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A. Jay Freeman, Tatyana Hofmekler, John-Paul Berauer, and Sirish Palle

Reflux

Gastroesophageal reflux (GER), the physiological passage of gastric contents into the esophagus, occurs in over two-thirds of otherwise healthy infants with daily "spitting-up" and represents a common topic of parenteral concern at well child visits within the first year (Lightdale and Gremse 2013). Gastroesophageal reflux disease (GERRD), is reflux associated with troublesome symptoms and is estimated to occur in 10–20% of infants and 5–8% of children in North America (Nelson et al. 2000; Dent et al. 2005). Peak incidence of GERD occurs for most patients around 4 months of age with only 5–10% of patients continuing to experience symptoms at 12 months (Martin et al. 2002). GERD can present in a variety of manners depending on age (see Table 10.1), and should be monitored closely in populations that are high-risk for GERD associated complications (e.g. patients which are neurologically impaired, obese, preterm infants and/or have chronic respiratory conditions) (Hassall et al. 2007).

Established and proposed extra-esophageal manifestations of GERD must be considered and evaluated for in patients suspected of having GERD. However, care must be exercised to not overestimate the effects of reflux on certain conditions. Specifically, recent systematic reviews have failed to show significant evidence associating GERD with apnea or the crying/irritable infant (Smits et al. 2014; Gieruszczak-Białek et al. 2015). Additionally, while GERD may effect wheezing and asthma, recent publications suggest the impact is much less than previously thought and additional pulmonary care for uncontrolled asthma and/or wheezing should not be delayed even with the addition GERD therapy (Sheikh et al. 1999; Littner et al. 2005; American Lung Association Asthma Clinical Research Centers et al. 2009; Kiljander et al. 2010, 2013).

Table 10.1 Common GERD symptoms by age

Infants	Older children and adolescents
Feeding refusal/ inadequate volumes by mouth	Abdominal/chest pain (heartburn)
Recurrent emesis	Recurrent emesis
Poor weight gain/failure to thrive	Dysphasia
Irritability	Asthma
Sleep disturbances	Recurrent pneumonia
Respiratory symptoms/ cough	Upper airway symptoms (cough, horse voice)

Modified and adapted from Lightdale and Gremse (2013)

A.J. Freeman (✉) • T. Hofmekler • J.-P. Berauer
S. Palle
Division of Pediatric Gastroenterology, Hepatology and Nutrition, Emory University School of Medicine, Atlanta, GA, USA
e-mail: afreem6@emory.edu

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Diagnostic Considerations

GERD is a clinical diagnosis and diagnostic testing is not generally required. Despite the development and validation of a number of GERD questionnaires, there remains no single symptom, cluster of symptoms or subjective tool to diagnose or predict esophagitis, other complications of GERD and/or determine which patients will respond to therapy. As no single test definitively diagnoses or excludes GERD, testing should be conducted only to exclude other diagnosis that may explain the patient's symptoms, evaluate for complications of GERD, to establish a causal relationship between GERD and other symptoms and/or monitor therapy effectiveness (Lightdale and Gremse 2013). Despite its wide-spread use, Upper GI tract radiographic imaging serves no role in the evaluation of reflux but rather may be useful in ruling out anatomical causes of persistent emesis (Vandenplas et al. 2009). Multiple intraluminal impedance (MII) has replaced traditional pH probes due to their ability to detect not only acid but also non-acidic reflux. This allows MII to access a number of key variables including; (1) anterograde and retrograde esophageal boluses, (2) volume, speed and length of reflux event, (3) temporal association between reflux event and specific symptom(s) and (4) effectiveness of GERD therapy. Lastly, endoscopy with esophageal biopsies may be used to determine the extent of mucosal damage secondary to GERD, evaluate for anatomical abnormalities and/or Barrett esophagus and exclude other conditions that may mimic GERD including EoE and infectious esophagitis (Hassall 2002).

Management

Life style modifications should be attempted as first line therapy against GERD. Milk protein sensitivity is often overlooked as a condition that can mimic GERD and a 2- to 4-week trial of maternal exclusion of milk and eggs is recommended for breastfeeding infants, or partially hydrolyzed or amino acid formula in formula fed infants assuming adequate weight gain and no respiratory compromise (Vandenplas et al. 2009). Additional overfeeding, seated or supine positions and environmental tobacco smoke should be avoided. Thickening of the infants formula with rice cereal (1 tablespoon per ounce) may also be attempted but all thickening agents should be avoided in preterm infants given the risk of developing necrotizing enterocolitis (Clarke and Robinson 2004). Although data suggests that reflux is decreased in infants in the prone position, the risk of sudden infant death syndrome far outweighs the benefits and therefore prone position should only be considered when the child is awake or directly observed (Vandenplas et al. 2009). In older children, dietary avoidance of caffeine, alcohol, spicy foods and other food triggers may be sufficient to control symptoms (Lightdale and Gremse 2013).

If lifestyle modifications fail, acid suppression with histamine$_2$ receptor antagonists (H2RAs) or proton pump inhibitors (PPIs) are often effective. Several studies have shown clinical benefit of H2RAs but they are often limited in their long-term use by either tachyphylaxis or patient tolerance making PPIs a better choice in those patients expected to be on longer acid suppressive therapy (Gremse 2004). PPIs are generally considered safe for long periods of time with highest efficacy when taken ~30 min before a meal (Rudolph et al. 2001; Chan et al. 2011; Kierkus et al. 2014). Additionally, children tend to metabolize PPIs faster than adults and often need higher per kilogram dosing or twice a day dosing (Kierkus et al. 2014). For break through symptoms while on acid suppression medication, over the counter antacids may be used to provide relief.

Prokinetic agents such as metoclopramide and erythromycin have become trendy in GERD therapy but there is insufficient data at this time to support their routine use in infants or older children (Vandenplas et al. 2009).

In patients with severe GERD in which lifestyle changes and medical therapy have failed and also have either; (1) growth failure or (2) risk for significant aspiration or other respiratory compromise, then transpyloric feeds via a nasojejunal tube or surgical management may be required, typically a fundoplication. Ideally a

patient should be seen by both a pediatric gastroenterology and a pediatric surgeon to ensure medical management has been optimized prior to undergoing surgery due to its risks and long-term complications.

Eosinophilic Esophagitis

Previously thought of as an extremely rare condition, eosinophilic esophagitis (EoE) is now known to be one of the most commonly diagnosed conditions during the assessment of feeding difficulties in children (Straumann et al. 2008). EoE has been described worldwide and effects all age groups with a prevalence between 1 and 5 per 10,000 persons in the United States and Europe, most commonly effecting white males with an onset from school age to midlife (Furuta and Katzka 2015). Among those patients undergoing endoscopic assessment for food impaction, prevalence rates of EoE increase dramatically to nearly 55% (Desai et al. 2005).

Pathogenesis

The exact cause of EoE remains unclear but increasing prevalence of disease has led to focused attention on environmental exposures. Several risk factors have been identified supporting environmental influences to the development of EoE including birth by cesarean section, prematurity, early antibiotic exposure during infancy, food allergies, lack of breast feeding, smoking exposure and residency in low population density areas (Jensen et al. 2013, 2014; Slae et al. 2015). Additionally, clustering amongst families, male predominance, strong twin concordance and genome-wide association studies (GWAS) all suggest a genetic component as well (Furuta and Katzka 2015). At the cellular level, it is believed that impaired barrier function (dilated intercellular spaces, increased epithelial permeability and down-regulation of proteins associated with barrier function and molecular adhesion) along with increased activity of type 2 helper T (Th2) cells represents the underlying cause of disease (Furuta and Katzka 2015). Repeated case series have shown environmental and food hypersensitivities, with symptomatic and mucosal responses to elimination of exposure and subsequent relapse upon reintroduction of antigen, further supporting the role of food and environmental hypersensitivity as an important component of the pathophysiology of EoE (Markowitz et al. 2003).

Presentation

Reflux symptoms are a common initial presentation for all patients with EoE, but other symptoms may be more non-specific and vary by age. Adolescents are more likely to present with classic symptoms of dysphasia and food impaction while younger children are more likely to present with feeding difficulties, nausea, emesis and failure to thrive. Due to patient accommodation, symptoms may be subtle including slow oral intake, cutting food into very small pieces, excessive lubrication of foods with sauces, diluting foods with increased fluid intake, fear of eating in public and avoidance of pills and/or certain foods which may cause dysphasia (Furuta and Katzka 2015).

Endoscopic evaluation is necessary for the diagnosis of EoE with an increased number of eosinophils in the esophageal epithelium representing the histologic hallmark of disease. Utilizing a cutoff value of 15 eosinophils per high-powered field results in a sensitivity of 100% and specificity of 96%, although patients with classic phenotypic features and lower levels of eosinophilia have been described (Ravi et al. 2011; Dellon et al. 2015). Although not diagnostic, the most common gross findings on endoscopy include white specks/exudate, mucosal edema, linear furrowing, esophageal rings and esophageal stricturing (see Fig. 10.1). Barium esophagography may also have a role in the evaluation of patients with EoE as up to 55% of children who had no signs of stricturing at time of endoscopy have been found to have esophageal narrowing on esophagography (Menard-Katcher et al. 2015).

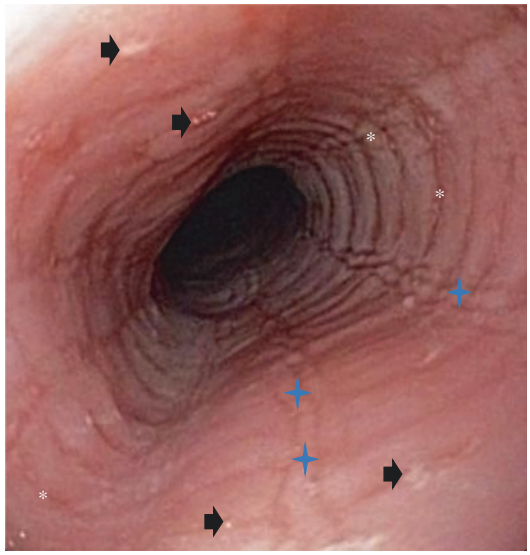

Fig. 10.1 Common histological appearance of EoE. Classic appearance of EoE with white specks/exudate (*black arrow head*), vertical furrowing (*blue stars*) and esophageal rings, also known as furrowing (*white asterisk*)

Table 10.2 Overview of EoE therapies

Therapy	Recommendation or dosage
Elemental diet therapy	Amino-acid based formula for 4–6 weeks
Elimination diet therapy	
Six-food elimination	Elimination of milk, wheat, eggs, soy, seafood and nuts
Four-food elimination	Elimination of milk, wheat, eggs and soy
Allergy testing-based	Not recommended
Proton pump inhibitors (Omeprazole[a])	10–20 kg body weight: 10 mg twice a day >20 kg body weight: 20 mg twice a day
Glucocorticosteroids	
Fluticasone	220–440 µg twice a day
Budesonide	0.25–0.5 mg twice a day

Modified and adapted from Furuta and Katzka (2015)
[a]An alternative, equivalent PPI may be used

Management

The management of EoE can be summarized as the "3 D-approach": Diet, Drugs and Dilation (D'Alessandro et al. 2015). Although the goal of therapy is clinical and histological remission, this is rare and clinical improvement along with significant reduction of mucosal eosinophilia are considered signs of effective therapeutic response (Dellon et al. 2013).

Diet

An elemental diet represents the therapy with the highest clinical response with nearly 90% of children demonstrating clinical improvement and is associated with histological remission. Patients are placed on an amino-acid based formula for 4–6 weeks. If clinical and histological response is seen, foods are slowly reintroduced one-food group at a time every 5–7 days. If no reoccurrence of symptoms is seen, endoscopic evaluation is performed to ensure histological disease progression is not seen before reintroducing each new food group. If a specific food elicits clinical symptoms or increased mucosal eosinophilia, then that food should be excluded form the patient's diet (Peterson and Boynton 2014; D'Alessandro et al. 2015).

In older children a 4- or 6-food elimination diet may be attempted and has been shown to have an approximately 70% rate of clinical response (see Table 10.2). Similar to the elemental diet, selected foods are eliminated from the diet and are only reintroduced after clinical and histological response are confirmed by endoscopy with those foods eliciting clinical symptoms and/or increased mucosal eosinophilia removed from the patient's diet (Rodríguez-Sánchez et al. 2014).

Allergy, skin-prick driven therapy has been shown to have much poorer response rates with only 45% of patients showing sustained response and therefore is not routinely recommended (Arias et al. 2014).

Drugs

Proton-pump Inhibitor (PPI) use is a mainstay of EoE therapy. As essentially all patients experience reflux-like symptoms, lack of PPI response is the only current method to rule out gastroesophageal reflux as a cause of the patient's

symptoms (Furuta and Katzka 2015). Additionally, nearly 40% of patients with histologically confirmed EoE experience a clinical response to PPI therapy alone and therefore is considered first-line therapy in all patients with EoE (Molina-Infante et al. 2015).

The use of systemic corticosteroids results in high rates of remission but long-term use is limited by relapse after tapering of the medication and side effects. Therefore, systemic steroids may be used to rapidly induce remission but should not be considered as a long-term therapeutic option (Mukkada and Furuta 2014). Topical steroids (fluticasone and budesonide) have also shown significant response rates with much lower side effect profiles as compared to systemic steroids and is now considered first-line therapy after a PPI trial (Contreras and Gupta 2014; Gupta et al. 2015). The preferred route of administration is via an oral viscous solutions with sucralose creating a slurry consistency, although several alternatives to sucralose have been show to be effective as well including applesauce and honey (Lee et al. 2016).

Dilation

Strictures are a common finding among patients with EoE with several studies showing endoscopic dilation to be safe and efficacious (D'Alessandro et al. 2015). Although dilation may result in rapid symptom relief, it does not affect esophageal inflammation and should be considered an adjunct therapy only to appropriate dietary and/or medical interventions (Kavitt et al. 2014).

Celiac Disease

Introduction and Epidemiology

Prevalence of celiac disease in pediatric patients is similar to that of adults, effecting approximately 1% of the population (Newton and Singer 2012). Celiac disease is defined as "chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals" (Ludvigsson et al. 2013). Classic celiac disease presents with symptoms suggestive of malabrsoption: diarrhea, steatorrhea, weight loss, and/or growth failure (Ludvigsson et al. 2013). However, there has been an increasing number of non-classical cases that present with a number of intestinal and extra-intestinal manifestations (Rampertab et al. 2006).

Pathogenesis and Immunology

The pathogenesis of Celiac disease is linked to a combination of genetic, environmental and immunological risk factors, although no clear pathway for each has ever been defined (Tran 2014). The microbiome has been studied extensively with mixed results both in favor and opposed to its role in the development of Celiac disease (de Meij et al. 2013).

Genetics and Risk Factors

The common human leukocyte antigen (HLA) class II gene (DR3, DR5/DR7, or DR4) known as HLA-DQ2 and HLA-DQ8 located on chromosome 6p21 is associated with Celiac disease (Gutierrez-Achury et al. 2011). HLA typing is not helpful in establishing a diagnosis of Celiac disease but can be useful to exclude the diagnosis in high-risk patients or group of patients. Patients that do not have the HLA-DQ2 or HLA-DQ8 molecules have a negative predictive value near 100%, thus essentially ruling out the diagnosis of celiac. It is important to remember that many children with the proper HLA typing may not have celiac disease at the time of testing, but are still at risk to develop the disease later in life (Tran 2014).

Multiple risk factors have been associated with having an increased risk of gluten intolerance (see Table 10.3) and if present should prompt screening for Celiac disease (see diagnosis section below) (Husby et al. 2012). Alternatively, breast feeding has been suggested to be protective (Størdal et al. 2013).

Table 10.3 Factors associated with an increased risk for Celiac disease

Signs
Unexplained elevated transaminases without known liver disease
Iron deficiency anemia
Pubertal delay
Poor growth
Diagnoses
Type I DM
Selective IgA deficiency
Down's syndrome
Autoimmune liver disease
Dermatitis herpetiformis
Intussusceptions
Eosinophilic esophagitis
Irritable bowel syndrome
Behaviors/family
Introduction of gluten after age 6 months
Relatives with celiac disease

Diagnosis

In addition to patients with increased risk factors, patients with symptoms of diarrhea, poor growth, stunting, delayed puberty, amenorrhea, nausea or vomiting, chronic abdominal pain, fatigue and/or recurrent aphthous stomatitis should be screened for Celiac disease (Husby et al. 2012). Patients are most commonly screened for celiac disease with serological tests and this should be done while the patient is consuming a gluten containing diet. Celiac panels are particularly expensive, and generally not as helpful. It is better to select specific serological tests to check in patients (Hill et al. 2016). Immunoglobulin A (IgA) anti-tissue transglutaminase (TTG) can have a sensitivity of 98% if done in a reliable lab with an established upper limit of normal. Endomysial antibody IgA should be done in a lab with reference standards of a pediatric population (Husby et al. 2012). Deaminated gliadin peptide (DGP IgG) has comparable specificity and lower sensitivity as the EMA IgA. In children under age 2, the TTG IGA and EMA have a higher chance of being inaccurate. For this reason in kids <2 years, they should have a TTG IGA and DGP IGG tested. False negatives will occur with IgA deficiency so total IgA is usually collected when a screening TTG-IgA is collected for the first time for any patient (Hill et al. 2016).

An esophagogastroduodenoscopy is usually preformed to confirm the diagnosis in patients with concerning serology. Biopsies are taken from duodenal bulb and affected tissue will be patchy. The degree of villous atrophy is graded on the Marsh criteria (3c being most severe and 0 being normal). In patients where the routine pathology is inconclusive, anti T-cell receptor gamma delta (TCRγδ) positive intraepithelial lymphocytes detection can be performed on formalin fixed paraffin imbedded in small bowel biopsies. The (TCRγδ) will remain elevated even on gluten free diet (Tran 2014).

Although not routinely the standard of care within the United States, in 2012 the European society of Pediatric Gastroenterology, Hepatology and Nutrition offered times when endoscopy could be avoided for a diagnosis. Pediatric patients with signs or symptoms suggestive of celiac, high anti-TTG IGA titers (>10 times the ULN) should be offered a second blood test to check for EMA. If it is positive, then the diagnosis of celiac can be made without endoscopic conformation. It is also advised to check for HLA types in these patients (Husby et al. 2012).

Treatment

The treatment for celiac disease is a gluten free diet. Unfortunately, about 25% of patients continue to experience symptoms despite a gluten free diet (Paarlahti et al. 2013). Patients should plan to have less than 20 parts per million (ppm; 6 mg equivalent) of gluten per day. Some patients require new appliances that have been gluten free. Following a gluten free diet can add additional stress to all family members involved as this frequently affects the entire family. Gluten free diets tend to be higher in fat and should be avoided unless a diagnosis of celiac disease is made.

Functional Gastrointestinal Disorders

Background

Functional GI Disorders (FGID) are better defined as *Disorders of the Gut-Brain Interaction* and can affect anyone from young age through

adulthood. FGIDs did not always receive scientific rigor until the last several decades and so scientific historic data is lacking. However, with increasing categorization and scientific interest, research is suggesting several complex processes such as microbial dysbiosis, altered mucosal immune function, visceral hypersensitivity and central nervous system dysregulation all contributing to the etiology of FGIDs (Drossman and Hasler 2016). With emerging understanding, it is important to keep in mind that functional disorders can coexist, or even be worsened, with other underlying gastrointestinal pathologies (Hyams et al. 2016).

Most recently, the Rome IV criteria were published in the Journal of Gastroenterology (Drossman and Hasler 2016), updating the typical definitions and treatments of FGIDs. The full list of pediatric FGIDs is seen in Table 10.4. Here we will focus on functional diarrhea, functional constipation and functional abdominal pain.

Table 10.4 Pediatric functional gastrointestinal disorders

G. Childhood functional GI disorders: neonate/toddler
G1. Infant regurgitation
G2. Rumination syndrome
G3. Cyclic vomiting syndrome (CVS)
G4. Infant colic
G5. Functional diarrhea
G6. Infant dyschezia
G7. Functional constipation
H. Childhood functional GI disorders: child/adolescent
H1. Functional nausea and vomiting disorders
H1a. Cyclic vomiting syndrome (CVS)
H1b. Functional nausea and functional vomiting
H1b1. Functional nausea
H1b2. Functional vomiting
H1c. Rumination syndrome
H1d. Aerophagia
H2. Functional abdominal pain disorders
H2a. Functional dyspepsia
H2a1. Postprandial distress syndrome
H2a2. Epigastric pain syndrome
H2b. Irritable bowel syndrome (IBS)
H2c Abdominal migraine
H2d. Functional abdominal pain—NOS
H3. Functional defecation disorders
H3a. Functional constipation
H3b. Nonretentive fecal incontinence

Table adapted from Drossman and Hasler (2016)

Neonate/Toddler Functional GI Disorders

Functional symptoms in infants and toddlers can be a result of normal development, as in the case of infant regurgitation, or it can be a "maladaptive behavioral response to an internal or external stimuli", as in the case of functional constipation. Young children cannot distinguish between emotional and physical distress, and both can result in similar behavior. Because young children are unable to express themselves clearly, physicians must rely on caregiver's history and clinical insight for diagnosis and treatment. For this reason, in the management of functional disorders, it is of the outmost importance that clinicians develop a trusting relationship between the caregivers and themselves. Conversations should include the assessment of family dynamic and inquiry on how disruptive the FGID is to the family relationship. Treatments and interventions should certainly be targeted to the child, but should also consider and attend to the family as well.

Functional Diarrhea

Diagnostic criteria for functional diarrhea are in Table 10.5. Physiologically, children with functional diarrhea maintain normal hydration, electrolyte balance and glucose absorption, and there is no steatorrhea (Milla et al. 1978). Etiology is typically nutritional: overfeeding, excessive fruit juice intake, excessive fructose intake, low fat diet, and/or excessive sorbitol intake. Stools can become progressively less formed throughout the day and may have undigested food or

Table 10.5 Diagnostic criteria for functional diarrhea

Must include all of the following:
1. Daily painless, recurrent passage of 4 or more large, unformed stools
2. Symptoms last more than 4 weeks
3. Onset between 6 and 60 months of age
4. No failure to thrive if caloric intake is adequate

Table adapted from Benninga, et al. (2016)

mucous. If the patient is growing well, malabsorption is unlikely. No specific treatment is indicated other than reassurance (Benninga et al. 2016).

Functional Constipation

Functional constipation (FC) is the result of a child having repeated voluntary attempts to withhold feces in an attempt to avoid defecation due to a fear. The fear can be due to a previous discomfort, pain, or other negative experience associated with defecation (Tabbers et al. 2014). In children, one episode of painful stool due to a diet change can be the initial negative experience that can result in withholding in the future. Continued retention of feces in the colon results in continued water absorption from the stool causing the fecal matter to become harder and more painful to evict. Diagnostic criteria for FC are listed in Table 10.6.

Differential diagnosis for FC in childhood should include anatomical obstruction, Hirschsprung's disease, spinal problems, metabolic and neuroenteric abnormalities. Hirschsprung's disease should be suspected in those infants that did not pass meconium passage in the first 24 h of life. Barium enemas may be unhelpful until after 4–6 weeks of life and colonic distention has taken place. Rectal suction biopsy is the gold standard for diagnosis although anorectal manometry is sometimes appropriate if extreme short segment Hirschsprung's disease is suspected (Benninga et al. 2016).

Treatment for FC should include education of the caregivers, reassurance, and implanting interventions early when symptoms start. Duration of treatment can be months to years in certain situations. Pharmacological treatments should include stool softeners such as polyethylene glycol, lactulose or milk of magnesia. Stool softners will soften the actual stool making it less painful for the child. Over time, the goal would be to minimize the discomfort and normalize defecation for the child. Although these medications are commonly prescribed in children, there is no large well-designed randomized trial studying these interventions. Additionally, no randomized control studies exist that study dietary supplement or laxatives in infants and toddlers (Benninga et al. 2016). However, laxatives such as senna, are frequently added in combination with stool softners. There is all together limited data on probiotics in children. Reports evaluating cow milk allergy causing constipation have been inconsistent with conflicting data (Iacono et al. 2006; Kiefte-de Jong et al. 2010). It is reasonable to consider a 2–4 week trial of hypoallergenic formula in infants and toddlers in whom laxative treatment failed (Tabbers et al. 2014). Behavior techniques such as strict toilet training should be avoided due to potential to cause additional anxiety. For preschoolers, reward system with "stars" can work to provide incentive.

Table 10.6 Diagnostic criteria for functional constipation

Must include 1 month of at least 2 of the following in infants up to 4 years of age:
1. 2 or fewer defecations per week
2. History of excessive stool retention
3. History of painful or hard bowel movements
4. History of large-diameter stools
5. Presence of a large fecal mass in the rectum.
In toilet-trained children, the following additional criteria may be used:
1. At least 1 episode/week of incontinence after the acquisition of toileting skills
2. History of large-diameter stools that may obstruct the toilet

Table adapted from Benninga, et al. (2016)

Functional Disorders of Childhood and Adolescence

Functional Nausea and Functional Vomiting

Functional Nausea and Vomiting are new diagnoses that present in the Rome IV criteria. Diagnostic criteria are listed in Table 10.7. Their inclusion was based on clinical experience with having patients complaining of these symptoms without underlying pain that would otherwise make the diagnoses of functional dyspepsia. These patients may experience autonomic symptoms such as dizziness, sweating, pallor and tachycardia. Postural orthostatic tachycardia

Table 10.7 Diagnostic criteria for functional nausea and vomiting

H1b1. Functional nausea
Must include all of the following fulfilled for the last 2 months:
1. Bothersome nausea as the predominant symptom, occurring at least twice per week, and generally not related to meals
2. Not consistently associated with vomiting
3. After appropriate evaluation, the nausea cannot be fully explained by another medical condition
H1b2. Functional vomiting
Must include all of the following:
1. On average, 1 or more episodes of vomiting per week
2. Absence of self-induced vomiting or criteria for an eating disorder or rumination
3. After appropriate evaluation, the vomiting cannot be fully explained by another medical condition

Table adapted from Hyams et al. (2016)
[a]Criteria fulfilled for at least 2 months before diagnosis

should be considered during the workup. Additionally, anatomical variations (such as malrotation), gastroparesis, and pseudo-obstruction should also be considered and evaluated for if necessary. Electrolytes, calcium, cortisol and thyroid hormone levels should all be evaluated. Psychological evaluations are important in these children (Hyams et al. 2016).

There is no established treatment for patients with nausea and vomiting. Cognitive behavioral therapy and/or hypnotherapy can be helpful. Cyproheptadine has been shown to be helpful in functional dyspepsia with nausea. Gastric electric stimulation can be considered in severe cases under the guidance of a specialized neurogastroenterologist (Benninga et al. 2016).

Functional Abdominal Pain Disorder and Irritable Bowel Syndrome

Previously known as "abdominal pain related functional gastrointestinal disorder" the term has now been changed to "functional abdominal pain disorders". There is emphasis to use specific names to differentiate between various functional disorders (Table 10.4) and to acknowledge that more than one functional disorder may occur at the same time (Hyams et al. 2016).

Irritable bowel syndrome is a type of functional abdominal pain disorder and it is divided into diarrhea predominant, constipation predominant, constipation and diarrhea predominant, and unspecified. Diagnosis criteria are in Table 10.8. For patients with constipation and abdominal pain, it is recommended to treat constipation first. If there is continued discomfort, then patient should be treated for irritable bowel syndrome—constipation predominant (Hyams et al. 2016).

Etiology for IBS is still thought to be a disease of the brain gut syndrome. Sensitizing medical events such as abdominal distention, inflammatory processes (infections and allergies), and motility problems superimposed with a potential genetic predisposition can lead to changes in pain processing and develop visceral hypersensitivity. Visceral hypersensitivity in combination with sensitizing psychosocial events such as depression, family stressors, coping problems and secondary gains can all lead to abdominal pain and other gastrointestinal complaints (Iovino et al. 2009; Saps et al. 2009). During evaluation of IBS, other pathologies causing a mucosal disease and/or malabsorption should be considered. Alarm symptoms listed in Table 10.9 should be warrant further investigation for etiologies such as celiac, inflammatory bowel disease, and other (Hyams et al. 2016). Fecal calprotectin is being used increasingly to evaluate for mucosal inflammation that is commonly present in patients with

Table 10.8 Diagnostic criteria for irritable bowel syndrome

Must include all of the following:
1. Abdominal pain at least 4 days per month associated with one or more of the following:
(a) Related to defecation
(b) A change in frequency of stool
(c) A change in form (appearance) of stool
2. In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not irritable bowel syndrome)
3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

Criteria fulfilled for at least 2 months before diagnosis
Table adapted from Hyams et al. (2016)

Table 10.9 Potential alarm features in children with chronic abdominal pain

Family history of inflammatory bowel disease, celiac disease, or peptic ulcer disease
Persistent right upper or right lower quadrant pain
Dysphagia
Odynophagia
Persistent vomiting
Gastrointestinal blood loss
Nocturnal stools
Arthritis
Perirectal disease
Involuntary weight loss
Deceleration of linear growth
Delayed puberty
Unexplained fever

Clinical judgment should be exercised, putting what might be considered an alarm sign into the whole context of the history and physical exam
Table adapted from Hyams and Di Lorenzo Gastro; 1456–1468

inflammatory bowel disease (Henderson et al. 2012).

There are few randomized control studies for IBS. However, there is evidence to try probiotics (Zhang et al. 2016), peppermint oil (Pittler and Ernst 1998; Grigoleit and Grigoleit 2005; Khanna et al. 2014), FODMAP (Fermentable, Oligo-, Di, Mono-saccharides And Polyols) diet (Halmos et al. 2014). In addition to pharmacotherapy and food interventions, cognitive behavior therapy, relaxation techniques, biofeedback and hypnotherapy have all been found to be helpful (Bursch 2008).

Functional Constipation

Functional constipation in childhood and adolescents is similar to that in toddlerhood. As in the younger child, the triggering event is frequently a painful experience with defecation or social occurrences that become more meaningful at this age. Repeated withholding leads to continued absorption of water from the feces while they are in the colon and thus resulting in a hard stool mass. This mass becomes more painful to pass and causes a continued cycle of withholding due to the associated pain (Hyams et al. 2016).

Diagnosis of constipation should ideally be made by history and physical exam. Digital rectal exam are frequently, but not always useful in evaluations degree of stool burden in the rectum. Regular abdominal x-rays should be avoided except in those patients where physical exam and history are not sufficient. Barium enemas should not be used early in the evaluation process. Laboratory screening with hypothyroidism, celiac and hypercalcemia are not indicated without other concerning symptoms (Hyams et al. 2016).

Treatment should comprise of rectal disimpaction and then a routine regiment to avoid reaccumulation. Disimpactions can either be done by large amounts of polyethylene glycol or rectal enemas. Routine regiments should include small amounts of polyethylene glycol as a stool softener and/or a stimulant such as Senna. Unfortunately, those children that suffer with fecal incontinence require long term follow up without always full resolution of symptoms (Hyams et al. 2016). At 2 year follow up, 29% of patients with fecal incontinence were free of soiling at 2 years following intensive therapy (Tabbers et al. 2014). High fiber diets have not been shown to improve constipation.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is an emerging inflammatory condition of the gastrointestinal (GI) tract in children that includes Crohn's disease (CD) and ulcerative colitis (UC). UC and CD are grouped together as they have similar epidemiology, immunologic, genetic, clinical features and diagnostic features but they differ in treatment and prognostic approach. In this section, we will use a common IBD approach where appropriate but differentiate CD from UC wherever necessary.

Epidemiology

Worldwide, population studies show that IBD is unevenly distributed with the highest disease rates occurring in developed nations like Europe and North America (Lashner 1995; Lakatos

2006). However recent many small series on IBD epidemiology published form Asia, Eastern Europe and South America show increased incidence. Data published from Canada and United Kingdom show an increased incidence of IBD in second and third generation immigrants especially from South Asia. Based on few systematic, population- based studies the incidence of IBD in the pediatric population is estimated to be around 7–12 per 100,00 children in North America (Kugathasan et al. 2003). IBD in children differs from adults with more cases seen among males patients and CD comprises about 2/3 of all new IBD diagnosis, where as in adults prevalence of CD and UC are equal (Perminow et al. 2006).

Pathophysiology

The underlying etiology of IBD is not well understood. Environmental, genetic, microbial and immune factors have been proposed as underlying causes (Oliva-Hemker and Fiocchi 2002). Over 200 genetic loci have been discovered that are linked to IBD suggesting an underlying genetic component, yet the changing epidemiology of IBD implies that, in addition to genetic susceptibility for disease, environmental triggers such as diet and commensal microbiota signatures may likely impact disease presentation and ultimate phenotypic expression.

Clinical Presentation

UC and CD are both chronic inflammatory diseases of the gastrointestinal tract with periods of remission and flares. Although UC and CD share many similarities, they each have distinguishing characteristics depending on location of involvement, disease extend and extra intestinal manifestations (Baldassano and Piccoli 1999). In UC, inflammation is continuous starting in the rectum and extending proximally to varying extents and this inflammation only involves mucosa of the colon. In contrast, CD typically exhibits transmural inflammation and can be located anywhere in the GI tract, from mouth to anus. Additionally, inflammation in CD is often patchy which can be helpful in distinguishing UC from CD. The most common site of involvement for Crohn's disease is the terminal ileum but more than 2/3 pediatric patients have some colonic involvement and up to 10–15% have only colonic disease. In approximately 10% of cases it is difficult to distinguish UC from CD and these patients are diagnosed with "indeterminate colitis".

The most common presentation of UC is diarrhea, rectal bleeding and abdominal pain while CD is more likely to present with more subtle and varied abdominal pain, diarrhea, poor appetite, and weight loss. The insidious onset and nonspecific presentation can often cause a delay in the diagnosis of CD.

Abdominal pain is the single most common presenting symptom in IBD, but may have several other less obvious presentations such as growth failure, anemia, arthralgias and rashes without notable GI symptoms (Fish and Kugathasan 2004; Heuschkel et al. 2008). Knowing the varied presentations of IBD can aid in early referral and initiation of treatment (see Table 10.10).

Extra-intestinal Manifestations

Although usually more rare, many extra-intestinal manifestations have been reported in the literature. Up to 25–30% of patients exhibit extra-intestinal manifestations that cause varying degree of morbidity and mortality. The exact etiology of these conditions is unknown but autoimmune reactions, induction of immune complexes and inflammatory response, and genetic factors are all postulations. Extra-intestinal manifestations can correlate with GI symptoms but some will be present even in GI remission. The most common extra-intestinal manifestations are listed in Table 10.11.

Evaluation

If IBD is suspected, laboratory tests that should be ordered to include complete blood count

Table 10.10 Potential "red flags" on history and exam suspicious for inflammatory bowel disease

History	Physical exam
Abdominal Pain	Pallor/anemia
Distant from umbilicus	
Interferes with sleep	
Discrete, acute episodes	
Precipitated by eating	
Dysphasia/Odynophagia	
Involuntary weight loss	Decreased growth velocity
Rectal bleeding	Delayed puberty/maturation
Nocturnal stooling	Oral ulcerations
Extra-intestinal manifestations	Abdominal tenderness/mass
Recurrent low-grade fevers	
Erythema nodosum	
Pyoderma gangrenosum	
Joint pain/swelling	
Severe eye pain/ Persistent conjunctivitis	
Unexplained jaundice	
Strong family history of IBD	Perianal fistula/fissures

Table 10.11 Extra-intestinal manifestations of IBD

Extra-intestinal locations	Symptoms
Skin	Erythema nodosum
	Pyoderma gangrenosum
Mouth	Aphthous stomatitis
	Gingivitis
Eye	Uveitis
	Episcleritis
Bone	Spondyloarthritis/axial arthritis
	Osteoporosis/osteopenia
	Finger clubbing
Hepatobiliary	Sclerosing cholangitis
	Chronic hepatitis
	Fatty liver
	Pancreatitis
Blood	Anemia
	Thrombocytosis
Vascular	Thromboembolism
	Deep vein thrombosis
Kidney	Renal calculi (oxalate or uric acid)
	Amyloidosis

(CBC), erythrocyte sedimentation rate (ESR), albumin, aminotransferases, C reactive protein (CRP), iron studies, and stool calprotectin. The four lab tests that are most commonly abnormal and good indicators of the presence of IBD are the elevated ESR (>20 mm/h) or CRP, thrombocytosis (>400,000), decreased albumin level (2.0–3.5 g/dL), and decreased haemoglobin level indicating iron deficiency anemia. If any of these labs are abnormal, referral to a specialist should be made in a timely manner so that the diagnosis is confirmed with further work up (Mack et al. 2007).

Serologic markers such as anti-Saccharomyces cervisiae (ASCA), pANCA (anti-neutrophil cytoplasmic antibodies), antibody to outer membrane protein (Anti-OmpC) and others are used by few clinicians to identify IBD subtypes in cases where there is a significant overlap in the results after conventional diagnostic work up. Currently there is no sufficient evidence in use of these serological markers for therapeutic strategies or monitoring treatment response of IBD patients (Zholudev et al. 2004).

The diagnosis of inflammatory bowel disease is dependent on endoscopic, histological, and radiological findings. Radiography is necessary at diagnosis to determine extent of disease, location of disease, and severity. In the past, upper gastrointestinal series (UGI) with small bowel follow through was the "gold standard". However, technology has made great strides in the last

decade and other modalities like magnetic resonance imaging (MRI) and computed tomography scans (CT) are now standard of care with pelvic MRI the imaging modality of choice for perianal disease (Sauer et al. 2016). Most children with IBD receive multiple radiological exams throughout their life, increasing their lifetime exposure, making MRI especially promising in the pediatric population because of the lack of ionizing radiation (Fig. 10.2).

Video Capsule Endoscopy (VCE) has been a crucial addition in imaging in IBD. VCE allows small bowel visualization with no radiation and is well tolerated in the pediatric population. In most cases it requires no sedation; in the young/small child endoscopy may be necessary to place the capsule in the small bowel via endoscopy but in larger/older children this is not necessary. This technology has made evaluation of the small bowel more sensitive and can aid in diagnosing suspected IBD and distinguishing between UC and CD.

Endoscopy with biopsy is the most sensitive and specific evaluation of the colon and terminal part of ileum for evidence of IBD. Endoscopy aids in diagnosing IBD, differentiating between UC and CD, and assessing extent and severity of disease. After diagnosis, it is used to monitor response to therapy (mucosal healing), for cancer surveillance, and to perform therapeutic procedures, such as stricture dilatation (Beattie et al. 1996). Several studies showed that performing an esophagogastroduodenoscopy during the work-up for pediatric IBD resulted in higher rates of confirming a diagnosis and is now considered standard practice. Macroscopic findings may include patchy or continuous inflammation, ulcerations, nodularity, and strictures (Fig. 10.3).

Histology

Combined together with macroscopic appearance of the mucosa, biopsies aid in the diagnosis of IBD and differentiation between UC and CD. During endoscopy and colonoscopy,

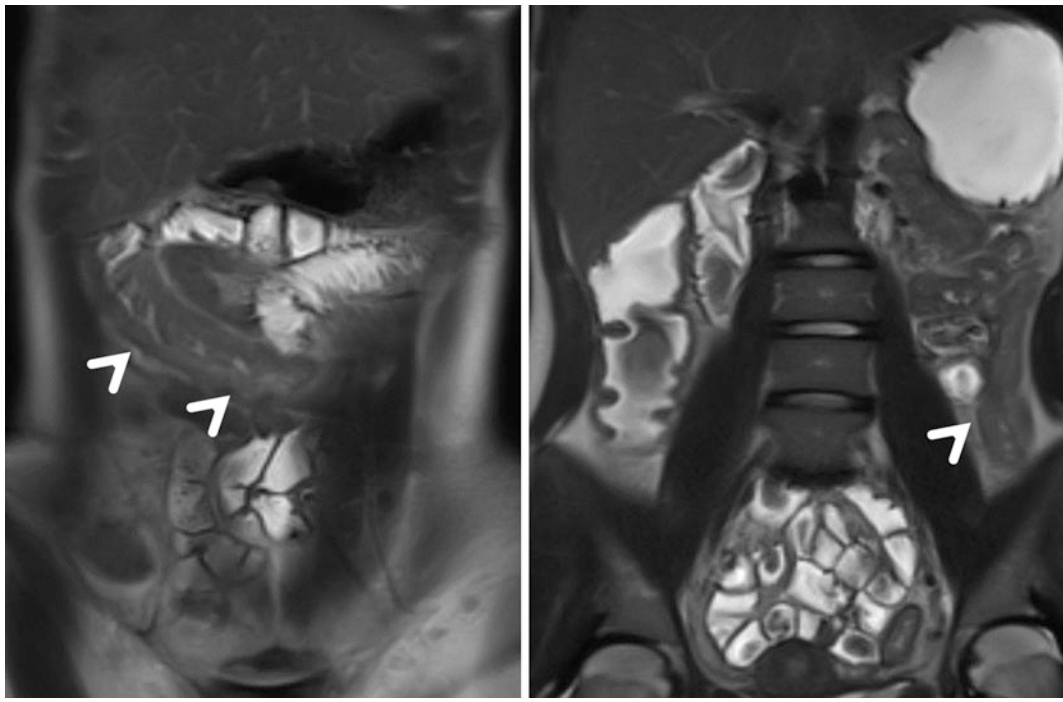

Fig. 10.2 MRE of patient with Ulcerative Colitis. MRE of ulcerative colitis—sequential coronal T2 weighted showing thickened transverse colon and featureless thick walled descending colon

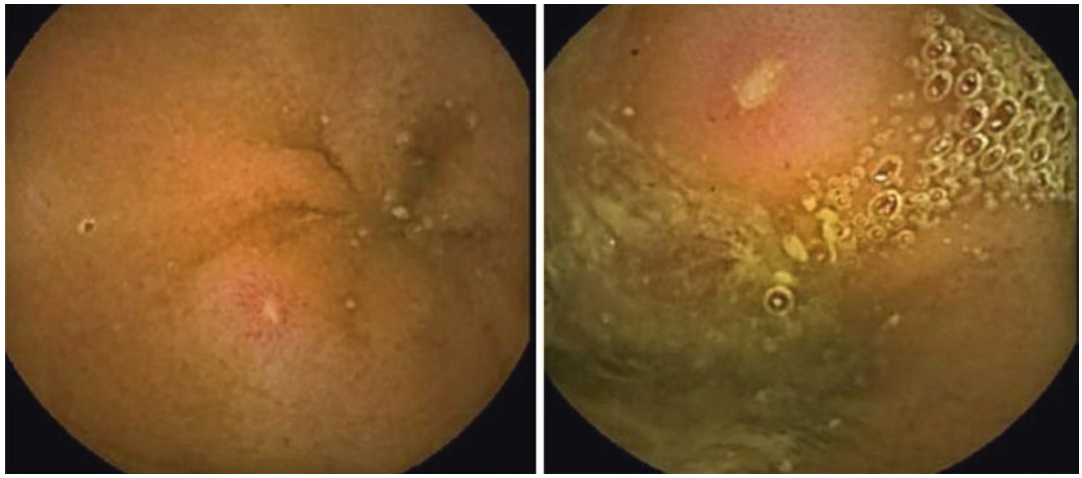

Fig. 10.3 Video capsule endoscopy images of ulcers in the small bowel suggestive of Crohn's disease. Video capsule endoscopy showing large ulcers with erythematous base in the small bowel of a patient with CD

biopsies are usually obtained from all areas, even in the absence of obvious lesions because histological abnormalities, sometimes granulomas, can be present in biopsies of "normal" appearing tissue. Certain histological findings are helpful in confirming an IBD diagnosis and distinguishing between UC and CD. Presences of noncaseating granulomas are pathognomonic for CD; however, 60% of the times biopsies will not show granulomas and the diagnosis is made based on radiological, histological, or endoscopic findings.

Management

Before the year 2000 the main therapy was corticosteroids, with few other options. Currently classes of drugs used to treat IBD include amino salicylates, immunomodulators and biologics. These classes have allowed practitioners to greatly decrease their dependence on steroids. There is a recent increased focus on IBD pathways and genetics which will ideally allow focussed targeting of disease pathways in the future with hopes that such targeting will lead to better outcomes with fewer adverse effects. Many treatment medications overlap between UC and CD but there are some clear indications that differ.

Corticosteroids

Corticosteroids still remains the main therapy for the induction of remission in moderate to severe CD and UC by providing rapid improvement of inflammation (Beattie et al. 1996). There is not much evidence to suggest that they provide mucosal healing, hence they should not be used as maintenance therapy. They are typically started along with a maintenance therapy to induce remission; while the maintenance drug takes effect, the steroids are gradually weaned. IV steroids can be used in severe UC and CD to induce remission. Rectal steroid enemas can be used for proctitis and sigmoid disease with no systemic side effects (Wang et al. 2016). The other formulations of steroids like oral budesonide, which has first pass metabolism, can be used to minimize systemic adverse effects. Systemic steroids have many adverse effects in children, particularly the effects on growth, immunity and adrenal suppression. For these reasons, plus lack of efficacy in maintenance of remission and mucosal healing in IBD, they should be used only as short period of time, ideally less than 3 months.

Aminosalicylates

Aminosalicylates (ASAs) are a wide group of medications that all contain a 5-aminosalicylate (5-ASA) moiety. These medications have shown to be effective in induction and maintenance of

remission in mild to moderate UC and are the first line of therapy in these cases (Wang et al. 2016). They may also have some benefit in maintenance of remission in mild CD. Because ASAs have varying delivery systems which determine the segment of bowel targeted, it is imperative to understand disease location prior to initiation of this therapy. In general these therapies are well tolerated. Main adverse effects are headache and rash: rare but serious side effects include pancreatitis, hepatitis, colitis and low sperm count in males.

Immunomodulators

Azathioprine and its metabolite 6-mercaptopurine (6-MP) are primarily used for steroid refractory CD and as maintenance of remission in moderate to severe UC and CD (Markowitz et al. 2000; Hyams et al. 2007; Turner et al. 2011). These drugs are not used in the induction of remission because they act slowly and may take up to 3 months to reach maximal effect. Most often they are started in conjunction with steroids in moderate to severe disease and when used in this way can minimize the steroid use. Adverse effects of these drugs are idiosyncratic and dose dependent. Idiosyncratic adverse effects are pancreatitis, fevers, and myalgias. Dose dependent adverse effects include infection, bone marrow suppression, and elevated liver enzymes (Kirschner 1998). Patients must be monitored for these side effects.

Methotrexate has shown to be effective in inducing and maintaining remission in adult patients with CD (Turner et al. 2011). So far, there have been no controlled trials of methotrexate use in paediatric CD but reports from retrospective reviews have shown good remission rates in patients that fail 6-MP or are intolerant to azathioprine. Methotrexate is a known teratogen, so birth control counselling must be given to all females of childbearing age who are started on this therapy.

Biologic Therapies

Biologics have revolutionized the treatment and management of IBD dramatically. One class of these drugs is the anti-tumour necrosis factor alpha (TNF alpha) agents. TNF alpha is a cytokine involved in systemic inflammation and can stimulate the acute phase reaction. Infliximab blocks the action of TNFα by preventing it from binding to its receptor in the cell and was the first in this class to be approved in paediatric IBD. This biologic is used in children with moderate to severe UC and CD (Hyams et al. 2007; Turner et al. 2011). Infliximab is also effective in fistulising and perianal CD (Bernstein et al. 2010). Since infliximab is chimeric, it can cause formation of antibodies against the drug and decrease efficacy. The most common adverse effects for infliximab include infusion reactions, infections, and ALT elevations. Infusion reactions are usually mild and respond to antihistamine therapy.

Another anti-TNF agent, adalimumab, has been approved for treatment of IBD in adults and recently approved for paediatrics CD (Sandborn et al. 2012). Adalimumab has decreased occurrence of antibody formation and is given as a subcutaneous injection. Biologic therapies can reactivate latent *Mycobacterium tuberculosis* and all patients must have a documented negative PPD or quantiferon gold before starting therapy. Other more serious complications with anti-TNF drugs are increased risk for malignancy. Infliximab has a black box warning regarding hepatosplenic T-cell lymphoma (Kotlyar et al. 2011), which is a rare and often fatal T-cell lymphoma that has been reported in approximately 12 US cases. All patients had IBD and predominantly were young males. All these patients had received infliximab in conjunction with azathioprine and/or 6-mercaptopurine. For this reason, these agents should not be used concurrently in young males, until other options are exhausted and the benefits outweigh the risks. Other malignancies that have been associated with anti-TNF agents include lymphoma and leukaemia.

Surgical Management

IBD first line treatment remains medical therapy. Indications for surgery are relatively similar between ulcerative colitis and Crohn's disease, however, the approach and the outcomes differ. Indications for surgery include fulminant colitis,

massive haemorrhage, perforation, stricture, abscess, fistula (in Crohn's disease), toxic megacolon, failure of medical therapy, steroid dependency, and dysplasia. Additional indications for surgery in paediatric patients include growth and pubertal delay as children often demonstrate post operative catch up growth.

The current standard surgical procedure for UC is total colectomy followed by ileoanal pull-through with anal anastomosis (IPAA) (Tilney et al. 2006). The majority of patients with Crohn's disease will need surgery during their life, although this number is decreasing due to advances in medical therapy. As recurrence rates of CD are very high within 5 years of surgery the aim of the surgery is to resect as little bowel as possible. This is also the reason CD is a relative contraindication to IPAA.

Outcomes

IBD is a relapsing disease that has high morbidity but low mortality. Most children with IBD lead active normal lives, with no limitations. However, patients with IBD are at increased risk for some malignancies. In UC the greatest risk is colonic dysplasia/cancer. The risk has been estimated to be up to 25% after 30 years of disease. Risk factors for development of colorectal cancer in UC patients are long duration of disease, early onset, chronic inflammation, family history of colorectal cancer, and primary sclerosing cholangitis. Patients with colonic CD share the same risk factors as UC patients. CD patients are known to have slight increased risk of lymphoma over their lifetime.

Nutrition

One primary area of progress in pediatric nutrition has been a unifying effort to define pediatric malnutrition better. The World Health Organization (WHO) defines malnutrition as "the cellular imbalance between the supply of nutrients and energy and the body's demand for them to ensure growth, maintenance, and specific functions" (de Onís et al. 1993). In pediatric children, the repercussion of malnutrition can be profound because of child's need for growth and development (Mehta et al. 2013). International studies have linked malnutrition to majority of childhood deaths in developing countries (Pelletier et al. 1993, 1995). However, in developed countries, there is less precise data. One problem has been a lack of unifying definition. The American Society of Parenteral and Enteral Nutrition (A.S.P.E.N) working group put forth guidelines to use five domains to help define malnutrition. The five domains include anthropometric parameters, growth, chronicity of malnutrition, etiology and pathogenesis, and developmental or functional outcomes (Fig. 10.4) (Mehta et al. 2013).

Anthropometric measurements should include a weight, height, body mass index (BMI) (for children 2 years and older) and mid arm circumference (MAUC) on admission to a hospital. Triceps skin fold (TSF) and mid-arm muscle circumference (MAMC) measurements can be considered. Serial measurements should be collected throughout an admission and plotted on appropriate growth charts. Head circumference should be measured for children under age 2 years. Ideally a single trained individual would be doing these measurements. Children under age 2 should have their lengths measured lying down on a length board. For older children that cannot stand, tibia lengths, knee height and/or arm span can be used. Infants and young children should be weighted with minimal clothing. Children that cannot be moved should be weighed in beds with special technology especially designed for this. Because using the proper growth chart is important, children under 2 years should be plotted on the WHO growth chart. The CDC growth chart should be used for children 2–20 years. Premature children should have their corrected age used while plotting their growth up until age 3 years. Z-scores should be used to express individual variables in relation to the population (Mehta et al. 2013).

Growth should be assessed with dynamic changes in weight and length velocity over time. A decline in the z-score by more than 1 can be an indication of failing growth. Once growth failure is established, etiology and interventions should

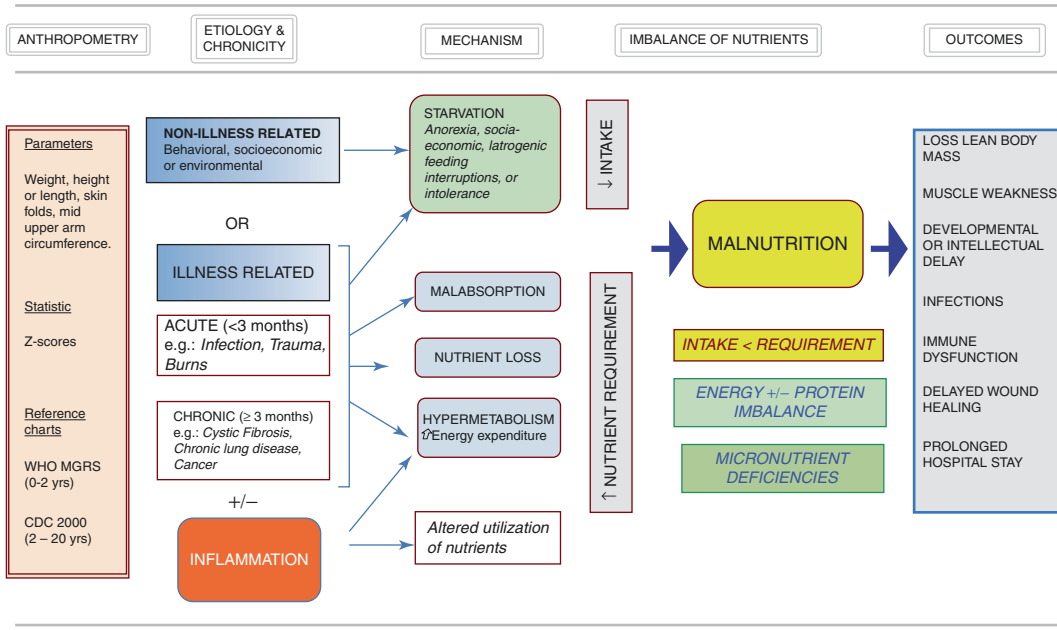

Fig. 10.4 Defining malnutrition. Adapted from Mehta et al. (2013)

be discussed and interventions provided based on the diagnosis. Chronicity of malnutrition needs to be established. Children with malnutrition for less than 3 months are considered to have acute malnutrition. Malnutrition for 3 or more months is considered chronic. Chronic malnutrition can be characterized by stunting, which may be irreversible and may present before 3 months if the degree of malnutrition is severe (Mehta et al. 2013).

If a disease process is directly responsible for malnutrition, it should be identified. Additionally, the mechanism(s) leading to malnutrition should be described. For example, if the malnutrition is due to decreased intake/starvation, increased requirement, excessive losses or failure to absorb. Because inflammation can increase the need for calories and decrease the bioavailability of nutrition, inflammatory makers should be measured when they are applicable. Development is a critical part to all pediatric patients. Developmental assessment should be considered in patients with chronic malnutrition. Muscle mass measurements should also be done via anthropometric measurements or body composition measurements. Measures of muscle strength are important but are not always uniform or reproducible with physical exams (Mehta et al. 2013).

Intestinal Rehab and Short Gut Syndrome

Definition and Pathogenesis

Intestinal failure results when patients cannot depend on their intestines to maintain protein-energy, fluid, electrolyte or micronutrient balance. This can be the consequence of obstruction, dysmotility, congenital defects, diseases associated with loss of absorption, or surgical resection resulting in short gut syndrome (O'Keefe et al. 2006). More recently, other definitions have been suggested, including measurements of fecal energy loss, amount of parenteral nutrition needed for growth, and amount of functional remaining gut mass, however measurements are still in early stages and not accepted clinically (Ruemmele et al. 2006). While short gut syndrome as a consequence of necrotizing enterocolitis in infancy has historically been the most common cause of intestinal failure in pediatric

patients, gastroschisis is now becoming a more common diagnosis (Fig. 10.5). However, many patients continue to have multiple underlying factors contributing to their intestinal failure making them have a spectrum of underlying pathologies to address (Fig. 10.6).

General Management Approach

Management of intestinal failure individuals needs to be centered to the underlying pathogenesis and cause of intestinal failure. In most cases of short gut syndrome and dysmotility, efforts need to be centered to promote gut adaptation or process by which the residual bowel increases absorption of fluids, electrolytes and nutrients to compensate for the loss of functional bowel. Structural adaptation should occur by which the absorptive area physically increases in size. Functional adaption should occur as the intestine slows the transit of time to allow for more absorption (Thompson et al. 2011). Adaptation will be promoted by maximizing general nutrition and enteral exposure to complex nutrients and minimizing infections. Adaptation in infants is maximized in the 3–4 years after bowel resection. For this reason, it is important to maximize parenteral nutrition to have overall growth, encourage gut exposure to nutrition, and minimize central line infections, which these patients are at increased risk for.

Parenteral Nutrition Management

Parenteral nutrition should be managed carefully by experienced individuals. Ideal growth should be maintained at approximately the 25th percentile. Multidisciplinary teams are ideal for this oversight to provide maximal input in ordering proper components. Intravenous drug shortages are common and require expertise in maneuvering the various components in parenteral nutrition to least affect the patient. In general there have been few new additions to be able to add to

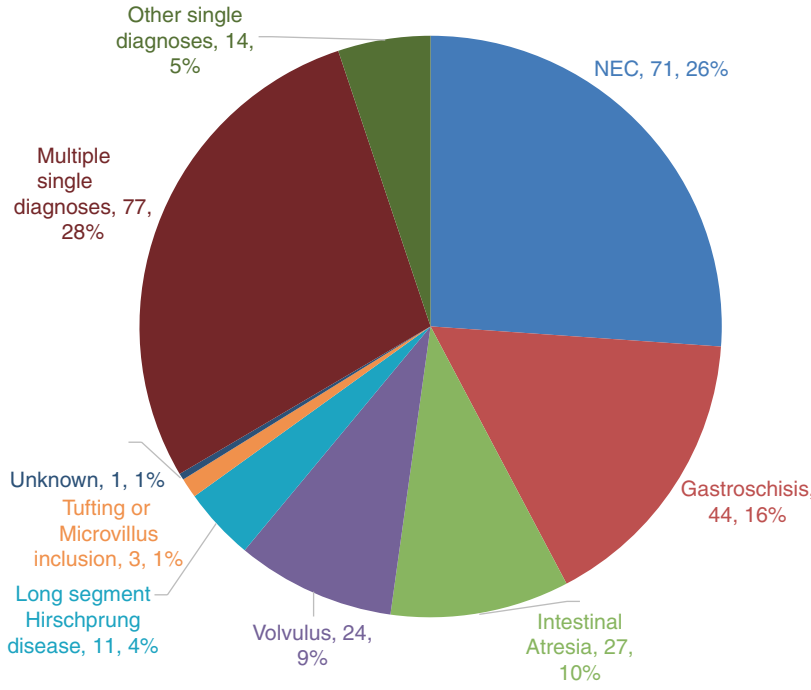

Fig. 10.5 Primary diagnosis of patients with intestinal failure. Primary diagnoses of patients with intestinal failure from the pediatric intestinal failure consortium (N = 272) (Adapted from Squires et al. (2012)

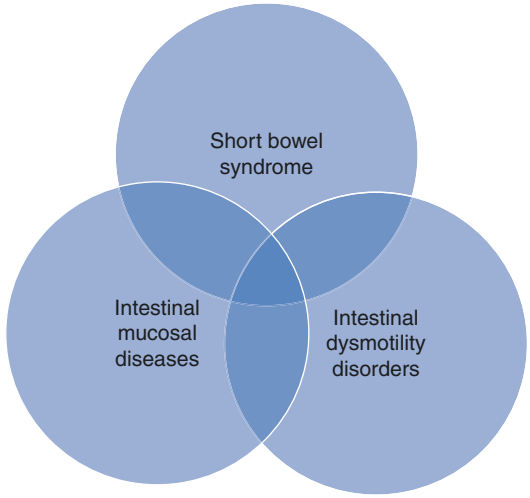

Fig. 10.6 Underlying causes of intestinal failure. Spectrum of underlying causes that cause intestinal failure in pediatric patients. Examples of short bowel syndrome include consequences of surgical resection due to congenital defects and necrotizing enterocolitis. Examples of intestinal mucosal disease include microvillus inclusion disease, tufting enteropathy, autoimmune enteropathy. Examples of Intestinal dysmotility include chronic internal pseudo obstruction syndrome. Hirschsprung's disease can be a dysmotility disorder but also result in short gut syndrome based on the extent of bowel involved. Aggressive Crohn's disease may result in surgical short bowel syndrome along with intestinal mucosal disease

parenteral nutrition in the recent past. Best advances have been in understanding how to best utilize the components of parenteral nutrition that we have.

As an example, over the last 10 years new insight has been made in how to utilize soy based lipids in parenteral nutrition. Parenteral nutrition associated liver disease (PNALD) is one of the most worrisome complications of chronic parenteral nutrition and lipid minimization of soy based oil emulsions to 1 or 0.5 mg/kg/day has been shown to decrease PNLD. Long-term studies are still needed to determine the final outcome of patients receiving lipid minimization. Extreme lipid minimization may precipitate essential fatty acid deficiencies and this should be monitored for by the triene to tetrane ratio. By decreasing the amount of lipid in parenteral nutrition, dextrose quantities have needed to be increased to compensate for the calories. Unfortunately, high concentration of dextrose, which may also be hepatotoxic over time, and GIR is recommended to be maintained below 15 mg/kg/min. For this reason, there must be closer attention to patient's clinical changes in adjusting the parenteral nutrition.

Fish oil based lipid infusions are not available outside of clinical trials in the United States. However, in countries where it is available, the preparation is also known to prevent PNALD. More longitudinal studies are needed, but there is current evidence showing similar results of preventing liver disease as in lipid minimization.

In addition to macronutrients, micronutrient must also be carefully tracked. Despite having micronutrients added directly to parenteral nutrition, Yang et al. (2011) showed that 50% of patients still experience micronutrient deficiencies with copper, iron and selenium being among the most common deficiencies. Regular micronutrient monitoring should take place for any patient on chronic parenteral nutrition.

Enteral Nutrition Management

No consensus exists on types of formulas that would be most appropriate for infants with intestinal failure. In general, consideration needs to be placed on the remaining gut and degree of functionality of the remaining gut. Increased exposure to enteral nutrition is known to improve adaptation by stimulating hyperplasia, promoting peristalsis and stimulates flow of GI secretions and secretion of humoral factors. However, it is not known whether continuous or bolus feeds are best. Breast milk is known to bolster the immune system and contain immunoglobulins, nutrients, hormones and growth factors to help with intestinal growth (Andorsky et al. 2001; Raphael and Duggan 2012). When breast milk is not available, formula should be used. There is no consensus on types of formulas to use but more complex nutrients are associated with improved adherence. Higher Medium Chain Triglyceride formulas have been theorized to improve absorption by bypassing the lymphatics and are able to be absorbed in the colon.

However, they have not shown to decrease time on parenteral nutrition and create a higher osmotic load to patients that could result in increased stooling. Long chain fatty acids are known to produce adaptation better but are less efficiently absorbed (Jeppesen and Mortensen 1998; Raphael and Duggan 2012). Thus formulas must the geared to the individual patient.

Central Access Preservation

Central lines become the lifeline for intestinal failure patients. Preventing central line associated infections (CLABSI) is critical in preserving vascular access. Patients enrolled in multidisciplinary clinics for intestinal failure patients have shown to have lower rates of CLABSI. Ethanol lock therapies have been established as a novel practice associated with decreasing CLABSI. There have been studies that showed increased line breaks with some regiments of ethanol lock therapy, but more studies are needed to understand if this is only seen in higher concentrations or more frequent use of ethanol.

Surgery

Bowel lengthening surgery should be preserved only for the situations when a patient is unable to be advanced in their feeds. The Serial Transverse Enteroplasty procedure is the most common bowel lengthening surgery and could be done in areas of dilated bowel. However, in patients with underling dysmotility disorder such as gastroschisis, outcomes may be guarded since it is dysmotile bowel that is being lengthened. Thus, although the length is increased, the functionality may still be poor.

Transplant

Transplantation for small bowel or dual small bowel and liver are rare in the United States. On average less than 100 occur per year due to advances in careful parenteral nutrition preparation and avoidance of PNALD. Nevertheless, patients should be evaluated if they have limited vascular access, advancing PNALD, or no chance of coming off parenteral nutrition.

Neonatal Cholestasis

Background

Neonatal cholestasis, characterized clinically by the prolonged occurrence of jaundice in the newborn period, is defined physiologically as a decrease in bile formation or flow due to impaired hepatobiliary membrane transport systems or mechanical obstruction of bile flow (Balistreri 1985). The resulting accumulation of biliary constituents within the liver and bloodstream are important pathophysiologic mechanisms implicated in both acquired and hereditary forms of cholestasis. While neonatal jaundice due to unconjugated hyperbilirubinemia is common, affecting up to 84% of term newborns (Kelly and Stanton 1995; Bhutani et al. 2013), and not usually harmful to infants, cholestatic jaundice (conjugated hyperbilirubinemia) must always be considered a pathological state signifying hepatobiliary dysfunction. With an incidence of approximately 1 in 2500 live births (Balistreri 1985), cholestatic liver diseases comprise a rare, yet critical, group of disorders. Left untreated, many of these disorders lead to progressive fibrosis of the liver and, ultimately, cirrhosis. Timely differentiation of neonatal cholestasis from simple unconjugated hyperbilirubinemia is one of the major challenges facing clinicians during the evaluation of the jaundiced infant because in the early stage, the infants can look very healthy except for their jaundice. Early recognition by the primary care provider and prompt referral to a pediatric gastroenterologist who can perform an appropriate diagnostic evaluation to identify the cause may ameliorate potentially catastrophic outcomes related to delayed diagnosis.

Pathogenesis

Decreased canalicular secretion of a broad range of biliary constituents that are normally excreted

into bile and retention of these potentially noxious substances within the liver is the fundamental pathophysiologic defect in all forms of cholestasis (Trauner et al. 1998). These substances include bile salts, glucuronide conjugates (e.g. bilirubin diglucuronide), heavy metals (e.g. copper), inorganic anions (e.g. bicarbonate and chloride), phospholipids, exogenous drugs, and environmental toxins (Boyer 2007). Disturbances of normal hepatobiliary transport and bile composition due to alterations in the uptake, conjugation, or excretion of these compounds result in the formation of "toxic bile" and subsequent hepatocellular and/or bile duct injury (Trauner et al. 1998, 2008). Moreover, retention of bile acids within the hepatocyte cause damage to intracellular membrane component, mitochondrial dysfunction, and hepatocyte cell death by apoptosis and necrosis. Secondary effects of cholestasis result from a deficiency of micelle-forming bile acids within the intestinal lumen that are essential for dietary lipid and fat-soluble vitamin absorption.

Presentation

The hepatic and systemic effects of chronic cholestasis are profound and widespread. Most infants with cholestatic liver disease present during the first month of life with jaundice often the most readily apparent sign of liver disease (Suchy et al. 2002). While jaundice occurs more commonly in the neonatal period than at any other time of life, neonatal jaundice due to a physiological delay in maturation of the bilirubin conjugation pathway or in association with breastmilk feeding is common in the first 2 weeks of life, where as neonatal cholestasis must be considered in any infant who remains jaundiced beyond the age of 14–21 days or who develops jaundice within the first month of life. Pale or acholic stools are the hallmark sign of cholestasis and suggest an obstructive process such as biliary atresia but may not be present with partial or evolving biliary obstruction. The presence of deeply pigmented stools makes biliary atresia unlikely. Parental reports of the stool color often overestimate the degree of pigmentation; therefore, medical practitioners should directly observe the stool (Matsui and Ishikawa 1994). Dark urine (normally colorless in the newborn) is a common non-specific indicator of conjugated hyperbilirubinemia, but is not pathognomonic.

The impact of bile acid deficiency may result in steatorrhea, poor weight gain, or fat-soluble vitamin deficiency from dietary lipid and fat-soluble vitamin malabsorption. Vitamin D deficiency can cause rickets and some infants present with bleeding or bruising secondary to coagulopathy caused by liver failure or vitamin K deficiency. Some causes of neonatal cholestasis have specific abnormalities associated with their underlying etiology, such as dysmorphic facies and congenital heart disease (e.g. Alagille's syndrome), skin lesions and chorioretinitis (e.g. CMV, HSV, toxoplasma), abdominal mass (e.g. choledochal cyst), and hypotonia or abnormal reflexes (e.g. mitochondrial disorders). Hepatosplenomegaly can occur in infants who have storage diseases or cirrhosis. In some cases, progression to end-stage liver disease can cause serious life-threatening complications such as portal hypertension, variceal bleeding, ascites and peripheral edema, or hepatic encephalopathy although these are less common during the neonatal period.

Etiologies

In the 1970s, up to 65% of infants presenting with cholestasis were diagnosed with "idiopathic neonatal hepatitis" (Balistreri 1985). By the turn of the century, improved diagnostic methods and advances in molecular genetics have decreased this category to no more than 15% (Balistreri and Bezerra 2006). Biliary atresia remains the most common cause, consistently accounting for approximately one third of all cases in multiple reports over several decades (Suchy 2004; Balistreri and Bezerra 2006; Hoerning et al. 2014). Various forms of inherited cholestasis syndromes occur in 10–20% of cases. Approximately 10% are caused by alpha1-antitrypsin deficiency. Other inborn errors of metabolism comprise about 20% of all cases. Congenital infections, including the so-called "TORCH" infections, account for only 5% of cases.

Diagnosis

The initial detection of neonatal cholestasis lies in the domain of the primary care provider and depends primarily on the recognition of prolonged jaundice. A thorough physical examination and direct observation of urine color, and, most importantly, stool color, is an essential aspect of the primary assessment of the jaundiced infant, as acholic stool and dark urine often indicate the presence of conjugated hyperbilirubinemia.

To differentiate benign causes of jaundice from neonatal cholestasis, the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition recommend measurement of total and direct (conjugated) serum bilirubin levels if jaundice is accompanied by dark urine or light stool or if it persists beyond 2 weeks of age (American Academy of Pediatrics Subcommittee on Hyperbilirubinemia 2004; Fawaz et al. 2016). Breast-fed infants who can be reliably monitored and who have an otherwise normal history (i.e. no dark urine or light stools) and physical examination may be asked to return at 3 weeks of age and, if jaundice persists, have the serum bilirubin fractionated at that time. Considering the clinical complexity to determine whether or not a direct fraction exceeds a percentage of the total bilirubin level, a direct bilirubin value greater than 1.0 mg/dL, regardless of the total bilirubin level, should be considered abnormal (Rosenthal et al. 1986). Any infant with cholestatic jaundice should be immediately referred to a pediatric gastroenterologist who can conduct a diagnostic evaluation to identify a specific cause.

Of note, ultrasonography is useful to identify anatomic abnormalities such as choledochal cysts. The diagnosis of biliary atresia cannot be made reliably with an ultrasound scan, although the finding of an absent or atretic gallbladder is suggestive.

Management

Prompt identification of infants who have medically treatable forms of cholestasis (e.g. UTI, galactosemia, hereditary tyrosinemia, congenital hypothyroidism) as well as those amenable to surgical intervention (e.g. biliary atresia, choledochal cyst) is crucial to avoid irreversible end-organ dysfunction. The quintessential example is the timing of hepatoportoenterostomy in patients who have biliary atresia. In a recent report from the Japanese Biliary Atresia Registry, the likelihood of success of the Kasai procedure and survival with native liver was highest in children who underwent the procedure in the first 30 days of life (Nio et al. 2003). Even when specific therapy is not available, infants who have cholestasis may benefit from early medical management to prevent long-term complications associated with chronic liver disease. Additionally, advanced experience of the center in caring for complex liver disease in neonates has been shown to correlate with improved outcomes (Kelly and Davenport 2007). Therefore it is imperative that primary care providers identify a center of excellence in order to refer patients in which complex neonatal liver disease is suspected.

Malnutrition secondary to impaired absorption of fats, impaired metabolism of proteins and carbohydrates, and increased hepatic metabolism is common in cholestatic infants and adversely affects their outcome, and should be monitored by frequent anthropometric assessment. Nutritional support and supplementation with fat-soluble vitamins is recommended in all children with cholestasis. Caloric intake should be approximately 125% of the recommended dietary allowance based on ideal body weight (Suchy 2004). If breast feeding does not promote growth, cholestatic infants should receive a formula containing medium-chain triglycerides such as Pregestimil® or Alimentum®, because these triglycerides can be directly absorbed from the small intestine into the portal circulation without requiring modification by bile acids (Fawaz et al. 2016). Specialized infant formula and diets may have a role in select cases (e.g. galactosemia, hereditary fructose intolerance, and hereditary tyrosinemia). For infants with continued poor growth, formulas can be concentrated or have additional carbohydrates or fats added to increase caloric density (Fawaz et al. 2016). Oral feeding is the preferred route of formula intake; however, if patients are unable to

ingest the needed calories, nasogastric tube feeding should be initiated, generally continuous overnight feeding. Parenteral nutrition is rarely necessary; however, if there is severe protein-energy malnutrition, feeding intolerance, and/or malabsorption, provision of parenteral nutrition, in combination with enteral nutrition, improves nutrient delivery and does not invariably worsen cholestasis (Fawaz et al. 2016).

Infants with cholestasis require supplementation with fat-soluble vitamins administered orally as water-soluble preparations (Suchy et al. 2002). Doses of at least 2–4 times the recommended daily allowance are typically required to produce therapeutic plasma concentrations. Serum levels should be routinely monitored to guide dosing. No single multivitamin preparation is adequate for all cholestatic infants; most will need additional vitamins K and E, and many will need vitamins D and A beyond a multivitamin preparation. Occasionally, intramuscular vitamin D is required. Vitamin supplementation should be continued for at least 3 months after resolution of jaundice (Venigalla and Gourley 2004).

Ursodeoxycholic acid (UDCA), a hydrophilic bile acid, has been found to have beneficial effects on many forms of cholestasis. Although its mode of action is not completely understood. UDCA is generally used as first-line therapy for pruritus due to cholestasis, parenteral nutrition-induced cholestasis, α1-antitrypsin deficiency, and after successful surgery for biliary atresia (Dani et al. 2015). The most common side effect is diarrhea, which usually responds to dose reduction. UDCA can be discontinued when cholestasis has resolved. In infants with moderate to severe pruritus due to cholestasis, cholestyramine (240 mg/kg/day), a bile acid sequestrant, or rifampicin (5–10 mg/kg/day) may also be recommended.

Nonalcoholic Fatty Liver Disease

Background

With the rapidly increasing prevalence of childhood obesity around the world, morbidity and mortality related to its complications is on the rise (2000). During the past 30 years, the percentage of children in the United States (U.S.) aged 6–11 years who were obese nearly tripled from 6.5% in 1980 to 17.7% in 2012 (National Center for Health Statistics (US) 2012; Ogden et al. 2014). Over the same time period, the percentage of adolescents aged 12–19 years who were obese quadrupled from 5% to 20.5%. Racial and ethnic disparities exist, with higher rates observed among African-American and Hispanic children compared to Caucasian children and the highest rate for 6–11 year old Hispanic boys (48.7% are overweight or obese).

Concurrent with the national epidemic of childhood obesity, epidemiologic data collected from 1988 to 2010 demonstrate that the prevalence of nonalcoholic fatty liver disease (NAFLD) among adolescents increased in parallel, becoming the most common cause of chronic liver disease in both adults and children in the past decade (Younossi et al. 2011; Welsh et al. 2013). Currently, NAFLD affects approximately 10% of the pediatric population in the U.S., reaching rates as high as 38% among obese children and adolescents (Schwimmer et al. 2006). This represents an estimated seven million children with chronic liver disease who are at increased risk of liver failure, cardiovascular disease, and liver cancer in adulthood.

According to the United Network for Organ Sharing database, nonalcoholic steatohepatitis (NASH)-related cirrhosis was the third most common indication for liver transplantation in patients younger than 65 years of age during the period from 2007 to 2010 (Kemmer et al. 2013). Although most liver transplants were not performed before the age of 18 years, many of these cases were likely the consequence of childhood NAFLD. Due to the alarming trends in childhood obesity and the improved management of chronic viral hepatitis, NAFLD is expected to become the most common indication for liver transplantation in the near future (Charlton et al. 2011). Improving our understanding of the etiopathogenesis of NAFLD, early identification of patients through non-invasive diagnostic methods, and the development of targeted therapies may reduce the burden of disease and eliminate the need for liver transplantation.

Pathogenesis

NAFLD encompasses a broad histological spectrum of disease activity ranging from simple steatosis, which is mostly non-progressive, to NASH, a state characterized by hepatic necroinflammation and/or fibrosis with variable risks for progression to cirrhosis and hepatocellular carcinoma (Adams et al. 2005; Vernon et al. 2011). While the pathogenesis of liver injury remains uncertain, a growing body of literature suggests a role for genetic and epigenetic factors in the development and progression of NAFLD. In the majority of patients, NAFLD is also associated with metabolic risk factors such as insulin resistance and atherogenic dyslipidemia; it is thus considered the hepatic manifestation of the metabolic syndrome (Adams et al. 2005). Although both excessive body mass index (BMI) and central obesity are common and well-documented risk factors for NAFLD, neither is necessary for the development of NAFLD. Familial clustering as well as racial and ethnic differences in the prevalence of NAFLD indicates that genetic factors influence the development and progression of NAFLD, but environmental factors are also likely to influence development and progression as well (Kitamoto et al. 2013).

Knowledge about the natural history and evolution of histologic changes in pediatric NAFLD is still evolving. Based on the currently available evidence from adult natural history studies, patients with simple steatosis exhibit very slow, if any, histologic progression, while approximately 20% of patients with NASH ultimately develop cirrhosis, usually over an average of 21.3 years (Singh et al. 2015). However, NAFLD in children may be more severe compared to that in adulthood and a subset of patients rapidly progress (Molleston et al. 2002; Holterman et al. 2013). Children as young as 2 years of age have been reported with NAFLD, and NASH-related cirrhosis has been reported as early as 8 years of age (Schwimmer et al. 2005). In addition to liver-related complications, NAFLD is associated with extrahepatic morbidity and mortality. Nonhepatic associations include cardiovascular, metabolic, pulmonary, and psychological disorders. Cardiovascular disease is the most common cause of death in NAFLD patients (Chacko and Reinus 2016).

Presentation

During the pre-cirrhotic stage, most children with NAFLD are asymptomatic (Lewis and Mohanty 2010). Typically, NAFLD is first suspected in a person found incidentally to have elevated serum aminotransferases or abnormalities suggestive of hepatic steatosis on routine imaging while undergoing evaluation for unrelated reasons such as abdominal pain (Mofrad et al. 2003; Farrell and Larter 2006). Rarely, patients may present with fatigue, malaise, or vague abdominal discomfort due to hepatomegaly and stretching of the hepatic capsule (Choudhury and Sanyal 2004).

Physical examination may reveal acanthosis nigricans, which indicates the presence of insulin resistance, or hepatomegaly, which is often difficult to appreciate due to central obesity (Schwimmer et al. 2003). Once a patient develops cirrhosis, they may display cutaneous stigmata of liver disease (e.g. palmar erythema, spider nevi) or features of hepatic decompensation, which include jaundice, pruritus, ascites, edema, variceal bleeding, and encephalopathy.

Diagnosis

The diagnostic criteria for NAFLD include: (1) presence of hepatic steatosis detected either by imaging or histology, (2) absence of significant alcohol consumption, and (3) appropriate exclusion of other causes for hepatic steatosis and coexisting chronic liver disease (Chalasani et al. 2012). Competing etiologies for hepatic steatosis include viral hepatitis, particularly hepatitis C virus, severe malnutrition, provision of parenteral nutrition, autoimmune hepatitis, and use of steatogenic medications such as anabolic steroids. Given the relatively young age at diagnosis, consideration to the possibility of genetic disorders such as alpha-1 antitrypsin deficiency, Wilson's disease, cystic fibrosis, and various inborn errors of metabolism are more relevant for children. It is important to recognize that, because of the high prevalence of childhood obesity, NAFLD can coexist with other chronic liver diseases (Nascimbeni et al. 2013).

Laboratory Evaluation

In clinical practice, serum alanine aminotransferase (ALT) concentration is most commonly used as the initial screening test for NAFLD, despite suboptimal sensitivity and specificity (Schwimmer et al. 2013). Even in the presence of significant histological abnormalities, a substantial number of NAFLD patients have normal transaminase levels (Molleston et al. 2014), indicating that ALT alone is not an ideal screening test for NAFLD. Elevations of aspartate aminotransferase (AST), alkaline phosphatase, and gammaglutamyl transpeptidase (GGT) are common but not useful as screening tools for NAFLD (Mofrad et al. 2003).

In persons with suspected NAFLD, exclusion of other causes of chronic liver disease often includes virological testing for hepatitis viruses A, B, and C, EBV, and CMV, a battery of serologic markers for autoimmune hepatitis (e.g. ANA, anti-LKM-1, anti-SMA, p-ANCA, and IgG), determination of alpha-1 antitrypsin phenotype and serum ceruloplasmin concentration in addition to other specific tests as directed by the clinical history and physical examination (Vajro et al. 2012). In the absence of autoimmune hepatitis, autoantibodies are positive in a significant proportion of children with NAFLD (Patton et al. 2008). Although their clinical significance is uncertain, their presence requires liver biopsy to discriminate between the two conditions. In patients with NAFLD, it is reasonable to assess for dyslipidemia and diabetes mellitus, because NAFLD may indicate the presence of these diseases.

Radiologic Evaluation

Imaging studies including ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) are useful in demonstrating hepatic steatosis, at least when hepatic fat accumulation is moderate to severe (Saadeh et al. 2002). However, these tests cannot detect the differences between NASH and NAFLD. Transabdominal US is acceptable as the first-line imaging modality for NAFLD because of its universal availability, affordability, and lack of radiation exposure. However, its relatively low sensitivity for detecting mild steatosis, operator-dependency, and poor image quality in obese patients are major limitations (Mottin et al. 2004). Newer US-based methodologies such as transient elastography or FibroScan®, which measure liver stiffness noninvasively, have shown promising ability to stage liver fibrosis but are not available outside of large academic medical centers (Yoneda et al. 2008). Both MR spectroscopy (MRS) and MRI-proton density fat fraction (MRI-PDFF) accurately detect and quantify steatosis (Schwimmer et al. 2015). At this time, MR-based methods are not widely used for screening because of the high cost, limited availability, and lack of validated thresholds for diagnosis of NAFLD. CT is highly sensitive and specific, but its cost together with radiation exposure prevents its widespread application.

Histologic Evaluation

Despite its invasiveness, liver biopsy remains the gold standard for the diagnosis and staging of NAFLD (Vos 2016). Histopathologic evaluation of the liver is the only diagnostic test that reliably identifies and quantifies hepatic steatosis, steatohepatitis, and fibrosis, thereby distinguishing NAFLD from NASH as well as other forms of liver disease.

While controversy remains about who should have a liver biopsy and when in the diagnostic evaluation liver biopsy should be used, there is universal agreement that liver biopsy should not be performed in all patients. The clinical practice guidelines on NAFLD from the American Association for the Study of Liver Diseases, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), and European Society for Pediatric Gastroenterology, Hepatology and Nutrition suggest that a liver biopsy be obtained when the diagnosis is uncertain, before pharmacological or surgical treatment is undertaken, and in cases of clinically suspected advanced liver disease (Chalasani et al. 2012; Vos 2016).

Screening

Early diagnosis of NAFLD in children may help prevent the development of chronic liver disease during adulthood (Schwimmer et al. 2013). The American Academy of Pediatrics and NASPGHAN, in their most recent guidelines,

recommend screening for NAFLD with ALT levels beginning between ages 9–11 years for all children whose BMI is ≥95th percentile and for those with a BMI between the 85th and 94th percentile with additional risk factors (e.g. central adiposity, insulin resistance, diabetes, dyslipidemia, sleep apnea, or family history of NAFLD) (BarlowExpert Committee 2007; Vos 2016). Screening can be considered in younger patients with risk factors such as severe obesity or a family history of NAFLD or hypopituitarism. When the initial screening test is normal, repeat screening should be performed every 2–3 years if risk factors remain unchanged or sooner if clinical risk factors increase in number or severity.

Management

The management of pediatric NAFLD is aimed at preventing progression toward more advanced forms of disease, regression of steatosis, and improvement in any underlying metabolic risk factors. Currently, the principal treatment for NAFLD is lifestyle modification by diet (directed by a registered dietician) and exercise (Vos 2016). Recommendations regarding pharmacological therapy are limited by a small number of randomized controlled trials (RCTs) and insufficient information to assess the risk-benefit ratio. Regardless of age, behavioral and/or pharmalogical therapy should commence immediately after the diagnosis of NAFLD for all children. Taking into consideration the severity of NAFLD, the degree of obesity, and the presence of comorbidities, the clinician must individualize treatment accordingly. Comorbidities such as obesity, diabetes mellitus type 2, hypertension, and dyslipidemia are managed concurrently as part of the therapy for NAFLD (Chalasani et al. 2012). It should be highlighted that the pharmacological treatment of metabolic risk factors, particularly with statins, is not contraindicated in NAFLD (Chalasani 2005). If the patient becomes cirrhotic, standard treatment of cirrhosis, including liver transplantation in the decompensated state, is offered.

Weight loss surgery (WLS) is a hot topic but is not recommended as a primary treatment for NAFLD but is becoming more common for severely obese (BMI ≥35 kg/m^2) adolescents with non-cirrhotic NAFLD and other serious obesity-related health conditions (Chalasani et al. 2012; Vos 2016). NAFLD has been proposed as a criterion for WLS in several published adolescent bariatric surgery guidelines (Nobili et al. 2015). However, no studies have examined the histological outcomes of WLS in the pediatric NAFLD population, and only one has reported on the progression of liver disease post-operatively, using ALT as a surrogate marker (Holterman et al. 2012). Therefore, the impact of bariatric surgery on NAFLD outcomes in children is difficult to quantify. In addition, there is concern for subacute liver failure secondary to massive steatohepatitis as a result of rapid weight loss after bariatric surgery (D'Albuquerque et al. 2008). Therefore, bariatric surgery referral should never be considered without the direct input of an experienced pediatric hepatologist.

Viral Hepatitis

Viral hepatitis is a broad term that describes inflammation of the liver from any viral source. Thousands of viruses may be implicated in inducing hepatic inflammation and likely represents an under diagnosed cause of nonspecific transaminase elevation. The mass majority of cases result in spontaneous, and often unrecognized, resolution of hypertransaminemia but in rare cases may progress to acute liver failure (ALF). In the largest studied cohort of pediatric patients experiencing ALF, Squires, et al. reported 20% of pediatric patients presenting in ALF where ultimately diagnosed with a viral etiology. A further 49% of patients had an indeterminate cause of their ALF, many of which may have been secondary to an undiagnosed viral causes (Squires et al. 2006). With the exception of Herpes simplex virus, therapy is symptomatic with liver transplant reserved for the most severe cases in which hepatic synthetic function appears to be irreversibly compromised.

While a seemingly innumerable number of viruses may lead to an acute hepatitis, chronic viral hepatitis in children is almost exclusively caused by either Hepatitis B or C. However, the landscape of these two diseases is rapidly and radically evolving as improved hygiene practices, blood supply monitoring and the widespread use of vaccines has greatly impacted the prevalence rates of Hepatitis B, while unprecedented success rates of Hepatitis C antiviral drugs is sure to lead to decreased chronic carrier rates as well as long-term complications such as cirrhosis and hepatocellular carcinoma (HCC) (Corte et al. 2016).

Hepatitis B

The majority of cases of chronic Hepatitis B (defined as positive Hepatitis B surface Antigen, or HBsAg, for 6 months or longer) occur via maternal transmission as risk of chronicity is highest among newborns who contract the virus (90%) as compared to children less than 5 years of age (25–30%) and adolescents or adults (<5%) (McMahon et al. 1985; Tassopoulos et al. 1987). The disease course in children is typically asymptomatic with preserved growth and psychological development, but close monitoring is required as 3–5% of children will develop cirrhosis and 0.01–0.03% developing HCC during childhood (Chang et al. 1995, 2005).

Prevention

Vaccination is the most effective measure to prevent the transmission and spread of Hepatitis B (Sokal et al. 2013). Administration of monovalent vaccine within the first 24 h of life followed by 2 or 3 (preterm infants <2000 g) doses of monovalent or combined vaccine with a minimum interval of 4 weeks results in about 95% seroprotective response (anti-HBs ≥10 mIU/ml) (WHO Publication 2010). If mother is a chronic carrier, vaccination alone is not sufficient to avoid vertical transmission and hepatitis B immunoglobulin (HBIG) is recommended in addition to vaccine, resulting in 90% protection rate in newborns born to Hepatitis B e Antigen (HBeAg) positive mothers (98% if HBeAg negative) (Lee et al. 2006; WHO Publication 2010). Breastfeeding has not been shown to be a significant risk in transmission of the virus from mother to newborn who have received proper immunoprophylaxis and in the absence cracked and/or bleeding nipples, should be encouraged to breastfeed (Shi et al. 2011).

Monitoring and Therapy

The decision to start therapy for children with chronic hepatitis B is based on ALT levels, HBeAg positivity, DNA levels, liver histology, family history of HCC and a possible co-existing liver disease (Sokal et al. 2013). Serum ALT, viral DNA load and HBeAg/Anti-HBe levels should be obtained every 6 months and HCC surveillance with hepatic ultrasound should be performed yearly. ALT levels (1.5× upper level or normal or >60 IU/L, whichever is lower) for over 6 months, high DNA levels (>20,000 IU/ml), family history of HCC and/or evidence of cirrhosis should all prompt evaluation by an experienced pediatric hepatologist to determine the possible need for therapy (Sokal et al. 2013). Given the evolving landscape of antiviral therapies with numerous ongoing clinical trials, treatment strategies are beyond the scope of this review and should be determined by an experienced hepatologist.

Hepatitis C

There is an estimated 3.5 million people infected with hepatitis C (HCV) in the United States with nearly half of all infected people unaware (Holmberg et al. 2013; Denniston et al. 2014). Higher incidence rates of disease during the 1970s and 1980s has resulted in updated guidelines from the Center for Disease Control and Prevention (CDC) resulting in broader screening mechanisms to detect those patients with undiagnosed, asymptomatic HCV infection (Mahajan et al. 2013). Given that the most common source of infection among children is via vertical transmission, an increased recognition of disease burden among adults/parents has prompted an increase in screening of children of infected

mothers with early recognition of disease in many instances (Corte et al. 2016).

Screening

Any child born to a HCV positive mother, regardless of the child's age or clinical condition, should be screened for HCV infection. While the mother's viral load at time of delivery directly effects transmission rates, generally speaking about 1 in 20 children born to a HCV positive mother will contract the virus (Corte et al. 2016). Although less common in children, other populations in which to consider HCV screening include; patients with prolonged elevation of their serum ALT levels, history of illegal injected drug use, and needle stick, sharp accident or mucosal exposure to a HCV positive individual.

Initial screening lab of choice is a serum HCV antibody (IgG). There are some limitations to this screening test though in that it does not become positive until 6–8 weeks after acquisition and thus not an appropriate choice in acute liver failure screening, does not differentiate acute versus chronic disease and is not useful in patients <18 months of age when maternal antibodies are still present in the blood (Mack et al. 2012). All patients with a positive HCV antibody screen or are being evaluated for acute liver failure should undergo testing with HCV RNA to confirm or rule-out infection. In all patients with positive HCV RNA testing, referral to an experienced hepatologist is indicated for further workup including determine virus genotype, consideration of possible of co-infections and decision on whether therapy is indicated or not.

Monitoring

The invention of direct-acting antiviral agents has revolutionized the therapy of HCV in both adults and children with multiple pediatric studies showing sustained viral remission rates >90%, far superior and with less side effects than previous interferon and ribavirin based therapies (Corte et al. 2016). However, given that 20% of patients will spontaneously clear the virus in the first 3 years of life and only 2% of patients will progress to cirrhosis by the end of adolescents, therapy may be delayed in many instances (Bortolotti et al. 2008). In these instances routine screening and anticipatory guidance become imperative. Patients should undergo annual examination with a focus on education and anticipatory guidance (see Table 10.12) and

Table 10.12 General guidelines for patients with hepatitis C

Topic	Recommendations
Household contacts	Okay to share: sharing food, drink, utensils, clothes/towels, toilet seats Avoid sharing: toothbrush, nail clippers, shaving supplies, glucometers, any personal item that may be contaminated with blood
Non-household contacts	No contraindication to attending day care, school, camps, playgrounds, community pool or participating in contact and non-contact sports
Casual contact	No contraindication to kissing, hugging or holding-hands
Sexual contact	Monogamous sexual contact is non contraindicated while unprotected sexual activity with multiple partners is highly discouraged
Other activities	Tattoos, body piercing, illicit drug use and use of alcohol should be avoided
Blood spills	Gloves should be worn to clean all spills. Thoroughly clean with a dilution of 1 part household bleach to 10 parts water (refer to www.CDC.gov)
Minor cuts	Universal precautions
Vaccines	Should receive all age-appropriate vaccines including Hepatitis A & B
Obesity	Obesity may further burden hepatic health and affect response to HCV therapy
Pregnancy	Universal screening is not recommended and transmission rates similar between vaginal or cesarean deliveries. Prolonged rupture of membranes and use of fetal scalp probes should be avoided as they may increase transmission rates
Breastfeeding	Not contraindicated unless mastitis or bleeding is present

General guidelines for parents of and children with hepatitis C (adapted from Mack et al. (2012)

laboratory evaluation of serum aminotransferases, total and direct bilirubin, albumin, HCV RNA level, complete blood count with platelets and prothrombin time/international normalized ratio (Mack et al. 2012). Additionally, annual to biannual screening for HCC should be performed via abdominal ultrasound or serum alpha-fetoprotein. Any abnormalities and/or concerns should be communicated with an experienced hepatologist.

Pediatric Acute Liver Failure

The liver is the second-largest organ in the human body and performs more than 500 vital functions including gluconeogenesis, synthesis of plasma proteins and coagulation factors, drug metabolism, and conversion of ammonia into urea (Boyer et al. 2011). Specialized macrophages located in the hepatic sinusoids known as Kupffer cells are intimately involved in the liver's response to infection, toxins, ischemia, and other stresses (Bilzer et al. 2006). The liver is also the body's largest gland, responsible for the production and secretion of bile, an alkaline compound that aids in digestion via the emulsification of lipids, and cholesterol, which serves as a precursor for the biosynthesis of steroid hormones and bile acids (Boyer et al. 2011).

Liver failure occurs when massive destruction of the hepatic parenchyma results in impairment of any one of these critical functions (Bucuvalas et al. 2006). Fortunately, a significant proportion of hepatocytes must be damaged before liver failure occurs and spontaneous recovery is possible, owing to the liver's unique regenerative ability. However, the outcome of pediatric acute liver failure (PALF) is generally poor, and one-half of patients die or require liver transplantation (LT) (Squires et al. 2006). According to the PALF Study Group, PALF is defined as coagulopathy not corrected by the administration of vitamin K with an International Normalized Ratio (INR) >1.5 in patients with hepatic encephalopathy, or >2.0 in patients without encephalopathy, within 8 weeks of onset of symptoms in the absence of preexisting liver disease (Squires et al. 2006).

Pathogenesis

Acute liver failure (ALF) results from rapid death or injury to a large proportion of hepatocytes, leaving insufficient hepatic parenchymal mass to sustain liver function. The pathophysiological mechanisms that lead to ALF are yet to be fully elucidated. However, acute hepatic necrosis is the most common mechanistic pathway of a variety of insults to the liver (Taylor and Whitington 2016). In 1999, the PALF Study Group was formed to develop a database that would facilitate an improved understanding of the etiopathogenesis, treatment and outcome of ALF in children. A report of the first 348 patients enrolled in the PALF registry found that the etiologic categories of non-acetaminophen-induced ALF in children were similar to adults and included metabolic, infectious, and immune-mediated conditions as well as drug injury (Squires et al. 2006).

Acute acetaminophen (APAP) toxicity was the most common identifiable cause of ALF in children ≥3 years (21%) (McGill et al. 2012). Non-APAP drug-related ALF was recognized primarily in older children. In most of these cases, the mechanism of injury leading to ALF is thought to be an idiosyncratic drug reaction. An infectious etiology was identified in 6% of patients, with herpes simplex virus (HSV) and Epstein-Barr virus (EBV) the most common identifiable infections in children <3 years and ≥3 years, respectively (Squires et al. 2006). Autoimmune hepatitis (AIH) also accounted for 6% of patients and occurred in all age groups. A metabolic cause for ALF was established in 18% of children <3 years of age. This group of diseases can lead to structural liver damage as a result of acute or progressive accumulation of toxic metabolites within the liver (Hansen and Horslen 2008). Unfortunately, an indeterminate cause of ALF was assigned to 54% of children <3 years of age and 49% overall (Taylor and Whitington 2016). Replacement of hepatic parenchyma with nonfunctioning tissue is an occasional cause of PALF with hepatic hemangioma, leukemia, and various other liver tumors representing the most prominent etiologies. Hypoxic-ischemic liver injury is an uncommon cause of ALF, but never in the absence of other

major organ dysfunction. Gestational alloimmune liver disease (GALD), the most common cause of neonatal ALF, is caused by transplacental passage of maternal alloantibody that activates fetal complement and leads to the formation of a membrane attack complex, resulting in hepatocyte injury (Whitington 2012).

It is unclear why some individuals recover from ALF spontaneously while others die or require LT. The final outcome is likely dependent on the underlying etiology, modifying effects of host factors, and whether or not the massive parenchymal loss can be compensated by liver progenitor cell (LPC)-mediated regeneration. Due to the rapid and severe course of the disease, several factors may determine whether LPC-dependent liver regeneration can save the failing liver, including the number of activated cells, speed of cell proliferation, and direction of cell differentiation (Weng et al. 2015). These critical issues are awaiting further investigation.

Presentation

Jaundice is the presenting symptom in most children with ALF. A prodromal phase indistinguishable from that of acute viral hepatitis, associated with non-specific symptoms of malaise, nausea, vomiting, anorexia, and abdominal discomfort, may precede the appearance of jaundice. As the disease progresses, most patients develop hepatic encephalopathy (HE), a complex neuropsychiatric syndrome that encompasses a spectrum of disease ranging from excessive sleepiness or confusion to severe psychomotor retardation or loss of consciousness. HE is classified into four grades based on the degree of impairment reflected by neurologic, psychiatric and physical findings (Ferenci et al. 2002). HE is particularly difficult to assess in young children and neonates. Infants may present initially with poor feeding, irritability, inconsolable crying, and altered sleep patterns, with frank features of HE manifesting late in the course of the disease.

Coagulation abnormalities related to decreased synthesis of clotting factors as well as qualitative platelet abnormalities are seen in ALF and may result in gastrointestinal or mucocutaneous bleeding (Kurtovic et al. 2005). The bleeding tendency accounts for increased risk of morbidity and mortality in patients with ALF undergoing diagnostic or therapeutic invasive procedures. Multiple organ failure is a complication of ALF with substantial renal dysfunction occurring in more than 50% of patients with ALF (Bernal and Wendon 2014). ALF often results in impaired glycogen storage and a diminished ability for gluconeogenesis. Therefore, ALF should be considered in children who are hypoglycemic and, likewise, children who are diagnosed with ALF should be monitored closely for hypoglycemia (Krasko et al. 2003). Findings on physical examination may include jaundice, hepatosplenomegaly, ascites, dilated abdominal veins secondary to portal hypertension, and cutaneous stigmata of chronic liver disease (e.g. spider nevi, palmar erythema, and leukonychia).

Diagnosis

Encephalopathy may be absent, late, or unrecognized in children (Chen et al. 2003). Therefore, the diagnostic emphasis in PALF is placed on the presence of coagulopathy that is not correctable by the administration of parenteral vitamin K. The PALF Study Group used an INR > 2.0 as the primary defining feature of ALF in young children where hepatic encephalopathy cannot be reliably determined (Squires et al. 2006). Because ALF progresses rapidly, patients require prompt medical evaluation and treatment, preferably in a tertiary referral center that performs liver transplantation and is experienced in treating pediatric liver disease. The diagnostic evaluation of these critically ill patients is challenged by many factors, including the lack of consensus on an age-appropriate evaluation, the short time interval between presentation and outcome, and limitations on the maximum allowable blood draw volume.

A wide range of laboratory studies is required to determine the etiology, severity, and prognosis in pediatric patients with ALF. The initial laboratory evaluation can be divided into three areas:

(1) basic screening tests to assess hematological, renal, and electrolyte abnormalities; (2) liver-specific biochemical and function tests; and (3) diagnostic tests indicated for signs and symptoms suggestive of a specific pathology. Proactive coordination of these tests is necessary to ensure that high-priority tests are performed expeditiously.

Serum aminotransferase levels do not correlate with the severity of the disease (Giannini et al. 2005). Their degree of elevation varies during the course of injury and may depend on the mechanism. It is important to note that a decrease in aminotransferase levels alone does not have prognostic value, since both resolution and massive hepatic necrosis may cause a similar biochemical picture. Both direct and indirect serum bilirubin levels are usually elevated. Typically, conjugated hyperbilirubinemia is present. Hypoalbuminemia, prolongation of the prothrombin time, and hypoglycemia are markers of synthetic liver dysfunction. Serum creatinine levels have been recognized as strong predictors of survival and the need for LT. The correlation between ammonia levels and the severity of HE remains controversial (Ong et al. 2003).

A comprehensive summary of the specific diagnostic tests for the cause of ALF is beyond the scope of this review. Unfortunately, the tendency is to attempt to rule out every known cause of liver disease with exhaustive and expensive testing. A well-thought workup is far more useful. Priority should be guided by the age of the patient and those conditions amenable to specific therapies. Even if no specific therapy exists, establishing a diagnosis may have important implications regarding the decision to proceed with LT and/or offer genetic counseling for heritable diseases that predispose to early cirrhosis (Whitington and Hibbard 2004). While some disorders such as GALD and galactosemia have characteristic clinical presentations, a detailed history and physical examination cannot be overlooked or abbreviated. Exposure to contacts with infectious hepatitis, accurate medication reconciliation, or a family history of Wilson's disease, α-1 antitrypsin deficiency, infectious hepatitis, infant deaths, or autoimmune conditions might lead to a specific diagnosis. Despite recent improvements, current practice indicates that the diagnostic evaluation in children with ALF is often insufficient and the precise etiology remains unidentified in approximately 50% of cases (Narkewicz et al. 2009).

Management

In the absence of a condition known to respond to specific therapy (e.g. acute APAP toxicity, HSV, GALD, tyrosinemia, galactosemia, AIH), the medical management of PALF is largely supportive (Squires et al. 2006). Medical treatment is focused on monitoring and supporting the physiological functions of the liver as well as prompt identification and treatment of complications as a bridge to spontaneous recovery or LT. A multidisciplinary approach and early referral to a pediatric liver transplantation center with an experienced hepatologist, transplant surgeon, and intensivist are essential.

Vital signs, including continuous blood oxygen saturation, should be carefully monitored. Metabolic, hematologic, and coagulation parameters should be monitored daily, or more frequently in an unstable child, until the patient becomes stable. Serial neurologic examinations performed at regular intervals are essential to characterize the degree and progression of HE. The use of benzodiazepines and other sedative medications must be avoided in non-intubated patients to prevent worsening or interference with assessment of the neurological status. If sedation is required, agents with a short half-life such as midazolam, propofol, or dexmedetomidine are preferred. Placement of a central venous catheter allows for measurement of central venous pressure, administration of fluids, medications, and blood products, and frequent laboratory monitoring. Any child who has grade III or IV encephalopathy should be intubated (Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics et al. 2013).

General supportive care includes correction of any fluid, electrolyte, and acid-base disturbances. Intravenous fluids should be tailored to the

clinical status of the patient and restricted to 85–90% of maintenance volumes to avoid fluid overload (Squires 2008). The classic signs and symptoms of hypoglycemia are often obscured, especially in the presence of encephalopathy; therefore, blood glucose levels should be monitored regularly. Oral or enteral nutrition is preferred to parenteral nutrition if it can be done in a safe manner and there is a functional gastrointestinal tract. Protein restriction is not recommended for children with HE. If a metabolic condition is suspected, all nutrition should be discontinued for 24 h and then restarted keeping the specific condition in mind (Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics et al. 2013).

One of the most serious complications of ALF is intracranial hypertension as a result of cerebral edema and HE, which can cause irreversible neurologic damage, and death (Cochran and Losek 2007). Classic signs of intracranial hypertension, such as papilledema and loss of pupillary reflexes are not always clinically apparent and radiographic evidence of cerebral edema frequently occurs late and does not reliably detect intracranial hypertension (Hirsch et al. 2000). Direct intracranial pressure (ICP) monitoring is the most accurate method to monitor changes in intracranial pressure in ALF patients. However, ICP monitoring is not routinely recommended due to the risk of local complications and lack of survival benefit (Vaquero et al. 2005). Management of intracranial hypertension often reflects the preferences of individual centers and may include positioning the head of the patient at >30° from horizontal, hyperventilation of intubated patients to a PCO_2 of <35 mmHg, infusion of hypertonic saline to maintain serum sodium at 145–155 mmol/L, mannitol infusions for surges of ICP exceeding 20 mmHg, maintenance of mild-moderate hypothermia, and bowel decontamination with lactulose or neomycin to reduce ammonia levels. If lactulose is administered, care should be taken to avoid over distension of the abdomen, which can interfere with a liver transplant procedure, if required.

Routine correction of coagulopathy with fresh frozen plasma (FFP) and other procoagulation products such as recombinant factor VIIa is not recommended, as they often obscure the trend of INR as a prognostic marker and impair medical decision making regarding LT. However, replacement is indicated in patients with clinically significant bleeding or prior to invasive procedures (Rahman and Hodgson 2001). Risks associated with FFP include volume overload and transmission of infectious agents via large donor pools. Cryoprecipitate may be helpful in patients with significant hypofibrinogenemia (<100 mg/dL). Platelet transfusion is not recommended unless a threshold platelet count of 10–20 × 10^9 L^{-1} is reached or there is significant bleeding and platelet count <50 × 10^9 L^{-1} (Drews and Weinberger 2000). Prophylactic use of proton pump inhibitors aid in the prevention of gastrointestinal bleeding (Polson et al. 2005).

Due to impaired immune function, bacterial and fungal infections are common and a leading cause of mortality (Wade et al. 2003). An active uncontrolled infection is also a relative contraindication for LT. Surveillance cultures should be obtained upon admission and with any unexplained deterioration in clinical status. Empiric administration of broad-spectrum antibiotics is recommended when the likelihood of impending sepsis is high (Stravitz et al. 2007). Empiric antibiotics are also recommended for patients with ALF listed for LT, since immunosuppression after liver transplant is imminent. Fluconazole or amphotericin should be added for suspected or proven fungal infection.

Renal dysfunction occurs in many patients with ALF and is usually multifactorial with components of acute tubular necrosis, hypovolemia and even hepatorenal syndrome. Avoidance of nephrotoxic agents, including aminoglycosides and non-steroidal anti-inflammatory drugs is critical. If progressive renal failure ensues, continuous venovenous hemofiltration is preferred over standard hemodialysis due to less dramatic fluid shifts. Use of plasmapheresis and therapeutic plasma exchange have been advocated in children with ALF to improve coagulopathy and prevent bleeding complications while allowing for adjustments of fluid, electrolyte, and acid-base balance (Singer et al. 2001).

Because ALF in children can progress rapidly, a timely decision to proceed to LT is needed to prevent sequelae. Unfortunately, existing prognostic scoring systems based on biochemical markers and/or clinical features, including the King's College Criteria, have not been shown to be useful for predicting survival or death in PALF (Shanmugam and Dhawan 2011).

Approximately 10–15% of pediatric liver transplants are performed for ALF (Squires et al. 2006). Although post-transplant survival in PALF remains lower than that observed for children who receive liver transplants for other causes, pediatric liver transplant recipients have the highest survival rate for any solid organ (Baliga et al. 2004). Contraindications to LT are active uncontrollable sepsis, severe cardiopulmonary disease, multisystem organ failure, extrahepatic malignancy, and severe neurological impairment. Artificial and bioartificial liver support devices such as the Molecular Absorbent Recirculating System (MARS) and Extracorporeal Liver Assist Device (ELAD), which temporarily perform normal hepatocyte functions, are currently undergoing development for PALF as a means of bridging patients to either transplantation or spontaneous recovery during native liver regeneration.

Pancreatitis

Over the last two decades the incidence of pancreatitis among children has been on the rise. A lack of historical pediatric data represents a major limitation in determining the degree of this increase but several studies out of the United States, Mexico and Australia have all shown a significant increase in the number of hospital admission for pediatric pancreatitis (Bai et al. 2011). Establishing the true incidence of pediatric pancreatitis is further complicated by a vast difference in incidence reports amongst hospitals which is felt to be due to variations in institutional management of acute abdominal pain, particularly in emergency units (Zsoldos et al. 2016). Despite the likely under reporting of acute pancreatitis (AP) in children, retrospective analysis suggests the true incidence of disease to be approximately 13.2 cases per 100,000 children in the United States (Morinville et al. 2010).

Although the increase in disease burden is well recognized for pediatric pancreatitis, data on pathophysiology, etiologies, management and clinical outcomes is continuing to take shape. The majority of available data is based almost exclusively from the adult literature, yet pancreatitis among adults is likely a very different disease than that seen in children given the differences in etiological backgrounds (Abu-El-Haija et al. 2014). Among adult patients with AP, alcohol and biliary etiologies predominate while genetic, anatomic, metabolic and toxic causes are much more prevalent amongst pediatric patients (Husain et al. 2016). Fortunately, a greater amount of attention has been focused recently on addressing pediatric specific pancreatitis concerns with large, pediatric-centered consortium such as INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure) and PINEAPPLE (Pain in Early Phase of Pediatric Pancreatitis) already significantly increasing our understanding of the disease process and burden.

Presentation

Abdominal pain is the most common initial presentation of AP affecting 80–95% of patients, with nausea or vomiting noted in up to 80% of cases (Bai et al. 2011). Importantly though, infants and toddlers are less likely to present with abdominal pain (43–93%) and/or emesis (29–76%), but have a higher likelihood of presenting with abdominal distention (16%) or fever (40%), both of which are rare in older patients (Kandula and Lowe 2008; Park et al. 2010). Biochemical presentation may also differ by age. In older patients the sensitivity of amylase to detect AP ranges from 50% to 85% with lipase felt to be approximately 75% more sensitive (Park et al. 2010). However, among infants and toddlers, studies suggest 100% of patients will have elevated lipase levels with only approximately 50% having elevated amylase levels (Kandula and Lowe 2008). Amylase remains an important marker in the detection of AP though as several

reports exist of patients with radiographic evidence of pancreatitis with isolated elevation of their amylase seen (Werlin et al. 2003; Bai et al. 2011).

Etiologies

While the pathophysiology remains obscure and largely theoretical, several risk factors are known to increase a patient's risk of developing AP. Risk factors typically fit into one of the following four categories: (1) Metabolic, (2) Environmental, (3) Genetic, or (4) Anatomical/Obstructive.

Metabolic

Hypertriglyceridemia, hypercalcemia and chronic renal failure are all considered significant risk factors for the development of AP and acute recurrent pancreatitis (ARP). Triglyceride levels >1000 mg/dL represent an absolute risk, while levels >500 mg/dL represent an absolute risk for the development of AP (Bălănescu et al. 2013; Christian et al. 2014). A threshold for hypercalcemia imparting a risk for AP has yet to be established but hypercalcemia associated with primary hyperparathyroidism, high IV calcium during cardiac surgery or parenternal nutrition administration, and ectopic secretion of calcium-mobilizing hormones such as seen acute lymphoblastic leukemia have all been associated with the development of pancreatitis (Husain et al. 2016). Autopsy studies have shown significant pancreatic disease among patients with end stage renal disease. However, determining the diagnosis of pancreatitis in patients with chronic renal failure may difficult due to the impaired clearance of amylase and lipase leading to the recommendation that levels 3× ULN are needed in order to the make diagnosis in this specific patient population (Husain et al. 2016).

Environmental

To date no studies have shown a clear association between smoking and/or alcohol use and the development of pancreatitis among children, although as one might imagine data on the subject is scarce (Husain et al. 2016; Kumar et al. 2016). Drug-induced pancreatitis is felt to represent a small proportion of all pancreatitis cases (0.3–2%) but is an important consideration for patients on certain medications which include certain antibiotics, nonsteroidal anti-inflammatory agents, immunomudulators, certain chemotherapeutic agents, antiepileptic drugs, antihypertensives, antihyperglycemics and antiviral therapies (Nitsche et al. 2012). Directly establishing drug-induced pancreatitis is often difficult requiring a withdrawal and monitor approach. Utilization of drug-induced pancreatitis algorithms, such as that proposed by Trivedi, may be of use to the clinician to more accurately recognize drug-induced pancreatitis (Trivedi and Pitchumoni 2005).

Genetic

Cystic fibrosis transmembrane conductance regulator (CFTR), pancreatic secretory trypsin inhibitor (SPINK1), cationic trypsinogen (PRSS1) and chymotrypsin C (CTRC) represent the major genetic causes of ARP and chronic pancreatitis (CP) in children. A recent review of the INSPPIRE database showed 48% of patients with ARP and 73% of patients with CP had at least one mutation on one of these pancreatitis-associated genes. The most common mutation associated with ARP was CFTR (34% of patients) while PRSS1 was the most commonly seen mutation among patients with CP (46%) (Kumar et al. 2016).

Anatomic/Obstructive

Approximately 1/3 of patients with ARP or CP are felt to have an anatomic or obstructive etiology (Kumar et al. 2016). Although surgical intervention is required in certain anatomical conditions, many obstructive etiologies may safely be managed by ERCP, which has been shown to be safe and effective in pediatric patients (Enestvedt et al. 2013; Halvorson et al. 2013; Saito et al. 2014).

Management

Historically, management of pancreatitis has been based on adult recommendations but more recently pediatric driven data is emerging suggesting new approaches may be warranted.

Acute Pancreatitis

Pain management is an integral part of AP management with narcotics often considered the drug of choice. However, determining when to introduce enteral nutrition and how aggressive to be with IV hydration have been highly debated topics in pediatric AP research. Recent pediatric studies have shown that aggressive IV hydration (1.5–2× maintenance) over the first 48 hours and early enteral nutrition (within 48 h) were not only safe but also resulted in shorted hospital stays and decreased risk of developing severe AP (Szabo et al. 2015). Additionally, those patients who consumed a high fat intake experienced lower pain scores as compared to those place on a fat restricted diet (Abu-El-Haija et al. 2016).

Chronic

Pain control is the mainstay of therapy for patients with CP and without proper oversight may result in narcotic addiction. Therefore, neuropathic pain control with tricyclic antidepressants, gabapentin or pregabalin are preferred (Pohl and Uc 2015). The use of proton-pump inhibitors, antioxidants and pancreatic enzymes for pain control have been proposed but none have been thoroughly studied or shown to be of benefit in pediatric pancreatitis. In severe cases of ARP and CP in which pain becomes unmanageable, total pancreatectomy with islet autotransplantation may be a viable option (Bellin et al. 2016).

Endoscopy

Pediatric esophagogastroduodenoscopy (EGD) was first described in the 1970's and has transformed from an infrequently performed procedure with significant risk to the routine, often outpatient procedure that it is viewed as today (Friedt and Welsch 2013). The majority of Advances in pediatric endoscopy have resulted in physicians becoming less reliant on invasive surgical measures and advancing imaging techniques such CT and MRI, which are frequently less sensitive and specific, to diagnose and treat a variety of gastrointestinal disorders. Future advancements promise to further decrease the need of invasive procedures requiring sedation and/or anesthesia while simultaneously improving diagnostic and therapeutic efficacy.

Esophagogastroduodenoscopy

From 1985 to 2005 there was over a 12-fold increase in the number of pediatric EGD's performed (Franciosi et al. 2010). Expanding diagnostic and therapeutic indications for EGD has resulting in further growth of the field with EGD becoming viewed as a routine procedure in many larger institutions (see Table 10.13 for common indications for EGD). Growth in interventional technologies has been particularly influential in changing the way we treat a number of conditions including, but not limited to, foreign body ingestions and acute gastrointestinal bleeding.

Foreign Body Ingestion

Although patients with a retained foreign body may present with drooling, pain, stridor, refusal to eat, dysphasia, stridor, wheezing or respiratory distress, approximately 50% of pediatric foreign body ingestions will present without symptoms (Temiz 2015). Coins represent the most common accidental ingestion in children in the western hemisphere, accounting for ~70% of ingestions (Peters et al. 2015). While a number of other toys, jewelry, food products (e.g. bones) and other common objects can be ingested, special attention much be shown to any object stuck in the esophagus for over 24 h, button batteries and high-powered Neodymium magnets (e.g. Buckyballs®) given the potential risk of bowel perforation and should prompt immediate referral to a pediatric center with advanced endoscopy capabilities (see Fig.10.7).

Upper Gastrointestinal Bleeding

Life threatening gastrointestinal bleeding is a rare occurrence in pediatrics and is best treated by an advanced endoscopist at a pediatric tertiary care center. Interventions are dependent upon the size of the child, the site of the bleed and the judgment of the endoscopist (Rahman et al. 2015). Bleeding is typically characterized as variceal or non-variceral. Variceal bleeding is

Table 10.13 Common indications for pediatric EGD

Diagnostic	Therapeutic
Abdominal pain/functional disorders	Foreign body/Bezoar removal
Weight loss/failure to thrive	Enteral tube placement
Dysphasia/odynophagia	Dilation
Diarrhea/malabsorption	Banding/injection of varices
Emesis/hematemesis	Non-variceal bleeding control
Iron deficiency anemia	Polypectomy
Enteropathy/suspected celiac disease	Botox/other injections
Suspected/surveillance inflammatory bowel disease	

Common diagnostic and therapeutic indications for performing an EGD in pediatric patients (Adapted from Rahman et al. (2015))

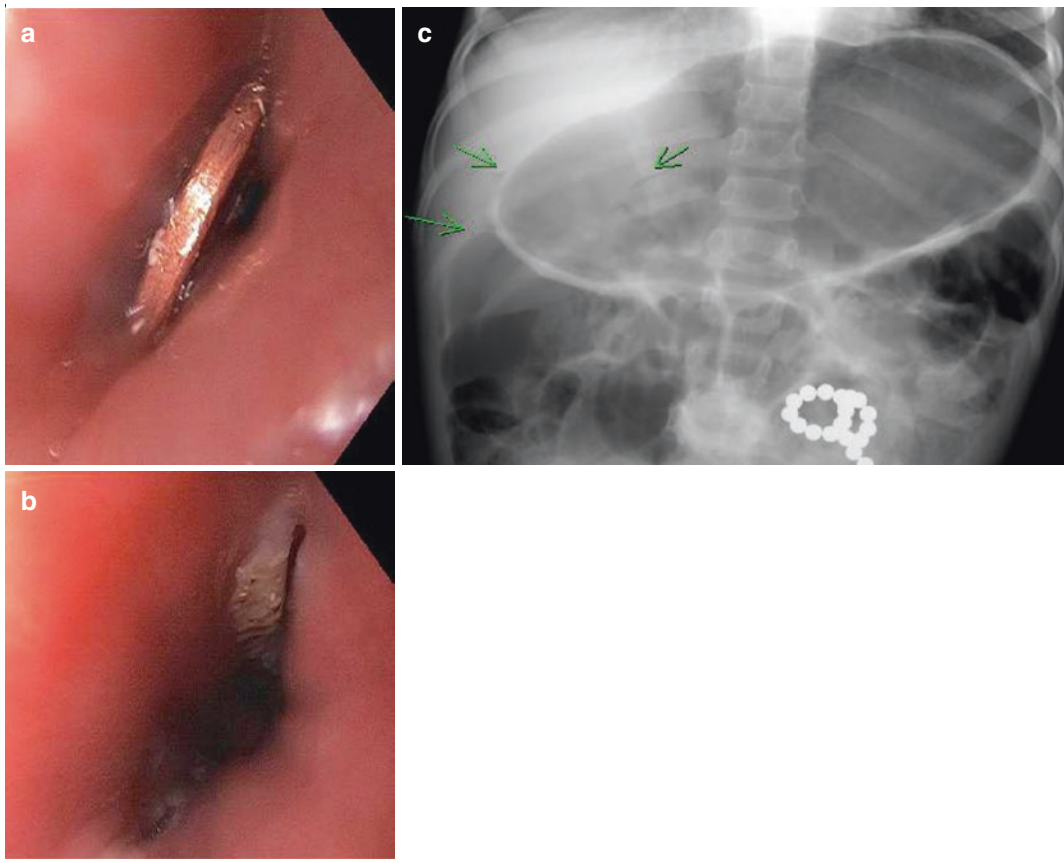

Fig. 10.7 Coin and neodymium magnet ingestions. (**a**) EGD image of penny ingested in a 2 year old >30 h before presentation to the emergency room with resulting linear ulcer (*B-blue asterix*) after extraction. (**c**) Shows abdominal x-ray of a neodymium magnet ingestion in a 5 year old with free air seen below the diaphragm (*green arrows*) from resulting intestinal perforation

typically managed with IV octreotide and endoscopic banding or sclerotherapy (Thomson and Belsha 2016). Non-variceal bleeding is typically treated with two of the following classes of interventions; (1) injection therapy (e.g. adrenaline, sclerosing agents, fibrin glue or normal saline), (2) Mechanical therapy (e.g. endoscopic hemoclips) or (3) Thermo-coagulation (e.g. hot biopsy

forceps, gold probe or argon plasma coagulation) (Thomson and Belsha 2016).

Future Directions

A specific focus of endoscopic research has been to decrease the need for surgical intervention in patients with severe gastroesohpageal reflux disease (GERD). Two exciting techniques that have been developed are endoluminal gastroplication and iatrogenic stricture formation through radiofrequency energy as replacements for surgical fundoplications (Rahman et al. 2015). While initial results are promising, years more research is required before these modalities will be determined to have any potential use in pediatric reflux therapy.

Endoscopic Retrograde Cholangiopancreatography (ERCP)

ERCP has been established as an effective diagnostic and therapeutic tool for pancreaticobiliary disorders in pediatrics. The invention of smaller diameter duodenoscopes in the late 1980s allowed for ERCP use in the pediatric population with several studies reporting outcomes in pediatrics is not statistically different than that seen in the adult population (Enestvedt et al. 2013; Halvorson et al. 2013; Troendle et al. 2015; Giefer and Kozarek 2015; Yıldırım et al. 2016). The primary impediment to pediatric ERCP is finding a pediatric endoscopist trained in ERCP or an adult endoscopist with appropriate sized duodenoscopes and access to a center with experience performing ERCP in children.

Evaluation of the Small Intestine

Previously felt to be "unreachable", the invention of video capsule endoscopy (VCE) and balloon enteroscopy has provided advanced endoscopist two new tools to access for mucosal changes in the small intestine. With balloon enteroscopy, the endoscopist also has the added capability to perform biopsies of distal small bowel and perform therapeutic measures similar to those that are capable with EGD. Investigation of obscure GI bleeds or unexplained anemia, investigation of IBD and surveillance of polyposis syndromes are the main indications for both modalities (Zevit and Shamir 2015). Like many of the other interventions outlined in this section, VCE and balloon enteroscopy are best performed at pediatric tertiary centers by pediatric gastrointestinal providers with experience utilizing these modalities. Future directions include VCE dedicated to evaluate the esophagus and colon in order to decrease the number of endoscopy procedures that require anesthesia.

Colonoscopy

While a number of advancements have occurred in upper endoscopy and small bowel imaging, colonoscopy has remained essentially unchanged and continues to serve more as a diagnostic tool. The main pediatric indications for colonoscopy remain: (1) Hematochezia, (2) Abdominal pain, (3) Diarrhea and (4) Polypectomy/polyp screening (Park 2010).

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