An Update on Pediatric Gastroenterology and Nutrition:  
A Review of Some Recent Advances

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Pediatric gastroenterology and nutrition continues to be a dynamic subspecialty. Ongoing research, at the bench and bedside, has led to revolutionary changes in both the diagnosis and the therapeutics of many gastrointestinal (GI) disorders. From the development of hydrolyzed and elemental formulas to the introduction of probiotics into infant formulas, the science of clinical nutrition continues to evolve.

This review provides the primary care physician an update on common GI conditions and their treatment paradigms in this millennium, focusing on advances in the last decade or two.

Gastroesophageal Reflux: Newer Techniques and Therapies

Introduction

Gastroesophageal reflux (GER) can be defined as the movement of the gastric contents into the esophagus. It is a common pediatric disorder that can affect as many as 50% of infants from birth to 3 months of age. The majority of those infants “outgrow” their reflux by 12 months.1

GER occurs when the lower esophageal sphincter relaxes transiently, allowing contents to pass into the esophagus.2 Infants are especially prone to develop reflux due to the short length of the esophagus, recumbent position, and the relatively small gastric capacity.

Clinical Presentation

The most common presenting symptom of GER in infants is vomiting, which may be associated with arching and irritability. While complications are uncommon, they can result in failure to thrive, food refusal, apparent life-threatening events, reactive airways disease, recurrent aspiration pneumonia, and chronic cough. Sandifer syndrome is a rare presentation of reflux that is manifested as repetitive stretching and arching movements that may be mistaken for seizures.

Diagnosis

Detailed history and physical examination are key elements in diagnosing GER. Testing, if necessary, should be tailored to the individual patient to address the specific concerns raised. Upper GI contrast studies can be helpful in identifying a structural abnormality. Esophageal pH monitoring is useful in quantifying the amount of acid reflux and the association of esophageal acidification with the child’s symptoms. Wireless pH monitoring can now be performed through the use of a capsule with a radio transmitter that can be endoscopically positioned in the distal esophagus.3 It is recognized that “not all reflux is acidic” and newer technology is attempting to solve this dilemma by allowing detection of nonacid regurgitation into the esophagus. Multichannel intraluminal impedance relies on the detection of electrical impedance generated by the motion of material such as food or secretions. The presence of multiple electrodes along the esophagus allows gathering of information on which direction movement of the object is occurring. Therefore, the signal would detect downward movement during swallowing and upward movement during regurgitation.
Upper endoscopy with esophago-gastro-duodenoscopy is useful to directly examine the mucosa of the esophagus (Fig 1) for complications as well as conditions that mimic GER such as eosinophilic esophagitis. The severity of esophagitis can be graded endoscopically, which can aid in steering the therapeutic intervention in an appropriate direction. Significant complications due to reflux, such as esophageal strictures, Barrett’s esophagus (premalignant), and esophageal cancer, albeit rare in children, can be evaluated during endoscopy. esophago-gastro-duodenoscopy can also be a useful therapeutic tool for esophageal strictures, which can be treated by endoscopic balloon dilation (Fig 2).

Management

Reassurance and lifestyle changes may be all that is necessary in uncomplicated physiologic reflux. The mainstay of treatment in children with reflux disease is acid-suppressive therapy. The use of antacids should be limited to short-term therapy between 8 to 12 weeks. Histamine-2 receptor antagonists such Cimetidine, Famotidine, Nizatidine, and Ranitidine can be helpful in suppressing gastric acid secretion. However, some children may require the more superior healing effect of proton pump inhibitors such as Omeprazole, Lansoprazole, Esomeprazole, Pantoprazole, and Rabeprazole. Surface agents (eg, Sucralfate) and prokinetic agents (eg, Metoclopramide, Erythromycin at low doses) have a limited role in managing children with reflux. Surgical therapy is usually indicated after failure of medical therapy and in the presence of significant complications of reflux-like chronic esophagitis, peptic strictures, and failure to thrive.

The Treatment of Chronic Constipation in Children

Introduction

Chronic constipation is a common worldwide problem. It has been estimated that over 16% of North American 22-month-olds suffer from constipation and it accounts for almost 25% of all visits to pediatric gastroenterologists. It is equally prevalent in girls and boys. The purpose of this review is to discuss the treatment modalities currently available for children with this common malady.

Definitions

Baker and coworkers defined constipation as “a delay or difficulty in defecation, present for >2 weeks, and sufficient to cause significant distress to the
patients.” More recently, there have been several international meetings of experts in the field of functional bowel disorders, where a more detailed description of constipation has been suggested. The Rome criteria (Table 1) divide pediatric constipation into two age groups, infants and toddlers, and those with developmental age of at least 4 years or older. In both age groups, consistency and hardness of bowel movements are important in defining constipation. In children greater than 4 years of age, fecal soiling or encopresis can be considered a symptom of constipation. Encopresis affects about 2.2% of children older than 4 year of age.9

Differential Diagnosis

While the vast majority of patients with chronic constipation have a functional basis, organic problems can also predispose the child to chronic constipation (Table 2). Anatomic abnormalities such as an imperforate anus, anal stenosis, and an anterior displaced anus can all be identified on physical examination. Hypercalcemia, diabetes mellitus, and hypothyroidism have all been shown to cause constipation. Neuropathic causes of constipation include hypotonia, hypertonia, spinal cord abnormalities, and sacral agenesis.

Hirschprung’s disease was first reported by Hirschsprung in 18889 and is characterized by a lack of ganglion cells. It is a rare cause of intractable constipation. Fecal soiling occurs in a distinct minority of these patients, but recurrent fecal impaction may not be uncommon.6 One of the first signs of this disorder in neonates is the delayed passage of meconium. Meconium passage in the first 24 hours occurs in 90% of normal newborns, but in only 10% of patients with Hirschsprung’s disease. A plain prone cross-table lateral X-ray, barium enema, anal manometry, and a suction rectal biopsy can suspect a diagnosis of Hirschsprung’s. It is confirmed by a full-thickness biopsy. For the vast majority of patients, a history and physical is all that is needed in the evaluation of chronic constipation. Patients that require further evaluation include those with prolonged fever, vomiting, diarrhea, severe abdominal distension, anorexia, weight loss, or poor weight gain. Associated complaints such as urinary incontinence may signify a spinal cord abnormality. Any suspicion of child abuse (presence of perianal warts, bruising) should always be pursued. Bloody stools, without evidence of anal fissure, or severe acute constipation should also be explored further for surgical obstructions, inflammatory bowel disease, polyps, and hemorrhoids.6,10-12

Treatment

Mild chronic constipation is treated with dietary manipulations, limiting fat in the diet and increasing whole grains, fresh fruits, and vegetables. While increasing fluid intake is often suggested, there is no clear evidence that this is of benefit. A fiber supplement or high fiber diet may also be of benefit with the goal of providing an additional 20 to 30 g of fiber per day. However more significant constipation, especially

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**Table 1.** Chronic constipation: Rome III criteria

<table>
<thead>
<tr>
<th>Infants and Toddlers:</th>
<th>Children with developmental age of 4-18 years</th>
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<tbody>
<tr>
<td>At least 2 of the following:</td>
<td>At least 2 of the following:</td>
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<tr>
<td>2 or less defecation per week</td>
<td>Two or less defecation per week.</td>
</tr>
<tr>
<td>At least one episode of incontinence after the acquisition of toilet training skills</td>
<td>At least one episode of fecal incontinence per week</td>
</tr>
<tr>
<td>History of excessive stool retention</td>
<td>History of retentive posturing or excessive volitional stool retention</td>
</tr>
<tr>
<td>History of painful or hard bowel movements</td>
<td>History of painful or hard bowel movements</td>
</tr>
<tr>
<td>Presence of a large fecal mass in the rectum</td>
<td>Presence of a large fecal mass in the rectum</td>
</tr>
<tr>
<td>History of a large diameter stool that may obstruct the toilet</td>
<td>History of large diameter stools that may obstruct the toilet</td>
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</tbody>
</table>

**Table 2.** Causes of chronic constipation

<table>
<thead>
<tr>
<th>Functional</th>
<th>Organic</th>
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</thead>
<tbody>
<tr>
<td>Developmental – cognitive disorders, ADD</td>
<td>Anatomic – imperforate anus, pelvic mass, anal stenosis, anterior displaced anus</td>
</tr>
<tr>
<td>Situational – coercive toilet training, phobias, abuse</td>
<td>Intestinal disorders – Hirschsprung’s, pseudo-obstruction, celiac disease</td>
</tr>
<tr>
<td>Dietary – low residue in diet</td>
<td>Metabolic/Endo – Hypercalcemia, Hyperkalemia, Diabetes mellitus, Hypothyroidism</td>
</tr>
<tr>
<td>Drugs/Medications – Pain meds(narcotics), antacids</td>
<td>Neuropathic – Hypotonia, Hypertonia, Spinal cord abnormalities, Sacral agenesis</td>
</tr>
<tr>
<td>that predominantly contain aluminum and calcium, blood pressure meds (calcium channel blockers), antiparkinson drugs, antispasmodics – (levsin, bentyl), antidepressants, iron supplements, diuretics, anticonvulsants.</td>
<td>Drugs:</td>
</tr>
<tr>
<td>Connective Tissue disorders – Ehlers Danlos</td>
<td>that predominantly contain aluminum and calcium, blood pressure meds (calcium channel blockers), antiparkinson drugs, antispasmodics – (levsin, bentyl), antidepressants, iron supplements, diuretics, anticonvulsants.</td>
</tr>
</tbody>
</table>
| Other – Cystic Fibrosis, Cow-Milk protein intolerance |}
when accompanied by fecal soiling (encopresis), typically requires two phases of therapy, combining medical and behavioral modalities.\textsuperscript{11,12} The first phase of treatment is the “cleanout.” Lack of effective cleanout is often the reason for persistent problems.\textsuperscript{13} Stool softening, is important but may only worsen the problem of soiling if the initial cleanout is not adequate. An abdominal X-ray is helpful to evaluate fecal load in a child who is difficult to examine. The cleanout can be accomplished by oral medications, which is typically the preferred route by patients. Oral regimens may include magnesium citrate, bisacodyl tablets, or even repeated doses of Miralax and is usually accomplished over 2 to 5 days, depending on the severity of constipation. At times, repeated cleanouts separated by 1 to 2 weeks may be necessary. When oral therapy is difficult or ineffective, treatment with enemas may be required. We have often found that when a firm, large fecal mass is palpated, the only effective cleanout is with nasogastric GoLYTELY® (PEG-3350 and electrolytes for oral solution) at a rate of 25-40 mL/kg/h until the patient’s bowel movements are clear.\textsuperscript{14,15}

The second phase in treatment is the maintenance phase, where behavioral and medical therapy is combined to facilitate regular defecation. Stool softening can be accomplished in infants and younger children\textsuperscript{16} with Miralax,\textsuperscript{12} lactulose, or milk of magnesia. Care must be taken in using mineral oil in children less than 2 years or those with GER because of the risk of significant lung injury if aspirated. Older children that can swallow pills can utilize docusate sodium, available over the counter, or Lubiprostone (Amitiza), a chloride channel agonist.

Behavioral treatment or bowel training is often overlooked but is a significant part of any successful treatment regimen.\textsuperscript{17} Regular toileting is accomplished by asking that the patient sit for 5 minutes on the toilet at the end of each meal. This takes advantage of the gastro-colic reflex, which improves the likelihood that defecation will accompany toileting efforts. Positive feedback from parents to children at this time, as well as training aids to improve “pushing” such as blowing up balloons, are often helpful at this time.

\textbf{Alternative Therapies}

When standard treatment options fail, other modalities, including medical and surgical options, are considered. While several prokinetic agents have been found to be useful in treating chronic constipation, many have been recalled due to concerns with cardiac rhythm abnormalities. Both Cisapride and Tegaserod\textsuperscript{18} were found to be effective in treating patients with defecation disorders; however, both have subsequently been withdrawn from regular use due to intestinal ischemia and cardiovascular side effects. Erythromycin, a motilin agonist, has some efficacy in treating motility problems in general and constipation in particular.\textsuperscript{19} Several studies have suggested a potential benefit of probiotics in treating constipation; however, the only double-blind placebo-controlled study evaluating this option, utilizing Lactobacillus GG, failed to show any benefit.

Surgical interventions are reserved for the most recalcitrant patients. Colostomy is rarely performed; however, appendicostomy, or the Malone Procedure, has been utilized with some success.\textsuperscript{20,21} Originally intended for use in meningocele patients, this strategy to initiate colonic lavage has been utilized in otherwise normal children suffering from long-term encopresis. Access to the cecum has also been obtained percutaneously (Button Cecostomy) by interventional radiologists or endoscopists, obviating the need for surgery.\textsuperscript{20}

\textbf{Long-Term Outcome}

Van Ginkel and Buller\textsuperscript{22,23} followed 418 children with chronic constipation and found that 41% of children have problems for longer than 1 year, and 30% have symptoms persisting past puberty. Voskuil and coworkers suggested slow improvement of encopresis: 29% resolved after 2 years, 65% after 5 years, and 90% after 10 years.\textsuperscript{24} Overall, recovery rates around 50% at 1 year and 75% after 5 years are reasonable expectations.\textsuperscript{25}

\textbf{Chronic Abdominal Pain and the Rome III Criteria}

Chronic abdominal pain is one of the more common presenting complaints in pediatric gastroenterology. It comprises 1 to 4% of all pediatric office visits.\textsuperscript{26} Approximately 13% of middle school children and 17% of high school children are symptomatic with chronic abdominal pain.\textsuperscript{27} The diagnostic criteria have improved with time. The condition was initially described by Dr. Apley, a pediatrician from England in 1958 that defined chronic abdominal pain as three episodes of pain over 3
weeks severe enough to interfere with daily activities and associated with positive emotional disturbance and negative physical findings.28 This definition was vague; inciting a group of scientists to get together in Rome in 1990 and establish diagnostic criteria for defining functional GI disorders. It has been revised since then, most recently in 2006 as the Rome III criteria (Table 3).7,8

The advantage of the Rome III criteria is that it provides an organized approach to the diagnosis and helps in the management of the specific condition. However, it is often criticized for absent gold standards and objective biomarkers of disease severity.

Functional GI disorders are a composite of several physiological components including dysmotility, visceral hypersensitivity, inflammation of intestine, abnormally increased or altered bacterial flora of intestine, and dysregulation of the brain-gut axis.29

### TABLE 3. Rome III criteria for functional bowel disorders associated with abdominal pain or discomfort in children

<table>
<thead>
<tr>
<th>Functional Dyspepsia</th>
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<tbody>
<tr>
<td>All of the following must be present at least once per week for at least 2 months before diagnosis:</td>
</tr>
<tr>
<td>1. Persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus).</td>
</tr>
<tr>
<td>2. Pain not relieved by defecation or associated with the onset of a change in stool frequency or stool form (ie, not irritable bowel syndrome).</td>
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<tr>
<td>3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the symptoms.</td>
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<table>
<thead>
<tr>
<th>Irritable Bowel Syndrome</th>
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<tr>
<td>All of the following must be present at least once per week for at least 2 months before diagnosis:</td>
</tr>
<tr>
<td>1. Abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with two or more of the following at least 25% of the time:</td>
</tr>
<tr>
<td>- Improved with defecation</td>
</tr>
<tr>
<td>- Onset associated with a change in frequency of stool</td>
</tr>
<tr>
<td>- Onset associated with a change in form (appearance) of stool</td>
</tr>
<tr>
<td>2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the symptoms.</td>
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<table>
<thead>
<tr>
<th>Childhood Functional Abdominal Pain</th>
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<tbody>
<tr>
<td>All of the following must be present at least once per week for at least 2 months before diagnosis:</td>
</tr>
<tr>
<td>1. Episodic or continuous abdominal pain</td>
</tr>
<tr>
<td>2. Insufficient criteria for other functional gastrointestinal disorders</td>
</tr>
<tr>
<td>3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the symptoms.</td>
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</table>

Childhood Functional Abdominal Pain Syndrome must include childhood functional abdominal pain at least 25% of the time and one or more of the following:

1. Some loss of daily activity
2. Additional somatic symptoms such as headache, limb pain, or difficulty sleeping

### TABLE 4. Warning symptoms and signs in patients with abdominal pain, suggestive of an underlying organic etiology "RED FLAGS"29

<table>
<thead>
<tr>
<th>Red Flags</th>
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<tbody>
<tr>
<td>...</td>
</tr>
<tr>
<td>1. Weight Loss</td>
</tr>
<tr>
<td>2. Fever</td>
</tr>
<tr>
<td>3. Mouth sores</td>
</tr>
<tr>
<td>4. Joint pain</td>
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<tr>
<td>5. Skin rashes</td>
</tr>
<tr>
<td>6. Nocturnal frequency of pain</td>
</tr>
<tr>
<td>7. Dysuria</td>
</tr>
<tr>
<td>8. Hematemesis</td>
</tr>
<tr>
<td>9. Dysphagia</td>
</tr>
</tbody>
</table>

| ... |
| 1. Respiratory symptoms |
| 2. Anemia |
| 3. Delayed puberty |
| 4. Family history of inflammatory bowel disease |
| 5. Blood in stools |
| 6. Diarrhea |
| 7. Constipation |
| 8. Recurrent vomiting |

...
the Rome III criteria has been shown to improve the diagnostic accuracy for detecting organic disease (eg, inflammatory bowel disease) with a sensitivity of 85% and sensitivity of 71%.34

**Treatment**

Treatment depends on the specific Rome III classification. Patients in whom a diagnosis of dyspepsia is established should be given a trial of H2 blockers (eg, Ranitidine) or proton pump inhibitors (eg, Omeprazole) and prokinetic agents (eg, Metoclopramide) should be added if they are showing signs of dysmotility such as gas and bloating.29 A trial of low-dose antidepressant can also help decrease visceral hypersensitivity (tricyclic antidepressants, selective serotonin reuptake inhibitors).29 However, this is the group of patients who may require upper endoscopy at some point to rule out an organic etiology, if these symptoms persist and they are unable to be weaned off acid suppression.

**Irritable Bowel Syndrome (IBS)**

IBS is divided into two categories: patients with constipation-predominant IBS or diarrhea-predominant IBS.7,8,35,36 It is important to obtain a detailed history in patients with IBS regarding anxiety and depressive symptoms. They should be counseled regarding adequate intake of fiber and water. IBS with constipation predominance may benefit from use of stool softener or laxatives as well. Selective serotonin reuptake inhibitors (SSRIs) are a good choice for IBS with constipation.35 In diarrhea-predominant IBS they should be counseled regarding decreasing the intake of juices, gum, sorbitol, and large meals. Patients with diarrhea-predominant IBS may have an increased incidence of lactose intolerance. They have some improvement on a lactose-free diet but it does not prove a causal relationship. Tricyclic antidepressants with noradrenergic activity are useful for patients who have diarrhea-predominant IBS particularly if associated with symptoms of pain and depression. SSRIs such as Lexapro (escitalopram oxalate) are used in adult patients with diarrhea-predominant IBS.35 There is insufficient data available for pediatric patients. Selective nor-epinephrine reuptake inhibitors (SNRIs) like Cymbalta (duloxetine) have been used in pediatric patients with chronic abdominal pain syndrome (IBS pain predominant).35

IBS, which is post infectious, may benefit from a course of antibiotics, such as metronidazole or rifaximin. Limited data are available in the pediatric population for use of probiotics in IBS (described in section on Probiotics).

**Functional Abdominal Pain**

This is a group of pediatric patients defined by the Rome III criteria that may have somatic complaints, significant enough to affect their quality of life and to miss school.7 It is important in this group of patients to explain the pathogenesis of disease, the brain-gut axis dysregulation, and presenting it as a positive diagnosis without significant organic complications.7,8,29 It is imperative to reassure the parents and minimize unnecessary diagnostic workup. There are recent data showing benefit from hypnotherapy. This is the group of patients who will benefit from referral to a psychologist for relaxation techniques and other coping mechanisms. It is also imperative to educate the school about this diagnosis to prevent unnecessary school absenteeism and promote a positive environment, with the goal of improving the quality of the child’s life.

In summary, abdominal pain is more complex than presented by Apley decades ago. The Rome III criteria will help promote clinical recognition and legitimization of specific functional GI disorders and help achieve optimum treatment for these patients.

**Overweight and Obesity in Children and Adolescents**

Over the last four decades, the rising concern for the tripled prevalence of overweight in children has provided new insight into the etiologic factors, medical morbidities, and multifaceted paradigms for the treatment, and strategies for prevention of this “new age” pandemic. Presently, there is no accurate and realistic method for measuring body fat. Body mass index (BMI—weight in kilograms divided by height in square meters, kg/m²) is used to define overweight. It has been correlated with medical morbidities like systolic hypertension, insulin resistance, etc. in children and adults.37

Experts at the Center for Disease Control and Prevention have suggested specific nomenclature for the
overweight child. A BMI above the 85th percentile is considered at risk for overweight. A BMI over the 95th percentile is considered overweight.

This review focuses primarily on the morbidities (Table 5) of being overweight in childhood and describes new data from the initial experience with bariatric surgery in children.

A single-prong approach to treat childhood obesity has failed because of its multifactorial etiopathogenesis. Factors associated with being overweight in childhood include dietary trends (easy availability and consumption of high caloric content foods that are highly processed and contain high carbohydrates), sedentary lifestyle, decreases in structured physical activity (increased television watching, use of computer and video games), psychosocial stressors, genetically heritable factors (Pro-opiomelanocortin [POMC] and Melanocortin 4 receptor [MC4R] gene) and cultural trends.38

The medical evaluation of an overweight child includes accurate anthropometry and BMI calculation, a detailed nutritional history, physical activity chart, and a behavioral and medical history. Medication history should include the use of atypical antipsychotic medication, mood stabilizers, anticonvulsants, and SSRIs, which are known to affect weight and appetite. It is also important to obtain a family history of overweight and obesity, type II diabetes, and cardiac, pulmonary, neurovascular, biliary, neoplastic, and endocrine disease.

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Description</th>
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<tbody>
<tr>
<td>Systolic Hypertension</td>
<td>Systolic blood pressure greater than 95th percentile for age and gender</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>Obstructive sleep Apnea, Pulmonary hypertension</td>
</tr>
<tr>
<td>Endocrine disease</td>
<td>Insulin resistance, Type II Diabetes mellitus, Polycystic ovarian disease</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Blount’s disease, Slipped capital femoral epiphysis (SCFE), Non-alcoholic fatty liver disease (NAFLD), Non-alcoholic steatohepatitis (NASH).</td>
</tr>
<tr>
<td>Bone and Joint disease</td>
<td>Depression, Atypical eating disorders, Social phobias and low self esteem</td>
</tr>
<tr>
<td>Spectrum of fatty liver disease</td>
<td>Headaches, visual disturbances</td>
</tr>
<tr>
<td>Spectrum of fatty liver disease</td>
<td>Gastroesophageal reflux disease (GERD), Cholelithiasis, Constipation</td>
</tr>
<tr>
<td>Nocturnal enuresis</td>
<td>Breast, ovarian, colon and prostate (in adults)</td>
</tr>
</tbody>
</table>

### Treatment

While nutritional therapy with exercise has shown good short-term results in children, behavioral therapy along with the above has shown promise for long-term weight loss maintenance. In children, the effect of the above strategies in reducing medical morbidities and prevention of developing further disease is not yet clear.

Weight loss surgery has evolved as a more aggressive but efficacious means of immediate and longer term weight loss that reduces morbidities like diabetes, hypercholesterolemia, and obstructive sleep apnea.39 The two common bariatric surgeries include laparoscopic adjustable gastric banding (LAGB) and laparoscopic gastric bypass. The complication rate and adverse events are decreasing with increasing experience with the surgery. About 10% of patients have significant complications of these procedures, which include anastomotic strictures, incisional hernias, and gallstone formation requiring cholecystectomy. Anastomotic leaks, staple line disruptions, and dumping syndrome can occur but have been reduced to 1 to 2% each by modifications in surgical technique.40,41 A fifth of patients may regain most of their weight on long-term follow-up after gastric restrictive surgery.

In children and adolescents, there are less data on the success, efficacy, and adverse event rate. However, compared with initial outcomes from the early 1980s, there has been a significant improvement in the success and safety of these procedures.41 In a study of 10 adolescents 17 years or younger with obesity-related morbidities who underwent gastric bypass surgery, 9 of 10 adolescents had weight loss in excess of 30 kg (mean weight loss was 53.6 ± 25.6 kg). Obesity-related morbidities resolved in all adolescents. Late complications requiring operative treatment occurred in four of the adolescents.42 In an excellent review of indications and therapeutic approaches available for the overweight adolescents, the following recommendations were drawn for bariatric surgery: Surgical management may be warranted for very severely obese adolescents who have serious obesity-related comorbid conditions and who have, in the opinion of their primary care providers, experienced failure of organized attempts to achieve sustained weight loss. Surgical therapy should be tailored to the individual patient’s needs, on the basis of the patient’s maturity level and the severity of comorbid conditions. It is essential for patients and their families to realize that...
bariatric surgery is not a cure for obesity but instead is an effective weight loss tool when patients comply with recommended dietary and physical activity regimens. Highly trained and skilled bariatric surgeons must play an integral role within multidisciplinary adolescent bariatric teams, to ensure safe and effective application of bariatric surgical procedures for adolescents.

The first US Food and Drug Administration (FDA)-approved trial of LAGB for 10 morbidly obese adolescent children with medical morbidities was published in 2007. The study enrolled subjects with a mean BMI of 50 ± 13, with a variety of morbidities to include sleep apnea, hypertension, dyslipidemia, metabolic syndrome, and steatohepatitis. All the patients lost 30 ± 13% of their excess body weight, with complete resolution of hypertension and near complete resolution of metabolic syndrome. There was also a significant improvement in the quality of life score and depression score.43 Retrospective data from the same group showed weight loss rates of up to 42% at 36 months.

Another study evaluated a larger sample (n = 73, 54F) of pediatric patients (13-17 years) with a mean BMI of 48 kg/m². The excess weight loss was 61 ± 27% at 2 years. One patient experienced a gastric perforation after a reoperation for band replacement; an additional patient requested band removal because of restriction intolerance after a slip. A total of six patients developed band slippage, and three patients developed symptomatic hiatal hernias. Nutritional complications included asymptomatic iron deficiency, asymptomatic vitamin D deficiency, and subjective hair loss. In 21 patients who had reached 1-year follow-up, there were 51 identified comorbid conditions. Of these, 35 (68.5%) were completely resolved, 9 (17.5%) were improved, 5 (10%) were unchanged, and 2 (4%) were aggravated after 1 year. There was no mortality in the follow-up time, thus rendering a conclusion that LAGB is an effective and relatively safe procedure in children with morbid obesity.43,44

Celiac Disease in Special Pediatric Conditions

A recent issue of this journal has presented a detailed review of celiac disease.45 Here we briefly emphasize the “at-risk” population. Conditions with an increased prevalence of celiac disease include children with first- and second-degree relatives with celiac disease, selective IgA deficiency, Downs syndrome, Turner’s syndrome, Williams syndrome, autoimmune thyroiditis, and Type I diabetes. The American Diabetes Association recommends routine screening for celiac disease in all children with type I diabetes. There is a commercially available genetic test that has helped define “gray zone” cases of celiac disease. It is particularly helpful when absent, making celiac disease extremely unlikely. However, a diagnosis of celiac disease cannot be made only with a positive genetic screen, as 33 to 40% of the normal population is positive for HLA-DQ2/DQ8.

Drug-Induced Intestinal Injury: Nonsteroidal Anti-Inflammatory Drugs (NSAID)

With expanding indications for continued NSAID use and empiric non-FDA labeled use of this group of drugs, there is increasing evidence of intestinal injury associated with their use. Historically gastric and duodenal ulcers were the only association. Present clinical data suggest a more expansive profile of intestinal diseases ranging from small bowel and colonic ulcerations to intestinal enteropathies.

The prevalence of small intestinal ulcerations was 8.4% in adults with no correlation between small bowel involvement and gastroduodenal disease.46 Intestinal perforation in adults on slow release NSAID has been well documented and suggests an alteration in target site from the stomach to mucosal injury in the small intestinal tract.47 The high-risk group in children appears to be preterm neonates, particularly after indomethacin exposure. Premature infants treated medically for patent ductus arteriosus closure had a 10 times higher risk of intestinal perforation, anywhere along the intestinal tract as compared with matched controls.48 Prolonged use of NSAID in adults has also been linked to intestinal strictures irrespective of ulcerative lesions with multiple thin web-like diaphragms being pathognomonic lesions.49

NSAID enteropathy and colitis is defined as a disturbance of the small intestinal function associated with NSAID use in the absence of macroscopic pathology due to diffuse alterations in intestinal inflammation and increased mucosal permeability.49 Seventy percent of NSAID users are believed to be at least partially affected by an enteropathy with features
of iron deficiency anemia, protein-losing enteropathy, and lipid malabsorption. Chronic use of NSAID may cause various forms of colitis (eosinophilic, collagenous, pseudomembranous, and nonspecific colitis), whose symptoms include watery and/or bloody diarrhea.\textsuperscript{50} Disease is more prominent on the right side of the colon. Graded evidence proves that NSAID use is known to activate UC.\textsuperscript{51} Hence cautious use of NSAID is recommended in all patients with known inflammatory bowel disease.

**Inflammatory Bowel Disease**

Over a million Americans suffer from inflammatory bowel disease (IBD) with about 10 to 25\% in the pediatric age group.\textsuperscript{52} The gold standard for the diagnosis of IBD in children remains endoscopic evaluation with tissue histology. However, less invasive modalities such as serological biomarkers, wireless capsule endoscopy, and advanced imaging are being developed with acceptable sensitivity and specificity.\textsuperscript{53}

**Diagnostic Modalities**

Laboratory screening commonly reveals an elevated sedrate or C-reactive protein, more often in Crohn’s disease than ulcerative colitis (UC), but normal values do not exclude a diagnosis of IBD as occurs in over 25\% of children with inflammatory bowel disease.\textsuperscript{54,55} Fecal markers of inflammation (eg, lactoferrin, calprotectin, PMN-elastase, etc.), specifically fecal calprotectin, is strongly associated with disease activity in childhood UC and Crohn’s disease.\textsuperscript{56} However, the primary role of these markers is in differentiating IBD from superimposed symptoms of IBS.

**Serological Biomarkers**

Five biomarkers are commercially available for this type of analysis (Prometheus Laboratories, San Diego, CA). They include the following: anti-Saccharomyces cerevisiae (ASCA) IgG and IgA, anti-Escherichia coli outer membrane porin C IgA, antipseudomonas fluorescens Crohn’s disease-related protein IgA, antiflagellin IgA, and antiperinuclear antineutrophil IgG with DNase sensitivity used to improve specificity. The prevalence of IBD-specific antibody markers in children and young adults is shown in Table 6.

A pediatric study demonstrated that a sequential serodiagnostic strategy was accurate in differentiating IBD from non-IBD in 84\% of patients presenting with nonspecific symptoms suggestive of IBD but with a normal physical examination. A positive test sequence was predictive of IBD in 90\% of patients and a negative sequence predicted the absence of disease in 80\%.\textsuperscript{57,58} Other evidence indicates that increasing degrees of immune reactivity to microbial antigens is associated with a more severe course and increased frequency of complications in patients with Crohn’s disease. A shorter time to onset of a complication was also noticed in this group. Higher ASCA levels are associated with younger age of disease onset, stricturing and penetrating disease, and need for surgery in both adults and children with Crohn’s disease.\textsuperscript{59} A recent retrospective pediatric study found that the combination of erythrocyte sedimentation rate and hemoglobin has a higher positive-predictive value and is more sensitive, more specific, and less costly than commercial serologic testing, as a screening strategy for IBD.\textsuperscript{60}

Wireless capsule endoscopy (WCE) can be performed in young children though most will require the placement of the capsule in the duodenum by endoscopy. Presently WCE can be used for determining disease recurrence in postoperative Crohn’s disease,\textsuperscript{61} but its use in the diagnosis of suspected IBD awaits prospective controlled trials in children.

**Imaging**

Abdominal ultrasound using high-resolution probes can detect bowel wall thickening, fibro-fatty infiltration of mesentery, enlarged nodes, and prestenotic dilation. Doppler ultrasound allows depiction of inflammatory hyperperfusion and morphological changes of the intestinal wall at sites of inflammation\textsuperscript{62} with sensitivity similar to small bowel series.

Magnetic resonance imaging (MRI) enterography is very useful for identifying transmural inflammation and bowel fistulae. In a study of contrast-enhanced MRI enterography for children with known or sus-
pected Crohn’s disease, the sensitivity and specificity of MRI for the positive diagnosis of Crohn’s disease were 100 and 83%, respectively. It is a well-tolerated, effective, noninvasive method in the evaluation of known or suspected Crohn’s disease in children.\(^63,64\)

While computerized tomography is an excellent tool for detecting disease and complications (eg, abscess), its use is limited by the significant radiation exposure. Computerized tomography enterography correlates with endoscopic severity and C-reactive protein in patients with Crohn’s disease and provides a noninvasive option to endoscopy when looking for disease activity.\(^64\)

**Therapeutic Advances**

The medical management of IBD has dramatically improved with better pharmacotherapeutic understanding of available medications as well as the emergence of biological agents.

For mild to moderate UC, the 5-amino salicylic acids have shown efficacy in inducing a response in 50-90% of adult patients and maintaining remission in 70-90%. The role of 5-amino salicylic acids in Crohn’s disease remains controversial.\(^65,66\)

Corticosteroids are indicated for moderate to severe UC in children. While response rates exceed 80%, dependency is seen in almost 50%.\(^67\) In children with Crohn’s disease the response rates mimic UC but dependence is seen in about a third with less than 8% requiring surgery within the first year.\(^68\)

Immunomodulator use in children with IBD is now becoming the standard of care for maintaining remission. Fifty percent of children with UC and 75% of children with Crohn’s disease are on immunomodulators within 2 years of diagnosis. While their efficacy when appropriately used and dosed remains unchallenged, caution needs to be exhibited before starting Azathioprine or 6-Mercaptopurine. These and other immunomodulator therapies like Methotrexate, and less commonly, Cyclosporine and Tacrolimus, need close monitoring of blood counts and drug levels to prevent adverse reactions (leucopenia, hepatotoxicity, pancreatitis, hepatic fibrosis, renal dysfunction, and lymphoma).

Biologic therapy (Infliximab, Adalimumab, Natalizumab) has revolutionized both the quality of life and the treatment paradigm for moderate to severe Crohn’s disease and UC refractory to standard therapy. Infliximab has been FDA approved since 2006 for children with moderate to severe Crohn’s disease with response rates of 89% at 10 weeks. It is well supported from adult and pediatric trials that continuing scheduled infusions are essential for maintaining remission. While anecdotal use continues, the use of infliximab for moderate to severe UC in children presently is in a phase IV clinical trial. Extra-intestinal manifestations like erythema nodosum, vasculitis, arthritis, and uveitis have also been shown to remit to biologic therapy when standard therapy has failed.\(^69\) These medications are contraindicated in children with active tuberculosis, serious infection, opportunistic infection (eg, herpes zoster, cytomegalovirus), and history of demyelinating disease, malignancy, or congestive heart failure. The two other agents, adalimumab and certolizumab, have shown similar response rates and are believed to cause less allergic reactions because they are fully humanized. The association between biologic therapies and malignancy remains controversial. Natalizumab is a humanized antibody against cell adhesion molecule α-4 integrin and has been anecdotally used in a small number of children with Crohn’s disease with a good efficacy.

Probiotics have failed to show reproducible efficacy in Crohn’s disease and is presently only indicated for the prevention and treatment of pouchitis.\(^70\)

**Treatment of Persistent Diarrhea and Travelers’ Diarrhea**

Persistent diarrhea is defined by the World Health Organization as an episode that begins acutely and lasts 14 days or more.\(^71-73\) With prevalence ranging from 5 to 25% it is a cause of significant morbidity in children. Poor nutrition appears to be a high-risk factor in predisposing an infectious agent into persistent diarrhea. Compounding vitamin A and zinc deficiency have been shown to be independent risk factors as well. The use of antibiotics for acute diarrhea has been implicated as a risk factor for developing persistent symptoms.\(^74-76\) Infectious agents like enteroadherant E coli has been often incriminated. Less compelling evidence suggests a role for Shigella, enterotoxigenic E. coli, and Campylobacter. Cryptosporidium and Giardia lamblia need to be considered in children with persistent diarrhea. Among viruses, rotavirus has been associated with a higher incidence in causing persistent diarrhea.\(^77\) In developed countries postinfectious enteropathy, bacterial overgrowth, and intestinal atopy predispose to similar
symptoms. Nitazoxanide (Alinia®) is efficacious in the treatment of Giardia and Cryptosporidium. The FDA has approved Rifaximin, a newer nonabsorbable oral antibiotic, for traveler’s diarrhea.

Zinc supplementation of 20 mg daily during the acute diarrhea episode significantly reduces the duration, severity, and risk of persistence of symptoms. Zinc supplementation also reduces the number of episodes in subsequent 2 to 3 months. The addition of amino acids to glucose-based oral rehydrating solution (ORS) has been proposed to create a “super ORS.” The addition of amylase-resistant starch has shown a beneficial profile with production of short-chain fatty acids, which improves absorption, but further clinical studies are needed before universal recommendation. Thus, when diarrhea persists for longer than 14 days, the above therapy options can be implemented.

Upper Gastrointestinal Bleeding

Gastrointestinal bleeding is a rare but alarming symptom in children. In newborn infants, the etiology may vary from benign conditions such as swallowed maternal blood or a cracked nipple to more serious lesions like duodenal ulceration, esophagitis, or gastritis. Treatment with antisecretory medications leads to favorable outcomes within 24 to 48 hours. Other causes include vascular anomalies, coagulopathies associated with vitamin K deficiency, metabolic disorders, and infections.

In older children bleeding may be secondary to mucosal disease of the upper GI tract such as gastritis, esophagitis, gastroduodenal ulcers, Mallory Weiss tear, esophageal or gastric varices, a vascular anomaly, GI duplication, coagulopathies, infections, and NSAIDS-induced intestinal lesions.

Medical management varies from observation in a child who had a small bleed with a stable hematocrit and no signs of active bleeding to aggressive management in a child with active bleeding. Initial management in a child with active bleeding includes stabilization, volume resuscitation, and correction of electrolytes and bleeding diathesis if present. Initial laboratory data include complete blood count, chemistry panel, and bleeding studies. An elevated blood urea nitrogen (BUN) is also suggestive of an intraluminal bleed. Oral as well as parenteral proton pump inhibitors (eg, esomeprazole) have been shown to decrease the incidence of rebleeding. Endoscopy along with parenteral PPIs have led to better outcomes compared with either intervention alone. Octreotide, a somatostatin analog, is beneficial in bleeding secondary to increased portal pressures since it decreases splanchic pressure without compromising blood flow to kidneys.

Diagnostic and Therapeutic Endoscopy

An upper GI bleed by definition is the bleeding proximal to the ligament of Treitz and an esophagogastroduodenoscopy not only helps establish the diagnosis 90% of the time, but also helps treat the condition and decrease the mortality and morbidity associated with it. An esophagasto-duodenoscopy done within 24 hours of initial symptoms leads to better outcome as compared with a delayed esophagastro-duodenoscopy.

There are no prospective data available in the pediatric literature for endoscopic management of an upper GI bleed. However the same techniques used for hemostasis in adults are also used in children and there are case reports from the pediatric literature to support these techniques. The main limitation in the pediatric patient is the size of the operating channel, which is 2 mm in a standard pediatric gastroduodenoscope. These channels can be used for sclerotherapy and Argon Laser catheters but are not compatible with a heater probe or a cautery probe. The endoscope with 2.8-mm operating channels cannot be used in children less than 2 years of age.

Endoscopic Hemostasis Technique

Endoscopic therapy is indicated for actively bleeding blood vessels or pigmented protuberances in an ulcer base. Injection therapy can be accomplished by using agents such as epinephrine or saline. Epinephrine in 1:10,000 or 1:20,000 dilution is the most common agent used in the pediatric population since it has the least side effects. However, systemic hypertension and tachycardia secondary to systemic absorption after esophageal injection has been reported. Epinephrine is injected 1 to 3 mm away from the blood vessel circumferentially at three to four sites. A sclerotherapy needle is used to inject varices with sclerosants such as ethanol, ethanolamine, and sodium morrhuate that cause direct tissue injury and thrombosis. Another class of tissue sealants is thrombin, fibrin, and cyanoacrylate glues.

A combination of epinephrine and sclerosant agents can be used; however, it increases risk of complications. The volume of these agents has not been
established for the pediatric population. Injection therapy has also been successfully used in combination with thermal coagulation.88

**Mechanical Methods for Hemostasis**

Endoscopic metallic clips have been used in upper GI bleeding for Mallory Weiss tears, ulcers, Dieulafoy lesions, gastric angiectasias, and gastric tumors.89 Mechanical hemostasis has been shown to be superior when combined with epinephrine in high-risk bleeding ulcers.90 Limitations are related to device setup, endoscopy technique, and manipulation of deployment device.

**Endoscopic Band Ligation**

The procedure entails placing an elastic band endoscopically over a vein after it has been suctioned into a cylindrical device. It is preferred over sclerotherapy for bleeding esophageal varices because of a decreased incidence of esophageal stricture and rebleeding compared with standard sclerotherapy. The procedure has to be repeated every 2 to 3 weeks until there is complete obliteration of varices.

**Thermal Hemostasis**

This is an endoscopic technique for hemostasis that is achieved by passing intermittent or continuous electrical current through the tissue at a bleeding site. There are two types of probes used: monopolar or bipolar probes. The electrical current produces high energy inside the cells, which leads to coagulation and subsequently shrinkage of bleeding vessels.

For small blood vessels the heat is applied directly. In large bleeding vessels the current is applied circumferentially around the vessel. The disadvantage of the monopolar probe is an increased risk of perforation and poor visibility due to clot adherence.

Bipolar hemostasis catheter is more popular because of better safety and hemostasis effectiveness. There is less risk of tissue perforation and less risk of tissue damage.

**Argon Plasma Coagulation (APC)**

This is a noncontact form of thermal coagulation using a monopolar probe. Electrical current is passed to the targeted tissue through ionized argon gas. The risk of tissue injury increases if the probe touches the tissue. The advantage of APC is that it can be used with the standard pediatric gastroduodenoscope. The smallest probe is 1.5 mm. The other advantage is that there is a decreased risk of tissue injury, perforation, and penetration with this technique. APC used for endoscopic techniques have been found to be safe in the pediatric population.91,92 Complications reported were scarring in stomach after treating a hemangioma in the stomach with APC and also submucosal gas, which developed as a result of the catheter touching the mucosa.93 The disadvantage is the cost of equipment.

**Combined Therapy**

Combined therapy is defined as an endoscopic hemostatic technique with injection therapy. Epinephrine helps with vasoconstriction and provides a better field of vision for application of thermal energy. Combination therapy is more effective for control of GI hemorrhage than either modality alone.

**Polyps and Polyposis Syndromes**

Major progress has been made in understanding the molecular pathogenesis of polyposis syndromes. Broadly classified as Adenomatous polyposis syndromes, they include Familial adenomatous polyposis; Gardner syndrome, Turcot syndrome, and Hamartomatous polyps to include Juvenile polyposis; Bannayan-Riley-Ruvalcaba syndrome; Cowden’s disease; Peutz-Jeghers syndrome; and mixed polyposis syndrome.

**Isolated Adenomas**

If an adenoma (Tubular or villous) diagnosis is made for an isolated or small number of polyps in a child or an adolescent, the following recommendations should be considered: (1) looking for a history of familial adenomatous polyposis (FAP), although a family history may be absent in sporadic forms of this disease; (2) history of familial colorectal cancer; and (3) employing postpolypectomy surveillance colonoscopy as proposed for adults by the Agency for Health Care Policy and Research Consortium.

Surveillance94 is suggested every 3 to 6 months for large sessile adenomas, annually for numerous adenomas, and every 3 to 5 years for multiple or solitary tubular adenomas.

**Familial Adenomatous Polyposis**

FAP is the most common polyposis syndrome in children. With a lifetime neoplastic risk of 100%, most patients develop adenomas by their teenage years with malignancy in the third to fourth decade.95
Individuals who should be offered genetic testing for adenomatous polyposis syndromes are as follows:

- 100 colorectal adenomas; first-degree relatives of patients with FAP
- 20 cumulative colorectal adenomas; first-degree relatives of patients with attenuated FAP at-risk individuals

**Screening Guidelines**

- APC gene mutation (+): flexible colonoscopy annually starting at age 10 to 12 years
- APC gene mutation (−): flexible sigmoidoscopy at age 25 years

If a patient’s genotype is not available, an annual flexible sigmoidoscopy or colonoscopy starting at age 10 to 12 years, then 2 years starting at age 35, then as per the guidelines for average-risk individuals starting at age 50.

Affected individual’s upper GI surveillance every 3 to 4 years and annually if upper tract polyps are identified. Annual physical examination and routine blood tests are needed to be performed per screening guidelines.

**Juvenile Polyps**

Three or more juvenile polyps or any number of polyps occurring in the context of a family history of juvenile polyposis or colon cancer have been proposed as a criterion for a risk of colon cancer.96

**Juvenile Polyposis Syndrome Screening Suggestions**

- Screen all first-degree relatives starting at age 10 or earlier if symptomatic.
- If positive for Juvenile Polyposis Syndrome, screening colonoscopy every 2 years.

These screening advances and genetic identification have been critical in the early identification and prevention of malignant complications associated with these syndromes.

**Genetic Factors in Chronic Pancreatitis in Children**

The earliest suggestion that chronic pancreatitis is an inherited disease came from studies by Comfort and Steinberg in the middle of the century.97 Since then, continuous genetic studies have revealed multiple mutations and susceptibility loci for triggering and propagating pancreatic inflammation.

Up to a third of chronic pancreatitis in children are of an idiopathic etiology. The American Gastroenterology Association has defined a working classification of risk factors for chronic pancreatitis. They include toxic-metabolic, genetic, autoimmune, recurrent, severe acute pancreatitis, and obstruction.98 This review focuses on the newer genetic etiology, describing indications for, and availability of, genetic testing for children with chronic pancreatitis.

The major genetic factors include mutations in the cationic trypsinogen gene (PRSS1), mutations in the pancreatic trypsin inhibitor gene, mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR), UDP glucuronyl transferase (UGT1A7), and genes altering the inflammatory process.

Depending on the mutation, hereditary pancreatitis is inherited in an autosomal-dominant pattern with up to 80% phenotypic penetrance.99,100

Clinically it is important to differentiate between familial and hereditary pancreatitis. Familial pancreatitis is used to describe any cause that occurs in a family with an incidence greater than would be expected by chance; hereditary pancreatitis should be restricted to patients with a gain of PRSS1 mutation or unexplained pancreatitis in a subject from a family in which pancreatitis phenotype seems to be inherited as an autosomal-dominant disorder.101

According to the consensus report, genetic testing in children less than 16 years for PRSS1 mutations is indicated after the following102:

- An episode of documented pancreatitis of unknown etiology and severe enough to require hospitalization
- Two or more documented episodes of pancreatitis of unknown etiology
- Documented episodes of pancreatitis occurring in a child with a relative known to carry a hereditary pancreatitis mutation.
- A child with recurring abdominal pain of unknown etiology where hereditary pancreatitis is a distinct clinical possibility
- Chronic pancreatitis of unknown etiology
- The significance of a positive genetic screen, inheritance, variable clinical course, malignancy risk, and avoidance of smoking, drugs and alcohol should be part of counseling.
Probiotics

Use in Disease Prevention and Treatment

Probiotics are live microorganisms that can offer benefit to the consuming host. Probiotics can reduce inflammation and its consequences especially in the intestinal mucosa (Michail S, Onady, G, Stolfi, A, et al. Unpublished data, 2008). They can serve as potential therapeutic options for specific pediatric disorders. Some of these disorders will be discussed in this section.

Allergy. The effect of probiotics in allergy has focused on either treatment or prevention of atopic dermatitis. Meta-analyses describing this role suggest a modest transient benefit in treating atopic dermatitis. Preventive effect was limited to a subset of patients. Currently, there is no role for probiotic use in asthma and there are conflicting reports regarding the efficacy of probiotics in allergic rhinitis.

Infections. Probiotics have no role in eradicating or preventing Helicobacter pylori infection but may be beneficial in reducing potential side effects encountered during traditional therapy.

The use of probiotic agents in other infections such as acute infectious diarrhea results in reduction of the duration of the acute symptoms by about 1 day. Necrotizing Enterocolitis. Systematic reviews suggest a promising role for probiotics in prevention of stage 2 or greater necrotizing enterocolitis in preterm infants with a reduction in the risk of death and a shorter time to achieve full enteral nutrition.

Inflammatory Bowel Disease. Several studies have been published that examine the effect of probiotics in Crohn’s disease, UC, and pouchitis. While adult data suggest some beneficial effect for probiotics, current pediatric studies have been quite disappointing; showing no role for probiotics in the treatment of children with Crohn’s disease.

The most promising role for probiotics in inflammatory bowel disease lies in the prevention and treatment of pouchitis. Pouchitis occurs as a complication following colectomy and ileal pouch anal anastomosis for UC. VSL#3, which is a mixture of eight different probiotic agents, has shown some efficacy in preventing the onset of pouchitis and may be helpful in mild active pouchitis.

Irritable Bowel Syndrome. Several adult studies suggest a therapeutic role for probiotics in treating patients with IBS. In pediatrics, there are only two trials published to date. Bausserman reported that the probiotic Lactobacillus GG administered to 50 children, for six weeks, was not superior to placebo in relieving abdominal pain. However, the children receiving probiotics had a lower incidence of perceived abdominal distension. The second pediatric study by Gawronska and coworkers showed efficacy with a 4-week therapy of Lactobacillus rhamnosus GG in treating FAP in children.

Summary

In summary, probiotics may prove to be attractive tools in managing several pediatric disorders in the future. Currently, there is some modest benefit seen in conditions such as acute infectious diarrhea where the duration of illness can be reduced by 1 day, pouchitis, and atopic dermatitis. More studies are needed to address many questions that remain unanswered such as safety and bioavailability of probiotics, accuracy of product labeling, and testing for reproducibility of retrieval of the probiotic in the GI tract, dose-response effects, and the use of “mixes” versus single-strain probiotic agents among many others.

Nutrition

Extensively Hydrolyzed and Elemental Formulae

Formula can be divided into several different categories using a number of different strategies. One commonly used classification is dependent on the type of protein content of the formula. To this end, there are cow-milk-based protein formulae, soy, hydrolyzed protein, and amino acid formulae (Table 7). The most common clinical indication for the use of hydrolyzed or amino acid formulae is food protein allergy, malabsorptive disorders, Crohn’s disease, and transpyloric tube feeding. The use of such formulae to induce remission for Crohn’s disease is controversial. A recent Cochrane review could not demonstrate that enteral nutrition was as effective as corticosteroid therapy in inducing remission of active Crohn’s disease. The type of protein content of the formula did not affect the outcome of Crohn’s disease activity.

Symptoms of food protein allergy can be immunoglobulin E (IgE) or non-IgE mediated. Presenting symptoms related to IgE sensitization include urticaria, eczema, wheezing, angioedema, rhinitis, vomiting, or more severely, an anaphylactic reaction. Non-IgE-associated disorders seen during consump-
tion of cow’s milk, soy, or any other offending dietary proteins include malabsorption,\textsuperscript{115} eosinophilic proctocolitis,\textsuperscript{115} enterocolitis, eosinophilic esophagitis,\textsuperscript{116} pulmonary hemosiderosis,\textsuperscript{117,118} and colic.\textsuperscript{119}

The prevalence of milk protein allergy ranges from 1 to 17%.\textsuperscript{120,121} Breastfeeding is believed to protect against development of atopic disease in high-risk infants\textsuperscript{122} and should be strongly encouraged. However, when breast-feeding is not possible or unavailable, “hypoallergenic formula” can be considered.

The mainstay of therapy of infants and children with food allergy is avoidance. Therefore, infants allergic to cow’s milk should not be given formula containing intact animal protein. Soy formulas can be a reasonable alternative. However, clinicians need to be aware that 8 to 14% of infants with symptoms of IgE-associated cow’s milk allergy will also react to soy,\textsuperscript{123,124} with an even higher prevalence of cross-reaction between cow’s milk and soy proteins (25-60%) among those infants with proctocolitis and enterocolitis.\textsuperscript{125,126} However, anaphylactic reactions with soy are uncommon as compared with cow’s milk. Extensively hydrolyzed formulas can be reasonable choices in infants who are severely sensitized. The majority of those infants (>90%) tolerate extensively hydrolyzed formulae, such as Neutramigen, Alimentum, and Pregestamil.\textsuperscript{127} The use of free amino acid-based infant formula should be reserved for those infants who continue to react to extensively hydrolyzed formula.

Extensively hydrolyzed and amino acid formulas are excellent nutrition options for infants, and toddlers who consume them exclusively over a long period of time grow well. Many of these specialized formulae are quite expensive and should be used under the supervision of physicians for specific clinical scenarios.

**Probiotics in Infant Dietetics**

Probiotics have become ingredients of dietetic products in the United States as well as many other countries. A medical position paper examining the effect of probiotic bacteria in dietetic products for infants has been published as a Commentary by the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition.\textsuperscript{128,129} The committee reviewed all publications pertaining to the use of probiotics in infants and found several randomized controlled trials that suggested a limited and short-term clinical benefit for the use of probiotics in infant dietetics. The committee recommended that more rigorous scientific data would be necessary before concluding that probiotic supplementation would be used to prevent or treat pediatric diseases.

**Growth.** Issues related to growth of infants consuming probiotic-supplemented formula have been evaluated in several studies. While there has been no concern regarding growth delay during these trials, most of the studies have not provided sufficient growth data and relevant information to allow the reader to reach the same conclusion.

**Safety.** The safety of probiotics in general, and in infants, especially preterm infants, has been investigated in a limited number of controlled trials. The findings this far suggests that probiotics are generally safe. However, there have been isolated reports of fungemia and bacteremia in children receiving probiotic products. Issues related to modifying the immune system so early in life and potential long-term consequences remain to be resolved and additional studies are needed.

**Prebiotics and Infant Dietetics**

Prebiotics are nondigestable carbohydrates, which when ingested, can promote the growth of probiotic bacteria in the gut. Symbiotic is a term that refers to the combined use of prebiotics and probiotics. Human breast milk contains a variety of oligosaccharides that are believed to be an important factor.

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**TABLE 7. Examples of formulae classified by type of protein**

<table>
<thead>
<tr>
<th>Type of protein</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact cow’s milk protein</td>
<td>Infant: Enfamil®, Similac®, Lactofree®, EnfaCare®, Neosure®, Enfamil® AR. Pediatric: Pediasure®, Compleat® Pediatric, Kindercal®</td>
</tr>
<tr>
<td>Soy protein</td>
<td>Infant: Prosobee®, Isomil®, Good Start®, Soy, Isomil® DF Toddler: Bright Beginnings®</td>
</tr>
<tr>
<td>Amino Acid</td>
<td>Infant: Neocate® infant, Elecare® Pediatric: Neocate® One +, Neocate® Jr, Pediatric EO28®, Vivonex® Pediatric, Elecare®</td>
</tr>
</tbody>
</table>
in the pattern of microflora colonization of breastfed infants. Breastfed infants predominantly harbor lactobacilli and bifidobacteria, whereas formula-fed infants predominantly harbor Enterobacteria and Gram-negative organisms.

The European Society of Pediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition has published recommendations regarding the use of prebiotic in infant dietetics. The committee found evidence to support short-term effects of ingesting prebiotics on stool microflora of infants with an increase in the number of bifidobacteria. However, there was no evidence to support a major clinical or long-term benefit. The committee was unable to determine whether the increase in the number of bifidobacteria in the gut was related to any “functional outcome, eg, immune or inflammatory modulation”.

There are a small number of good studies that assess the beneficial effect of prebiotics or oligosaccharides when added to the diet of infants and children. The benefit reported by some of these trials has been modest and limited. One study reported the development of softer stools in infants consuming prebiotic dietetics. The benefit does not seem to be universal or persistent for all trials.

Other conditions such as infectious diarrhea have been studied as well. In one large randomized trial, the effect of oligofructose in reducing infectious diarrhea or other infectious disorders could not be confirmed.

Furthermore, the committee could not support a recommendation using prebiotics, such as fructooligosaccharides, inulin, and other nondigestible carbohydrates, in oral rehydration solutions.

**Summary**

The subject of adding probiotics or prebiotics to infant foods is fascinating and deserves investigation. However, much of the evidence remains preliminary. There is little evidence in favor of a beneficial effect of prebiotics in dietetic products. Prebiotics can increase the number of bifidobacteria in the stools. The clinical benefit appears to be modest and mostly related to softening stools. The long-term benefit of prebiotic use has not been evaluated. Expert Committee opinion concludes: “there is no published evidence of other clinical benefits of adding prebiotic oligosaccharides to dietetic products for infants.”

**Endoscopic Advances (Diagnosis and Therapy)**

**The Use of Wireless Capsule Endoscopy In Children**

**Introduction.** WCE is the most significant advancement for less-invasive evaluation of the small intestine in recent history. WCE allows direct visualization of mucosal lesions that are not apparent by traditional contrast radiography such as upper GI series or small bowel dual contrast studies. It is less invasive and more easily tolerated than push enteroscopy or double balloon enteroscopy, the other currently available modalities for endoscopic small bowel visualization. Since the approval of WCE by the FDA in 2001 for adults, and 2003 for children, over 500,000 patients have been safely evaluated by this unique modality. The purpose of this review is to describe this new technology and discuss the indications and advantages of WCE over standard radiologic and endoscopic techniques in children.

**Technology, Complications, Contraindications.** The PillCam® SB video capsule is vitamin sized, measures $11 \times 26 \text{ mm}$ (Fig 3) and weighs less than 4 g. It provides resolution down to 0.1 mm; an upper GI typically identifies lesions 0.5 mm or larger. The capsule is composed of four light-emitting diodes, a lens, color camera chip, radiofrequency transmitter, antennae, and two batteries lasting 8 hours. Pictures are transmitted to a receiver worn by the patient at a

![FIG 3. Given® wireless capsule. (Color version of figure is available online.)](image-url)
rate of two images per second, generating more than 50,000 pictures per study.

Patient preparation includes a 10- to 12-hour fast the day before the procedure. Clear liquids can be given 2 hours into the procedure, and a light meal at 4 hours. An array of sensors are attached to the patient’s abdomen and the data recorder to a belt around the patient’s waist (Fig 4). The sensors locate the capsule during the study to within 6 cm. The capsule is either swallowed or placed endoscopically, and the patient can then resume daily activities. After 8 hours the patient returns; the recording device is removed, and the recorded pictures are downloaded. The pill passes naturally with a bowel movement, usually within 24 hours.

Proprietary software is utilized to analyze the images, which includes a blood indicator to identify areas of the bowel that may be bleeding, with an estimated accuracy (measure of conformity between a quantity and its actual value) of 81%. More recent software upgrades include photo recognition of common lesions to aid in detection and diagnosis.

Patients older than 10 years of age can often swallow the capsule with only water; however, endoscopic placement of a capsule has been reported in patients as small as 2.5 years old, weighing 12 kg. The primary complication of WCE is capsule retention, defined as a capsule present internally for a minimum of 2 weeks. This has occurred in approximately 1.5% of patients with obscure GI bleeding and 5% of patients with Crohn’s disease. Possible predictors of retention are NSAID use, Crohn’s disease, previous small bowel obstruction, resection, or surgery.

Contraindications to capsule endoscopy currently include pregnancy, strictures or fistulae, presence of cardiac pacemaker, defibrillator, or other implanted medical device.

**Indications.** The general indication for WCE is to evaluate for suspected small bowel disorders. This can be further broken down into three categories: (1) diagnostic; (2) therapeutic monitoring; and (3) surveillance.

**Diagnostic. Small bowel disease.** In 28 pediatric patients with suspected small bowel disease WCE was found to be more sensitive than radiographic or endoscopic investigations and led to alteration in management in 64% of the patients evaluated.

**Abdominal pain.** There are divergent opinions as to the usefulness of WCE in evaluating nonspecific abdominal pain in children. In a prospective study evaluating 10 children with functional abdominal pain investigators found significant abnormalities in 4/10 children previously evaluated by laboratory and radiographic studies. Barden and coworkers studied 20 patients with chronic abdominal pain after a workup that included normal upper and lower endoscopy. In addition, three-quarters of their patients had specialized imaging studies, liver and kidney panels, complete blood count, and erythrocyte sedimentation rate. No significant abnormalities were found, suggesting a lack of benefit of capsule endoscopy in this group of patients.

**Celiac disease.** A pilot study found that the characteristic findings of villous atrophy were seen in all 10 untreated celiac patients evaluated by capsule endoscopy. In a similar study looking at 43 patients with both biopsies and capsule endoscopy in the evaluation of celiac disease, they reported a sensitivity of 87.5% and specificity of 90.0%. The positive-predictive value was 96.5% and negative-predictive value was 71.4%. This suggests a role for WCE in patients with suspected celiac disease but with negative initial findings on upper endoscopy. Further studies to answer this question are pending.

**Inflammatory bowel disease.** WCE was used by Arguelles-Arias and coworkers to diagnose IBD in pediatric patients with a clinical suspicion of IBD, but
with negative endoscopic as well as radiographic (UGI/SBFT) findings. Seven of 12 patients (58.3%) had WCE studies consistent with IBD. WCE detects small bowel lesions better than dual contrast computed tomography scans in patients with known Crohn’s disease and occult GI bleeding.\textsuperscript{143} Leighton and coworkers found that WCE has an incremental yield above 30% versus other imaging modalities in looking for small bowel Crohn’s disease.\textsuperscript{144} They found WCE useful in (1) determining the extent and severity of small bowel disease; (2) postoperative recurrence; (3) documenting posttherapy mucosal healing; and (4) ruling out active small bowel disease in the clinical setting of a functional disorder.

**Obscure GI bleeding.** Obscure GI bleeding is one of the main indications for performing WCE. The annual incidence of GI bleeding is about 1 per 1000.\textsuperscript{145} Obscure GI bleeding, defined as bleeding of unknown origin that persists or recurs after a negative initial evaluation including large and small bowel endoscopy, occurs in 5% of children presenting with GI bleeding. Multiple studies have confirmed the superiority of WCE in this diagnosis with a sensitivity and a specificity of up to 95%.\textsuperscript{146} Repeat studies may even prove helpful as demonstrated in patients with an initially negative WCE for obscure GI bleeding. Repeat WCE was able to detect a new lesion in up to 11/24 (75%) of patients and in 15/24 (62.5%) led to changes in patient management.\textsuperscript{147}

**Monitoring Therapy.** Capsule endoscopy has been used to monitor treatment in a severe case of Henoch–Schoenlein purpura.\textsuperscript{148} Medication changes were guided by the appearance of the small bowel disease. WCE in a 8-year-old after allogenic hematopoietic cell transplantation for acute lymphoblastic leukemia with voluminous bloody diarrhea identified diffuse small bowel disease with erosions and bleeding, consistent with graft-versus-host disease.\textsuperscript{149} The patient responded to more intensive graft-versus-host disease therapy.

**Surveillance.** Improved surveillance for polyp formation by WCE in hereditary polyposis syndromes has been demonstrated but is not currently approved as standard of care. WCE has helped identify polyps in children with polyposis syndromes as demonstrated in two patients with hamartomatous polyp syndromes (Cowden’s and Puezt–Jegher syndrome) not originally visualized by GI endoscopy.\textsuperscript{150} In 4 patients with Puezt–Jegher and 16 with FAP studied with MRI and WCE,\textsuperscript{151} WCE was superior to MRI in finding polyps less than 15 mm, and the only modality visualizing polyps less than 5 mm. Similar results were found in 29 patients with FAP and 11 with Puezt–Jegher.\textsuperscript{152}

**Summary**

WCE is a new tool available for use in the pediatric patient, which has improved our ability to visualize mucosal lesions in the small intestine that are not apparent by traditional endoscopic or radiographic modalities. The capsule in its current form has been utilized in patients as small as 12 kg and 2.5 years of age. Increased diagnostic acumen, the ability to monitor therapy in small bowel disease, and the accuracy of surveillance in hereditary polyposis syndromes may all improve in the future with use of this 4 g camera.

**Narrow Band Imaging**

**Introduction**

It is a high-resolution new endoscopic imaging technology that utilizes optical filters and light wavelengths of narrow bands to enhance the microvasculature of mucosal surfaces. The white light goes through a XENON lamp and is dispersed into a narrow band blue light wavelength of 415 nm, which is absorbed by hemoglobin and displays the superficial capillary network while the green light wavelength of 540 nm penetrates the deeper tissue. This is then reflected back into a device attached to the endoscope and then goes through a video processor to generate a single color image.

**Advantages**

It can be used simultaneously with endoscopy with no limitation of visual field and does not require a dye.

**Indications**

It will help detect early changes in the microvasculature and mucosal abnormalities in dysplastic lesions, which can be missed by routine colonoscopy. In the pediatric population it will be utilized in surveillance colonoscopy of patients with UC to detect high-grade dysplasia, as well as early detection of Barrett’s esophagus,\textsuperscript{153} which is seen, though infrequently, in children.
Chromoendoscopy

Introduction

It is a new emerging endoscopic technique that uses dyes during endoscopy to enhance visualization of abnormal-appearing mucosa accessible to endoscope.

Advantage

There is no special expensive equipment required. In addition to the dye, a spray catheter is used. Some of the dyes or stains that have been used are Lugol’s solution, Toludine Blue, Methylene Blue, Crystl Violet, Indigo Carmine, Congo red, and Phenol Red.

Indications

Chromoendoscopy may have a role in the pediatric population for detection of villous atrophy in celiac disease, surveillance colonoscopy in patients with UC for early detection of high grade dysplasia, detection of Barrett’s esophagus, and differentiating adenomatous polyps from hyperplastic polyps.

Endoscopic Ultrasound

Introduction

Endoscopic ultrasound is a combination of endoscopy and ultrasonography, using a high-frequency ultrasonic transducer passed through the operating channel of the endoscope.

Advantage

It has evolved as a safe and reliable imaging modality for a spectrum of upper GI disorders. It has been particularly useful in characterization of submucosal lesions that are inaccessible to conventional endoscopic biopsy. It has been particularly useful in staging of pancreatic malignancies in adults.

Indications

In the pediatric population endoscopic ultrasound has been used for diagnosis of superior mesenteric artery syndrome, Henoch–Scholen purpura, and, more recently, high-resolution endoscopic ultrasound was used to diagnose unclear cases of pyloric stenosis. Its use continues to expand in defining congenital lesions of the pancreatic and biliary tree. Studies are underway to assess the sensitivity of this modality in differentiating between UC and Crohn’s disease.

Endoscopic Retrograde Cholangio Pancreatography (ERCP)

Introduction

ERCP is a procedure used for the diagnosis and interventional therapies used in pancreatic and biliary disease. It has been somewhat underutilized in pediatric patients primarily due to the lower incidence of pancreatic and biliary disease in children. Presently pediatric ERCPs are performed at major centers around the country.

The first successful ERCP was performed by Waye in 1976 and since then several series of pediatric patients undergoing ERCP has been published. Guelrud and coworkers evaluated infants with neonatal cholestasis over a 12-year period. With the availability of new equipment for pediatric infants (PJF-240 videoduodensoscope), he was able to optimally perform an ERCP with a success rate of 90% and no significant complications, thus establishing its safety in neonates when performed by an endoscopist experienced in the procedure.

Indications are systematically listed in Table 8.

Conclusion

In summary, there have been numerous recent advances in pediatric gastroenterology. The above re-

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**Table 8. Clinical indications where ERCP has been used**

<table>
<thead>
<tr>
<th>Biliary Disorders</th>
<th>Pancreatic Disorders</th>
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<tbody>
<tr>
<td><strong>Diagnostic</strong></td>
<td><strong>Therapeutic</strong></td>
</tr>
<tr>
<td>Neonatal cholestasis</td>
<td>Sphincterotomy</td>
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<tr>
<td>Biliary atresia</td>
<td>Stone extraction</td>
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<tr>
<td>Choledochal cyst</td>
<td>Stricture dilation</td>
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<tr>
<td>Primary Sclerosing cholangitis</td>
<td>Stent placement</td>
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<tr>
<td>Biliary obstruction: Choledocholithiasis</td>
<td>Biliary drainage</td>
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<tr>
<td>Sphincter of Oddi manometry</td>
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<tr>
<td><strong>Diagnostic</strong></td>
<td><strong>Therapeutic</strong></td>
</tr>
<tr>
<td>Congenital pancreatic duct anomalies</td>
<td>Stent placement</td>
</tr>
<tr>
<td>Pancreas divisum</td>
<td>Pseudocyst drainage</td>
</tr>
<tr>
<td>Duodenal duplication</td>
<td>Stone removal</td>
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<tr>
<td>Cystic dilations etc.</td>
<td>Stricture dilation</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
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</table>
view has highlighted a few of the more common conditions seen in general pediatric and pediatric gastroenterology practices.

The last two decades have seen the introduction of potent acid suppression therapy with proton pump inhibitors (eg, Omeprazole) into the treatment paradigm of pediatric and infant gastroesophageal reflux disease. The use of Miralax® has shown both efficacy and safety in the treatment of functional constipation in children and adolescents. The ROME III criteria has helped stratify patients with abdominal pain previously grouped together as functional GI disorders. This enables a better understanding, minimizes a detailed workup, and maximizes the quality of life of these patients with medication, dietary, and behavior modification therapies.

The search for less invasive, yet accurate, diagnostic techniques continues for disorders like inflammatory bowel disease. Potent biologic therapies targeting cytokines and inflammatory molecules have introduced mucosal healing as the standard for therapy. Probiotics continue to evolve, with newer indications. They have shown a modest benefit in acute infectious diarrhea and atopic dermatitis. In IBD they have shown a benefit in the treatment and prevention of pouchitis in adults only.

In nutrition, the last two decades have witnessed the advent of elemental formulas. This development has improved intestinal and nutritional rehabilitation in children with significant protein allergy and malabsorption. The prevention and treatment of obesity and medical morbidities of overweight with a team approach is now available in most centers. Studies that examine the severity of this epidemic and cost-effective strategies to control it are underway at both a local and a national level.

Finally, the field of diagnostic and therapeutic endoscopy has seen an exponential evolution in new technology. The invention of the less invasive wireless capsule has enabled us to visualize previously unreachable areas of the small intestine. The patency capsule (self-dissolving) awaits clinical trials in pediatrics. Double balloon enteroscopy and endoscopic retrograde cholangiopancreatography continue to be explored for pediatric indications.

The next few decades will witness further advances in genomics and proteomics, enabling clinicians to predict disease phenotype, clinical course, outcomes, and pharmacologic response in various conditions. Motility studies will further stratify patients with chronic abdominal pain and suspected dysmotility, based on objective findings.

The “next big thing” in GI endoscopy is natural orifice transluminal endoscopic surgery. Still in its infancy, this new approach uses existing flexible endoscopic instrumentation to puncture the wall of the stomach to gain access into the peritoneal cavity to perform various procedures. Thus far, the use of this technique for diagnostic exploration, liver biopsy, cholecystectomy, splenectomy, and tubal ligation has been reported in animal models. These, among other inventions, continue to excite both the research and the clinical communities in pediatric gastroenterology across the globe.

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