

# Chronic Diarrhea

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**Objectives** After completing this article, readers should be able to:

1. Describe how to prevent intractable diarrhea of infancy.
2. Characterize the causes of chronic, acquired diarrhea.
3. Recognize and diagnose the severe, rare congenital diarrheas.
4. Discuss factitious diarrhea and its signs and symptoms.

## Introduction

Although this review focuses primarily on issues that a pediatric practitioner in the United States or Canada may need to consider when faced with a patient who has protracted diarrhea, we should not ignore the role that North American pediatric practices play in world health. The harm done within and beyond our borders by the once common practices of withdrawing or diluting the feedings of infants who had diarrhea and overusing intravenous hydration and bottle-feeding have yet to be corrected fully. Implementation of the core concepts contained in the American Academy of Pediatrics (AAP) Practice Parameter for Acute Gastroenteritis (1996) is incomplete, although much progress has been made.

Recurrent, chronic, infantile diarrhea, acting in concert with malnutrition, causes the death of 4.6 million children globally each year. Prolonged diarrhea is a threat to life whenever or wherever safe food and water are not provided due to inadequate supply, ignorance, or malice. The near elimination of this lethal outcome of diarrhea in the United States and Canada is attributable, in part, to the successes of agriculture and public health measures in the 20th and 21st centuries that have made food abundant and safer. Also, in the last 25 years, the following specific preventive measures have reduced further the number of infants who have this condition: 1) renewed emphasis on breastfeeding, 2) reduction in the use of partial starvation regimens during diarrheal episodes, and 3) increased availability of age-appropriate infant food for children living in poverty (Special Supplemental Food Program for Women, Infants and Children) (WIC).

In the developing world, the downward spiral of diarrhea and undernutrition often ends in death; in the presence of modern western medical care, the condition usually is reversible, even in its late stages. Once an infant is recognized as having intractable diarrhea of infancy (IDI), enteral therapy with a lactose-free, sucrose-free, medium-chain triglyceride formula often allows recovery. If enteral therapy fails, parenteral nutrition becomes necessary and curative.

Full implementation of the AAP guidelines for treatment of acute gastroenteritis and the expansion of the WIC program to cover all who may benefit eventually should eliminate this potentially fatal form of chronic diarrhea within the United States, although it will reappear whenever understanding of its cause and prevention are forgotten.

## Definition

No limit of duration is employed consistently to separate acute and chronic diarrhea. Diarrhea caused by proven or assumed acute infectious agents seldom lasts more than 2 weeks, but awareness of the differences in the duration due to the common infectious agents can be useful in identifying patients who have more serious problems.

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**Table 1. Duration of Uncomplicated Viral Diarrhea**

Agent	Duration	
	Average (d)	Range (d)
Rotavirus	6*	1 to 10
Enteric adenoviruses	11	1 to 22
Astrovirus	5	1 to 8
Torovirus	5	1 to 5
Norwalk-like	2	1 to 4

\*Rotavirus and astrovirus diarrhea may continue for months in children who have defects in T-cell function (eg, DiGeorge syndrome, cartilage-hair hypoplasia syndrome)

### Viral Diarrheas

Diarrhea caused by the viral agents commonly found in United States children seldom continues for more than 2 weeks (Table 1). The average duration of diarrhea is 6 days for rotavirus, 11 days for enteric adenoviruses, 5 days for astrovirus, fewer than 5 days for torovirus, and 2 days for Norwalk-like agents. Rarely, rotavirus or astrovirus infection may continue for months in children who have defects in T-cell function.

### Bacterial Diarrheas

Diarrhea due to bacteria lasts longer (average 14 d), with a substantially longer duration seen with some agents (Table 2).

Nontyphoidal *Salmonella* infection, when acquired in the first weeks after birth, may lead to many months of recurrent diarrhea, intermittent positive stool cultures, and undernutrition. Antibiotic treatment is needed if bacteremia or meningitis is present, but the duration of the enteric infection and degree of growth impairment is not influenced favorably by such treatment. Infants may reach a point where parenteral nutrition is employed to prevent undernutrition.

*Aeromonas* and *Plesiomonas* sp are associated with diarrheal illness and extraintestinal infections and have a particular predilection for immunocompromised children who are exposed to untreated fresh and saltwater and shellfish. Quinolone antibiotics and trimethoprim-sulfamethoxazole are recommended therapy.

*Yersinia* is a gram-negative bacillus found in rodents, birds, and other animals. Infection is acquired by ingestion of contaminated, undercooked, or unpasteurized foods. Outbreaks associated with seasonal holidays have occurred in bottle-fed infants whose caretakers had handled raw pig intestines (chitterlings). *Yersinia* caused one epidemic of acute appendicitislike illness in children who had ingested chocolate milk at school.

As in *Aeromonas* and *Yersinia* infections, enteric pathotypes of *Escherichia coli* are likely to cause acute, self-limiting illness, but the diarrhea may evolve to a chronic course due to persistent injury to the bowel. Enterotoxigenic and mucosa-adherent *E coli* cause a watery diarrhea that may lead to prolonged diarrhea due to mucosal damage or persistence of the primary infection. The enterohemorrhagic pathotype that produces Shiga toxin causes acute colitis and the hemolytic-uremic syndrome.

Outbreaks of disabling watery diarrhea lasting for more than 1 year are experienced periodically. The first carefully studied episode was in Brainerd, Minnesota. Epidemiologic evidence suggested unpasteurized milk or undertreated municipal water as the source, but the agent (Brainerd agent) is presumed to be infectious, although it has not yet been identified. Travelers and Israeli soldiers have developed a similar illness.

### Nonviral, Nonbacterial Diarrheas (Table 3)

#### *Giardia lamblia*

*G lamblia* cysts usually are ingested from unwashed hands that were in contact with infected feces; outbreaks result from contaminated drinking water, recreational pools, pets, and rarely, food. A high index of suspicion for the diagnosis should be maintained for those caring for diapered children in child care, older children returning from camp, children who have immunodeficiencies,

**Table 2. Bacterial Causes of Chronic Diarrhea**

Organism	Sources	Duration
<i>Aeromonas</i> sp	Untreated water	1 wk to 1 y
<i>Campylobacter</i> sp	Raw poultry, diarrheic animals, unpasteurized milk, birds, water, ferrets	5 d to chronic
<i>Clostridium difficile</i>	Antibiotic use; can be nosocomial	10% have relapses
<i>Plesiomonas shigelloides</i>	Untreated water, shellfish	2 wk to months
<i>Salmonella</i> sp	Poultry, fecal-oral, water	5 d to months in infants
<i>Yersinia enterocolitica</i>	Handling of raw pig intestines (chitterlings)	3 wk to 3 mo
Brainerd diarrhea agent	Unpasteurized milk, water	Many months

Table 3. Parasitic Causes of Chronic Diarrhea

Organism	Sources	Duration
<i>Giardia lamblia</i>	Diapered infants, fecal-oral, water supplies	2 wk to years
<i>Cryptosporidium parvum</i>	Child care, petting zoos, swimming pools	1 to 2 wk (mean, 1 to 10 d), with occasional reports of 6 wk
<i>Cyclospora cayetanensis</i>	Raspberries from Central America, water, unpasteurized apple cider	1 wk to 1 mo or more
<i>Entamoeba histolytica</i>	Fecal-oral, water	Weeks
<i>Isospora belli</i>	Fecal-oral, water	Chronic
<i>Strongyloides stercoralis</i>	Developing countries, Appalachia, fecal-oral	Chronic
<i>Blastocystis hominis</i>	Uncertain if a pathogen	

and any child whose diarrhea lasts for more than 5 days, especially if associated with other signs and symptoms of giardiasis (Table 4). The diarrhea is voluminous and odoriferous but seldom contains blood.

Giardiasis, the most common protozoan-caused diarrhea in North America, causes a protracted but usually self-limiting diarrhea in well-nourished, immunocompetent children. Given the frequency of reinfection (35% in some child care studies), coinfection with other enteric pathogens, and common lack of symptoms, the exact duration of symptoms in an uncomplicated case has been hard to establish. Some of the best information on signs and symptoms comes from a study of a single point outbreak in previously healthy and well-nourished adult skiers. The average duration of diarrhea was 44 days, and the average weight loss was 9.7 lb (4.3 kg). Frequent

recurrences of diarrhea punctuated by periods of normalcy occurred in 25% of the cases (Moore et al, 1969).

Although most people who have acute giardiasis become asymptomatic within 6 weeks of onset, a few otherwise healthy children develop prolonged diarrhea with weight loss of 10% to 15%, failure to grow, and stunting for 2 years or more. Why the infection in these apparently immunocompetent and well-nourished children is not controlled or why it eventually becomes controlled is not known. Diagnosis and therapy are associ-

ated with catch-up growth in case reports.

Diagnosis has been made easier by the widespread availability of fecal *Giardia* antigen tests, a simpler, less expensive, quicker test that, usually combined with a similar antigen test for cryptosporidia, largely has replaced the less sensitive and more labor-intensive microscopic examination of fecal concentrate (“O and P”). Before the advent of the fecal antigen tests, the much lower sensitivity of the microscopic tests performed in hospital and commercial laboratories often led to invasive testing that employed biopsy capsules, endoscopic biopsies, and “string tests.” At one time, the most sensitive test for *Giardia* was inspection of a mucosal impression smear taken from a well-oriented duodenal biopsy specimen that had been obtained with a Crosby-Kugler capsule or similar instrument. Because capsule biopsies have been replaced almost completely over the last decade by the much smaller biopsies obtained by upper endoscopy, this no longer may be considered the most sensitive test. Current biopsies are more difficult to orient for the impression smear. The sensitivity of the current duodenal biopsies in detecting *Giardia* trophozoites has not been determined, but it is likely to be less than that of the capsule samples and possibly a single fecal antigen test.

Because fever, leukocytosis, eosinophilia, and radiographic abnormalities usually are absent in giardiasis, an infectious cause for the diarrhea may not be considered. In occasional children, diarrhea is absent, with malaise being the only symptom. Rarer presentations of giardiasis include anasarca (protein-losing enteropathy) and retinal degeneration. *Giardia* sometimes are found in anatomic sites other than the proximal small bowel,

Table 4. Signs and Symptoms of Giardiasis\*

- Diarrhea (64% to 100%)
- Malaise, weakness (72% to 97%)
- Abdominal distention (42% to 97%)
- Flatulence (35% to 97%)
- Abdominal cramps (44% to 81%)
- Nausea (14% to 79%)
- Foul-smelling, greasy stools (15% to 79%)
- Anorexia (41% to 73%)
- Weight loss (53% to 7#%)
- Vomiting (14% to 35%)

\*From data from Walterspiel JN and Pickering LK, and Moore GT, et al.

but probably are innocent, transient visitors in those locations.

Metronidazole in a dose of 15 mg/kg for 10 days is the current treatment for giardiasis in the United States. Asymptomatic children generally are not treated; screening of schoolmates or family contacts is useful only if an epidemiologic study is in process.

### *Cryptosporidium parvum*

This protozoan causes watery diarrhea that often continues for 2 weeks and occasionally for longer. The infection results from ingestion of the organism from fecal contamination of the hands of caretakers, directly from animals, or from water in recreational settings. Chlorine is ineffective; the sand filtering necessary for removal seldom is carried out at water parks, swimming pools, or petting zoos. Large outbreaks have occurred when municipal water supplies are contaminated. Chronic and debilitating diarrhea occurs in the immunocompromised host.

The recently introduced combined *Giardia-Cryptosporidium* fecal antigen tests have better sensitivity than previous procedures. The diagnosis can be confirmed through microscopic examination of a Kinyoun acid-fast stain of feces, and the organism sometimes is seen in intestinal biopsies. The conventional ova and parasite examination seldom detects this infection. The incidence of coinfection with *Giardia* in immunocompetent adults is low (2%).

Diarrhea caused by both *Cryptosporidium* and *Giardia* can be treated with nitazoxanide oral suspension for 3 days.

### *Cyclospora cayetanensis*

*Cyclospora* is a unicellular coccidian parasite recognized in 1979 to be a cause of diarrhea. It causes watery, explosive diarrhea that may continue for a month or more and may become chronic with severe weight loss in immunocompromised individuals. Sources include contaminated water and food, especially fragile items of fresh produce that cannot be washed rigorously after harvesting. Outbreaks have occurred from unpasteurized apple cider and imported raspberries. Diagnosis is based on identification of oocysts in acid-fast stained fecal specimens. Trimethoprim-sulfamethoxazole has proven an effective therapy in controlled trials.

## Diarrhea in Infants

### IDI

IDI also is known as postenteritis enteropathy, protracted diarrhea of infancy, secondary disaccharidase de-

ficiency, global mucosal dysfunction, and “slick gut” syndrome. Enteric infection and associated compromise of intake and absorption lead to a variable loss of digestive and absorptive capacity in infants. The mildest variant of this effect is transient lactose intolerance. In its most severe form (IDI), even the least challenging feedings are not tolerated and, if parenteral nutrition is not possible, death occurs.

Recurrent episodes of diarrhea and failure to regain weight in an infant (usually <6 mo old) should suggest this diagnosis. Suspicion should be raised further by the absence of breastfeeding, the administration of diluted or clear liquid feedings, or restriction of intake in a misguided effort to reduce diarrhea or vomiting.

Diagnostic pitfalls abound. Highly absorptive diapers may mask the presence of watery diarrhea, even in a hospitalized child. The failure to gain weight and recurrently low serum bicarbonate concentration in the infant who has IDI may result in miscategorization of the condition as renal tubular acidosis, which can delay therapy and compromise survival. A delay in diagnosis and intervention until all alternatives have been ruled out can kill. The practitioner must make the diagnosis and initiate therapy without a positive laboratory or pathologic result.

Diagnosis is based on the physician’s awareness of the entity, reasonable exclusion of alternative explanations (Table 5), and eventually, the patient’s response to nutrition therapy and return to full health. Intestinal biopsy findings are nonspecific, and the procedure in small, malnourished infants carries a much higher likelihood of perforation with serious consequences. Intestinal biopsy

## Table 5. Differential Diagnosis of Prolonged Diarrhea of Infancy

- Intractable diarrhea of infancy
- Enteric infection
- Immunodeficiency disease
- Hirschsprung disease
- Cystic fibrosis
- Celiac disease
- Congenital short gut (malrotation)
- Congenital chloride diarrhea
- Congenital sodium diarrhea
- VIPoma
- Acrodermatitis enteropathica
- Autoimmune enteropathy
- Microvillus inclusion disease
- Tufted enteropathy
- A-beta-lipoproteinemia

## Table 6. Entities Diagnosed by Small Bowel Biopsy

- Microvillus inclusion disease
- Congenital chloride diarrhea
- Congenital sodium diarrhea
- Autoimmune enteropathy
- Tufted enteropathy
- Celiac disease

should be deferred until the infant fails to respond to nutrition intervention. If the diarrhea continues, the remaining conditions, all much rarer than IDI, can be established only by biopsy (Table 6). In as many as 10% to 25% of infants whose diarrhea persists despite appropriate enteral and parenteral nutrition, no diagnosis can be established, even after extensive testing.

IDI can be prevented in most cases by adherence to the AAP guidelines for treatment of acute gastroenteritis, but a few infants nevertheless develop the syndrome. Initial treatment usually is administration of a full-strength lactose-free, sucrose-free formula, which may be sufficient to allow weight gain and recovery of the intestinal lining. Diarrhea may continue during this therapy but should not be a barrier to continuing full feedings; intravenous supplementation of salts and water may be needed transiently to maintain hydration. For some patients, parenteral nutrition may be necessary. The clinician must decide when the risks of continuing the enteral feedings exceed the risk of parenteral nutrition and institute intravenous nutrition; 3 to 4 weeks of parenteral nutrition may be needed before full enteral feeding can be accomplished. Neither the exact duration of parenteral feeding nor the usefulness of small concurrent enteral (“trophic”) feedings has been studied critically and prospectively.

Because infants who have IDI have no underlying chronic illness, complete recovery is the usual outcome, although secondary disaccharidase deficiency may persist for 18 months or longer.

Awareness of this increasingly rare entity in the United States is waning except in children’s hospitals that provide care for large numbers of infants who have diarrhea or where faculty and trainees devote part of their service to sites in the developing world.

### Rare But Serious Causes of Protracted Diarrhea in Infancy

**ANATOMIC ABNORMALITIES.** Chronic diarrhea and slow growth are the presenting problems in some chil-

dren who have intestinal malrotation. The causes are: 1) chronic obstruction of intestinal lymphatic and venous drainage due to chronic volvulus, 2) congenital foreshortening of the small bowel, and 3) an associated defect of intrinsic enteric innervation and bowel motility.

Children who have chronic small bowel obstruction with stasis due to congenital or acquired bowel stenosis may have diarrhea due to malabsorption, inflammation, or bacterial overgrowth in the bowel segment involved.

The diagnosis of patients who have anatomic causes of chronic diarrhea usually is based on an expertly conducted and interpreted upper gastrointestinal radiographic series and small bowel follow-through. The presence of malrotation or of congenitally short small bowel often is not appreciated initially on a routine study performed in a nonpediatric hospital.

**MICROVILLUS INCLUSION DISEASE.** Microvillus inclusion disease (MVID) causes high-volume watery diarrhea, with onset in the first postnatal days. The diagnosis is based on the finding of villus atrophy and intracytoplasmic inclusions lined by intact microvilli in intestinal biopsy material. The pathophysiology is understood incompletely, but autophagocytosis of apical membranes suggests a defect in enterocyte migration and exfoliation. Occurrence in siblings and in progeny of consanguineous marriages as well as the pattern of inheritance in groups sharing common ancestors (Navajo) suggests that MVID is an autosomal recessive disease.

No curative therapy is known. The infants are dependent on parenteral nutrition, but diarrhea continues and death usually occurs in infancy. Small bowel transplantation has been attempted.

**CONGENITAL CHLORIDE DIARRHEA.** Congenital chloride diarrhea (CLD) (Darrow-Gamble syndrome) is due to a mutation in the *DRA* gene encoding a transporter protein. This genetic defect causes profuse, watery, chloride-rich diarrhea beginning in utero. Prenatal ultrasonography shows multiple dilated, fluid-filled intestinal loops and marked polyhydramnios. Stool chloride concentration ( $>90$  mEq/L [ $90$  mmol/L]) may be diagnostic as early as the fourth day after birth. Fecal chloride can be measured in the hospital laboratory, permitting early diagnosis and therapy. The characteristic hypokalemia with metabolic alkalosis also provides an important diagnostic clue but is present inconsistently when the infant is younger than 6 months of age.

CLD is inherited recessively. Clusters occur in Finland, Poland, and the Persian Gulf and in immigrants from those areas (1:5,000 in Saudi Arabia). The condi-

tion was described initially by two United States pediatricians.

Treatment consists of providing sufficient salts and water to replace the diarrheal losses, initially intravenously and later orally. If the diagnosis is made and severe dehydration avoided, growth and development often are normal.

**CONGENITAL SODIUM DIARRHEA.** Congenital sodium diarrhea is caused by a defect in a jejunal sodium/proton exchange that results in severe watery diarrhea. As in CLD, the first manifestations are polyhydramnios and dilated fetal intestine, with the onset of diarrhea immediately after birth. Only 11 patients have been reported. It appears to be an autosomal recessive disease. To date, search for mutations in the known sodium/proton exchanger genes has failed.

**TUFTED ENTEROPATHY.** This disorder presents with watery diarrhea in the first weeks after birth. The intestinal biopsy reveals focal epithelial “tufts,” teardrop-shaped groups of enterocytes, and shortening of the microvilli without inclusions. There is no known effective therapy.

**ACRODERMATITIS ENTEROPATHICA.** Acrodermatitis enteropathica (AE) is characterized by chronic diarrhea, undernutrition, and a rash primarily involving the perioral, perianal, and perineal areas. Serum zinc and alkaline phosphatase concentrations are low, and the signs and symptoms resolve after oral or parenteral zinc therapy. The hereditary form of AE is rare and follows an autosomal recessive pattern. Mutations in a gene (SLC39A4) that encodes a protein that has features characteristic of a ZIP zinc transporter have been found in families who have this form of AE. Zinc supplementation must be continued to prevent relapse.

Identical clinical manifestations occur in patients who become zinc deficient due to other illnesses, including IDI, cystic fibrosis, exclusively breastfed preterm or term infants, anorexia nervosa, and Crohn disease.

Iatrogenic AE may occur when an inadequate supply of zinc is provided to patients who have special needs. This deficiency has occurred in infants receiving special diets for methylmalonic aciduria, propionic aciduria, and ornithine transcarbamylase deficiency and in children undergoing dialysis or receiving parenteral nutrition when zinc supplementation is inadequate.

**AUTOIMMUNE ENTEROPATHY.** Autoimmune enteropathy is another rare but life-threatening chronic diarrhea

whose onset occurs in the first year after birth. Among the bowel biopsy findings are total villus atrophy and inflammatory cells, including eosinophils, in the epithelium. The condition is distinguished from celiac disease by the absence of a response to gluten elimination and from MVID by the absence of inclusions. Nonintestinal immune-mediated problems, such as type 1 diabetes, hypothyroidism, hemolytic anemia, membranous glomerulonephritis, autoimmune hepatitis, and rash, are common. Treatment with prednisone, azathioprine, cyclophosphamide, tacrolimus, and prolonged parenteral nutrition is associated with an estimated 50% recovery rate.

There have been too few patients scattered over too many years and centers to have allowed a randomized trial of immunosuppression regimens. Many of the children have increased serum antiepithelial cell antibodies.

**VIPoma AND WDHA.** Vasoactive intestinal polypeptide (VIP), a hormone secreted by some tumors (Table 7), causes chronic, high-volume, watery diarrhea, hypokalemia, and alkalosis (WDHA) syndrome. In the pediatric age range, 1- to 3-year-olds are affected most often. Initial misdiagnoses are the common infections, lactose intolerance, or chronic nonspecific diarrhea of infancy (CNSD) and irritable bowel syndrome (IBS). Later in the course, the secretory nature of the diarrhea, persistence of diarrhea during periods of interrupted oral intake, abdominal distention disproportionate to the child’s nutritional state, and growth arrest suggest the condition. Diagnosis is established by measurement of serum VIP, which is strikingly elevated (eg, 3,200 pmol/L [ $<270$  pmol/L]) or imaging studies that show a mass in the adrenal gland or along the sympathetic ganglia in the abdomen or thorax. The diarrhea

Table 7. Vasoactive Intestinal Polypeptide-secreting Tumors

Pediatric

- Ganglioneuroma
- Ganglioneuroblastoma
- Pheochromocytoma
- Mastocytoma
- Non-beta cell hyperplasia
- Medullary thyroid carcinoma

Adult

- Pancreatic non-beta cell islet neoplasm

Table 8. Diarrhea in Immunodeficiency Diseases

Condition	Diarrhea Type/Onset
Human immunodeficiency virus infection	30% have diarrhea or malabsorption. Cryptosporidia and <i>Giardia</i> are common. In the absence of proven infection, elevated serum VIP suggests hormonal cause.
Severe combined immunodeficiency syndrome (Rag1, Rag2, JAK3, ZAP-70, Omenn S)	50% have protracted diarrhea with onset in early infancy; cryptosporidia and prolonged rotavirus.
X-linked agammaglobulinemia	Onset late in first year up to age 5 y. <i>Campylobacter jejuni</i> , <i>Giardia</i> .
Hyper IgM immunodeficiency	50% have protracted diarrhea. Cryptosporidia are common. Tonsils and other lymphoid organs are enlarged.
Common variable immunodeficiency	<i>Giardia</i> and <i>Campylobacter jejuni</i> are common.
Chronic granulomatous disease	Mild watery to severe bloody diarrhea. <2 years old, Crohnlike colitis.
Wiskott-Aldrich syndrome	Bloody diarrhea at birth; inflammatory bowel disease-like course.
Major histocompatibility complex class II deficiency	Death in infancy due to diarrhea/malabsorption; 96% have diarrhea with proven and unproven infections, including <i>Giardia</i> , cryptosporidia, <i>Candida</i> sp, <i>Salmonella</i> sp, <i>Cytomegalovirus</i> .
Selective IgA deficiency	Possible increased sign of chronic giardiasis.
Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome	Intractable diarrhea in first year

ceases and the serum VIP concentration drops to normal within a few days of tumor resection.

In children, the underlying lesion most often is a ganglioneuroma or ganglioneuroblastoma with a relatively mature cell type; resection often is curative. The syndrome also has been reported in metastatic neuroblastoma and has appeared after chemotherapy when it was not present before. The tumor typically is found in an adrenal gland or elsewhere in the retroperitoneal space and occasionally in the mediastinum or neck. The tumor is revealed by computed tomography or conventional radiographs; it may be calcified.

In adults, the syndrome usually is caused by a malignant pancreatic islet cell tumor that frequently is metastatic at diagnosis.

The less common VIP-secreting tumors may be suspected in the presence of the cutaneous manifestations or a family history of an underlying syndrome (eg, neurofibromatosis-1, multiple endocrine neoplasia I, mastocytoma) associated with those tumors.

Intractable diarrhea in patients infected with human immunodeficiency virus can be associated with a modest elevation of VIP. Improvement after octreotide therapy has been reported in these cases, suggesting that VIP may be causal.

**IMMUNODEFICIENCY DISEASES.** Protracted diarrhea is a common complication of a number of immunodeficiency states and may be the dominant or presenting manifestation in infants. Evaluation of infants who have protracted or life-threatening diarrhea should include a

careful family history and a focused physical examination that includes the tonsils, lymph nodes, spleen, and skin. Scrutiny of the peripheral blood smear may reveal absence of mature lymphocytes or polymorphonuclear leukocytes, although more complex analysis often is required. The major immunodeficiencies associated with chronic diarrhea are listed in Table 8. The course of several of these conditions presenting in early life is fulminant and fatal; life-saving interventions often can be instituted if the diagnosis is considered early.

**FACTITIOUS DIARRHEA.** Intentional poisoning of infants and children with osmotic agents (Epsom salts, magnesium citrate, propylene glycol) and irritants (ipe-cac, bisacodyl, phenolphthalein) can cause chronic diarrhea, growth arrest, and death. The criminal usually is a parent, most often the child's mother. She frequently is well-informed about the medical diagnostic process and conceals her role in creating the illness behind a mask of concern, challenging even the most experienced practitioner's diagnostic ability. This problem is particularly difficult to recognize when superimposed on established medical intervention (eg, central venous catheter, gastrostomy) or prior proven chronic illness.

The clinical characteristics are watery or bloody diarrhea that usually resolves when the patient is admitted to the hospital for study. Hypokalemia and alkalosis from chronic loss of potassium and or surreptitious feeding of baking soda may be misinterpreted as evidence for a VIP-secreting tumor. Ipecac poisoning causes diarrhea as well as vomiting, and biopsies at colonoscopy showing

### Table 9. Chronic Nonspecific Diarrhea (CNSD)/Irritable Bowel Syndrome (IBS)

#### Symptoms

- Onset: 6 to 18 months of age
- Loose, explosive bowel movement containing food particles
- Bowel movement frequency: 6 to 12/d
- Growth: Normal (if not on restrictive diet)

#### Red Flags (Not Compatible With CNSD/IBS)

- Hematochezia or melena
- Persistent fever
- Weight loss or growth arrest
- Anemia

#### Diet

- Restrict apple juice and pear nectar (trial only)
- Restrict lactose (trial only)

#### Laboratory Studies

- tTG or EMA
- Fecal *Giardia* antigen

#### Therapy

- Reassurance
- Lifestyle modifications
- Avoidance of restrictive diets

inflammation may be misinterpreted as inflammatory bowel disease. Cardiomyopathy from emetine may be misdiagnosed as a systemic mitochondrial disease.

Diagnosis is difficult. Study of the electrolyte and osmotic composition of feces can reveal the presence of one of the osmotic agents, and emetine can be found in feces, gastric contents, blood, and urine. These studies should not be attempted without expert guidance. A carefully maintained record of custody of the specimen from bedside to the final reference laboratory is needed if the evidence is to hold up against legal challenge.

Phenolphthalein was withdrawn by the United States Food and Drug Administration from over-the-counter sales in 1999, and shifts in the management of poisoning have reduced the availability of ipecac. These changes may reduce the incidence of those specific poisonings, although osmotic cathartics remain widely available.

The term “poisoning” is preferable to “Munchausen-by-proxy syndrome.” The latter is interpreted by some attorneys and judges as maternal psychiatric illness, displacing the focus from the legal action needed to protect the child.

### Table 10. Presentations of Celiac Disease

- Slow weight gain
- Fecal impaction
- Iron deficiency
- Hypertransaminasemia
- Osteomalacia/fractures
- Delayed puberty
- Anasarca/hypoalbuminemia
- Recurrent intussusception
- Alopecia areata
- Dermatitis herpetiformis
- Fatigue
- Depression

### Diarrhea in Older Children

Many of the entities that cause chronic diarrhea in older children were covered in another article in *Pediatrics in Review* (Pietzak and Thomas, 2003).

#### Chronic Nonspecific Diarrhea

CNSD (toddler’s diarrhea; IBS, infant variant) is a very common condition. The diagnosis is based on history and physical examination findings. Often, the primary care physician successfully offers reassurance without making a specific diagnosis. In the absence of red flags (Table 9), reassurance is a good practice.

#### Disaccharidase Deficiency

Lactase deficiency after enteritis may persist for many months, sometimes overlapping with the onset of the genetically determined form of lactase deficiency that occurs in older children and adults of African, Asian, or Middle Eastern ancestry.

#### Celiac Disease

Probably due to anorexia and limited intake, diarrhea in patients who have celiac disease often is absent or overshadowed by other symptoms (Table 10).

#### Cystic Fibrosis

Cystic fibrosis may present with chronic watery diarrhea or infrequent, loose, voluminous bowel movements in older children. Acquired zinc or lactose intolerance may dominate the clinical presentation.

#### IBS

The symptoms of IBS, adult variant are found in 10% to 20% of the adult population, most of whom never seek

## Table 11. Irritable Bowel Syndrome Diagnostic Criteria (Rome II)

In children old enough to provide an accurate history of pain, at least 12 weeks, which need not be consecutive, in the preceding 12 months of:

- 1) Abdominal discomfort or pain that has two of three features:
  - a) Relieved with defecation
  - b) Onset associated with a change in frequency of stool
  - c) Onset associated with a change in form (appearance) of stool
- PLUS
- 2) No structural or metabolic abnormalities to explain the symptoms

medical care. The pediatrician should make the diagnosis positively (Table 11) because it provides substantial reassurance and liberty from misguided therapies.

### Suggested Reading

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## PIR Quiz

Quiz also available online at [www.pedsinreview.org](http://www.pedsinreview.org).

1. Which of the following pairs correctly matches an organism with its most likely source of infection?
  - A. Adenovirus – unpasteurized milk.
  - B. *Cryptosporidium parvum* – contaminated swimming pool.
  - C. *Giardia lamblia* – undercooked pork.
  - D. *Plesiomonas* – raw pig intestines.
  - E. *Yersinia* – contaminated well water.
2. You are evaluating a 7-year-old girl in your office who has a 6-week history of watery, foul-smelling diarrhea. She also has experienced some bloating and cramping but no weight loss. She just returned from summer camp. You suspect giardiasis. Which of the following tests is the simplest and most reliable in helping you confirm your diagnosis?
  - A. Duodenal biopsy.
  - B. Fecal *Giardia* antigen test.
  - C. Fecal ova and parasites.
  - D. Stool culture.
  - E. String test.
3. Which of the following diarrheal diseases is *most* likely to present after 6 months of age?
  - A. Congenital chloride diarrhea.
  - B. Congenital sodium diarrhea.
  - C. Microvillus inclusion disease.
  - D. Tufted enteropathy.
  - E. VIPoma.
4. You are evaluating a 6-month-old boy in the hospital. He has had several episodes of watery diarrhea since the age of 3 months, at which time he was hospitalized for rotavirus infection. He has been receiving an oral electrolyte solution primarily because his mother has been reluctant to start him again on his regular milk-based formula. His weight at 3 months was 5.6 kg; his current weight is 6.2 kg. Except for mild dehydration, findings on his examination are normal. His electrolyte concentrations are normal, with the exception of a serum  $\text{HCO}_3^-$  of 12 mEq/L (12 mmol/L). Which of the following is the *best* next step in management?
  - A. Complete bowel rest and initiation of parenteral nutrition.
  - B. Continuation of his milk-based formula with additional zinc supplementation.
  - C. Initiation of a full-strength lactose-free, sucrose-free formula.
  - D. Initiation of an immunologic evaluation.
  - E. Stool for *Giardia* fecal antigen and culture.
5. A 14-month-old boy presents to your office with a history of diarrhea, according to his mother, for “his whole life.” A review of his chart reveals two prior infections with *Giardia* and one episode of *Campylobacter jejuni* infection. His weight is 8 kg (<5th percentile), and his physical examination reveals shotty cervical adenopathy but no other abnormalities. Which of the following is the *most* likely diagnosis in this toddler?
  - A. Acrodermatitis enteropathica.
  - B. Celiac disease.
  - C. Chronic nonspecific diarrhea of childhood.
  - D. Common variable immunodeficiency.
  - E. Postenteritis enteropathy.