Chronic Diarrhea

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ARTICLE

Chronic Diarrhea

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IMPORTANT POINTS

1. **The differential diagnosis of chronic diarrhea varies markedly with age.**
2. **The most common cause of chronic diarrhea in small infants is formula protein intolerance.**
3. **There is up to a 50% crossover in intolerance between cow milk and soy protein formulas.**
4. **In toddlers, the first intervention in chronic diarrhea is usually the trial of a high-fat, low-carbohydrate diet that includes whole cow milk.**
5. **Lactose intolerance is rarely a problem in infants and toddlers who have chronic diarrhea.**

Evaluation of a child who has diarrhea requires an understanding of the pathophysiology of the condition. Diarrhea is defined most commonly as either an increase in the frequency or a decrease in the consistency of the stool. Because stool number, volume, and consistency vary considerably among individuals, or in the same individual, the definition is inherently imprecise. Normal infants pass about 5 to 10 g/kg of stool daily, and stool volumes in excess of 10 g/kg per day are considered diarrhea. Adults average about 100 g/day, and stool loss greater than 200 g/day in older children and adults constitutes diarrhea. From a parental standpoint, the presence of diarrhea usually is assessed by subjective evaluation of stool frequency and consistency.

Pathophysiology of Diarrhea

Diarrhea often is subdivided in terms of pathophysiology (Table 1). Osmotic diarrhea, secretory diarrhea, motility disturbances, and inflammatory processes are the primary mechanisms through which diarrhea occurs. In many instances, more than one mechanism is at fault.

Osmotic diarrhea is relatively common in children. This term implies that malabsorption of an absorbable solute creates an osmotic load in the distal small intestine and colon, resulting in increased fluid losses. This commonly occurs when carbohydrates, relatively small osmotically active particles, are malabsorbed. Malabsorption of carbohydrates in infancy usually is caused by diffuse mucosal injury. Congenital defects in carbohydrate absorption are relatively rare. More typically, excess intake of hypertonic juices by toddlers results in osmotic diarrhea. In this instance, the diarrhea rapidly ceases when the offending substance is withdrawn.

Secretory diarrhea in its purest sense is diarrhea that continues even when the patient is not being fed; it results from enhanced secretion of water and electrolytes into the lumen relative to the amount of fluid and electrolytes absorbed. Pure secretory diarrhea typically does not manifest intestinal inflammation; occult blood and white blood cells are absent from the stool. Secretory diarrheas may occur in congenital disorders of fluid and electrolyte metabolism such as congenital chloridorrhea, mucosal disorders such as microvillus inclusion disease, and certain tumors such as ganglioneuroblastoma.

Motility disorders may cause diarrhea, but they rarely cause malabsorption. The absorptive capacity of the small intestine is sufficient to absorb most nutrients, even when transit is rapid. Perhaps the most common motility-induced diarrhea in the pediatric age group is irritable colon of infancy or chronic nonspecific diarrhea. Disorders that result in decreased intestinal motility, such as chronic idiopathic intestinal pseudo-obstruction syndrome or Hirschsprung disease, may result in severe bacterial overgrowth in the small intestine, with mucosal injury and inflammatory diarrhea.

Inflammatory diarrhea is relatively common in the pediatric age group, especially associated with acute diarrheal disorders that are likely to be infectious. Chronic inflammatory conditions such as ulcerative colitis and Crohn disease also occur in the pediatric age group. Exudation of mucus, protein, and blood into the gastrointestinal lumen may contribute to fecal water, electrolyte, and protein loss. Inflammatory diarrheas often are accompanied by secretory, osmotic, and even motility-induced components.

Chronic Diarrhea in the Infant

The differential diagnosis of chronic diarrhea changes markedly with age (Table 2). In the young infant, perhaps the most common cause of chronic diarrhea is formula protein intolerance. Diffuse intestinal mucosal injury begins before 6 months of age and, in severe cases, is associated with malabsorption and malnutrition. The incidence of protracted formula protein intolerance, which develops into intractable diarrhea of infancy, has decreased rather markedly in recent

TABLE 1. Major Types of Diarrhea by Mechanism

TYPE	EXAMPLE
Osmotic	Lactase deficiency
Secretory	Neuroendocrine syndrome
Motility	Irritable bowel syndrome
Inflammatory	Crohn disease

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TABLE 2. Common Causes of Chronic Diarrhea

Infants
• Formula protein intolerance
Toddlers
• Irritable colon of infancy
• Protracted viral enteritis
• Giardiasis
Children/Adolescents
• Ulcerative colitis
• Crohn disease
• Primary acquired lactose intolerance

years. This probably is due to the introduction of new, improved, extensively hydrolyzed therapeutic infant formulas, increased use of breastfeeding, and a tendency to feed children more aggressively during diarrheal states, thus preventing the occurrence of malnutrition and its adverse effect on mucosal healing. The actual mechanism and genetics are poorly understood, but this disorder is commonly familial.

Infants who have formula protein intolerance frequently develop enterocolitis, with inflammation in both the small bowel and colon. It usually begins at about 2 weeks to 2 months of age, with a symptom constellation consisting of vomiting, irritability, diarrhea, and occasionally, bloody stools. Stools sometimes test positive for reducing substances, suggesting small bowel mucosal injury and carbohydrate malabsorption. Stool pH may be <5.5 for the same reason, and stool leukocytes can be present, which suggests colitis. A variety of histologic abnormalities can be seen in the small intestine, primarily partial villus blunting and flattening and an increase in inflammatory cells. The lesion, however, is patchy, and small bowel biopsy often does not reveal the true extent of the injury.

Most patients who have cow milk protein-sensitive enterocolitis respond well to protein hydrolysate formulas. Occasionally, amino acid formulas may be required and deserve a trial.

If these patients do not respond to therapeutic formulas, they may develop intractable diarrhea of infancy and require a combination of continuous enteral and parenteral nutrition (Figure). The previous practice of placing such patients on extended periods of bowel rest has been shown to be inappropriate. Enteral feeding generally heals the mucosal lesion more rapidly, especially if an extensively hydrolyzed or amino acid enteral feeding formula is used. Most patients who have severe milk protein sensitivity also are intolerant of soy formula. Lack of understanding of this concept has led to overuse of soy formulas. These infants tend to outgrow the allergic response between 1 and 2 years of age.

In young infants who develop symptoms of vomiting and diarrhea when milk is ingested, it is invariably the protein, not the lactose, that is creating the problem, and use of a lactose-free formula in such infants is inappropriate. Vomiting and diarrhea are common in infants and are most often infectious. When these symptoms persist for longer than 1 week, intolerance of formula or some other protein should be suspected, and use of a protein hydrolysate formula is indicated.

An intractable diarrhea-like syndrome may develop in older infants following infectious enteritis and is characterized by mild malabsorption, impaired growth, and low-grade inflammation on small intestinal biopsy. Hypocaloric, high-carbohydrate diets may be a participating factor in the poor growth. Some of these infants may develop a secondary cow milk protein intolerance that resolves in a few months. Intolerance of cow milk by this group of patients is more likely due to a secondary allergic reaction to the protein than to lactose malabsorption. A high-fat, low-carbohydrate diet is suggested in these cases.

Other rare causes of chronic diarrhea in infants include microvillus inclusion disease, tufting enteropathy, and a disorder known as syndromatic enteropathy, which is characterized by mild villus abnormalities on light microscopy in association with brittle, unmanageable hair, characteristic facies, and a subtle defect in antibody production. Autoimmune enteropathy also may cause severe mucosal injury and protracted malabsorption, but this usually presents after 6 months of age.

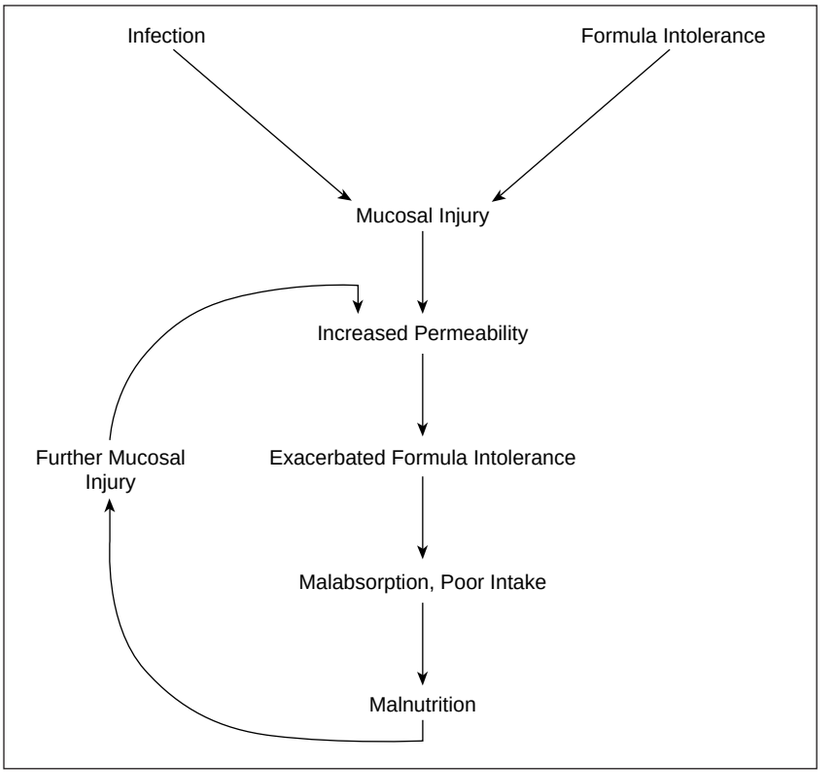

FIGURE. Vicious circle of pathophysiology in intractable diarrhea.

For any infant who has intractable diarrhea, one needs to consider the possibility of Hirschsprung disease, which occasionally can present with enterocolitis, and Munchausen syndrome by proxy, in which maternal administration of laxatives to infants produces an intractable diarrhea-like syndrome. In the case of Munchausen by proxy, the small intestinal biopsy typically is normal, and separation of the child from the caretaker results in abrupt cessation of symptoms. Parents of these infants often appear overly concerned and constantly are with the child.

Congenital transport of nutrients may cause diarrhea from birth in congenital chloridorrhea, congenital glucose galactose malabsorption, and congenital sucrase isomaltase deficiency. Diarrhea from birth only occurs when the infant is fed a sucrose-containing formula. In each instance, small intestinal biopsy is normal.

Chronic Diarrhea in the Toddler

The differential diagnosis of chronic diarrhea changes during the latter part of the first year of life and into the second year. The most common cause of chronic diarrhea in this age group is irritable colon of infancy, also known as chronic nonspecific diarrhea. This disorder is believed to be a variant of irritable bowel syndrome. It is not uncommon to find a family history of irritable bowel in parents or siblings.

Patients who have this disorder typically exhibit intermittent loose, watery stools. The presentation can vary from two to three mushy stools on one day to five to ten watery stools on other days. The intermittent nature of the diarrhea often is helpful in making the diagnosis. Stools usually are not expelled at night, although it is not uncommon to have a very watery stool immediately upon awakening in the morning. These children manifest normal growth if they are not placed on hypocaloric diets in an attempt to control the diarrhea. Because of the intermittent nature of the diarrhea, they often are misdiagnosed as having food allergies or recurrent episodes of viral enteritis. The assumption of food allergy is strengthened in the minds of the parents by the common presence of vegetable or other food particles in the stool, which are simply a manifestation of rapid transit.

The mechanism for diarrhea in this disorder appears to be altered gastrointestinal motility. Despite relatively rapid transit, absorption is intact and the child will grow well if fed adequately. Institution of a high-fat, low-carbohydrate diet is often helpful because of reduced dietary osmolality and the effect of ileal fat reducing intestinal motility. When fat reaches the ileum, secretion of gastrointestinal hormones, primarily peptide YY, slows gastric emptying and small intestinal transit, thereby providing some improvement in the child's diarrhea. We usually tell parents to encourage ingestion of meats, vegetables, butter, gravy, and whole milk and eliminate all simple sugars, especially sucrose and juices. Addition of fiber in the form psyllium mixed with applesauce also may aid in improvement.

Institution of a high-fat, low-carbohydrate diet that includes whole milk often results in significant improvement in toddlers who have diarrhea.

Another disorder in toddlers that closely mimics chronic nonspecific diarrhea is referred to as protracted viral enteritis. This disorder starts with a viral infection such as rotavirus. Institution of high-carbohydrate, low-fat feedings results in chronic hypocaloric, hyperosmotic ingestions that produce osmotic diarrhea. Low-grade mucosal injury often persists, and the patient may lose weight because of hypocaloric feedings. These children often consume large quantities of apple juice or other high-carbohydrate beverages and frequently drink large quantities of fluid. They respond dramatically to a high-fat, low-carbohydrate diet and reduced fluid intake. It is important to remember that lactase deficiency is an insignificant problem in most patients who have viral enteritis, and institution of a lactose-free diet usually is unnecessary. Whole milk is a good source of protein and fat, and its restriction from the diets of children who have persistent chronic diarrhea often results in hypocaloric, hyperosmolar feedings that exacerbate diarrhea.

Giardiasis is another disorder that closely mimics chronic nonspecific diarrhea. *Giardia* is a proximal small intestinal protozoal pathogen that causes mucosal injury, resulting in malabsorption and watery stools. It may be contracted through contaminated food or water or by person-to-person contact. The incidence varies greatly with geographic location, and children usually exhibit weight loss, loose runny stools, and crampy abdominal pain. Patients may lose weight initially because of chronic low-grade malabsorption. Diagnosis is difficult because pathogens are not always recovered from the stool. Results of stool examinations may be normal in up to 50% of patients. Enzyme-linked immunosorbent assay (ELISA) for *Giardia* antigen in the stool may be as sensitive, and a small intestinal biopsy that includes careful examination for *Giardia* often may be definitive.

Celiac sprue, otherwise known as celiac disease or gluten enteropathy, is believed to be a relatively rare disease, but it may be more common in North America than originally thought. This disorder results in chronic proximal small intestinal inflammation following ingestion of gluten, a protein in wheat, oats, barley, and rye. Patients usually present with poor growth, abdominal distention, chronic diarrhea, and weight loss. They are often poor eaters, as are all children who have any form of mucosal injury, because they become uncomfortable when they eat.

Celiac sprue usually is associated with significant failure to thrive, which can differentiate it from most other causes of toddler diarrhea. Screening studies are now available

for celiac disease, including immunoglobulin A (IgA) and IgG anti-gliadin antibodies, antireticulin antibodies, and antiendomysial antibodies. Because the condition requires lifelong restriction of gluten from the diet, a small intestinal biopsy is mandatory for confirming the diagnosis. It will reveal the classic findings of a flat small bowel mucosa. The presence of positive antibodies, a compatible biopsy, and an excellent response to a gluten-free diet obviates the need for further biopsies. These patients run a significant risk of gastrointestinal malignancies later in life, which can be avoided largely by strict elimination of gluten throughout life. Therefore, the diagnosis must be made with certainty and the diet rigidly maintained. One cannot overemphasize to patients that celiac disease is a lifelong condition that never is cured.

Cystic fibrosis often is considered in the differential diagnosis of chronic diarrhea, but these patients typically have greasy, foul-smelling stools and significant failure to thrive that frequently presents during infancy. Diagnosis can be confirmed or excluded by sweat chloride determination.

Other rare causes of diarrhea in toddlers include congenital sucrase isomaltase deficiency and secretory diarrhea from tumors. Inflammatory bowel disease, especially ulcerative colitis, may occur occasionally in toddlers.

Chronic Diarrhea in School-age Children

The differential diagnosis changes again as the child progresses into school age. Inflammatory bowel disease becomes more common, and disorders such as chronic nonspecific diarrhea and protracted viral enteritis are less common. Inflammatory bowel disease is probably the first consideration in the school-age child who has chronic diarrhea. After age 5, both Crohn disease and ulcerative colitis occur with similar frequency; the incidence of Crohn disease appears to be increasing. Children who have inflammatory bowel disease may present with blood and mucus in the stool and often with abdominal pain and cramping. Growth failure is common, especially in Crohn disease. Perianal disease, such as fissures or fistulas, are often present on physical examination, as is right lower quadrant tenderness in patients who have Crohn disease. Definitive diagnosis can be made more certainly with colonoscopy than with radiography, especially if the examination is performed by a skilled pediatric gastroenterologist who can intubate the terminal ileum.

Appendicitis in infants and children occasionally may cause diarrhea for several days or weeks, especially if perforation has occurred. Localized inflammation in the region of the cecum results in chronic inflammatory diarrhea, often associated with low-grade fever and abdominal tenderness.

Primary acquired lactase deficiency may present in the school-age child. Lactase levels begin to drop between the ages of 3 and 5 years in children destined to become lactose-intolerant. The child gradually develops flatulence, abdominal pain, and loose stools following ingestion of milk. The condition is extremely rare before 5 years of age and is a more common cause of abdominal pain than diarrhea.

A small number of cases of milk protein intolerance have been observed in older children, in which the ingestion of cow milk protein is followed by a sudden onset of diarrhea, abdominal pain, and vomiting. These patients have normal results on lactose breath hydrogen tests, abnormal small bowel histology following ingestion of milk protein, and usually a history of milk intolerance from birth. Exclusion of milk from the diet is curative.

Occasionally, patients who are constipated will be brought to the physician for evaluation of chronic diarrhea. These children develop fecal impaction with overflow incontinence, that is, encopresis. Soiling of the pants is interpreted by the parents as diarrhea. A key question to ask in obtaining a history from the parents of a child who has chronic diarrhea is where he or she stools. A school-age child who has diarrhea almost always can make it to the toilet. If he or she does not, encopresis should be the first consideration in the differential diagnosis.

Summary

The differential diagnosis of chronic diarrhea varies markedly with age. In infants, it is usually a problem with formula intolerance. Because there is up to a 50% crossover intolerance between milk and soy, the infant should be given an extensively hydrolyzed formula. If such intervention is delayed, he or she may develop intractable diarrhea of infancy. Most affected toddlers have either irritable colon of infancy or protracted viral enteritis with low-grade mucosal injury and are consuming hypertonic feedings. In either case, institution of a high-fat, low-carbohydrate diet that includes whole milk often results in significant improvement. Dietary lactose rarely is a problem. A likely cause of diarrhea among children and adolescents is inflammatory bowel disease. With the exception of toddlers, chronic diarrhea suggests the presence of significant organic disease.

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PIR QUIZ

11. Of the following, the *most* common feature of chronic nonspecific diarrhea (irritable colon of infancy) is:
    A. Guaiac-positive stools.
    B. Intermittent fever.
    C. Lactose intolerance.
    D. Nocturnal soiling.
    E. Normal growth pattern.

12. A 9-month-old infant has had seven watery stools per day for 6 weeks. A dietary record reveals that he takes 22-oz per day of apple and pear juice. The primary mechanism to explain this child's diarrhea is:
    A. Infectious.
    B. Inflammatory.
    C. Motility.
    D. Osmotic.
    E. Secretory.

13. Which of the following interventions is the *most* appropriate for treating toddlers who have irritable colon of infancy or protracted viral enteritis?
    A. Institute a high-carbohydrate, low-fat diet.
    B. Institute a low-carbohydrate, high-fat diet.
    C. Place at complete bowel rest and start total parenteral nutrition.
    D. Remove milk and milk products from the diet.
    E. Treat empirically with metronidazole.

14. A 2-month-old girl has extreme irritability, vomiting, diarrhea, and most recently, bloody stools. A switch from cow milk to soy-based formula did not improve her symptoms. Physical examination reveals a small, nonicteric girl. The abdomen is mildly distended, but there is no hepatosplenomegaly. The stools are grossly bloody and the clinitest result is 2+. The *most* likely cause for this infant's symptoms is:
    A. Biliary atresia.
    B. Celiac disease.
    C. Congenital lactase deficiency.
    D. Cystic fibrosis.
    E. Formula protein intolerance.

15. A 13-month-old infant has chronic diarrhea, poor appetite, irritability, and growth failure. She had been well previously, developing normally until diarrhea began at 8 months of age. Findings include weight less than the 5th percentile and length at the 25th percentile; cachectic appearance with wasted extremities and protuberant abdomen; albumin, 2.3 g/dL; and total protein, 4.0 g/dL. Stool is positive for reducing sugars and for split fats and repeatedly negative for enteric pathogens and ova and parasites. These findings are *most* consistent with:
    A. Celiac sprue.
    B. Cow milk, soy protein allergy.
    C. Crohn disease.
    D. Cystic fibrosis.
    E. Giardiasis.

16. A 9-year-old boy began soiling himself following a move 8 months ago. He previously had complaints of constipation, but his parents now are concerned about diarrhea. His physical examination is remarkable only for mobile masses in the left lower quadrant and a wet smear of stool in his underpants. Hard stool is present in the rectal vault and is negative for enteric pathogens, occult blood, leukocytes, and parasites. The *most* likely cause for his symptoms are:
    A. Crohn disease.
    B. Encopresis.
    C. Milk protein intolerance.
    D. Primary acquired lactase deficiency.
    E. Ulcerative colitis.

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