Recommendations for Evaluation and Treatment of Common Gastrointestinal Problems in Children With ASDs

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KEY WORDS

autism spectrum disorder, abdominal pain, constipation, diarrhea, gastroesophageal reflux disease

ABBREVIATIONS

ASD—autism spectrum disorder
GER—gastroesophageal reflux
PEG—polyethylene glycol
HLA—human leukocyte antigen
LBT—lactose breath test
Ig—immunoglobulin
GERD—gastroesophageal reflux disease
PPI—proton-pump inhibitor

Drs Buie and Fuchs made equal contributions to the development and preparation of this manuscript.

The guidance in this article is not intended to advocate for an exclusive course of treatment or to represent a standard of medical care. Individual circumstances will determine variations that may be appropriate.

www.pediatrics.org/cgi/doi/10.1542/peds.2009-1878D

doi:10.1542/peds.2009-1878D

Accepted for publication Sep 4, 2009

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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abstract

Children with autism spectrum disorders (ASDs) can benefit from adaptation of general pediatric guidelines for the diagnostic evaluation of abdominal pain, chronic constipation, and gastroesophageal reflux disease. These guidelines help health care providers determine when gastrointestinal symptoms are self-limited and when evaluation beyond a thorough medical history and physical examination should be considered. Children with ASDs who have gastrointestinal disorders may present with behavioral manifestations. Diagnostic and treatment recommendations for the general pediatric population are useful to consider until the development of evidence-based guidelines specifically for patients with ASDs. *Pediatrics* 2010;125:S19–S29

In 2008 a multidisciplinary panel that reviewed gastrointestinal aspects of autism spectrum disorders (ASDs) recommended that "individuals with ASDs who present with gastrointestinal symptoms warrant a thorough evaluation, as would be undertaken for individuals without ASDs who have the same symptoms or signs."[1] The prevalence of gastrointestinal symptoms in children with ASDs has been reported to range from 9% to 70% or higher.[1–3] Evidence-based guidelines for the evaluation of gastrointestinal symptoms are not yet available for children with ASDs.[1]

Consensus guidelines have been developed by medical societies for the management of commonly encountered gastrointestinal symptoms in the general pediatric population.[4–7] Few, if any, of these published documents addressed modifications in the diagnostic evaluation based on the needs of children with disabilities such as impaired language skills. Clearly, evidence-based information is needed to guide therapy for children with ASDs, but until these data exist, recommendations will be supported by the opinions of pediatric gastroenterologists from practices across the United States with substantive experience in the care of children with ASDs. For this article, 8 pediatric gastroenterologists reviewed published guidelines for the management of gastrointestinal symptoms that occur frequently in the general pediatric population. Then, on the basis of their clinical experience, they adapted current best practices to diagnostic evaluation and treatment for children with ASDs. These expert-opinion recommendations are presented for chronic abdominal pain, chronic constipation, chronic diarrhea, and symptoms of gastroesophageal reflux (GER).

The primary care provider or specialist is encouraged to use these recommendations as a guide for evaluation of the child with an ASD who presents with symptoms and/or signs that suggest abdominal distress. We also discuss the association of self-injurious behavior and disturbed sleep with underlying gastrointestinal pathology in an effort to raise awareness of atypical presentations of common gastrointestinal problems in individuals with ASDs.

CHRONIC ABDOMINAL PAIN

Differential Diagnosis

For practical purposes, chronic abdominal pain is defined as intermittent or constant abdominal pain that exceeds 1 or 2 months in duration, but for children with ASDs this remains a challenging assessment. Although underlying causes of chronic abdominal pain are frequently benign, parents are often worried that their child with an ASD is in gastrointestinal distress and that their practitioner should be concerned about missing a serious disease.

Evaluation

Generally, for children without ASDs between the ages of 4 and 18 years, functional abdominal pain can be diagnosed correctly by the primary care practitioner when alarm symptoms (Table 1)[5] are absent, results of the physical examination are normal, and stool does not contain occult blood. Evaluation of abdominal pain in a child with impaired communication skills is challenging. As yet there are no reliable signs or symptoms that enable the health care provider to distinguish between organic and functional disorders. Certain children with ASDs are able to communicate when they experience episodes of pain by using language or other communication tools. However, others have limitations in communication and may express abdominal pain in atypical behaviors or changes in state of being that may not be perceived as indicating the source of the discomfort. These behaviors include pressing on the abdomen and tapping on the areas of distress; changes in state of being include sleep disturbance,[8] self-injurious behavior, and aggression. The presence of any alarm symptom should initiate an evaluation, but even in the absence of alarm symptoms, a diagnostic evaluation (Table 2) or empiric trial of a therapeutic intervention (Table 3) may be considered.

TABLE 1 Alarm Symptoms or Signs That Warrant Consideration of Diagnostic Testing in Typically Developing Children Who Present With Chronic Abdominal Pain

Involuntary weight loss
Deceleration of linear growth
Gastrointestinal blood loss (visible or occult)
Significant vomiting, including
Bilious emesis
Protracted vomiting
Cyclical vomiting
Chronic severe diarrhea
Persistent right upper or right lower quadrant pain
Unexplained fever
Family history of inflammatory bowel disease
Abnormal or unexplained physical findings

Data source: American Academy of Pediatrics, Subcommittee on Chronic Abdominal Pain. *Pediatrics*. 2005;115(3):812–815.

Treatment Considerations

Education is an important part of treatment. In the absence of alarm symptoms, after an unrevealing diagnostic evaluation and failure of empiric treatment to resolve the symptom or behavior, it may be helpful for the practitioner to review with the family the child's symptoms and explain that although the pain is real, there is no evidence at present of a serious or chronic disease. The clinical picture can change over time, and individuals with ASDs should be reevaluated if their symptoms or signs change.

TABLE 2 Adaptation of Diagnostic Tests for Evaluation of Abdominal Pain or Chronic Diarrhea in Children With ASDs

Tests That May Be Difficult to Complete	Tests That May Be Easier to Complete (Be Selective)
Noninvasive tests	
Upper gastrointestinal series with small-bowel follow-through	Stool for enteric pathogens, ova/parasites, *Giardia* antigen, *C difficile* toxin
72-h fecal-fat collection	Stool: guaiac, electrolytes/osmolarity (if secretory diarrhea), split and neutral fat, calprotectin, lactoferrin, trypsinogen, α-1-antitrypsin, elastase
LBT	Serum: electrolytes, liver function tests
	Assessment of nutritional status (if appropriate): anthropometry, 25-OH vitamin D
	Abdominal radiograph (assessment of bowel gas pattern and retention of stool)
Tests that require anesthesia	
—	Upper endoscopy: biopsy looking for enteritis; disaccharidase assay (lactase or sucrase–isomaltase deficiency); secretin test
	Colonoscopy: biopsy looking for colitis

TABLE 3 Empiric Treatments for Abdominal Pain in Children With or Without ASDs

Trial of a strict lactose-free diet for 2 wk
Trial with a PPI for 2–4 wk
Trial with PEG 3350 for 4 wk

CONSTIPATION

Differential Diagnosis

Constipation is the occurrence for 2 weeks or so of a delay or difficulty in defecation. The causes of constipation are many and may be organic or nonorganic; medications can be a potential cause (Table 4).[7] Children with ASDs can have sensory processing abnormalities and develop stool-withholding behaviors or constipation related to altered pain responses. Even children with ASDs who have daily bowel movements may have retention of stool that is not evident to parents, teachers, or health care providers.

Evaluation

The evaluation of all children who present with constipation should include a thorough medical history and physical examination. Information from the history and physical examination usually enables the physician to determine if further evaluation is warranted or if functional constipation is present (Fig 1).[7] Determination of what the family or child means when they use the term "constipation," the frequency of bowel movements, the consistency and size of stools, and whether the child experiences abdominal pain is important. A history of stool-withholding behavior reduces the likelihood of there being a causative organic condition.

Components of a thorough physical examination are listed in Table 5.[7] For children with ASDs, the physical examination may not identify palpable stool in the left lower quadrant, and a careful rectal examination might not be feasible. Every attempt should be made to examine the rectum, although at times this cannot be accomplished. The rectal examination enables assessment of stool retention, anal tone, and occult mass, as well as the presence or absence of blood, and helps to reassure the family that their child's anatomy is normal. It need not be repeated on subsequent visits unless there is a change in the history or physical examination.

A plain radiograph of the abdomen may reveal a rectal fecal mass not palpable on the abdominal examination,[9]

TABLE 4 Differential Diagnosis of Constipation

- Nonorganic
  - Developmental
    - Cognitive handicaps
    - Attention deficit disorders
  - Situational
    - Coercive toilet training
    - Toilet phobia
    - School bathroom avoidance
    - Excessive parental interventions
    - Sexual abuse
    - Other
  - Depression
  - Constitutional
    - Colonic inertia
    - Genetic predisposition
  - Reduced stool volume and dryness
    - Low fiber in diet
    - Dehydration
    - Underfeeding or malnutrition
- Organic
  - Anatomic malformations
    - Imperforate anus
    - Anal stenosis
    - Anterior displaced anus
    - Pelvic mass (sacral teratoma)
  - Metabolic and gastrointestinal
    - Hypothyroidism
    - Hypercalcemia
    - Hypokalemia
    - Cystic fibrosis
    - Diabetes mellitus
    - Multiple endocrine neoplasia type 2B
    - Gluten enteropathy
  - Neuropathic conditions
    - Spinal cord abnormalities
    - Spinal cord trauma
    - Neurofibromatosis
    - Static encephalopathy
    - Tethered cord
  - Intestinal nerve or muscle disorders
    - Hirschsprung disease
    - Intestinal neuronal dysplasia
    - Visceral myopathies
    - Visceral neuropathies
  - Abnormal abdominal musculature
    - Prune belly
    - Gastroschisis
    - Down syndrome
  - Connective tissue disorders
    - Scleroderma
    - Systemic lupus erythematosus
    - Ehlers-Danlos syndrome
  - Drugs
    - Opiates
    - Phenobarbital
    - Sucralfate
    - Antacids
    - Antihypertensives
    - Anticholinergics
    - Antidepressants
    - Sympathomimetics
  - Other
    - Heavy-metal ingestion (lead)
    - Vitamin D intoxification
    - Botulism
    - Cow's milk protein intolerance

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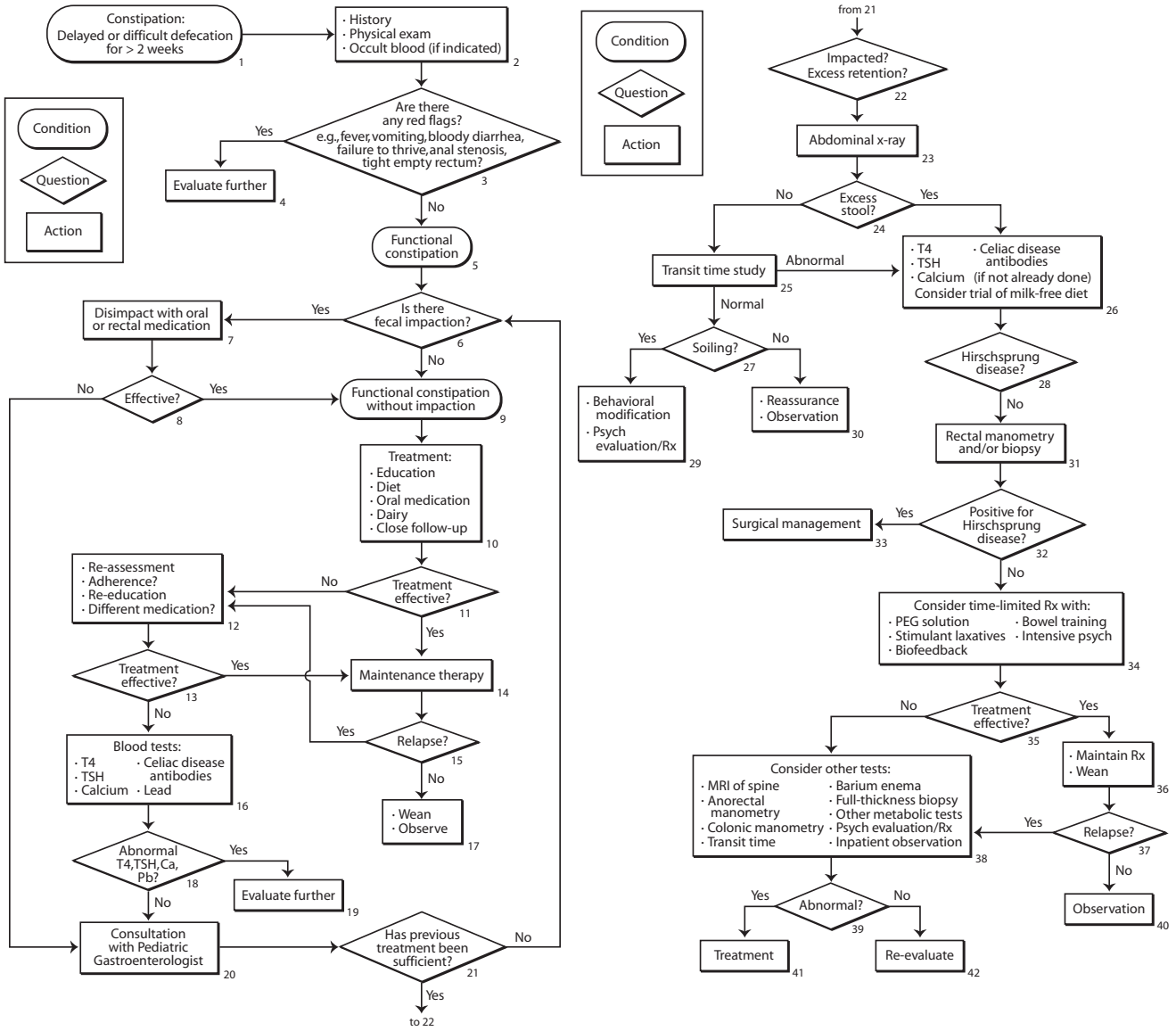

FIGURE 1

Algorithm for the management of constipation in children 1 year of age and older. T4 indicates thyroxine; TSH, thyroid-stimulating hormone/thyrotropin; Ca, calcium; Pb, lead; Rx, therapy; psych, psychological management. (Reprinted with permission from Constipation Guidelines Committee of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr.* 2006;43(3):e3.)

although evidence for the accuracy of a radiologic diagnosis of constipation is conflicting,[10] and routine radiography is not recommended.[11] If large amounts of stool are found on rectal examination, an abdominal radiograph is not needed to establish the presence of fecal impaction.[7]

Diagnostic clues can help to identify some organic causes of constipation. Hirschsprung disease is no less common in children with ASDs, and a history of delayed passage of stool after birth should raise suspicion of aganglionosis. Anatomic abnormalities such as an anterior displaced anus, which is more common in girls than boys, can be diagnosed by careful inspection of the rectum. Children with altered intestinal motility may have underlying mitochondrial disease.[12]

Recent studies have suggested a frequent association of ASDs and mitochondrial dysfunction.[13,14] Mitochondrial disorders are heterogeneous but characterized by impaired energy production.[15] There is no reliable biomarker specific for the screening and diagnosis of mitochondrial disorders.[15] The primary care physician should be alert to the presence of "red-flag" findings that raise clinical suspicion (Table 6) and warrant a baseline diagnostic evaluation.[15] Initial evaluation includes metabolic screening of blood and urine for all patients, metabolic

TABLE 5 Physical Examination of Children With Constipation

General appearance
Vital signs
Temperature
Pulse
Respiratory rate
Blood pressure
Growth parameters
Head, ears, eyes, nose, throat
Neck
Cardiovascular
Lungs and chest
Abdomen
Distension
Palpable liver and spleen
Palpable mass
Anal inspection
Position
Stool present around anus or on clothes
Perianal erythema
Skin tags
Anal fissures
Rectal examination
Anal wink
Anal tone
Fecal mass
Presence of stool
Consistency of stool
Other masses
Explosive stool on withdrawal of finger
Occult blood in stool
Back and spine examination
Dimple
Tuft of hair
Neurologic examination
Tone
Strength
Cremasteric reflex
Deep tendon reflexes

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TABLE 6 "Red-Flag" Findings in Mitochondrial Disease

Organ System	Selected Findings
Neurologic	Cerebral stroke-like lesions in nonvascular pattern
	Basal ganglia disease
	Encephalopathy
	Neurodegeneration
	Myoclonus
Cardiovascular	Hypertrophic cardiomyopathy with rhythm disturbance
	Unexplained heart block in child
	Cardiomyopathy with lactic acidosis (>5 mM)
	Dilated cardiomyopathy with muscle weakness
Ophthalmologic	Retinal degeneration with signs of night blindness, color-vision deficits, decreased visual acuity
	Ophthalmoplegia/paresis
	Fluctuating, disconjugate eye movements
	Ptosis
Gastrointestinal	Unexplained or valproate-induced liver failure
	Severe dysmotility
	Pseudo-obstructive episodes
Other	Unexplained hypotonia, weakness, FTT, and a metabolic acidosis (particularly lactic acidosis) in newborn, infant, or young child
	Hypersensitivity to general anesthesia

FTT indicates failure to thrive.
Adapted with permission from Haas RH, Parikh S, Falk MJ, et al. *Pediatrics*. 2007;120(6):1326–1333.

screening of spinal fluid for patients with neurologic symptoms, and clinical neurogenetic evaluation for patients with a developmental delay (Table 7).[15] In addition, neuroimaging, provocative testing, and DNA analysis may be part of an extensive evaluation.[16] The role of mitochondrial disorders in autism needs further definition.

Treatment Considerations

Pharmacotherapy added to behavior management for constipation is often beneficial.[17] Mineral oil, magnesium hydroxide, lactulose, sorbitol, polyethylene glycol (PEG), or a combination of lubricant (mineral oil) and laxative is recommended for the daily management of constipation in children (Table 8).[7]

CHRONIC DIARRHEA

Differential Diagnosis

Chronic diarrhea occurs when loose stools persist for 2 weeks or longer, with or without an increase in stool frequency. Most episodes of acute diarrhea resolve within a week's time and are frequently caused by self-limited infections. In contrast, the causes of chronic diarrhea are generally different and include more noninfectious causes than for acute diarrhea.

In the US general pediatric population, the most common causes of chronic diarrhea are functional disorders, malabsorption syndromes, inflammatory bowel disease (Crohn disease or ulcerative colitis), and chronic infections.[15] The causes of diarrhea in children on the autism spectrum are likely the same as in children without ASDs, and the differential diagnosis should be approached with similar rigor. Chronic nonspecific diarrhea of childhood can first present between 6 and 36 months of age and resolve by 60 months of age. It is characterized by loose and sometimes frequent stools and, importantly, the absence of other abnormalities such as growth failure, abdominal pain, and difficulty in passing stool. If the latter signs or symptoms are present, other causes of chronic diarrhea should be considered.

Evaluation

Guidelines for the diagnostic evaluation of chronic diarrhea have not yet been developed, but recommended approaches are available in standard pediatric gastroenterology texts.[18,19] These same approaches are relevant for the child with an ASD. A careful history and physical examination are important and include definition of the age at symptom onset and whether symptoms develop abruptly or gradually. Causes of chronic diarrhea in children are listed in Table 9.[20,21] Family history of allergy or atopic disease may increase the likelihood of cow's milk allergy. Celiac disease is more

TABLE 7 Baseline Screening Tests For Mitochondrial Disease: Initial Evaluation

Metabolic Screening of Blood and Urine for All Patients	Assessment of Systemic Involvement for All Patients	Metabolic Screening of Spinal Fluid for Patient With Neurologic Symptoms	Clinical Neurogenetic Evaluation for Patient With Developmental Delay
Basic chemistries	Echocardiogram	Lactate and pyruvate	Karyotype
Liver enzymes and ammonia	ECG	Quantitative amino acids	Fragile X syndrome testing
CBC	Ophthalmologic examination	Routine studies, including cell count, glucose, and protein measurement	Child neurology consult
Creatinine kinase	Audiology testing		Genetics consult
Blood lactate, pyruvate, and lactate/pyruvate ratio	Brain MRI		
Quantitative blood amino acids			
Quantitative urine organic acids			
Plasma acylcarnitine analysis			

Negative test results have a high false-negative rate. Thus, if the results are abnormal or if mitochondrial disease is still suspected, refer the patient to a mitochondrial center. CBC indicates complete blood count; ECG, electrocardiogram; MRI, magnetic resonance imaging.
Adapted with permission from Haas RH, Parikh S, Falk MJ, et al. *Pediatrics*. 2007;120(6):1326–1333.

TABLE 8 Medications for Use in Treatment of Constipation in Children

Medication	Dosage	Comments
Lactulose (70% solution)	1–3 mL/kg per d in divided doses	Well tolerated
Sorbitol (70% solution)	1–3 mL/kg per d in divided doses	Similar to lactulose but less expensive
Magnesium hydroxide (400 mg/5 mL, 800 mg/5 mL, or tablets)	3 mL/kg per d	Monitor for Mg toxicity, hypophosphatemia, hypocalcemia
Magnesium citrate (liquid, 16.17% Mg)	<6 y of age: 1–3 mL/kg per d; 6–12 y of age: 100–150 mL/d in single or divided doses; >12 y of age: 150–300 mL/d in single or divided doses	Monitor for Mg toxicity, hypophosphatemia, hypocalcemia
PEG 3350	1–1.5 g/kg per d for 3 d; maintenance: 1 g/kg per d (usual dose 17 g/d)	Palatable (can be dissolved in most fluids); not approved for use in infants
Phosphate enemas	<2 y of age: to be avoided; ≥2 y of age: 6 mL/kg up to 135 mL	May be psychologically traumatic; may damage rectal wall; may cause abdominal distention or vomiting; tetany with hyperphosphatemia/hypocalcemia; avoid if renal disease is present
PEG electrolyte solution	For disimpaction: 25 mL/kg per h (maximum: 1000 mL/h) via nasogastric tube until clear; maintenance: 10 mL/kg per d	Taste is an issue; may cause nausea, bloating, cramps, vomiting
Mineral oil	<1 y of age: not recommended; >1 y of age: maintenance 1–3 mL/kg per d	Safe alternatives are available; should be used only if other agents fail; lipoid pneumonia if aspirated; leakage of stool; concern about impairing absorption of fat-soluble vitamins has not been substantiated clinically
Senna (syrup, 8.8 mg sennosides per 5 mL)	2–6 y of age: 2.5 mL/d; >12 y of age: 5–15 mL/d	May cause permanent nerve or muscle damage, hepatitis, melanosis coli
Bisacodyl suppository (10 mg)		May irritate rectal mucosa
Bisacodyl tablets (5 mg)		Abdominal pain, diarrhea, hypokalemia
Glycerin suppositories		Minimal adverse effects except for stress caused from insertion

Mg indicates magnesium.
Adapted with permission from Constipation Guidelines Committee of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2006;43(3):e1–e13.

common in individuals with specific human leukocyte antigen (HLA) types and is, in part, genetically determined.

It is important to assess a child's growth and nutrition. Weight for length or height and BMI are the simplest indices of growth failure secondary to malnutrition. Poor weight gain may be a result of malabsorption or inadequate or inappropriate feeding: delayed growth may then be the result of a child being fed a dilute, hypocaloric formula or clear liquids in an effort to reduce diarrhea. In contrast, for infants or children who appear to be thriving or overweight while suffering from chronic diarrhea, a careful dietary record for 1 week may determine if a patient is being overfed or drinking excessive amounts of apple juice, pear nectar, or other fruit juices that are

TABLE 9 Causes of Chronic Diarrhea in Children

Cause	Comment
Enteric infection	MAI, *Isospora*, and *Microsporidia* occur in immunocompromised children, including those with inadequately treated HIV infection
Giardia lamblia	
Cryptosporidium parvum	
Cyclospora cayetanensis	
C difficile	
EAEC	
EPEC	
Mycobacterium avium-intracellulare complex	
Isospora belli	
Microsporidia	
Immunodeficiency	
Primary immunodeficiencies (enteric infection, including small-bowel overgrowth)	Primary immunodeficiencies are uncommon causes
Secondary immunodeficiencies (protein energy and micronutrient malnutrition, HIV infection)	Secondary immunodeficiencies, including HIV infection and malnutrition, are major causes worldwide
Abnormal immune response	
Celiac disease	
Colitis and enteropathy associated with food allergy	
Autoimmune disorders (autoimmune enteropathy, GVHD)	
Idiopathic inflammatory bowel disease	More common in developed countries
Crohn disease	
Ulcerative colitis	
Congenital persistent diarrhea	Structural defects?
Microvillus inclusion disease	Neonatal onset; rare
Tufting enteropathy	
Congenital chloride diarrhea	
Congenital disaccharidase (lactase, sucrase–isomaltase) deficiencies	
Congenital bile acid malabsorption	
Hereditary lactase deficiency	Onset after 3 y of age
Chronic nonspecific diarrhea of childhood	Onset between ages 6 and 36 mo and resolution by age 60 mo; child is otherwise thriving
Syndromic persistent diarrhea (associated with malnutrition)	Of greatest importance in developing countries and worldwide

MAI indicates *Mycobacterium avium-intracellulare*; EAEC, enteroaggregative *E coli*; EPEC, enteropathogenic *E coli*; HIV, human immunodeficiency virus; GVHD, graft-versus-host disease.

Adapted from Gibbons T, Fuchs GJ. Chronic enteropathy: clinical aspects. In: Cooke RJ, Vandenplas Y, Wahn U, eds. *Nutrition Support for Infants and Children at Risk*. Vol 59. Basel, Switzerland: Vevey/S Karger AG; 2007:89–104. Nutrition Institute Workshop Series: Pediatric Program and Steiner TS, Lima AAM, Nataro JP, Guerrant RL. *J Infect Dis*. 1998;177(1):88–96.

known to induce diarrhea. A functional cause of chronic diarrhea is suggested by protracted symptoms (>12 months) or lack of significant weight loss, nocturnal diarrhea, and straining with defecation.

Loose stool in children with ASDs may be misdiagnosed as diarrhea. Constipation is a common, albeit somewhat paradoxical, cause of loose stool and may be difficult to confirm by history or physical examination. Stool might not be palpable in the left lower quadrant, and a rectal examination may be challenging and traumatic for the child. A plain abdominal radiograph may be useful but not reflect the extent of retained stool. Frequently, an empiric trial with a stool softener, such as PEG 3350 (Miralax) for 2 to 4 weeks, supports the diagnosis by causing a change in behavior.

Lactose intolerance can be difficult to diagnose. A diagnostic trial of a strict lactose-elimination diet may identify children who are suspected of having lactose intolerance, but it is difficult to maintain, especially for a patient for whom food choices are limited. In addition, unless results are clear-cut, other diagnostic tests may be necessary. A lactose breath test (LBT), which requires an overnight fast and repeated collection of breath samples over 3 hours, can be difficult to perform on some children. An LBT is possible, though, for many children with ASDs if the child and family are adequately prepared and a tolerant, understanding staff member performs the test. Similar information can be obtained at the time of an upper endoscopy via tissue analysis for disaccharidase-specific activity.

Food allergy, another but less frequent cause of diarrhea, is often challenging to diagnose because most instances of intestinal food allergy are cell mediated rather than mediated by immunoglobulin E (IgE). IgE-based tests may not identify individuals who do not have atopic or immediate reactions, and IgG-based tests are of no value in assessing intestinal food allergy. Referral to an allergist for skin testing may be appropriate. Screening instruments are currently being developed to identify children with ASDs who are likely to have a food allergy.

Assessment for celiac disease should be performed for any child with an ASD and gastrointestinal symptoms. Testing at a minimum should include a total IgA level, tissue transglutaminase IgA antibodies with or without endomysial IgA antibodies. Antigliadin antibodies are less reliable and more likely to yield a false-positive result. Testing must show no evidence of insufficiency of IgA for antibody testing to be deemed reliable.

Children on a gluten-free diet should consider testing for celiac disease when gluten is reintroduced. Alternatively, even if a child is on a gluten-free diet, genetic testing for *HLA-DQ2* and *HLA-DQ8* is reliable if the results are negative and largely exclude a diagnosis of celiac disease. Because 35% of

the US population has *DQ2* or *DQ8* but not celiac disease, the presence of these alleles does not make a diagnosis of celiac disease. Genetic testing is especially valuable for excluding celiac disease in children on a gluten-free diet in whom antibody testing is not reliable.

Stool samples to test for enteric pathogens, ova/parasites, or occult blood can be obtained easily at the time of a lower endoscopy but otherwise may be difficult to collect. Biopsies of the colon and ileum are routinely obtained on endoscopy and determine whether there is acute or chronic mucosal inflammation.

Other relevant diagnostic tests are listed in Table 2. Stool guaiac identifies blood in the stool and suggests inflammatory bowel disease, *Clostridium difficile* infection, or perhaps allergy as a potential cause of the chronic diarrhea. Blood in the stool caused by colitis is often associated with an increase in fecal calprotectin and lactoferrin, proteins derived from polymorphonuclear leukocytes. Split or neutral fat in the stool suggests malabsorption that could be caused by pancreatic insufficiency (elevated neutral fat) or mucosal injury, such as in celiac disease (elevated split fat). Pancreatic insufficiency should also be suspected if trypsinogen or elastase levels in the stool are decreased. Protein-losing enteropathy that causes diarrhea is usually associated with increased α-1-antitrypsin in the stool and hypoalbuminemia. If the total peripheral lymphocyte count is also decreased, one should consider the rare condition intestinal lymphangiectasia. The occurrence of diarrhea when a child is fasting is suggestive of secretory diarrhea, in which case stool electrolytes and osmolarity are diagnostic and an evaluation for hormonal causes should be considered.

TABLE 10 Therapeutic Options for Chronic Diarrhea in Children

Therapy	Underlying Cause
Symptomatic therapy with antisecretory medication	Severe diarrheal disease as an empiric trial before end of diagnostic workup
	Severe idiopathic diarrhea
Drug therapy	Chronic intestinal infections and small-bowel bacterial overgrowth
	Malabsorption
	Inflammatory bowel diseases and autoimmune enteropathy
	Short-bowel syndrome and other chronic secretory diarrheal disorders
Surgery	Malrotation
	Stenosis
	Blind loops
Intestinal transplantation	Short-bowel syndrome
	Intestinal pseudo-obstruction and other disorders of defective intestinal motility
	Ultrastructural enterocyte abnormalities

Data source: Canani RB, Cirillo P, Terrin G. Chronic and intractable diarrhea. In: Guandalini S, ed. *Essential Pediatric Gastroenterology, Hepatology, and Nutrition.* New York, NY: McGraw-Hill Medical Publishing Division; 2005:41–42.

Treatment Considerations

Therapeutic interventions vary depending on the cause of chronic diarrhea; children without ASDs may receive a specific medical/surgical therapy or may be treated symptomatically (Table 10).[18] Physicians should exercise clinical judgment when considering the appropriate treatment option for children with ASDs.

GASTROESOPHAGEAL REFLUX DISEASE

GER, the term for passage of gastric contents into the esophagus, can produce diverse symptoms and complications, called gastroesophageal reflux disease (GERD) (Table 11).[4] Clinical practice guidelines for the management of GERD in the general pediatric population were published in 2001[4] and are currently being updated.[22] The following recommendations can be applied to children with ASDs and are based on the 2001 publication, with modifications ensuing from the clinical experiences of the authors.

Manifestations of GERD

During infancy, in contrast to nonpathologic reflux, GERD presents most frequently as an adverse effect of recurrent vomiting but also as apparent life-threatening events. As a child matures, other symptoms and signs of GERD include chest pain or heartburn, esophagitis, food refusal, and extraesophageal manifestations of the airway.

As in children without ASDs, the expression of disease related to GER can vary widely in children with ASDs. The manifestations listed in Table 11 may

TABLE 11 Complications of GER

Symptoms
Recurrent vomiting
Weight loss or poor weight gain
Irritability in infants
Regurgitation
Heartburn or chest pain
Hematemesis
Dysphagia or feeding refusal
Apnea or ALTE
Wheezing or stridor
Hoarseness
Cough
Abnormal neck positioning (Sandifer syndrome)
Findings
Esophagitis
Esophageal stricture
Barrett's esophagus
Laryngitis
Recurrent pneumonia
Hypoproteinemia
Anemia

ALTE indicates apparent life-threatening events.
Reprinted with permission from Rudolph CD, Mazur LJ, Liptak GS, et al; North American Society for Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr.* 2001;32(suppl 2):S4.

be identifiable in children with ASDs. However, certain children may express discomfort through problem behaviors, restriction of foods of specific texture, or simply pointing to their chest. Objective measures become important to elicit from the patient and family, such as the frequency and timing of regurgitation, the character and amount of material regurgitated, and the kinds of foods that are tolerated by the child.

Underlying Cause

The presenting symptom or sign is a clue to the underlying cause. Children with ASDs who have obstruction caused by, for example, malrotation or antral web may regurgitate many times an hour, whereas those individuals who have typical GERD may experience symptoms when they lie down at night or after meals. The vomiting of undigested foods suggests a delay in gastric emptying; hematemesis suggests the presence of inflammation or ulceration. In young children, a preference for liquids or a refusal to eat textured foods or foods that require chewing should raise suspicion of esophagitis.

Evaluation

Diagnostic evaluation begins with a careful history and physical examination. In some children more than 2 years of age, recurrent regurgitation or vomiting disrupts their participation in childhood activities. As for children without ASDs, an empiric trial of acid suppression may be of diagnostic value, but then the clinician may want to order an upper gastrointestinal series to exclude an anatomic abnormality, as well as upper endoscopy with biopsy to look for inflammation associated with GERD, allergy, or eosinophilic esophagitis. Other warning signals for additional diagnostic testing include gastrointestinal bleeding, abdominal tenderness, and fever.

A diagnostic trial of acid suppression, with an appropriate dose of a proton-pump inhibitor (PPI), should be considered before invasive studies. For many children with ASDs, who may have GERD undiagnosed for many years, a trial of acid suppression is beneficial. PPI medications should be given 30 minutes before the first meal of the day and, if 2 doses are prescribed, 30 minutes before the evening meal. Assessment of response to a PPI trial is somewhat subjective in children with ASDs and might depend on changes in behavior as perceived by care providers (parents, teachers, or health care providers).

If further diagnostic testing is pursued, upper gastrointestinal radiographs can be challenging for many children who are unable to cooperate with drinking barium and lying down quietly for the procedure. Because of these potential barriers, it can be difficult to identify anatomic abnormalities, such as a malrotation, annular pancreas, or antral inflammation or narrowing, that may be the cause of GERD-like symptoms.

Most children with ASDs are unlikely to tolerate placement of a transnasal pH probe for a prolonged period. A Bravo pH probe (Given Imaging Ltd, Yoqneam, Israel), which is endoscopically attached to the distal esophagus, may be better tolerated. For such children, upper endoscopy under general anesthesia is often the diagnostic test initially used and might provide information about other gastrointestinal conditions such as carbohydrate malabsorption or food allergy or intolerance. Endoscopy is usually reserved for children who are unresponsive to a diagnostic trial of gastric acid suppression or when other clinical factors, such as hematemesis or food refusal, support the scheduling of invasive tests.

Treatment Considerations

Treatment of GERD depends on the cause. Surgical therapy should be considered with a diagnosis of anatomic abnormality such as malrotation, whereas esophagitis may be treated best by prolonged acid suppression (see Table 12). Subsequent evaluation depends on the resolution and recurrence of an individual's symptoms. Upper endoscopy should be considered to follow children with long-standing GERD who may be at risk for developing complications such as esophageal stricture, Barrett esophagus, and esophageal cancer.

As in children without ASDs, GERD in children with ASDs can be a chronic problem, with waxing and waning of symptoms. The management of such children often requires continuity with advancing age and an appreciation by the health care team of the natural history of disorders that underlie GERD.

CONCLUSIONS

Children with ASDs can benefit from the adaptation of general pediatric guidelines for the diagnostic evaluation of abdominal pain, chronic constipation, and other gastrointestinal symptoms. The diagnostic evaluation begins with a thorough medical history and physical examination. The expression of disease can be as diverse in individuals with ASDs as in the general pediatric population. Health care providers also should be alert to behavioral manifestations of gastrointestinal disorders in patients with ASDs. Information from the medical history, including the presence of red-flag findings, the characterization or definition of a problem (as for chronic constipation), and the age of symptom onset (as for chronic diarrhea), can clarify the clinical picture and help determine the need for further evaluation.

TABLE 12 Acid-Suppressive Medications for Use in Treatment of GERD in Children

Medication	Dosage	Comments
Omeprazole (capsules[a] and oral suspension[a])	1–16 y of age: 5 to <10 kg, 5 mg/d; 10 to <20 kg, 10 mg/d; ≥20 kg, 20 mg/d; adult dosing: 20 mg/d for 4–8 wk	Adverse events of respiratory system, fever (from adult studies: headache, abdominal pain, nausea, diarrhea); capsules can be administered with applesauce
Lansoprazole (tablets[a], capsules[a], and oral suspension[a])	1–11 y of age: ≤30 kg, 15 mg/d for ≤12 wk; >30 kg, 30 mg/d for ≤12 wk; 12–17 y of age: 15–30 mg/d for ≤8 wk; adult dosing: 15–30 mg/d for ≤8 wk	Constipation, headache, abdominal pain, nausea, dizziness (from adult studies: diarrhea, abdominal pain, nausea, constipation); strawberry-flavored SoluTabs do not need to be swallowed; capsules can be administered with apple, orange, or tomato juice
Pantoprazole (tablets[a] and oral suspension[a])	—[b]; adult dosing: 40 mg/d for ≤8 wk	(From adult studies: headache, diarrhea, flatulence, abdominal pain)
Rabeprazole (tablets[a])	Adolescents ≥12 y of age: 20 mg/d for ≤8 wk; adult dosing: 20 mg/d for 4–8 wk	Headache, nausea (from adult studies: pain, pharyngitis, flatulence, constipation)
Esomeprazole (capsules[a] and oral suspension[a])	1–11 y of age: 10 or 20 mg/d for ≤8 wk; 12–17 y of age: 20–40 mg/d for ≤8 wk; adult dosing: 20 or 40 mg/d for 4–8 wk	Headache, diarrhea, abdominal pain, nausea, somnolence (from adult studies: headache, diarrhea, nausea, flatulence, abdominal pain, constipation, dry mouth)

[a] Delayed-release formulations.

[b] Safety and efficacy of pantoprazole have not been established for the pediatric population.

Diagnostic trials with empiric therapy (eg, PEG 3350 for chronic constipation, acid-suppressive therapy for GERD) may establish or support a specific diagnosis. Supervision by an experienced provider, including a nutritionist if the diagnostic trial is an elimination diet, is important for assessing the clinical response appropriately.

Many tests commonly performed in typically developing children, such as the LBT and standard pH probe monitoring, are challenging or not feasible for children with ASDs. In this population, a number of such tests are difficult to perform. For children who are unable to cooperate, performance of multiple tests during a single examination under anesthesia might be considered.

Well-designed trials are needed to develop an evidence base for optimal diagnostic and treatment strategies to manage gastrointestinal disorders in children with ASDs. Until then, application and, where necessary, adaptation of conventional recommendations for the general pediatric population are relevant to children with ASDs.

ACKNOWLEDGMENTS

This article is sponsored by the Autism Forum. The forum's goal in this initiative is to establish best practices for the care of co-occurring medical conditions that may affect the developmental outcome of persons with ASDs. Autism Forum programs are developed under the guidance of the Northwest Autism Foundation and in association with, and support of, the Autism Research Institute, Autism Society of America, and Easter Seals Oregon.

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FINANCIAL DISCLOSURE: *Dr Winter has consulting agreements with AstraZeneca, P&G, Salix Pharmaceuticals, Ltd, Takeda Pharmaceuticals North America, Inc, and UCB Inc Pharma and has received research grants from AstraZeneca, Centocor, Inc, P&G, Nutricia North America Inc, SHS, Takeda Pharmaceuticals North America, Inc, UCB Pharma, and Wyeth Pharmaceuticals; and the Autism Forum provided honoraria to all authors.*

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PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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