Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

better care could significantly reduce much of the morbidity and premature mortality associated with the disease. In the UK, high priority is currently being given to implementing national standards of diabetes care in order to reduce the high economic and human cost of diabetic complications.

See also: **Coronary Heart Disease**: Etiology and Risk Factor; **Diabetes Mellitus**: Treatment and Management; **Hyperlipidemia (Hyperlipidaemia)**; **Hypertension**: Physiology; **Obesity**: Etiology and Diagnosis

Further Reading

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Dialysis *See* **Membrane Techniques**: Principles of Reverse Osmosis; Applications of Reverse Osmosis; Principles of Ultrafiltration; Applications of Ultrafiltration

DIARRHEAL (DIARRHOEAL) DISEASES

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Background

Diarrhea is one of the most common health care problems in both developing and developed countries. Infectious diarrhea has been noted to constitute 10% of US pediatric outpatient visits; its estimated costs total nearly $1 billion annually. World Health Organization (WHO) statistics indicate that diarrhea is the second leading cause of death in the pediatric population, causing about 3 million deaths per year. Although a dramatic decrease in mortality was achieved through the introduction of oral rehydration therapy program in 1979, infectious diarrhea is still a major problem; a causative microorganism is identified in only about half of all such cases. The epidemiology of the microorganisms has not changed significantly over time.

Diarrhea is defined as an excessive loss of fluid and electrolytes in the stool. In newborns and infants, stool volume greater than $15\,g\,kg^{-1}\,day^{-1}$ is considered diarrhea. By approximately 3 years of age, the stool quantity reaches adult output, and from then on, an amount greater than 250 g per day is

considered diarrhea. Diarrhea can be categorized as acute or chronic, according to its duration; chronic diarrhea lasts more than 2 weeks. The etiology of diarrhea can be traced to both noninfectious and infectious agents such as viruses, bacteria, and parasites. Noninfectious etiologies include food allergies, malabsorption, inflammatory bowel disease, drugs, and endocrinopathies.

Pathogenesis of Diarrhea

Most dietary carbohydrates are ingested as di or polysaccharide and are hydrolyzed into monosaccharides prior to absorption. Carbohydrate in the bowel lumen attracts water, and under normal circumstances, water is subsequently absorbed. Whenever there is an excess of luminal carbohydrate, as in the case of malabsorption, net absorption of water is reversed, and diarrhea occurs. Osmotic and secretory diarrhea are differentiated, based on the pathogenesis (see etiology in Tables 1 and 2). Osmotic diarrhea is related to the presence of unabsorbed substances, such as lactose; nonabsorbable sugars, such as lactulose; or laxatives, such as magnesium. These osmotic solutes draw more water through the tight junctions into the gut lumen. Electrolyte absorption continues and is not influenced by intraluminal osmotic solutes. In osmotic diarrhea, the stool fluid has little sodium or potassium; osmolality is high; and the ion gap, calculated by the subtraction of stool osmolality by the doubled value of the sum of $Na + K$, exceeds $100\,mOsm\,kg^{-1}$. This type of diarrhea commonly ceases when fasting. In secretory diarrhea, typically, the amount of stool is voluminous, even when fasting. Stool osmolality is normal, and the ion gap is less than $100\,mOsm\,kg^{-1}$. The most common cause of secretory diarrhea is bacterial enteritis, such as *Escherichia coli* or *Vibrio cholerae*. The increase in net fluid and electrolyte secretion occurs when the pathogens adhere to, or invade, the enterocytes and produce toxins that enhance intracellular second messengers (cyclic AMP, cGMP, and/or Ca/protein kinases). These mediators activate protein kinase, which inhibit NaCl-coupled influx, and increase Cl efflux to the ion channels.

Table 1 Etiology of osmotic diarrhea

Impaired intraluminal digestion
Exocrine pancreatic insufficiency (cystic fibrosis, Shwachman–Diamond syndrome, etc.)
Decrease in bile acid pool (congenital absence of bile acid synthesis, ileal resection, Crohn's disease, etc.)
Congenital lipase deficiency
Congenital lactase deficiency
Adult-type hypolactasia
Sucrase-isomaltase deficiency
Congenital trehalase deficiency
Inflammatory villous atrophy (celiac disease, protein milk allergy, postgastroenteritis)
Malabsorption
Carbohydrate malabsorption (congenital glucose–galactose malabsorption, fructose malabsorption)
Fat malabsorption (abetalipoproteinemia, hypobetalipoproteinemia, etc.)
Laxative abuse
Increased colonic fermentation
Excessive sorbitol
Lactulose abuse
Increased consumption of simple carbohydrate (juice)

Table 2 Etiology of secretory diarrhea

Infection (bacterial toxins)
Enteroaggregative and enterotoxigeneic *E. coli*, cholera
Intestinal obstruction
Partial bowel obstruction, Hirschsprung's disease
Congenital ion transport defects
Congenital chloride transport defect, congenital sodium transport defect
Neuroendocrine tumors
Gastrinoma, VIPoma, somatostatinoma, mastocytosis, carcinoid tumor, medullary carcinoma of the thyroid
Ileal bile acid malabsorption
Nonosmotic laxative abuse
Idiopathic villous atrophy
Congenital microvillous atrophy
Autoimmune enteropathy or vasculitis

Acute Diarrhea

Acute diarrhea is generally associated with an enteric infection. Viral gastroenteritis primarily affects the proximal small intestine. It presents with watery diarrhea and vomiting, leading to dehydration. Enteritis that affects the small intestine, such as that caused by *Vibrio cholerae*, enterotoxigenic and enteroaggregative *Escherichia coli*, *Klebsiella pneumoniae*, *Giardia lamblia*, and *Cryptosporidium*, produces nonbloody, watery diarrhea. Infection with *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, enteroinvasive *E. coli*, and amoeba manifests with fever, abdominal cramps with tenesmus, and bloody mucoid stool. *Clostridium difficile*-associated diarrhea usually follows the use of broad-spectrum antibiotics. Usually, the course of the infectious diarrhea is self-limited and lasts no longer than 14 days.

Infectious Diarrhea

Viral Diarrhea

Rotavirus infection is the most common cause of dehydration in early infancy, particularly between 6 months and 2 years of age. The pattern of viral shedding spreads from shortly before, to possibly 2 weeks after, onset of illness. The infection is most common

during the winter in temperate climates. The viruses spread predominately via the fecal–oral route. Symptoms of rotavirus infection begin with fever, nasal congestion (30–50% of children), and emesis, followed by watery diarrhea without blood or mucus, which can last up to 5–7 days. Vomiting and fever typically disappear within 48 h of onset. Severe dehydration and death can occur in children with underlying malnutrition and short bowel syndrome. In tropical countries or endemic areas, rotaviruses are a cause of traveler's diarrhea. Severe and protracted diarrhea is seen in children with T-cell immunodeficiency and severe combined immunodeficiency (SCID), but rotavirus is not a common cause of diarrhea in children with human immunodeficiency infection. Asymptomatic infants, older children, and adults may shed the virus in their stools.

Diagnosis of rotavirus diarrhea is considered in young children with acute onset of vomiting and watery diarrhea. Viral particles can be detected in the stools by electron microscopy. A simple and inexpensive tool with enzyme-linked immunosorbent assay (ELISA) or latex agglutination can detect viral antigen in the stools.

Management of rotavirus diarrhea focuses on rehydration and contact isolation. Mild to moderate dehydration requires oral rehydration solution therapy. Intravenous fluid therapy is used in children with severe dehydration, recurrent emesis, and failed oral rehydration. Antibiotics and antidiarrheal drugs should not be given. Oral administration of human milk or human immune globulin-containing protective rotavirus antibody is indicated in low-birth-weight infants as passive prophylaxis and in children with immunodeficiencies who develop protracted rotavirus diarrhea.

Astroviruses are the second most important group of viral agents that cause diarrhea in young children. Transmission tends to occur from person to person through the fecal–oral route. Occasionally, contamination with water or shellfish has been reported. Most such infections have occurred in children younger than 4 years of age. Diagnosis is made with direct visualization by electron microscopy, but may not be as sensitive as for rotavirus. ELISAs are available in reference and research laboratories.

Enteric adenovirus diarrhea, which occurs year-round, mostly affects children younger than 2 years of age. Caliciviruses (or Norwalk viruses) and calicilike viruses are a common cause of water- and food-borne outbreaks of acute nonbacterial gastroenteritis, and are particularly associated with ingestion of shellfish and salads contaminated by infected kitchen-workers during food preparation. Transmission occurs from person to person via the fecal–oral route. Viral shedding lasts 5–7 days after the onset of illness but can extend up to 2 weeks, and may persist 4 days after the cessation of symptoms. The illness is indistinguishable from other viral gastroenteritis in children. Adults tend to have an abrupt onset of symptoms similar to those of staphylococcal food poisoning. Several other viruses cause gastroenteritis in children, including picornaviruses, coronaviruses, toroviruses, parvoviruses, parvo-like viruses, and unclassified small round viruses. Some of these viruses are occasionally responsible for outbreaks.

Bacterial Diarrhea

Bacterial infection in the gastrointestinal tract has a variety of manifestations, such as acute food poisoning, nonbloody, watery diarrhea; and dysentery. Antibiotic therapy is recommended in infections by certain bacterial pathogens, as shown in Table 3.

Salmonella Salmonellae are Gram-negative bacilli that are classified into groups A–E. *S. typhi* (group D)

Table 3 Recommended antimicrobial treatment for bacterial diarrhea

Diseases caused by pathogenic bacteria	*Antibiotic treatment*
Cholera	1. Tetracycline 50 mg kg^{-1} day^{-1}; maximum 2 g day^{-1} in four divided doses for 3 days (drug of choice for *V. cholera* 01 and 0139 Bengal): use of tetracycline under the age of 8 years may outweigh the side-effect of developing tooth coloring in resistant strain to other antibiotics 2. Doxycycline 6 mg kg^{-1}, maximum 300 mg, as a single dose 3. Trimethoprim-sulfamethoxazole (TMP-SMX) 8 mg kg^{-1} day^{-1} of trimethoprim if the strain is resistant to tetracycline
Shigellosis	Ampicillin, TMP-SMX, for 5 days
Enteropathogenic *E. coli* diarrhea	TMP-SMX For infants with mild diarrhea, nonabsorbable agents, such as neomycin and gentamicin, given three or four times a day for 5 days
Enteroinvasive *E. coli* diarrhea	TMP-SMX
Yersinia enteritis	Aminoglycosides, cefotaxime, tetracycline (< 8 years old), chloramphenicol, TMP-SMX
Salmonellosis or typhoid fever	Ampicillin, amoxycillin, cefotaxime, ceftriaxone, chloramphenicol, TMP-SMX
Pseudomembranous colitis (*C. difficile*)	Metronidazole 30 mg kg^{-1} day^{-1} in four divided doses for 7–10 days

and many other *Salmonella* serotypes cause bacteremia and typhoid fever, typically with gradual onset of fever, malaise, headache, and abdominal tenderness. Nontyphoidal salmonellosis can present with gastroenteritis ranging from a small volume of stools, to profuse bloody diarrhea and to severely watery stools. Most *Salmonella* infections are sporadic, but transmission occurs from person to person; via contaminated water and food of animal origin (e.g., poultry, red meat, eggs, and unpasteurized milk); and by contact with infected reptiles, such as pet turtles and iguanas. *Salmonella* infection frequently occurs in the extreme ages (younger than 5 and older than 70 years of age), and peaks early in the first year of life. Diagnosis is made by isolation of salmonellae from stool, urine, or blood specimen. Antimicrobial therapy is not recommended in uncomplicated cases of gastroenteritis. Infants less than 3 months of age, and children with complicated and invasive disease, malignancy, hemoglobinopathies, HIV infection, immunosuppressive state, or severe colitis, should be treated with antibiotics. A small number of persons infected with *Salmonella* can develop Reiter's syndrome.

Shigella Shigellae are Gram-negative, aerobic, nonmotile bacteria. Shigellae are easily transmitted from person to person and by the fecal–oral route. Ingestion of 10 shigellae can cause dysentery in adults. The bacteria can survive in water for up to 6 months. The infection tends to occur in children younger than 4 years of age. However, newborn infants can have a subclinical infection, and carriers are commonly found in developing countries. Day-care centers are sources of outbreaks in the developed world. Shigellosis often occurs during the rainy season. *Shigella flexneri* is the most common group in developing countries. The rectosigmoid and distal colon are more affected than the proximal part, which leads to bloody mucoid stools; however, some children present with high fever and watery diarrhea in the first 48 h, followed by abdominal cramps, tenesmus, and a small volume of blood and mucus in the stools. Complications with hyponatremia and hypoglycemia are commonly found in shigellosis. Lethargy and febrile seizures can precede diarrhea. Toxic megacolon, intestinal perforation, hemolytic uremic syndrome, pneumonia, and malnutrition can lead to death. Extraintestinal manifestations rarely occur in shigellosis. Sepsis and disseminated intravascular coagulation are infrequent complications but have high mortality rates. Shigellae can be isolated by a common stool culture, followed by biochemical and serologic tests to identify subgroups and serotypes.

Campylobacter *Campylobacter* is a group of spiral-shaped, motile, flagellated, Gram-negative bacilli that can be transmitted through food and water contaminated with material from infected animals or humans. *Campylobacter* is the most common bacterial cause of diarrheal illness in the USA; the majority of these cases stem from cross-contamination or consumption of raw or undercooked poultry. Most such human illness is caused by one species, *C. jejuni*. The bacteria adhere to the intestinal epithelium and produce enterotoxins, leading to secretory diarrhea. They can penetrate the cells and cause cellular damage and cell death, with subsequent bloody stools. The incubation period can last from 1 to 7 days. Symptoms start with nausea, vomiting, and abdominal pain with fever and myalgia, followed by watery diarrhea or bloody stools. Abdominal pain frequently resembles appendicitis in children older than 2 years of age. The diarrhea can last as long as 2 weeks. Extraintestinal manifestations associated with *C. jejuni* include Guillain–Barré syndrome. Direct examination of stools may demonstrate spiral-shaped organisms and fecal leukocytes. *Campylobacter* is microaerophillic, requiring special culture media and conditions. Correction of fluid and electrolyte imbalance is the sole therapy in this infection. The role of antibiotics is still controversial in complicated cases.

Clostridium difficile Pseudomembranous colitis is associated with a Gram-positive, spore-forming anaerobe that grows when the normal colonic flora is suppressed as a consequence of the use of broad-spectrum antibiotics. This organism produces toxins, particularly toxin A. Usually, it manifests with watery, nonbloody diarrhea and abdominal cramps. Occasionally, bloody mucoid stools may develop. Pseudomembranes may be seen on sigmoidoscopy. A fulminant colitis and toxic megacolon may develop, requiring surgical intervention. *C. difficile* can be found in the stools of young infants without causing any symptoms. Diagnosis is made by detection of toxin A in the stool. It has been seen, however, that in certain infections, toxin A is negative, but toxin B is positive; therefore, stools should be tested for this toxin as well.

***Aeromonas* species** *Aeromonas* species are Gram-negative, oxidase-positive bacilli that may be found in about 2% of children with diarrhea. The diarrhea is usually watery and self-limited; however, bloody stools and persistent diarrhea may occur.

Escherichia coli (E. coli) *E. coli* is part of the normal bacterial flora of the human gut. A few strains can cause gastroenteritis.

Enteropathogenic Escherichia coli *(EPEC)* EPEC consists of 12 serogroups. The EPEC strains do not

produce enterotoxins, but certain strains make Shiga-like cytotoxin. Children younger than 2 years of age are usually affected by EPEC and present with acute or chronic diarrhea, especially in developing countries. Diarrhea can be severe and, if untreated, can last up to 2 weeks. Vomiting and fever occur in 60% of children. Diagnosis can be made with commercial *E. coli* typing sera. Treatment consists of fluid replacement and correction of electrolyte imbalance and antibiotic therapy. Trimethoprim-sulfamethoxazole (TMP-SMX) is administered orally. Intravenous aminoglycoside is added if resistance to TMP-SMX is known. Fluoroquinones are not approved for use in children.

Enterotoxigenic Escherichia coli *(ETEC)* ETEC first adheres to the small intestinal mucosa, and then releases both heat-labile and heat-stable enterotoxins. ETEC is a common cause of nonbloody, watery diarrhea in children, and of traveler's diarrhea in developing countries. Adults in endemic areas do not tend to acquire this infection, probably because of the development of protective immunity. Children can present with rapid dehydration. Mortality is higher among malnourished patients. Patients rarely have fever, and stools do not contain blood or fecal leukocytes. The definitive diagnosis is made by isolation of *E. coli*, which produces enterotoxin and contains a gene encoding for enterotoxin production.

Enteroinvasive Escherichia coli *(EIEC)* EIEC is one of the causes of dysentery in developing countries. Occasionally, there are foodborne outbreaks in the developed world. The Shiga-like EIEC produces a clinical manifestation similar to shigellosis. These strains have the same biochemical characteristics and gene encoding for tissue invasion as *Shigella*. These bacteria invade colonic epithelium and cause ulcers that lead to blood and mucus in stools.

Enterohemorrhagic Escherichia coli *(EHEC)* EHEC infection has a unique presentation, with grossly bloody diarrhea, which is associated with *E. coli* serotype O157:H7. Most of these outbreaks have been related to consumption of contaminated beef. After ingestion of the contaminated food, the organisms adhere to the epithelium and produce cytotoxins, called Shiga-like toxins or verotoxins, which inhibit protein synthesis and result in cellular destruction. Children usually present with watery diarrhea, low-grade or no fever, and severe abdominal cramps. The diarrhea may become bloody. *E. coli* O157:H7 infection may cause hemolytic uremic syndrome in children, and thrombocytopenic purpura in adults. Treatment with antibiotics is not recommended, as some data suggest that antibiotic treatment will increase the incidence of hemolytic uremic syndrome.

Enteroaggregative Escherichia coli *(EAEC)* The EAEC organisms produce one or more enterotoxins that cause injury to the intestinal mucosa. The course may be acute, or it may be chronic, especially in infants. The diarrhea tends to be watery; however, bloody diarrhea may occur occasionally.

Yersinia enterocolitica *Yersinia enterocolitica* can cause inflammation in the ileum and colon and mesenteric adenitis, which mimics appendicitis. The infection occurs most frequently in children between 5 and 15 years of age. Clinical presentation is similar to other acute gastroenteritis. Bloody mucoid stools are found in some patients. This is a self-limiting infection, which, in uncomplicated cases, does not require antibiotics.

Vibrio cholerae Infection with *Vibrio cholerae* is manifested as an afebrile, painless, high-output, watery diarrhea that causes rapid dehydration and electrolyte imbalance, leading to hypovolemic shock within 4–12 h if no treatment is implemented. Stools are colorless with some mucus, and resemble rice water. Transmission occurs via consumption of raw or undercooked shellfish and dried fish. The incubation period is usually 1–3 days. Direct contact has not been described. Drugs of choice include tetracycline and doxycycline. TMP-SMX, erythromycin, or furazolidone may be considered in resistant strains.

Parasitic Infection

Except for giardiasis and cryptosporidiosis, intestinal parasitic infection is an uncommon problem in the developed world. The common mode of transmission is the fecal–oral route and ingestion of contaminated water or food. Infection with *Giardia lamblia* can be asymptomatic or present with nonbloody, watery diarrhea and steatorrhea. Normal hosts with *Cryptosporidium* and *Isospora belli* may present with nonbloody, self-limited diarrhea, whereas persistent diarrhea and malnutrition occur in immunocompromised hosts. The clinical spectrum of *Entamoeba histolytica* infection ranges from mild diarrhea to fulminant rectocolitis, and subsequently with frequent bloody mucoid stools. Roundworm infestation may cause watery diarrhea in tropical and subtropical regions Table 4.

Management Dehydration is the major complication in individuals with diarrhea who need fluid and electrolyte assessment. Rehydration and correction of concurrent fluid loss and electrolyte imbalance are

Table 4 Summary of parasitic infection and management

Disease and/or agents	*Endemic areas*	*Modes of infection*	*Diagnostic tests*	*Manifestations*	*Therapy*
Giardia lamblia	World-wide	Ingestion of contaminated water with feces containing cysts	Microscopic examination, *Giardia* antigen	Acute or recurrent abdominal pain, flatulence, anorexia, failure to thrive	Metronidazole, albedazole, furazolidone
Cryptosporidium parvum	World-wide	Fecal–oral route, ingesting water contaminated with oocysts	Microscopic examination, antigen by EIA	Watery diarrhea, abdominal cramps, vomiting, fever	Human serum immunoglobulin in immunocompromised host
Microsporidia	World-wide	Fecal–oral route, ingesting water contaminated with spores	Microscopic examination	Watery diarrhea in immunocompromised host	Albendazole, metronidazole, atovaquone, but recurrence of diarrhea after therapy is stopped
isospora belli	Tropics, subtropics	Fecal–oral route, ingesting water contaminated with oocysts	Microscopic examination	Protracted, foul-smelling, watery diarrhea, fever, vomiting in immunocompromised hosts	TMP-SMX, pyrimethamine
Cyclospora cayetanensis	World-wide	Fecal–oral route, ingesting water contaminated with oocysts	Microscopic examination	Protracted, watery diarrhea, fever, vomiting in immunocompromised hosts	TMP-SMX for 7 days
Entamoeba histolytica	World-wide	Fecal–oral route, ingesting water contaminated with cysts	Microscopic examination, PCR, isoenzyme analysis, antigen detection, serum antibody test	Watery diarrhea, then bloody mucoid stools, fever, liver abscess	Metronidazole, luminal amebicide with iodoquinol, paromomycin, or diloxaanide furoate
Dientamoeba fragilis	World-wide	Fecal–oral route, ingesting water contaminated with protozoa	Microscopic examination	Intermittent diarrhea, abdominal pain, anorexia	Iodoquinol, paromomycin, or tetracyclin
Balantidium coli	World-wide	Fecal–oral route, ingesting water contaminated with cysts	Microscopic examination, scraping lesions during sigmoidoscopy for histology is more sensitive	Recurrent bloody or mucoid diarrhea	Tetracyclin, or iodoquinol and metronidazole as alternatives
Blastocystis hominis	World-wide	Believed to be fecal–oral route, ingesting water contaminated with cysts	Microscopic examination	Associated with symptoms of bloating, abdominal pain, nausea, mild to moderate diarrhea	Metronidazole or iodoquinol
Trichuris trichiura	Tropics, subtropics	Eating embryonated eggs, from soils or food	Microscopic examination	Protracted diarrhea, rectal prolapse	Mebendazole 100 mg twice a day for 3 days
Strongyloides stercoralis	Tropics, subtropics	Penetration of the skin by infective larvae either from contact with infected soil or autoinfection	Microscopic examination, eosinophilia	Rash, cutaneous larva currens, mucoid voluminous stools, malabsorption, steatorrhea, pneumonitis	Thiabendazole 25 mg kg^{-1} per dose twice a day for 2 days
Trichinella spiralis	World-wide	Eating meat containing encysted larvae	Eosinophilia, bentonite flocculating test, muscle biopsy	Diarrhea, muscle tenderness, subungual petechial hemorrhages	*Trichinella spiralis*

Continued

Table 4 Continued

Disease and/or agents	*Endemic areas*	*Modes of infection*	*Diagnostic tests*	*Manifestations*	Therapy
Shistosoma mansoni, S. japonicum	*S. mansoni*: Africa, Brazil, Suriname, Venezuela,	Skin penetration	Microscopic examination	Pruritus, diarrhea, bloody stool abdominal pain, vomiting, peptic ulcer, portal vein hypertension	Single dose of praziquantel 40 mg kg^{-1} for *S. mansoni*, 60 mg kg^{-1} day^{-1} divided into two or three doses for 5 days
S. japonicum	Caribbean: Far east, South-east Asia				
Capillaria philippinensis	Philippines, Thailand	Eating uncooked infected fish	Microscopic examination	Protracted diarrhea, protein-losing enteropathy, ascites	Mebendazole, albendazole

Table 5 Composition of commonly used ORS for rehydration therapy in children

Solutions	*Sodium* ($mmol\,l^{-1}$)	*Potassium* ($mmol\,l^{-1}$)	*Chloride* ($mmol\,l^{-1}$)	*Base* ($mmol\,l^{-1}$)	*Glucose* ($mmol\,l^{-1}$)	*Osmolality*
WHO solution	90	20	80	30	111	310
ESPGHAN solution	75	20	65	30	139	310
Pedialyte (Ross Laboratories)	45	20	35	30	139	250
Resol Wyeth Ayerst	50	20	50	34	111	
Ricelyte	50	20	50	34	Oligosaccharides	
Infalyte Mead Johnson	50	25			Oligosaccharides	200
Gatorade	23.5	< 1	17	3	45 (glucose, sucrose, fructose mix)	330
Colas	1.6	< 1		13.4	50–150 (glucose, fructose mix)	550–750
Apple juice	5	32			120	730
Orange juice	< 1	50		50	120	
Chicken broth	250	8		0	0	500

Gatorade, colas, and juices are demonstrated for comparison, not advised for rehydration.

the mainstay of the therapy. Oral rehydration solution (ORS) therapy was successfully developed for this purpose in children who can tolerate enteral intake (Table 5). The principle is that glucose and amino acids are transported across the apical membrane of the enterocyte by contransporters. Unlike apical sodium–hydrogen exchange, nutrient–sodium cotransport is not affected by increased intracellular cyclic AMP levels, particularly in bacterial toxin-induced diarrhea. Inadequate potassium replacement can cause muscle weakness, paralytic ileus, and cardiac arrhythmia. Current oral rehydration therapy is safe and effective in children with mild to moderate dehydration and electrolyte imbalance. In severe dehydration, when the patient's vomiting is uncontrollable, or whenever there are associated conditions that interfere with oral intake, intravenous fluid rehydration may be required.

Feeding Feeding should be resumed as early as possible. Breastfeeding during diarrhea results in a shorter recovery period and improved nutritional status compared with fasting. Early and rapid reintroduction of a normal diet is recommended to maintain nutritional status, especially in malnourished children. Multiple studies have demonstrated that most eutrophic children do not need to have lactose eliminated from the diet, have the formula diluted, or undergo slow regrading of formula. Liquids that contain a high amount of simple sugars, such as fruit juices, should be avoided, because of their high osmolality. Although lactose malabsorption is rare in well-nourished infants, in some cases, lactose intolerance may delay recovery, especially in children with malnutrition, severe dehydration, or recent episodes of gastroenteritis. In these cases, a lactose-free formula may be beneficial. The addition of age-appropriate food has been shown to be well tolerated by infants and children with diarrhea.

Medications Antimicrobial agents are imperative in those who have infectious diarrhea, as described above. Agents such as loperamide and diphenoxylate, which reduce gut motility, do not alter fluid and electrolyte net balance, and are not recommended. Bismuth subsalicylate may decrease intestinal secretion, but bismuth and salicylate toxicity are worrisome. Clay adsorbents alter the appearance of the

stool without changing the water and electrolyte balance. Probiotics have been shown to shorten the duration of rotaviral diarrhea and prevent antibiotic-associated diarrhea. Zinc supplementation in malnourished children may reduce the duration and severity of diarrhea. Vitamin A and other micronutrients have yet to be proven efficacious for the treatment of diarrheal patients. Hyperimmune bovine antirotavirus colostrums may be given in selected cases to immunocompromised children.

Prevention Individuals who travel to high-risk areas or developing countries should avoid inappropriately prepared drinks, raw fruit and vegetables, and certain foods. Routine antibiotic use is not generally recommended, because of the risks of drug reaction, antibiotic-related colitis, and an increase in the incidence of resistant bacteria. Vaccines are being developed for better immunogenicity and fewer side-effects.

Chronic, Persistent, or Protracted Diarrhea

When the course of diarrhea continues over 14 days, it is considered to have become chronic. Chronic diarrhea can be caused by pathogenic organisms such as viruses, bacteria, or parasites acting on an individual who usually has risk factors such as malnutrition, associated illness, impaired immune status, intestinal mucosal injury, and/or bacterial overgrowth.

Chronic diarrhea may be congenital or acquired.

Congenital Microvillus inclusion disease (congenital microvillus atrophy), although rare, appears to be the most common cause of congenital intractable watery diarrhea. Diagnosis is based on intestinal biopsy demonstrating villous atrophy, crypt hypoplasia, and, on electron microscopy, microvillus inclusion in the enterocytes. Infants with this disease require total parenteral nutrition.

Tufting enteropathy presents in the first weeks of life with intractable watery diarrhea, but its onset is somewhat later than in microvillus inclusion disease. The remarkable finding is that the majority of the epithelial surface contains focal epithelial tufts (teardrop-shaped groups of closely packed enterocytes with apical rounding of the plasma membrane).

Congenital glucose–galactose malabsorption is a rare disorder with a defect of the glucose–sodium cotransporter system, leading to an increase in osmotic load in the intestinal lumen. Affected individuals, however, are capable of absorbing fructose, which becomes the source of dietary carbohydrate.

Congenital chloride diarrhea is a rare autosomal recessive condition. Maternal polyhydramnios is common. At birth, the infant develops rapid dehydration with marked abdominal distention. Stool chloride is $120\,\mathrm{mmol\,l^{-1}}$, and there is metabolic alkalosis. In congenital sodium diarrhea, clinical manifestations are similar to those of congenital chloride diarrhea, except for the fact that stool sodium is as high as $145\,\mathrm{mEq\,l^{-1}}$, and stool pH is alkaline as opposed to what is found in congenital chloride diarrhea.

Primary bile acid malabsorption is another extremely rare transport defect in the distal part of the ileum. Intractable diarrhea begins early after birth, followed by failure to thrive and fat malabsorption.

Hypobetalipoproteinemia is clinically indistinguishable from abetalipoproteinemia (Bassen–Kornzweig syndrome) and manifests itself with steatorrhea, failure to thrive, hypolipidemia, and acanthocytosis, which are present since infancy. The defect is an incapacity to form micelles, an important mechanism for fat transport into the enterocytes. Chylomicron retention disease may manifest similarly with steatorrhea and failure to thrive. Children with intestinal lymphangiectasia can suffer from steartorrhea, protein-losing enteropathy, and lymphopenia.

Disaccharidase enzyme deficiency can be diagnosed with a breath hydrogen test and confirmed by intestinal biopsy demonstrating normal histology and almost absent disaccharidase activity. Congenital sucrase–isomaltase deficiency becomes evident when sucrose or starch is introduced to the diet. Congenital lactase deficiency is a rare condition. Congenital glucoamylase deficiency has been reported in children with chronic diarrhea, which worsened with an oral starch challenge.

Impaired fat digestion tends to cause frequent bowel movements. Stools are foul-smelling, bulky, greasy, and float on the surface of the toilet water. This is one of the most common causes of failure to thrive in children. A sweat chloride test confirms the diagnosis of cystic fibrosis in some of these children. However, exocrine pancreatic insufficiency may occur in other diseases as well.

Acquired Chronic nonspecific diarrhea, or toddler's diarrhea, is seen in children between 6 and 36 months of age. Except for the history of watery stools, the children are healthy, and experience normal growth and development without abdominal pain. Diarrhea has been associated with initiation of broad-spectrum antibiotics, which change the normal intestinal flora, excessive fluid intake, and fruit juice (particularly apple juice) consumption.

Secondary lactase deficiency can be seen after acute gastroenteritis, particularly in malnourished individuals and those with recurrent episodes of diarrhea in the recent past. Acquired or late-onset lactase deficiency may begin in childhood or preadolescence, mainly in the nonCaucasian population, but it occurs

in many Caucasians as well. Reduction of lactase production is determined by genetic background and may lead to lactose intolerance, causing abdominal pain and/or diarrhea.

An abnormal intestinal villous surface prevents the absorption of digested nutrients, and leads to osmotic diarrhea and steatorrhea. Hypersensitivity to cows' milk or soy protein may cause partial villous atrophy in young infants. Frequent bloody mucoid stool, dehydration, and failure to thrive are not uncommon features. Total villous atrophy is found in celiac disease in infants who consume a diet containing gluten. Intestinal biopsy is the gold standard to make the diagnosis. Partial villous atrophy may be associated with intestinal infection such as *Giardia lamblia*, particularly in individuals with secretory IgA deficiency. Chronic diarrhea occurs often in individuals with congenital hypogammaglobulinemia, combined immunodeficiencies, and acquired immunodeficiency, at times associated with opportunistic infections. Crohn's disease and ulcerative colitis may present with chronic watery or bloody diarrhea. Crohn's disease presents systemic symptoms more often than ulcerative colitis. Enteroenteric and enterocolonic fistula may complicate cases of Crohn's disease with malabsorption and bacterial overgrowth. Infectious diarrhea can mimic exacerbation of inflammatory bowel disease.

Autoimmune enteropathy is a poorly understood syndrome with malabsorption and chronic diarrhea, which usually develops after 6 months of age and does not respond to a gluten-free diet. The presence of specific antienterocyte antibodies in serum can confirm this disorder.

Children with altered intestinal motility, such as partial obstruction or pseudoobstruction, may present with chronic diarrhea. Bacterial overgrowth also leads to diarrhea.

Certain tumors such as gastrinoma, VIPoma, ganglioneuroma, and ganglioneuroblastoma produce neurotransmitters that can cause secretory diarrhea. Tropical sprue can be seen among children who live in certain Caribbean countries, northern South America, Africa, and parts of Asia. Patients develop a diffuse lesion in the small intestine, which leads to malabsorption. Symptoms usually begin with fever, malaise, and watery diarrhea, which then subside. Subsequently, malabsorption and intermittent diarrhea follow and cause malnutrition. Small bowel biopsy demonstrates villus atrophy, an increase in crypt length, and chronic inflammatory cells in the lamina propria. Symptoms respond well to nonabsorbable sulfonamides or tetracycline for 3–4 weeks, folic acid and vitamin B_{12} therapy. When the investigation is thorough, but the etiology is still unknown or the resultant data are inappropriate, one should look for a condition of self-induced diarrhea. The use of stool laxatives can mimic chronic osmotic diarrhea. Determination of stool electrolytes, magnesium, and sulfate can be helpful in making the diagnosis. Creatinine may be detected in the stool in cases when urine is added to the stool by the patient or a caretaker to simulate diarrhea. A low stool osmolality suggests addition of water to the stool.

Management Treatment should be approached according to the pathophysiology of the diarrhea. The main goal is to prevent dehydration, malnutrition, its complications, and associated illnesses. Infection should be investigated and aggressively treated with appropriate antimicrobial agents. Empirical therapy for chronic diarrhea is considered when no specific treatment is available, based on the etiology of chronic diarrhea. Empirical trials of antimicrobial agents may be judiciously used in patients who have a high possibility of a condition leading to bacterial, viral, or protozoal infection. Bile acid-binding agents such as cholestyramine may decrease diarrheal output in children with primary bile acid malabsorption or high bile acid output-induced diarrhea. Reducing the intestinal transit time is helpful to allow the enterocytes to reabsorb fluid and electrolyte. Therefore, opiates are considered as antidiarrheal agents in those patients with noninfectious chronic diarrhea. Octreotide, a somatostatin analog used in tumor-induced secretory diarrhea, has been shown to decrease secretions. Parenteral nutrition should be the last resort for those who are unable to meet nutritional requirements with the enteral approach.

See also: ***Aeromonas***; ***Campylobacter***: Properties and Occurrence; Campylobacteriosis; ***Clostridium***: Botulism; ***Escherichia coli***: Food Poisoning; ***Salmonella***: Salmonellosis; ***Shigella***; **Vibrios**: *Vibrio cholerae*; **Viruses**

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DIETARY FIBER

Contents

Properties and Sources

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Background

Although dietary fiber has been known for more than 2000 years under various terms (e.g., bran, roughage), the term 'dietary fiber' first appeared in 1953 and referred to hemicelluloses, cellulose, and lignin. The term 'fiber' is somewhat misleading since only a fraction (cellulose) of dietary fiber is fibrillar in nature. To correct this misnomer, other terms (e.g., plantix) have been proposed, but despite these efforts, the term 'dietary fiber' has survived.

This section deals with several different aspects of dietary fiber, including its determination and many of its physiological effects. Most of this information is relatively new and is the result of progress in research brought about in the last 30 years. The first part of this article will focus on the nature and composition of dietary fiber, its properties, and examples of sources of dietary fiber. This is followed by a definition of dietary fiber. Although this should be a relatively straightforward description, there are many different viewpoints concerning the nature and physiological effects that dietary fiber should have. These will be discussed in relationship to the physiological effects of dietary fiber.

Chemical Structure

The composition and structure of dietary fiber differ from plant to plant. It is also a function of the portion of the plant that is edible and the stage of maturation and is largely composed of the cell wall (structural) components that give the plant physical stability. As such, it is made of highly interlinked sugar-based and phenolic-based polymers (hemicelluloses, pectic substances, phenolics, glycoproteins, and proteoglycans) in a matrix of amorphous structure with some enmeshed cellulose microfibrils. The cell-wall components are intimately linked together