2004; 9:174–176.

Section 7: Approach to the Jaundiced Neonate

1. Moyer V, Freese DK, Whitington PF, et al. Guideline for the evaluation of cholestatic jaundice in infants: recommendations of the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2004; 39:115–128.

OBJECTIVES

Functional Gastrointestinal Disorders with Abdominal Pain

1. Recognize the characteristic clinical presentation of functional abdominal pain in children.
2. Identify features of the history or physical examination that are not consistent with functional abdominal pain.

Vomiting and Regurgitation

1. Understand the distinction between vomiting and regurgitation.
2. Be aware of the range of gastrointestinal and non-gastrointestinal causes of vomiting.
3. Be aware of an age and presentation-appropriate approach to the neonate, infant, child and adolescent with vomiting.
4. Be aware of an approach to the investigation and management of infants with simple gastroesophageal reflux and complicated gastroesophageal reflux (GERD).

Chronic Constipation

1. Recognize normal variations in patterns of elimination in infants.
2. Be aware of the functional and organic causes of constipation.
3. Understand the mechanisms and management of functional constipation and encopresis.

Growth Failure and Malnutrition

1. Understand normal patterns of growth and normal feeding behavior in the infant.
2. Develop an approach to determine factors causing problems with growth in the infant.

Acute Diarrhea in Children

1. Understand the pathophysiology of acute diarrheal disease in the pediatric patient.
2. Be able to assess severity of dehydration in infants and children.
3. Understand the use of oral rehydration therapy for the management of acute diarrheal disease.

Cystic Fibrosis

1. Recognize the different gastrointestinal presentations of infants with cystic fibrosis.
2. Describe the presentations of hepatobiliary disease in infants and children with cystic fibrosis and understand the necessity of monitoring the child for development of liver disease.
3. Understand the management of pancreatic insufficiency.

Approach to the Jaundiced Neonate

1. Be aware of the factors contributing to physiological jaundice in the newborn.
2. Be aware of the various causes of unconjugated hyperbilirubinemia in infancy. Know the symptoms and sequelae of unconjugated hyperbilirubinemia. Be aware of the options for management.
3. Be aware of the various causes of neonatal conjugated hyperbilirubinemia.
4. Be aware of an approach (algorithm) for the investigation and management of neonatal hyperbilirubinemia.