CHRONIC DIARRHEA

Dr.FARIBORZI

Pediatric gastroenterologist

DEFINITION

- Chronic diarrhea is defined as stool volume of more than 10 grams/kg/day in infants and toddlers, or more than 200 grams/day in older children for more than 14 days .
- This typically translates to persistent loose or watery stools occurring at least three times a day, where the change in stool consistency is more important than stool frequency.

PREVALENCE AND MORBIDITY

- Diarrhea lasting more than two to four weeks occurs in up to 3 to 5 percent of the population worldwide. It is generally more frequent in males, with a male-to-female ratio of 1.2 to 2.6:1 in the age range of 6 to 24 months .
- In the developed world, the prevalence of chronic diarrhea is substantially lower.
- Most of these cases are self-limited, with fewer than 28 percent presenting for medical care. Fewer than 100 per 10,000 children are hospitalized in the United States for diarrheal disease.

PATHOPHYSIOLOGY

- The basic pathophysiology of all diarrheas is incomplete absorption of water from the intestinal lumen either because of a reduced rate of net water absorption (related to impaired electrolyte absorption or excessive electrolyte secretion) or because of osmotic retention of water in the lumen.

FUNCTIONAL DIARRHEA

- painless passage of three or more large, unformed stools during waking hours for four or more weeks, with onset in infancy or the preschool years, and without failure to thrive or a specific definable cause . This common, benign disorder has also been termed chronic nonspecific diarrhea of childhood or toddler's diarrhea.
- Children with functional diarrhea usually pass stools only during waking hours. Early morning stools typically are large and semi-formed, then stools become progressively looser as the day progresses . Virtually all children develop normal bowel patterns by four years of age

- In some cases, the diarrhea is associated with excessive intake of fruit juice, sorbitol, or other osmotically active carbohydrates, and will improve when the intake of these foods is moderated. Other than this precaution, restrictions to the diet or other interventions are not necessary or helpful. In particular, restriction of dietary fat may be counter-productive.
- If the evaluation suggests functional diarrhea:
- Reduce or eliminate fruit juice or other osmotically active carbohydrates. Apple, prune, and pear juice contain sorbitol and have a particularly high osmotic load.
- Liberalize the fat content of the diet to 35 to 50 percent of total calories

INFECTIOUS CAUSES

- Postenteritis syndrome : Most enteric infections in otherwise healthy children resolve within 14 days and do not develop into a chronic diarrhea illness. However, in a minority of patients, an acute gastroenteritis can trigger persistent diarrhea by causing mucosal damage to the small intestine, termed a "postenteritis syndrome" . The mechanisms underlying this syndrome are not fully understood.
- international guidelines discourage the use of hypoallergenic or diluted milk formulas during acute gastroenteritis.
- In some cases, treatment with probiotic bacteria may facilitate recovery from postenteritis syndrome

BACTERIA

- In immunocompromised patients, common infectious causes of acute diarrhea, such as Campylobacter or Salmonella, can cause persistent diarrhea. Chronic infections with these pathogens are uncommon in immunocompetent hosts. Bacterial cultures should be part of the initial diagnostic evaluation for all patients if the stool contains blood, or for immunocompromised patients regardless of fecal blood.
- In children recently treated with antibiotics, Clostridium difficile may cause a colitis characterized by "pseudomembrane" formation. The enzyme immunoassay available in most laboratories detects C. difficile toxins A and B with high specificity but only moderate sensitivity. Polymerase chain reaction (PCR) based diagnostic methods can enhance the detection rate

PARASITES

- Intestinal parasites are an uncommon cause of chronic diarrhea in developed countries, except among individuals with an immunodeficiency.
- Specific antigen assays for Giardia and examination from the stool for parasites is imperative for children with known immunodeficiencies or with a history of travel to endemic areas. These tests are also an appropriate step in the evaluation of immunocompetent children if initial testing fails to determine a cause of the chronic diarrhea.

IMMUNE DEFICIENCY

- Chronic diarrhea may present as a complication of a known immune deficiency such as HIV disease. In this case, the evaluation should focus on potential infectious causes of the diarrhea, particularly parasites and opportunistic infections such as Cryptosporidium, Isospora, and Cyclospora . These children also are at risk for persistent infectious pathogens that typically cause acute diarrheas, such as rotavirus.
- Chronic diarrhea also may be a presenting symptom of immune deficiency in a child. When a patient is infected with an unusual pathogen, or has multiple or recurrent infections of the gastrointestinal tract or elsewhere, further evaluation for immune deficiency is required.

ABNORMAL IMMUNE RESPONSE

- Celiac disease :
- (also known as gluten-sensitive enteropathy or nontropical sprue) is an immune-mediated inflammation of the small intestine caused by sensitivity to dietary gluten and related proteins in genetically sensitive individuals. The disorder is common, occurring in 0.5 to 1 percent of the general population in most countries.
- Celiac disease often presents as chronic diarrhea, with or without malnutrition, during late infancy or early childhood.

INFLAMMATORY BOWEL DISEASE

- Ulcerative colitis and Crohn's disease are idiopathic chronic inflammatory diseases (IBD) of the bowel. These disorders typically present with gradual onset of chronic diarrhea, with or without blood, from mid-childhood through adulthood.
- Infantile and very early onset IBD (onset at age less than six years) appears to be a distinct subset of these diseases, in which clinical and genetic characteristics can be unique compared with later-onset cases of IBD

ALLERGIC ENTEROPATHY

- An abnormal immune response to food proteins can cause a proctitis/colitis or an enteropathy.
- The former tends to present as bloody diarrhea and is frequently triggered by cow's milk protein in infants.
- The latter presents as non-bloody diarrhea and/or as failure to thrive.

EOSINOPHILIC GASTROENTERITIS

- Disorder that is sometimes but not always associated with an identifiable dietary antigen.
- Approximately one-half of patients have allergic disease, such as asthma, defined food sensitivities, eczema, or rhinitis; some patients have elevated serum IgE levels; rare patients have IgE antibodies directed against specific foods.

MICROSCOPIC AND COLLAGENOUS COLITIS

- Microscopic colitis typically presents with chronic watery nonbloody diarrhea. It typically occurs in middle-aged adults, but occasionally presents in children. The endoscopy is grossly normal, but histopathology reveals abnormal inflammatory findings, characterized by a collagenous colitis or lymphocytic colitis, sometimes with an eosinophilic infiltrate. In some cases, this disorder may represent an overlap with the eosinophilic gastroenteropathies.
- Microscopic colitis in children usually responds well to aminosalicylic acid (5-ASA) medications .
- Some cases in adults have been successfully treated with budesonide. Collagenous colitis is a related form of colitis that has been reported in a few children. The colon appears grossly normal, but biopsies show a thickened subepithelial collagenous band in the colonic mucosa.

AUTOIMMUNE ENTEROPATHIES

- Autoimmune enteropathies are rare disorders that may present as severe diarrhea during infancy or toddlerhood. The diarrhea may be isolated, or may occur in association with diabetes mellitus as part of the IPEX syndrome (**I**mmune dysregulation, **P**olyendocrinopathy and **E**nteropathy, **X**-linked), which is associated with mutations in the FOXP3 gene. IPEX is characterized by chronic diarrhea, which usually begins in infancy, dermatitis, autoimmune endocrinopathy (diabetes mellitus, thyroiditis). Antienterocyte antibodies may be present.)
- Autoimmune polyendocrine syndrome 1 (APS-1), also known as autoimmune polyendocrinopathy-candidiasis ectodermal dystrophy (APECED), is one of several autoimmune disorders caused by mutations in the autoimmune regulator gene (AIRE). Features include hypoparathyroidism and adrenal insufficiency, and about 25 percent of patients develop autoimmune enteritis.

CHOLERHEIC DIARRHEA

- Patients who have undergone resection of the terminal ileum have impaired absorption of bile acids. If sufficient bile acids enter the colon, they may cause a secretory diarrhea.
- Similarly, patients who have had a cholecystectomy can develop cholerheic diarrhea because the continuous drainage of bile into the small bowel may overcome the terminal ileum's reabsorptive capacity.
- Cholerheic diarrhea also may be caused by rare congenital defects in bile acid malabsorption.

GASTROINTESTINAL PROTEIN LOSS

- Mucosal disease :Protein losses may be caused by inflammatory exudation through mucosal erosions (eg, inflammatory bowel disease), or by increased mucosal permeability without erosions (eg, celiac disease).
- Lymphatic obstruction :Obstruction of the intestinal lymphatics impairs lymph flow and increases pressure in the intestinal lymphatics. This leads to leakage of lymph into the intestinal lumen, reduced recirculation of intestinal lymphocytes into the peripheral circulation, and decreased absorption of fat-soluble vitamins.
- Primary intestinal lymphangiectasia is characterized by diffuse or localized ectasia of enteric lymphatics.
- Secondary intestinal lymphangiectasia may be caused by cardiac diseases, and chemotherapeutic, infectious, or toxic substances that are associated with inflammatory processes that cause retroperitoneal lymph node enlargement, portal hypertension or hepatic venous outflow obstruction.

BOWEL OBSTRUCTION OR DYSMOTILITY

- Hirschsprung's disease :This disorder may present with dysmotility and diarrhea, and may progress to life-threatening toxic megacolon. Infants presenting with a history suggestive of Hirschsprung's disease should be evaluated promptly with abdominal plain films, followed by barium contrast studies and/or rectal suction biopsies.
- Intestinal pseudoobstruction : This disorder of intestinal motility typically presents with constipation, but patients also may have periods of diarrhea, particularly if bacterial overgrowth supervenes.

CONGENITAL SECRETORY AND OSMOTIC DIARRHEAS

- Congenital diarrhea can be caused by a variety of inherited disorders that disrupt nutrient digestion, absorption, or transport, enterocyte development and function, or enteroendocrine function.
- Evaluation — If a congenital diarrhea is suspected, stool electrolytes, pH, fat, and reducing substances should be measured. A trial of fasting should be performed to determine if the diarrhea is secretory or osmotic. A marked decrease in stool output during fasting and high stool osmolarity (eg, more than 40 mOsm greater than the serum osmolarity) suggests an osmotic diarrhea .

CONGENITAL CHLORIDE DIARRHEA

- Affected individuals present in the neonatal period with hyponatremia, hypochloremia, and metabolic alkalosis; there may be a history of polyhydramnios. The diagnosis of CCD is based on the finding of excessive fecal secretion of chloride.

  Treatment consists of a high chloride intake to prevent volume depletion. Determining the optimal replacement dose is challenging because inadequate salt substitution paradoxically decreases diarrhea volume, and excessive salt administration also increases diarrhea volume by osmotic mechanisms . In some cases treatment with the proton pump inhibitor omeprazole appeared to reduce the stool volume and the fecal excretion of sodium and chloride by decreasing gastric chloride secretion .

- in another report, butyrate appeared to be helpful . However, subsequent investigations suggest that the findings were artifacts of suboptimal salt substitution, and that these medications are not effective for treatment of CCD

CONGENITAL SODIUM DIARRHEA

- a syndromic form which includes choanal or anal atresia and is associated with mutations in the SPINT2 gene, which are not seen in patients with isolated CSD .
- The stool is alkaline and fecal sodium concentrations are high; metabolic acidosis and hyponatremia are typically present ; there may be a history of polyhydramnios.

MICROVILLUS INCLUSION DISEASE

- The disorder typically presents with intractable secretory diarrhea shortly after birth, rapidly progressing to hypotonic dehydration and metabolic acidosis . A milder form of MID presents a few months later. Some patients have been successfully managed with parenteral nutrition including replacement of the large fecal losses of fluid and electrolytes, followed by intestinal transplantation

TUFTING ENTEROPATHY

- also known as intestinal epithelial cell dysplasia.
- The disorder presents with secretory diarrhea shortly after birth; the diarrhea volume is often less than in MID, and may partially respond to fasting . Enteral feeding usually is unsuccessful; successful management with long-term parenteral nutrition and/or intestinal transplantation has been described.
- Chronic arthritis has also been reported in a case with a genetically supported diagnosis.
- patients with the typical clinical presentation of congenital tufting enteropathy, many had associated ophthalmologic findings, including superficial punctate keratitis or conjunctival erosions; conjunctival biopsies revealed epithelial parakeratosis and tufts .

OSMOTIC DIARRHEAS

- Glucose-galactose malabsorption:The diagnosis is suspected if the diarrhea resolves promptly when these sugars are eliminated, and confirmed by a positive glucose breath hydrogen test and normal intestinal biopsy. Treatment is with a fructose-based formula, and lifelong dietary restriction of the causative sugars.
- Congenital sucrase-isomaltase deficiency : Infants are asymptomatic if their diet contains only lactose (eg, exclusively breast-fed infants), but typically develop chronic diarrhea after sucrose-containing formulas or foods are introduced. Case reports describe effective treatment with sacrosidase.

- Enteric anendocrinosis : also known as congenital malabsorptive diarrhea 4) is caused by mutations in neurogenin-3 (NEUROG3) and is associated with a paucity of enteroendocrine cells in the pancreas and intestine . It is characterized by an osmotic diarrhea and later development of insulin-deficient diabetes, without anti-islet cell antibodies .
- Maldigestion of fat :Congenital defects in pancreatic enzyme activity and lipid trafficking tend to present with chronic fatty diarrhea (steatorrhea) due to fat malabsorption, often with failure to thrive during infancy.
- Cystic fibrosis : is the most common cause of pancreatic exocrine insufficiency in children. The disease may present at birth with meconium ileus, or may be suggested later by gastrointestinal symptoms of fat malabsorption, failure to thrive, rectal prolapse (particularly in the setting of diarrhea) or pulmonary symptoms.

CATEGORIZE THE DIARRHEA

- ●Watery diarrhea – Most cases of persistent watery diarrhea in children in resource-limited settings are caused by acute infections with enteric pathogens, usually in combination with under-nutrition. enteropathogens not usually associated with persistent diarrhea may present as acute or chronic infections.

- ●Bloody diarrhea – In resource-limited settings, most cases of acute bloody diarrhea are caused by *Shigella* spp (45 to 67 percent of cases), and *Campylobacter* (35 to 37 percent of cases) . *E. histolytica* is the most important non-bacterial pathogen, but is responsible for fewer than 3 percent of episodes. Most infections with these organisms result in acute diarrhea illnesses, and cause low-volume bloody stools, often associated with fever.

LABORATORY TESTING

- In cases where diarrhea has persisted more than two weeks, testing the stool for glucose and pH can be helpful in identifying those children with severe villous atrophy. This can be done easily at the bedside with a urine dipstick if available. Glucose test tape, nitrazine paper, and clinitest tablets also have been used. A stool glucose of greater than 2+ or a pH of less than 5.0 suggests substantial villous atrophy.

DIETARY MANAGEMENT

- Most children will respond to dietary management using locally available foods designed to provide approximately 150 kcals/kg/day and 10 percent of calories from protein .
- If possible, at least half the protein should come from an animal source such as milk, egg, or chicken.
- Additional potassium should be added to the diet to provide at least 5 mEq/kg per day.
- At first the diet should be given in frequent small amounts, for instance every three hours, in which the total amount mentioned above is divided into eight feedings. If children refuse food, a nasogastric tube may be necessary. Feeding should be continued, either orally or by nasogastric tube, during the night to avoid long periods without food.

- many infants and children with chronic diarrhea have secondary disaccharidase deficiencies, caused by mucosal damage. Consequently, a low-lactose diet and sometimes a diet also low in sucrose or total carbohydrates may be necessary. It is often sufficient to reduce lactose by mixing milk with cereals such as rice or noodles and giving small frequent feedings.

- Egg or pureed chicken have been successfully used and are palatable.

- Yogurt-based diets have also been used successfully .

MICRONUTRIENTS AND VITAMINS

- Children with chronic diarrhea and malnutrition are often deficient in vitamin A, zinc, folic acid, copper, and other vitamins and minerals . Deficiencies in these micronutrients can impair the function of the immune system and have a direct effect on small intestinal function and recovery.

- The WHO recommends zinc supplementation for children with diarrhea in resource-limited settings, at a dose of 10 mg daily for infants up to 6 months of age, and 20 mg daily for older infants and children, for 14 days. These recommendations are based on a variety of randomized trials in resource-limited settings, demonstrating that zinc supplementation reduced the severity and duration of acute and persistent diarrhea in children.

ANTIDIARRHEAL DRUGS

- Drugs that alter intestinal motility, including loperamide, codeine, and paregoric, are not recommended because they lack efficacy, are associated with potentially serious side effects, and possibly prolong the excretion of enteric pathogens .
- Similarly, some antiemetics may cause sedation that could interfere with oral rehydration therapy, and should not be given to children with diarrhea

PROBIOTICS

The authors concluded that probiotics appeared to hold promise as adjuvant therapy for persistent diarrhea but there was insufficient evidence to recommend their use at this time.

The probiotics used in the trials were lactobacillus strains plus saccharomyces boulardii and lactobacillus rhamnosus GG