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Garrett C. Zella and Esther J. Israel

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Garrett C. Zella, MD,*
Esther J. Israel, MD*

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Educational Gap

It is estimated that diarrheal illnesses are responsible for ~2 to 4 million childhood deaths worldwide each year, representing 13.2% of all childhood deaths worldwide.

Objectives

After completing this article, readers should be able to:

1. **Understand the pathophysiologic mechanisms involved in chronic diarrhea.**
2. **Know how to evaluate a child who has chronic diarrhea, including appropriate elements of history, physical examination, stool analysis, and blood testing.**
3. **Be familiar with the many disorders that cause chronic diarrhea, both with and without failure to thrive.**
4. **Know the therapies for the many causes of chronic diarrhea.**

Definitions

Chronic diarrhea is a common complaint in pediatric medicine and can pose a complex situation for practitioners and families. This complaint is both a symptom and a sign. (1) Although patients or their parents often assess the presence of diarrhea by reporting stool consistency and frequency, one can more scientifically define diarrhea as stool volume >10 g/kg per day in infants and toddlers, and >200 g/day in older children. (2) However, diarrhea should not be defined solely by stool weight. Some adolescents and adults may have up to 300 g of formed stool per day without any complaints. (3) The duration of symptoms necessary to define diarrhea as "chronic" also is not definitive. Most authors agree that 14 days of symptoms meets criteria, although others use a cut-off of 4 weeks. (4) An additional term, "persistent" diarrhea, acknowledges diarrhea lasting more than 14 days but implies a more abrupt onset compared with chronic diarrhea. Regardless of the specific term or number of days of symptoms, it should be understood that this definition should allow for the usual resolution of most causes of acute diarrhea.

Epidemiology

It is estimated that diarrheal illnesses are responsible for ~2 to 4 million childhood deaths worldwide each year. (5)(6) In 2002, the World Health Organization estimated that 13.2% of all childhood deaths worldwide were caused by diarrheal diseases, 50% of which were chronic diarrheal illnesses. (7) Large-scale studies indicate that the prevalence of chronic diarrheal illnesses worldwide ranges from 3% to 20%, and the incidence is ~3.2 episodes per child-year. (4)(8) Estimates in the United States are substantially lower at 0.18 episodes per child-year in children ages 6 months to 3 years. (9) In the United States, only ~25% of cases present for medical care, and fewer than 1% of children are hospitalized for diarrheal diseases. (10) The rotavirus vaccine may decrease hospitalizations by up to 66% in developing countries, because a substantial number of these hospitalizations are for rotavirus-associated diarrhea. (11)

Abbreviations

CCD:	congenital chloride diarrhea
CF:	cystic fibrosis
CNSD:	chronic nonspecific diarrhea
CSD:	congenital sodium diarrhea
IBD:	inflammatory bowel disease
IBS:	irritable bowel syndrome
IDI:	intractable diarrhea of infancy
TTG IgA:	tissue transglutaminase immune globulin A
ZES:	Zollinger-Ellison syndrome

*Pediatric Gastroenterology and Nutrition, Massachusetts General Hospital, Boston, MA.

Pathophysiology

The many causes of chronic diarrhea can be divided into four principle pathophysiologic mechanisms: osmotic, secretory, dysmotility associated, and inflammatory. Often, a single disorder will involve multiple overlapping mechanisms. Regardless of the cause, water in the intestinal lumen is incompletely absorbed either because net water absorption is decreased or because water is being held within the lumen by an osmotic gradient. Reduction in net water absorption by as little as 1% may be sufficient to cause diarrhea. (12)

Osmotic diarrhea is caused by a failure to absorb a luminal solute, resulting in secretion of fluids and net water retention across an osmotic gradient. This outcome can result from either congenital or acquired disease and is best exemplified by the common disorder of lactose malabsorption. (13) Other carbohydrates may be malabsorbed, either because of dissacharidase deficiencies or because the absorptive capacity of the intestine for that sugar may be overwhelmed by excessive consumption, eg, fructose and sorbitol. (14) Such excessive intake may be seen in young children drinking fruit juices. Dissacharidase deficiencies, such as lactase deficiency, are rarely congenital but more often are a result of gut mucosal injury secondary to some process later in infancy, such as an enteritis. (2) Pure osmotic diarrhea should cease when the offending dietary nutrients are removed. (1)

Secretory diarrhea occurs when there is a net secretion of electrolyte and fluid from the intestine without compensatory absorption. Endogenous substances, often called "secretagogues," induce fluid and electrolyte secretion into the lumen even in the absence of an osmotic gradient. Children with a pure secretory diarrhea will therefore continue to experience diarrhea even while fasting. Typically, secretagogues affect ion transport in the large and small bowel both by inhibiting sodium and chloride absorption and by stimulating chloride secretion via cystic fibrosis (CF) transmembrane regulator activation. Examples of secretory diarrhea include multiple congenital diarrheal disorders associated with identified genetic mutations that affect gut epithelial ion transport. (1) Congenital chloride diarrhea (CCD) is one such disorder.

Chronic diarrhea associated with intestinal dysmotility typically occurs in the setting of intact absorptive abilities. Intestinal transit time is decreased, the time allowed for absorption is minimized, and fluid is retained within the lumen. High-amplitude propagated contractions play a key role in motility disorders of the gut and have been found to be more frequent in patients with diarrhea-predominant irritable bowel syndrome (IBS). (15) Although diarrhea-predominant IBS may be diagnosed in older adolescents, toddlers commonly present with chronic nonspecific diarrhea (CNSD). Changes in small intestinal motility also have been implicated in causing CNSD. (16)

Inflammatory diarrhea may encompass all of the pathophysiologic mechanisms. Inflammation with resultant injury to the intestine may lead to malabsorption of dietary macronutrients which, in turn, creates a luminal osmotic gradient. Additionally, particular infectious agents may induce secretion of fluid into the lumen, and blood in the gut may alter intestinal motility. Diseases such as inflammatory bowel disease (IBD) and celiac disease exemplify this inflammatory mechanism. (13)

Evaluation of Chronic Diarrhea

History and Physical Examination

A careful history of the characteristics of the diarrhea is important in assessing the severity of the illness and in formulating a differential diagnosis. Stool frequency, volume, and appearance; the presence of blood or mucus; and the relationship to feeding or dietary intake should be documented. Also important is the presence or absence of abdominal pain, weight loss, rash, fatigue, vomiting, joint aches, or oral ulcers, among other extraintestinal symptoms. A 3-day diary of stool pattern, dietary intake, and associated symptoms can be helpful. One should inquire also about recent travel, exposure to new water sources, family history, and sick contacts.

Physical examination should include plotting of weight, height, and head circumference on a standardized growth chart. Signs of nutrient deficiencies should be sought, such as perianal dermatitis in zinc deficiency and leg deformity in vitamin D deficiency. The abdomen may reveal distension in malabsorption syndromes or small bowel bacterial overgrowth or may be exquisitely tender in an inflammatory state. Examination of the rectum is important also and may reveal perianal disease in IBD, guaiac positive stool in many disease states, or loss of surrounding subcutaneous tissue in celiac disease and other states of malnutrition.

Examination of Stool and Blood

Laboratory examination should begin with microbiologic studies for bacteria and parasites in the stool. Infection with bacteria such as *Yersinia*, *Escherichia coli*, and *Salmonella* may develop into chronic illness and can be detected by routine stool culture. Additionally, some stool

cultures may include testing for diarrhea-causing *Aeromonas* and *Plesiomonas*. *Clostridium difficile* toxin assay should be performed, especially in the setting of recent antibiotic use. Antigen detection for *Giardia* and *Cryptosporidium* are more sensitive and specific than routine microscopy-based "ova and parasite" examinations and therefore may be helpful if these infections are suspected. (17)

Analysis of the stool for electrolyte content and osmolarity may be helpful in distinguishing an osmotic from a secretory diarrhea. If there is a difference between the stool osmolarity and twice the sum of the concentrations of sodium and potassium in the stool of >50mOsm, the diarrhea is osmotic in nature. If this osmotic gap is <50mOsm, it is presumed that the diarrhea is secretory.

A 24-hour fast with intravenous hydration may be necessary to distinguish an osmotic diarrhea, with resolution of the diarrhea upon fasting. Continuation of the diarrhea while not ingesting anything suggests a secretory pathophysiology.

Inspection of the stool for the presence of leukocytes may indicate mucosal inflammation. Analysis for reducing substances may reveal carbohydrate malabsorption. Measuring the amount of elastase in the stool gives an indication of exocrine pancreatic function, with low fecal elastase suggesting pancreatic insufficiency.

If steatorrhea is suspected, more precise measurement of fecal fat requires a 72-hour collection of stool. Patients must consume adequate amounts of fat during the stool collection (>30 g/day in infants and >50 g/day in school-age children) and a coefficient of fat malabsorption of >5% is considered abnormal past infancy. The normal percentage can be up to 15% during infancy.

Blood tests should include routine complete blood cell count to evaluate for anemia and thrombocytosis, suggesting blood loss and inflammation, respectively. Evaluation of red blood cell characteristics may suggest vitamin B12 or folate deficiency in malnutrition. White blood cell count and differential and immunoglobulin analysis screen for immune disorders. Erythrocyte sedimentation rate and C-reactive protein support inflammation but are nonspecific. Elevated tissue transglutaminase immune globulin A (TTG IgA) antibody is sensitive and specific for celiac disease, but a low total serum IgA level may result in a false-negative test. Measurements of albumin and prealbumin may be obtained to reflect low dietary protein intake. (13) Levels of the fat soluble vitamins A, 25-OH vitamin D, vitamin E, and vitamin K (reflected by prothrombin time) may be measured if fat malabsorption is suspected.

Additional Testing

The value of radiologic studies in the context of chronic diarrhea is limited. Abdominal radiographs may show constipation or dilated small bowel loops. Computed tomography and MRI may be useful in IBD to show bowel wall thickening suggestive of mucosal inflammation. Breath hydrogen analysis, or "breath testing," can be used to examine for carbohydrate malabsorption. If not absorbed, lactose, sucrose, or lactulose given at the onset of testing reaches colonic bacteria, producing hydrogen that is measured in the breath. Endoscopy may be useful to reveal duodenal villous blunting and intraepithelial lymphocytes in celiac disease or evidence of ileal or colonic inflammation in infectious colitis or IBD. Small bowel biopsy during endoscopy also may reveal evidence of duodenitis in parasitic infections. However, stool testing for parasites is much less invasive and is more sensitive and specific than endoscopy.

Differential Diagnosis

It may be helpful to separate the wide differential diagnosis of pediatric chronic diarrhea into those illnesses that result in poor weight gain and those in which weight typically is maintained. The Table presents the features of the main causes of chronic diarrhea.

Chronic Diarrhea Without Failure to Thrive

Chronic Nonspecific Diarrhea of Childhood or Infancy

CNSD is the most common form of persistent diarrhea in the first 3 years after birth. (18) The typical time of onset may range from 1 to 3 years of age and can last from infancy until age 5 years. Patients with CNSD usually pass stool that is different in both consistency and frequency from that of other children. Affected children may pass 4 to 10 loose bowel movements per day without blood or mucus. Specific to CNSD is the pattern that these patients pass stools only during waking hours, typically beginning with a large formed or semiformed stool after awakening. As the day progresses, stools become more watery and smaller in volume. Transit time of enteral contents may be especially short, and parents frequently describe undigested food remnants in the stool. By definition, children with CNSD maintain their weights and heights. Although some affected children describe mild abdominal discomfort, most typically appear healthy and maintain a normal appetite and activity level. (19)(20)

Potential pathophysiologic mechanisms for CNSD include increased intestinal motility and osmotic effects of intraluminal solutes (eg, carbohydrates). (16) The role of ingested carbohydrates in CNSD has been emphasized in

Table. Causes of Chronic Diarrhea

Without Failure to Thrive	Major Clinical Features	Major Laboratory and Imaging Findings
CNSD	Daytime nonbloody, nonmucousy stools Normal growth Occurs in the first few years after birth	Normal laboratory and imaging results
Infectious colitis	Possible blood and/or mucus in stool Possible fever and/or abdominal pain Exposure to undercooked meat Contaminated water Occurs at any age	Positive stool culture, ova and parasite examination, or stool antigen test
Lactose malabsorption	Abdominal discomfort, bloating, flatulence Nonbloody stools Occurs beyond infancy	Elevated breath hydrogen concentration after lactose ingestion
Small bowel bacterial overgrowth	Abdominal discomfort Increased risk if ileocecal valve removed Occurs at any age	Elevated fasting breath hydrogen concentration (>20 ppm) Elevated early and late breath hydrogen concentration After lactulose ingestion
IBS	Alternating constipation with diarrhea Abdominal pain relieved by defecation Absence of weight loss, bloody stool, fever, or anemia Typically diagnosed in adolescence or later	Normal laboratory and imaging results
With Failure to Thrive		
IDI	Infectious colitis ruled out Higher risk in malnourished or immunodeficient patients In need of prompt nutritional support	Enteropathy by histology
Allergic enteropathy	Most commonly in response to cow or soy milk Growth failure is in sharp contrast to well infant with allergic colitis Stool may be guaiac positive	May have hypoalbuminemia and anemia Electrolyte abnormalities from diarrhea/vomiting Serum IgE may be elevated
Celiac disease	Up to 1/100 prevalence Severe cases have abdominal distension Myriad of presenting features	Elevated TTG IgA, antiendomysial IgA antibodies May be IgA deficient* Histologic villous blunting and intraepithelial Lymphocytes
IBD	Bloody stool more common in colitis Enteritis may cause nonbloody stool Stooling urgency, abdominal pain, fatigue	Elevated erythrocyte sedimentation rate, thrombocytosis Iron-deficiency anemia Hypoalbuminemia
Immunodeficiency state (various diseases)	Recurrent infections Young age, typically in infancy	Abnormal immunoglobulins (eg, low IgG, low IgA, high IgM) Lymphopenia Low antigen titers to previous immunizations
Congenital secretory diarrhea (Chronic chloride and chronic sodium diarrhea)	Maternal polyhydramnios Severe secretory diarrhea at birth Severe dehydration	CCD: hypochloremia and metabolic alkalosis CSD: hyponatremia and metabolic acidosis

Continued

Table. (Continued)

With Failure to Thrive		
Tufting enteropathy	Intractable watery diarrhea Severe growth failure	Electrolyte abnormalities Small bowel villous atrophy and crypt hyperplasia without inflammation
Microvillous inclusion disease	Diarrhea within first week after birth No history of polyhydramnios	Small bowel villous atrophy but no crypt hyperplasia or inflammation
Autoimmune enteropathy	Secretory diarrhea May coexist with other endocrinopathies	May have positive antienterocyte, antigoblet cell, or anticolonocyte serum antibodies
Neuroendocrine tumors	Secretory diarrhea	VIPoma: elevated serum VIP ZES: elevated fasting serum gastrin Carcinoid: elevated urine 5-hydroxyindoleacetic acid Elevated prostaglandin E2
Hirschsprung disease	Delayed passage of meconium Distended abdomen Explosive stool with rectal examination	Abnormal barium enema Absent ganglion cells on rectal biopsy
CF	Malabsorption of carbohydrate/fat/protein	Decreased fecal elastase Elevated fasting breath hydrogen if small bowel bacterial overgrowth present

IgE=immune globulin E; VIP=vasoactive intestinal polypeptide-secreting tumor.
* Leads to false-negative IgA-based antibody tests: TTG IgG may be useful in this setting.

light of a typical toddler's affection for fruit juices. Excessive intake of fruit juices, particularly those containing sorbitol or fructose (eg, apple, pear, cherry, and prune juices), may contribute to the stool osmotic load, thus causing or worsening diarrhea. (21)(22)

Reassurance is the cornerstone of therapy for CNSD. Parents should be reassured that their child is growing well and is healthy. Although no precise treatment for CNSD has been established, dietary intervention may be prudent. Fruit juice intake should be minimized or changed to types of juice with low sucrose and fructose loads. Beyond the restriction of fruit juice, possible helpful changes may be to liberalize fat to encourage normal caloric intake and to slow intestinal transit time, not to restrict fiber, and to assure adequate but not overhydration. (21)

Infectious Colitis

Although many infectious causes of diarrhea result in an acute presentation and short course, other pathogenic bacteria and parasites may cause chronic diarrhea. Viruses rarely cause diarrhea lasting more than 14 days and more typically range from 2 days (eg, Norwalk-like virus) to 11 days (enteric adenoviruses) in duration. (6) Rotavirus may cause diarrhea lasting up to 20 days. (11)

Salmonella is one of the most common causes of laboratory-confirmed cases of food-borne intestinal disease reported to the Centers for Disease Control and Prevention each year. (23) The infection usually is contracted from exposure to food of animal origin related to poultry, eggs, beef, and dairy products. Nontyphoidal *Salmonella* organisms typically cause gastroenteritis with diarrhea, abdominal cramping, and fever. *Salmonella* organisms typically are detected in routine stool culture for up to 5 weeks but may be excreted in stool for >1 year in 5% of patients. (24) Antibiotic therapy for uncomplicated nontyphoidal serotypes is not indicated because it does not shorten the disease duration and may prolong the duration of excretion of bacteria in the stool. (25) Antibiotics are appropriate, however, for treating children younger than 3 months of age or those with immunosuppressive diseases, given the increased risk for invasive disease (bacteremia, osteomyelitis, abscess, meningitis) in these populations. (23)

Yersinia enterocolitica and *Y pseudotuberculosis* cause chronic diarrhea less commonly than *Salmonella* in children in the United States. Infection typically occurs via exposure to food products, specifically pork (a major *Yersinia* reservoir) and dairy products but may occur with ingestion of other foods contaminated by these products. Diarrheal stool may contain blood, mucus, and leukocytes, reflecting mucosal inflammation. Symptoms may mirror appendicitis or ileal Crohn disease because *Yersinia* may affect the terminal ileum. Often the organism needs to

be sought specifically by laboratory personnel because it may not be part of each institution's routine stool culture. The efficacy of antibiotics in treating uncomplicated *Yersinia* infection has not been established. (26)

Other bacterial causes of chronic diarrhea include *Escherichia coli*, *Campylobacter*, *Aeromonas*, and *Plesiomonas*. Enteropathogenic *E coli* is a leading cause of chronic diarrhea in developing countries, sometimes associated with fever, abdominal pain, and vomiting. (27) Enteropathogenic *E coli* is one type of *E coli* disease in which antibiotic therapy has been shown to reduce morbidity and mortality in uncomplicated diarrheal disease. (28) Persistent bloody diarrhea with abdominal pain should raise suspicion for enterohemorrhagic *E coli*, particularly because enterohemorrhagic *E coli* may result in hemolytic-uremic syndrome, a potentially dangerous complication. *Campylobacter* often originates from poultry and may cause diarrhea for only 4 to 5 days, but relapses are common. Both *E coli* and *Campylobacter* can be isolated by routine stool culture.

Aeromonas, long considered a normal commensal organism, has been shown recently to cause secretory diarrhea with up to 20 watery stools per day. Symptoms are persistent in approximately one-third of patients. Antibiotics do not seem to be helpful in uncomplicated *Campylobacter* and *Aeromonas* illnesses. *Pleisomonas* can be found in fish, shellfish, cats, and dogs; also causes secretory diarrhea; and has a course that may be shortened by antibiotic therapy. (29)

The protozoa *Giardia intestinalis* and *Cryptosporidium* may affect immunocompetent as well as immunodeficient children and adolescents. Both infections may affect the duodenum and upper small bowel, leading to mild villous blunting, dissacharidase deficiency, and resultant osmotic and secretory diarrhea. Malabsorption of fat, protein, and carbohydrates may occur, worsening diarrhea. Both infections are linked to contaminated water and may be associated with childcare centers, exposure to wild animals, swimming in water parks or pools, or recent travel to developing countries. Symptomatic giardiasis should be treated, even in immunocompetent children, with tinidazole, metronidazole, or nitazoxanide as possible agents. *Cryptosporidium* infection generally does not need to be treated unless the patient is immunocompromised. However, nitazoxanide has been approved for treating immunocompetent children with diarrhea associated with *Cryptosporidium*. (30)

Disaccharide Intolerance

Lactose malabsorption is, by far, the most common type of disaccharide intolerance. Approximately 70% of the world's adult population has primary acquired lactase deficiency, resulting in lactose intolerance. Age of onset varies among populations, with one-fifth of Hispanic, Asian, and African American children becoming lactose intolerant before age 5 years. White children typically do not lose lactase function until after age 5 years, and often much later, during later teenage years or beyond. (31) Molecular studies have elucidated differences in messenger RNA expression among races that might explain population-based variations in lactase activity. (32) Congenital lactase deficiency is exceedingly rare and only a handful of cases have been published in the literature.

Secondary lactase deficiency results from small intestinal mucosal injury when lactase enzyme is lost from the tips of the villi. Causes include rotaviral infection, parasitic infection, celiac disease, Crohn disease, and other enteropathies. Many studies question the clinical significance of secondary lactase deficiency in diarrheal illnesses except in children who are <3 months or malnourished. (33) Symptoms of lactose intolerance are independent of the cause. Incompletely digested lactose reaches the dense colonic microbial population, which ferments the sugar to hydrogen and other gases, thereby causing gassy discomfort and flatulence. The nonabsorbed lactose serves as an osmotic agent, resulting in an osmotic diarrhea. Diagnosis can be made by a successful lactose-free diet trial of 2 weeks or by hydrogen breath-testing. Treatment entails minimizing lactose intake because the symptoms are dose-dependent and may not require complete removal of dietary lactose. Artificial lactase enzyme may be taken once the diagnosis has been made. (31)

Small Bowel Bacterial Overgrowth

The normal small intestine has relatively few bacteria residing within it (typically $<10^4$ cfu/cc). Various conditions such as short bowel syndrome, pseudoobstruction, bowel strictures, and malnutrition may result in overgrowth of aerobic and anaerobic bacteria in the small bowel. Symptoms of abdominal pain and diarrhea arise as bile acids are deconjugated and fatty acids hydroxylated by bacteria. These processes lead to an osmotic diarrhea. The diagnosis can be made by an early and late rise in breath hydrogen with lactulose testing as the undigested lactulose reaches the small bowel and then the colon. Treatment is with metronidazole or with nonabsorbable rifaximin. (34)

Irritable Bowel Syndrome

IBS, characterized by recurrent abdominal pain and altered bowel habits, is a common disorder that can present

during adolescence. Without any one specific pathophysiologic cause identified, IBS is considered a functional disorder defined by symptom criteria. (35)(36) The Rome III criteria define IBS as abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following features: improvement with defecation, onset associated with a change in frequency of stooling, and onset associated with change in the form of the stool. This strict definition may be used to define the syndrome precisely but typically is more useful in research rather than in everyday clinical medicine. The history often suggests the diagnosis, with abdominal pain often relieved with defecation. These patients do not have rectal bleeding, anemia, weight loss, or fever. It should be determined that celiac disease is not present. Treatment is often challenging. Antispasmodic agents, tricyclic antidepressants, and selective serotonin-reuptake inhibitors may improve symptoms. Some probiotics have been useful in adult and pediatric IBS, but results are not consistent. (37)

Chronic Diarrhea With Failure to Thrive

Intractable Diarrhea of Infancy

Persistent diarrhea after an acute episode of presumed infectious diarrhea is known as intractable diarrhea of infancy (IDI), postenteritis or postgastroenteritis diarrhea, postenteritis enteropathy, or "slick gut." This disorder is unique compared with CNSD because in IDI there is weight loss associated with malabsorption and histologic evidence of enteropathy. (38) IDI remains an important cause of morbidity and mortality in developing countries where children may be at nutritional risk. Children at particular risk include those who are young, who suffer malnutrition, or who have an altered immune state. (39) Osmotic diarrhea with increased fluid requirements secondary to carbohydrate malabsorption is common. Without nutritional support, patients may become severely ill.

IDI should be suspected in any infant with persistent diarrhea after an acute gastroenteritis. Other causes of chronic diarrhea should be sought but not at the expense of promptly supporting caloric needs. (6) Small bowel biopsy may reveal patchy villous atrophy and inflammatory infiltrates in epithelial and lamina propria layers. Caution should be exercised in obtaining biopsies because malnutrition increases the risks associated with endoscopy. Breastfeeding should continue unless lactose malabsorption is strongly suspected.

To prevent IDI, guidelines for managing acute gastroenteritis should be followed, which recommend avoiding formula dilution and promoting early feeding that reduces intestinal permeability and illness duration and improves nutritional outcomes. (40) Dietary protein and fat are important in recovery, but simple carbohydrates should be minimized. The BRAT diet (bananas, rice, applesauce, toast) in the management of diarrhea is unnecessary and nutritionally suboptimal. Refeeding syndrome is a risk for severely malnourished patients. Intravenous hydration may be necessary in treating IDI. Tolerance of enteral feeds and resolution of diarrhea typically occur within 2 to 3 weeks.

Allergic Enteropathy

Allergic enteropathy, or eosinophilic enteropathy, associated with failure to thrive, vomiting, and diarrhea, should be distinguished from allergic colitis occurring in otherwise healthy and thriving infants. As in allergic colitis, allergic enteropathy is induced by food proteins with the most common being cow milk and soy proteins. In allergic enteropathy, however, there is small intestinal mucosal damage resulting in malabsorption of protein, carbohydrate, and fat. Protein malabsorption may lead to hypoalbuminemia and diffuse swelling. Profuse vomiting and diarrhea may lead to severe dehydration, lethargy, and hypotension, mimicking sepsis in a young infant. Serum IgE levels may or may not be elevated. Protein hydrolysate or amino acid-based elemental formulas are necessary if breastfeeding on a restricted diet is not possible. Once the inciting dietary protein is removed, the enteropathy will resolve.

Celiac Disease

Celiac disease is an immune-mediated enteropathy that occurs in the setting of gluten ingestion in a genetically susceptible individual. With its prevalence in adults and children approaching 1% worldwide, celiac disease has become a more commonly diagnosed disorder. (41) However, the classic presentation of celiac disease in children with the triad of failure to thrive, diarrhea, and abdominal distension is being seen less frequently. (42) Because of family screening, more sensitive and easily accessible testing, and the recognition of the wide variety of presenting symptoms, identification of patients presenting with atypical symptoms is on the rise. (43)

Diagnosis should begin with establishing the presence of antiendomysial IgA antibodies, which have near 100% specificity, or employing newer and less expensive techniques for measuring enzyme-linked immunosorbent assay-based anti-TTG IgA antibodies. Diagnosis is confirmed by particular histologic findings in the duodenum,

including villous blunting and prominent intraepithelial lymphocytosis. Current treatment is with a diet free of wheat, rye, and barley. New potential therapies are being sought, including the use of gliadin-digesting recombinant enzymes.

Inflammatory Bowel Disease

Children and adolescents suffering from diarrhea, with or without weight loss, must be evaluated for IBD. Approximately 50% to 80% of children with Crohn disease will present with diarrhea, among other symptoms. In Crohn disease, stool may contain microscopic blood but may not be grossly bloody, especially in the absence of significant left-sided colonic disease. Diarrhea is more common in colonic disease and may be absent altogether in cases of isolated small bowel inflammation. In ulcerative colitis, diarrhea is a more consistent presenting feature, often insidious in its development but eventually developing hematochezia. Nocturnal diarrhea with urgency may be a sign of left-sided colonic inflammation in either Crohn disease or ulcerative colitis. Diarrhea associated with IBD typically improves with therapy as mucosal inflammation resolves.

Immunodeficiency States

Children with primary immunodeficiency states often present with chronic diarrhea. (44) X-linked agammaglobulinemia may result in diarrhea secondary to chronic rotaviral infections or recurrent giardiasis. IgA deficiency may lead to recurrent giardiasis and bacterial overgrowth, and is associated with a 10- to 20-fold increased incidence of celiac disease. (45) Chronic diarrhea is common also in hyper-IgM and human immunodeficiency virus syndromes and may be caused by infection with *Cryptosporidium parvum* in these diseases. Children with common variable immunodefiency often present with diarrhea and significant malabsorption along with severe recurrent life-threatening infections during the first months after birth. Intractable diarrhea with neonatal insulin-dependent diabetes should raise suspicion for the syndrome of immune dysregulation, polyendocrinopathy, and enteropathy (autoimmune), X-linked (IPEX syndrome). Glycogen storage disease type 1B and chronic granulomatous disease may present very similarly to Crohn disease, likely related to defective intestinal mucosal immunity. (46)

Congenital Secretory Diarrhea

Two very rare causes of secretory diarrhea in early infancy are CCD and congenital sodium diarrhea (CSD). Fewer than 15 patients with CSD and ~250 with CCD have been reported in the literature. (47) Both diseases present before birth with polyhydramnios resulting from in utero diarrhea. At birth, high-volume secretory diarrhea continues despite bowel rest and may cause life-threatening dehydration and electrolyte disturbances. CCD causes severe hypochloremia and a unique metabolic alkalosis, whereas CSD causes hyponatremia with alkaline stools resulting in metabolic acidosis. Stool electrolytes often aid in the diagnosis, and genetic testing can identify defective chloride transport genes in some patients with CCD. Aggressive fluid and electrolyte replacement is the mainstay of therapy for both diseases.

Tufting Enteropathy

Tufting enteropathy, also known as intestinal epithelial dysplasia, presents in the first few months after birth with growth failure and intractable watery diarrhea. (48) Significant electrolyte abnormalities may occur even before the severity of illness is recognized by caretakers. Histology of the small bowel reveals a unique picture of villous atrophy and crypt hyperplasia without significant inflammation. Closely packed enterocytes appear to create focal epithelial "tufts." A recent genomic study of children born with tufting enteropathy revealed mutations in the epithelial cell adhesion molecule EpCAM. (49) Affected infants typically become dependent on parenteral nutrition to allow normal growth and development. Small bowel transplant is potentially curative, but the associated morbidity and mortality are high.

Microvillous Inclusion Disease

Another rare cause of chronic secretory diarrhea in the neonatal period is microvillous inclusion disease, presenting with diarrhea so watery that it may be mistaken for urine. (48) Microvillous inclusion disease is the second most common cause of severe, protracted diarrhea in the first week after birth, after infectious causes are excluded. Contrary to what occurs in CCD and CSD, polyhydramnios typically is not seen. Histology reveals small bowel villous atrophy but without inflammation or expected crypt hyperplasia. Villin substance can be seen by immunostaining in affected cell cytoplasm, creating the "microvillous inclusions." Aggressive intravenous rehydration and electrolyte replacement are necessary to maintain life during infancy, followed by lifelong parenteral nutrition in most cases.

Autoimmune Enteropathy

Children with autoimmune enteropathy usually develop secretory diarrhea after the first 8 weeks after birth.

Another autoimmune disease, such as insulin-dependent diabetes, may be present in the setting of chronic diarrhea and poor growth, which should raise suspicion for IPEX syndrome. (48) However, autoimmune enteropathy may exist without extraintestinal manifestations. Diagnosis is made by documenting antienterocyte, anticolonocyte, or antigoblet cell antibodies in the blood, although the number of centers that perform this test is limited and the specificity of the test is unclear. Treatment is difficult but may be accomplished with immunosuppressive agents such as corticosteroids, 6-mercaptopurine, tacrolimus, and infliximab. (50)

Neuroendocrine Tumors

Neuroendocrine tumors affecting the gastrointestinal tract in children are rare. These tumors produce symptoms by the systemic effect of their secretory products. The neuroendocrine tumors produce secretory diarrhea and include vasoactive intestinal polypeptide-secreting tumor, or VIPoma; Zollinger-Ellison syndrome (ZES); tumors secreting prostaglandin E2; and carcinoid syndrome. VIP stimulates cyclic adenosine monophosphate activity, eventually resulting in intestinal secretion, similar to the effects of the cholera toxin. Therefore, the classic presentation of VIPoma is with profuse watery diarrhea (usually >20 cc/kg per day), hypokalemia, and achlorhydria (WDHA syndrome). ZES causes diarrhea because of high intestinal gastrin levels. Carcinoid tumors may secrete serotonin, bradykinin, and histamine, also leading to gastric acid hypersecretion and diarrhea. Once secretory diarrhea is established, the evaluation may include measuring the concentrations of serum VIP, fasting gastrin, and prostaglandin E2 levels, along with 24-hour urine 5-hydroxyindoleacetic acid for carcinoid tumor. Most VIPomas in children are ganglioneuromas or ganglioneuroblastomas, which can be identified radiographically. Operative resection is imperative but not always curative if the tumor has metastasized. (51)

Hirschsprung Disease

Diarrhea is present in approximately one-third of neonates born with Hirschsprung disease. (52) The diarrhea usually is a consequence of enterocolitis that occurs in the setting of bacterial stasis in the lumen. (53) Children may present with fever, diarrhea, and abdominal distension. Some children may appear acutely ill with explosive diarrhea, vomiting, rectal bleeding, and lethargy, whereas others may present with only loose stools and perianal excoriation. Hirschsprung disease should be suspected in any infant who does not pass meconium within the first 24 hours, which is the case in 94% of affected infants but in only 10% of healthy infants. Older infants may have poor growth, a distended abdomen, and explosive passage of stool with rectal examination. Older children with Hirschsprung disease usually do not have the fecal soiling and stool withholding behaviors that are common in functional constipation. Enterocolitis represents the most significant source of morbidity and mortality in Hirschsprung disease and deserves immediate treatment with intravenous antibiotics and supportive care.

Cystic Fibrosis

Diarrhea occurs in CF most commonly as a result of pancreatic insufficiency. Approximately 90% of patients with CF have pancreatic insufficiency. (54) Loss of exocrine pancreatic function leads to malabsorption of carbohydrates, fat, and protein because of dysfunctional amylases, lipases, and proteases, respectively. Such malabsorption leads to poor growth in addition to chronic diarrhea and possible steatorrhea. Patients with CF also have an increased incidence of small bowel bacterial overgrowth, possibly secondary to altered motility and thickened secretions, among other complex factors. (55) Fecal elastase can be used as a predictor of pancreatic exocrine function, with low levels indicating possible pancreatic insufficiency. Pancreatic enzyme replacement therapy may improve malabsorptive diarrhea in patients with CF.

Factitious Diarrhea

When inconsistencies arise among a patient's history, physical signs, and laboratory findings, the practitioner should consider the possibility of a factitious disorder. Many cases of factitious diarrhea induced by either the patient or patients' parents have been reported in the literature. (56)(57) Although laxative ingestion is the most common cause of factitious diarrhea, the ingestion of osmotic agents or even feces may induce diarrhea. Patients also may dilute stool to create the appearance of diarrhea. Munchausen by proxy syndrome (factitious disorder by proxy per Diagnostic and Statistical Manual criteria), in which the caregiver creates the child's illness, often includes factitious diarrhea induced with stimulant laxatives or even by syrup of ipecac poisoning. Such cases usually require hospital admission with careful observation after a full evaluation for organic causes of chronic diarrhea has been completed.

Summary

- The differential diagnosis for chronic diarrhea in children is broad. Pediatric clinicians can narrow these possible diagnoses beginning with a detailed history and physical examination.
- Particular attention should be paid to growth measurements to distinguish between chronic diarrhea with and without associated growth failure.
- Understanding the four basic pathophysiologic mechanisms of diarrhea also may aid in making a diagnosis. The four categories are osmotic, secretory, dysmotility associated, and inflammatory.
- Although specific therapies vary for each disease, the importance of maintaining nutrition demands particular emphasis. Whatever the cause of the diarrhea, each patient requires adequate caloric intake to allow healing of the initial insult, or at least to support the child while pursuing diagnostic and therapeutic interventions.

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1. A 2-year-old girl has had daily diarrhea for the past 3 months. She has a soft but formed stool in the morning and then has seven to eight episodes of increasingly soft-to-watery stools. Her parents at times see undigested food in her stools. She does not have loose stools at night. She eats a regular diet, drinks milk, water, and juice. She is growing well. She has not had blood or mucus in her stools and does not complain of abdominal pain. Her parents ask what is the next step in the evaluation and management of her diarrhea. Your best response is to recommend which of the following?

   A. Bowel rest with restricted caloric intake for 2 weeks.
   B. Eliminating juice intake.
   C. Hydrogen breath testing.
   D. Initiating treatment with artificial lactase enzymes.
   E. Obtaining stool cultures.

2. A 14-year-old girl has abdominal pain approximately weekly. During these episodes, she has multiple bowel movements that are looser than her usual stools. She relates that she feels better after she has a bowel movement. She has had no fever, rectal bleeding, or mucus in her stool. She has not lost weight. Her physical examination is normal. The best next step in the evaluation of her abdominal pain is

   A. Endoscopy.
   B. Upper gastrointestinal series with small bowel follow-through.
   C. Stool electrolyte content and osmolarity.
   D. Tissue transglutaminase immune globulin A test.
   E. 72-hour stool collection for measurement of fecal fat.

3. An 8-month-old girl is seen for daily loose stools for 4 weeks. Her older siblings also had diarrhea but recuperated after 10 days of illness. The infant has lost weight and is hospitalized for further evaluation. The diet you are most likely to recommend for this infant is

   A. Bowel rest with parenteral nutrition.
   B. BRAT diet (bananas, rice, applesauce, toast).
   C. Breastfeeding or regular formula.
   D. Oral rehydration fluids only.
   E. Restricted protein and fat intake.

4. A 5-month-old boy has been hospitalized for pneumonia. He has had diarrhea for 3 months, with frequent watery stools daily. He is losing weight. On physical examination, he is afebrile, thin, and listless. The evaluation you are most likely to initiate includes

   A. Enteral transit time study.
   B. Hydrogen breath testing.
   C. Immunoglobulin levels.
   D. Lactulose testing.
   E. 3-day dietary history.

5. A 3-month-old infant boy has emesis and diarrhea and is losing weight. His formula was changed to a soy-based product and after rehydration he is admitted to the hospital for further evaluation. The diet you are most likely to request for this infant is

   A. Bowel rest with parenteral nutrition.
   B. Cow's milk-based formula with artificial lactase enzyme.
   C. Diluted soy formula.
   D. Oral rehydration solution.
   E. Protein hydrolysate or amino acid-based elemental formula.

Chronic Diarrhea in Children

Garrett C. Zella and Esther J. Israel

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