Chapter 366

Acute Gastroenteritis in Children

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The term *gastroenteritis* denotes inflammation of the gastrointestinal tract, most commonly the result of infections with bacterial, viral, or parasitic pathogens (Tables 366.1 to 366.3). Many of these infections are foodborne illnesses (Table 366.4). Several clinical syndromes are often described because they have different (albeit overlapping) etiologies, outcomes, and treatments. **Acute gastroenteritis** (AGE) captures the bulk of infectious cases of diarrhea. The most common manifestations are diarrhea and vomiting, which can also be associated with systemic features such as abdominal pain and fever. **Dysentery** refers to a syndrome characterized by frequent small stools containing visible blood, often accompanied by fever, tenesmus, and abdominal pain. This should be distinguished from bloody diarrhea (larger volume bloody stools with less systemic illness) because the etiologies may differ. **Prolonged** (lasting 7-13 days) and **persistent diarrhea** (lasting 14 days or longer) are important because of their impact on growth and nutrition.

BURDEN OF CHILDHOOD DIARRHEA

Although global mortality due to diarrheal diseases has declined substantially (39%) during the past 2 decades, it remains unacceptably high. In 2015, diarrheal disease caused an estimated 499,000, or 8.6% of all childhood deaths, making it the 4th most common cause of child mortality worldwide. Over the same period, a smaller decline (10%) was observed in the incidence of diarrhea disease among children younger than 5 yr. Almost 1.0 billion episodes occurred in 2015 worldwide, resulting in an estimated 45 million childhood disability-adjusted life years. Approximately 86% of the episodes occurred in Africa and South Asia (63% and 23%, respectively). The decline in diarrheal mortality, despite the lack of significant changes in incidence, is the result of preventive rotavirus vaccination and improved case management of diarrhea, as well as improved nutrition of infants and children. These interventions have included widespread home- and hospital-based oral rehydration solution (ORS) therapy and improved nutritional management of children with diarrhea.

In addition to the risk of mortality, high rates of diarrhea can be associated with long-term adverse outcomes. Diarrheal illnesses, especially episodes among young children that are recurrent, prolonged, or persistent, can be associated with malnutrition, stunting, micronutrient deficiencies, and significant deficits in psychomotor and cognitive development.

PATHOGENS

Rotavirus is the most common cause of AGE among children throughout the world. Several other viruses occur less frequently. Norovirus and sapovirus are the 2 genera of *Caliciviruses* that cause AGE. Norovirus genogroup II, genotype 4 (GII.4) has predominated globally during the past decade. Among the more than 50 serotypes of adenovirus, 40 and 41 are most often associated with diarrhea. Astroviruses are identified less often (see Table 366.1).

Keywords
Diarrhea
gastroenteritis
rotavirus
Salmonella
Shigella

Table 366.1 Etiologies of Viral Gastroenteritis

ETIOLOGY	INCUBATION PERIOD	ACUTE SIGNS AND SYMPTOMS	DURATION OF ILLNESS	PRINCIPAL VEHICLE AND TRANSMISSION	RISK FACTORS	COMMERCIALLY AVAILABLE DIAGNOSTIC TEST
Caliciviruses (including noroviruses and sapoviruses)	12-48 hr	Nausea, vomiting, abdominal cramping, diarrhea, fever, myalgia, and some headache	1-3 days	Person-to-person (fecal-oral and aerosolized vomit), and food, water, and fomites contaminated with human feces.	Very contagious (chlorine and heat resistant); produces large outbreaks in closed settings such as cruise ships, and restaurants.	No. Testing of stool or vomitus using real time reverse transcriptase (RT)-quantitative PCR is the preferred method, available in public health laboratories. Immunoassays for norovirus have poor sensitivity. FDA-cleared multiplex PCR assays are available to detect these organisms. Norovirus genotyping (GI and GII) is performed by CDC.
Rotavirus (groups A-C), astrovirus, and enteric adenovirus (serotypes 40 and 41)	2-4 days	Often begins with vomiting, followed by watery diarrhea, low-grade fever	3-8 days	Person-to-person (fecal-oral), fomites. Aerosol transmission of rotavirus may be possible.	Nearly all infants and children worldwide were infected by 2 yr of age before vaccine introduction.	Yes. Rotavirus: immunoassay (preferred), latex agglutination, and immune-chromatography of stool. Enteric adenovirus: immunoassay. FDA-cleared multiplex PCR assays are available to detect these organisms.

CDC, Centers for Disease Control and Prevention.
Modified from Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, *MMWR* 53(RR-4):1–33, 2004.

The major bacterial pathogens that cause AGE are nontyphoidal *Salmonella* (NTS), *Shigella, Campylobacter*, and *Yersinia* (see Table 366.2). Five pathotypes of *Escherichia coli* infect humans: Shiga toxin–producing (STEC), also known as enterohemorrhagic (EHEC), enterotoxigenic (ETEC), enteropathogenic (EPEC), enteroaggregative (EAEC), and enteroinvasive (EIEC). Two serogroups of *Vibrio cholerae* (O1 and O139) produce epidemic cholera and cause nearly all sporadic cases. *Clostridium difficile* disease can be both nosocomial and community acquired in children. Bacterial pathogens that cause foodborne illness due to their ability to produce emetic and/or enterotoxins include *Bacillus cereus*, *Clostridium perfringens*, and *Staphylococcus aureus*. The significance of isolating *Aeromonas* and *Plesiomonas* in a diarrheal stool remains uncertain.

Giardia intestinalis, Cryptosporidium spp., *Cyclospora cayetanensis*, and *Entamoeba histolytica* are the most common parasites that cause diarrhea in the United States (see Table 366.3). At least 13 species of *Cryptosporidium* are associated with human disease, but *C. hominis* and to a less extent *C. parvum* are most common. The genus *Entamoeba* comprises 6 species that colonize humans, but only *E. histolytica* is considered a human pathogen. *G. intestinalis* (formerly *G. lamblia* and *G. duodenalis*) is a flagellate protozoan that infects the small intestine and biliary tract. Other protozoa that uncommonly cause AGE are *Isospora belli* (now designated *Cystoisospora belli*) and *Blastocystic hominis*.

EPIDEMIOLOGY IN THE UNITED STATES AND OTHER MIDDLE- AND HIGH-INCOME COUNTRIES

Risk Factors Related to Economic Development. Insufficient access to adequate hygiene, sanitation, and clean drinking water are the main factors leading to the heavy burden of AGE in developing countries. Nonetheless, infectious AGE remains ubiquitous in middle- and high-income countries, although the severe consequences have become uncommon. In fact, economic development poses its own risks for transmission of enteric pathogens. The ability to mass-produce and widely distribute food has led to large multistate outbreaks of AGE due to NTS, STEC, and other agents. Globalization has cultivated a taste for tropical fruits and vegetables, creating a mechanism for importation of novel pathogens. The increasing frequency of antimicrobial resistance among bacteria that causes AGE has been linked to the use of antibiotics as growth-promotors for animals bred for food. Recreational swimming facilities and water treatment systems have provided a vehicle for massive outbreaks of *Cryptosporidium*, a chlorine-resistant organism. Venues serving catered food to large groups of people, such as hotels and cruise ships, are conducive to outbreaks, as are institutions where hygiene is compromised, such as daycare centers, prisons, and nursing homes. Hospitalization and modern medical therapy have created a niche for nosocomial *C. difficile* toxin infection (Table 366.5).

Endemic Diarrhea. In the United States, rotavirus was the most common cause of medically attended AGE among children younger than 5 yr until the introduction of rotavirus vaccine for routine immunization of infants. Annual epidemics swept across the country beginning in the southwest in November and reaching the northeast by May, affecting nearly every child by the age of 2 yr. Since vaccine introduction, healthcare utilization for AGE has decreased markedly. Norovirus is the leading cause of AGE among children in the United States seeking healthcare, followed by sapovirus, adenovirus 40 and 41, and astrovirus (see Table 366.1).

Foodborne Transmission. The most comprehensive resource for describing the burden of bacterial and protozoal diarrhea in the United States is the Foodborne Diseases Active Surveillance Network (FoodNet) maintained by the Centers for Disease Control and Prevention (CDC) (see Table 366.4). FoodNet performs active laboratory-based surveillance of 9 bacterial and protozoal enteric infections commonly transmitted by food. Among children 0-19 yr of age in 2015, NTS was most common, followed by *Campylobacter* and *Shigella*, then STEC and *Cryptosporidium*. *Vibrio, Yersinia, and Cyclospora* were the least common (see Table 366.5). Children younger than 5 yr have the highest incidence of disease, and the elderly have the highest frequency of hospitalization and death. Only 5% of these infections are associated with recognized outbreaks.

Noninfectious agents may also cause foodborne gastrointestinal symptoms due to a direct toxic effect of the food (mushrooms) or contamination (heavy metals) (Table 366.6).

Diarrhea Outbreaks. The U.S. Foodborne Disease Outbreak Surveillance System quantifies enteric infections associated with foodborne outbreaks. In 2015, among all age groups, norovirus was the most common agent (46%), followed by NTS (23%). Less common are *C. perfringens* (6%), STEC (5%), *Campylobacter* (5%), and *S. aureus* (2%), followed much less often (each 1%) by *B. cereus*, *Clostridium botulinum, Shigella, Cryptosporidium, Yersinia, Listeria, Vibrio parahaemolyticus,* and *Shigella*. Outbreaks of enteric pathogens propagated by direct

Text continued on p. 2020

Table 366.2 Etiologies of Bacterial Gastroenteritis

ETIOLOGY	INCUBATION PERIOD	ACUTE SIGNS AND SYMPTOMS	DURATION OF ILLNESS	PRINCIPAL VEHICLE AND TRANSMISSION	RISK FACTORS	COMMERCIALLY AVAILABLE DIAGNOSTIC TEST
Bacillus cereus (preformed emetic toxin)	1-6 hr	Sudden onset of severe nausea and vomiting; diarrhea may be present	24 hr	Soil and water	Improperly refrigerated cooked or fried rice, meats	No. Reference laboratory used for outbreaks.
Bacillus cereus (enterotoxins formed in vivo)	8-16 hr	Abdominal cramps, watery diarrhea; nausea and vomiting may be present	1-2 days	Soil and water	Meats, stews, gravies, vanilla sauce	No. Reference laboratory used for outbreaks.
Campylobacter jejuni	1-5 days	Diarrhea, (10–20% of episodes are prolonged), cramps, fever, and vomiting; bloody diarrhea, bacteremia, extraintestinal infections, severe disease in immunocompromised	5-7 days (sometimes >10 days) usually self-limiting	Wild and domestic animals and animal products, including pets	Raw and undercooked poultry, unpasteurized milk, untreated surface water	Yes. Stool culture (routine in many laboratories, while others require a special request) is preferred; multiplex PCR.
Clostridium difficile toxin	Unknown—can appear weeks after antibiotic cessation	Mild to moderate watery diarrhea that can progress to severe, pseudomembranous colitis with systemic toxicity.	Variable	Person-person (fecal-oral), mostly within healthcare facilities	Immunosuppression, intestinal disease or surgery, prolonged hospitalization, antibiotics	Yes. PCR, immunoassay, tissue cytotoxicity.
Clostridium perfringens toxin	8-16 hr	Watery diarrhea, nausea, abdominal cramps; fever is rare	1-2 days	Environment, human and animal intestines	Meats, poultry, gravy, dried or precooked foods with poor temperature control	No. Reference laboratory used for outbreaks.
Enterohemorrhagic *Escherichia coli* (EHEC) including *E. coli* O157:H7 and other *Shiga* toxin–producing *E. coli* (STEC)	1-9 days (usually 3-4 days)	Watery diarrhea that becomes bloody in 1-4 days in ~40% of infections; in contrast to dysentery, bloody stools are large volume and fever/toxicity are minimal. More common in children <4 yr old.	4-7 days	Food and water contaminated with feces from ruminants; infected people and animals (fecal-oral); predominantly high-resource countries	Undercooked beef especially hamburger, unpasteurized milk and juice, raw fruits and petting zoos, recreational swimming, daycare. Antimotility agents and antibiotics increase risk of hemolytic uremic syndrome	Yes. Culture on sorbitol-MacConkey agar, immunoassay for O157:H7, or Shiga toxin PCR.†
Enterotoxigenic *E. coli* (ETEC)	1-5 days	Watery diarrhea, abdominal cramps, some vomiting	3-7 days	Water or food contaminated with human feces	Infants and young children in LMIC and travelers	Yes. Multiplex PCR,† or reference laboratory.
Salmonella, nontyphoidal	1-5 days	Diarrhea, (10–20% prolonged), cramps, fever, and vomiting; bloody diarrhea, bacteremia, extraintestinal infections, severe disease in immunocompromised	5-7 days (sometimes >10 days) usually self-limiting	Domestic poultry, cattle, reptiles, amphibians, birds	Ingestion of raw or undercooked food, improper food handling, travelers, immunosuppression, hemolytic anemia, achlorhydria, contact with infected animal	Yes. Routine stool culture (preferred), multiplex PCR.†
Shigella spp.	1-5 days (up to 10 days for *S. dysenteriae* type 1)	Abdominal cramps, fever, diarrhea Begins with watery stools that can be the only manifestation or proceed to dysentery.	5-7 days	Infected people or fecally contaminated surfaces (fecal-oral)	Poor hygiene and sanitation, crowding, travelers, daycare, MSM, prisoners	Yes. Routine stool culture (preferred), multiplex PCR†

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Staphylococcus aureus (preformed enterotoxin)	1-6 hr	Sudden onset of severe nausea and vomiting Abdominal cramps Diarrhea and fever may be present	1-3 days	Birds, mammals, dairy, and environment	Unrefrigerated or improperly refrigerated meats, potato and egg salads, cream pastries	No. Reference laboratory used for outbreaks.
Vibrio cholerae O1 and O139	1-5 days	Watery diarrhea and vomiting, that can be profuse and lead to severe dehydration and death within hours.	3-7 days	Food and water contaminated with human feces	Contaminated water, fish, shellfish, street-vended food from endemic or epidemic settings; blood group O, vitamin A deficiency	Yes. Stool culture (requires special TCBS media so laboratory must be notified). Rapid test is useful in epidemics but does not provide susceptibility or subtype so should not be used for routine diagnosis.
Vibrio parahaemolyticus	2-48 hr	Watery diarrhea, abdominal cramps, nausea, vomiting. Bacteremia and wound infections occur uncommonly, especially in high-risk patients, e.g., with liver disease and diabetes.	2-5 days	Estuaries and marine environments; currently undergoing pandemic spread	Undercooked or raw seafood, such as fish, shellfish	Yes. Stool culture. Requires special TCBS media so laboratory must be notified. Standard culture acceptable for wounds and blood.
Vibrio vulnificus	1-7 days	Vomiting, diarrhea, abdominal pain. Bacteremia and wound infections, particularly in patients with chronic liver disease (presents with septic shock and hemorrhagic bullous skin lesions)	2-8 days	Estuaries and marine environments	Undercooked or raw shellfish, especially oysters, other contaminated seafood, and open wounds exposed to seawater	Yes. Culture of stool requires TCBS agar; alert laboratory if suspected. Standard media acceptable for wound and blood cultures.
Yersinia enterocolitica and *Yersinia pseudotuberculosis*	1-5 days	Diarrhea, (10–20% prolonged), cramps, fever, and vomiting; bloody diarrhea, bacteremia, extraintestinal infections, severe disease in immunocompromised; pseudoappendicitis occurs primarily in older children.	5-7 days (sometimes >10 days) usually self-limiting	Swine products, occasionally person-to-person and animal-to-humans, water-borne, bloodborne (can multiply during refrigeration)	Undercooked pork, improper food handling, unpasteurized milk, tofu, contaminated water, transfusion from a bacteremic person, cirrhosis, chelation therapy.	Yes. Stool culture in special media and temperature. Not performed in many laboratories unless requested. Requires special media to grow. When clinically relevant, can isolate from vomitus, blood, throat, lymph nodes, joint fluid, urine, and bile.

[†]FDA-cleared multiplex PCR assays are available but generally not recommended for diagnosis in individual patients because of inability to determine antimicrobial susceptibility to guide treatment or speciate the organism for outbreak investigation.

FDA, Food and Drug Administration; *LMIC,* low and middle-income countries; *MSM,* men who have sex with men; *PCR,* polymerase chain reaction; *TCBS,* thiosulfate-citrate-bile salts-sucrose.

Modified from Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, *MMWR* 53(RR-4):1–33, 2004.

Table 366.3 Etiologies of Parasitic Gastroenteritis

ETIOLOGY	INCUBATION PERIOD	ACUTE SIGNS AND SYMPTOMS	DURATION OF ILLNESS	PRINCIPAL VEHICLE AND TRANSMISSION	RISK FACTORS	COMMERCIALLY AVAILABLE DIAGNOSTIC TEST
Cryptosporidium	1-11 days	Diarrhea (usually watery), bloating, flatulence, cramps, malabsorption, weight loss, and fatigue may wax and wane. Persons with AIDS or malnutrition have more severe disease.	1-2 wk; may be remitting and relapsing over weeks to months	Person-to-person (fecal-oral), Contaminated food and water (including municipal and recreational water contaminated with human feces.	Infants 6-18 mo of age living in endemic settings in LMIC, patients with AIDS, childcare settings, drinking unfiltered surface water, MSM, IgA deficiency	Request specific microscopic examination of stool with special stains (direct fluorescent antibody staining is preferable to modified acid fast) for Cryptosporidium. Immunoassays and PCR† are more sensitive than microscopy.
Cyclospora cayetanensis	1-11 days	Same as *Cryptosporidium*	Same as *Cryptosporidium*	Fresh produce (imported berries, lettuce)	Travelers, consumption of fresh produce imported from the tropics.	Specific microscopic examination of stool for Cyclospora; multiplex PCR.† May need to examine water or food.
Entamoeba histolytica	2-4 wk	Gradual onset of cramps, watery diarrhea and often dysentery with cramps but rarely fever. Can wax and wane with weight loss. Dissemination to live and other organs can occur.	Variable; may be protracted (several weeks to several months)	Fecal-oral transmission Any uncooked food or food contaminated by an ill food handler after cooking; drinking water	Persons living in or traveling to LMIC, institutionalized persons, MSM.	Microscopy of fresh stool for cysts and parasites on at least 3 samples; immunoassay is more sensitive; multiplex PCR.† Serology for extraintestinal infections
Giardia intestinalis	1-4 wk	Diarrhea, stomach cramps, gas, weight loss; symptoms may wax and wane.	2-4 wk	Any uncooked food or food contaminated by an ill food handler after cooking; drinking water	Hikers drinking unfiltered surface water, persons living in or traveling to LMIC, MSM, IgA deficiency	Microscopic examination of stool for ova and parasites; may need at least 3 samples; immunoassay is more sensitive. Multiplex PCR.†

†FDA-cleared multiplex PCR assays are available.

IgA, Immunoglobulin A; *LMID,* low- and middle-income countries; *MSM,* men who have sex with men; *PCR,* polymerase chain reaction.

Modified from Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, *MMWR* 53(RR-4):1–33, 2004.

Table 366.4 Incidence of Bacterial and Parasitic Food-Borne Infections in 2017 and Percentage Change Compared With 2014-2016 Average Annual Incidence by Pathogen FoodNet Sites,* 2014-2017†

	2017		2017 VERSUS 2014-2016	
PATHOGEN	**NO. OF CASES**	**INCIDENCE RATE§**	**% CHANGE¶**	**(95% CI)**
BACTERIA				
Campylobacter	9,421	19.1	10	(2 to 18)
Salmonella	7,895	16.0	–5	(–11 to 1)
Shigella	2,132	4.3	–3	(–25 to 25)
Shiga toxin–producing *E. coli***	2,050	4.2	28	(9 to 50)
Yersinia	489	1.0	166	(113 to 234)
Vibrio	340	0.7	54	(26 to 87)
Listeria	158	0.3	26	(2 to 55)
PARASITES				
Cryptosporidium	1,836	3.7	10	(–16 to 42)
Cyclospora	163	0.3	489	(253 to 883)

*Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, Tennessee, and selected counties in California, Colorado, and New York.
†Data for 2017 are preliminary.
§Per 100,000 population.
¶Percentage change reported as increase or decrease.
**For Shiga toxin–producing *E. coli*, all serogroups were combined because it is not possible to distinguish between serogroups using culture-independent diagnostic tests. Reports that were only Shiga toxin–positive from clinical laboratories and were Shiga toxin–negative at a public health laboratory were excluded (n = 518). When these were included, the incidence rate was 5.2, which was a 57% increase (CI = 33–85%).
CI, confidence interval; *FoodNet*, CDC's Foodborne Diseases Active Surveillance Network.
From Marder EP, Griffin PM, Cieslak PR, et al: Preliminary incidence and trends of infections with pathogens transmitted commonly through food—foodborne diseases active surveillance network, 10 U.S. sites, 2006-2017, *MMWR* 67(11):324–328, 2018 (Table 1, p. 325).

Table 366.5 Exposure or Condition Associated With Pathogens Causing Diarrhea

EXPOSURE OR CONDITION	**PATHOGEN(S)**
FOODBORNE	
Foodborne outbreaks in hotels, cruise ships, resorts, restaurants, catered events	Norovirus, nontyphoidal *Salmonella*, *Clostridium perfringens*, *Bacillus cereus*, *Staphylococcus aureus*, *Campylobacter* spp., ETEC, STEC, *Listeria*, *Shigella*, *Cyclospora cayetanensis*, *Cryptosporidium* spp.
Consumption of unpasteurized milk or dairy products	*Salmonella*, *Campylobacter*, *Yersinia enterocolitica*, *S. aureus* toxin, *Cryptosporidium*, and STEC. *Listeria* is infrequently associated with diarrhea, *Brucella* (goat milk cheese), *Mycobacterium bovis*, *Coxiella burnetii*
Consumption of raw or undercooked meat or poultry	STEC (beef), *C. perfringens* (beef, poultry), *Salmonella* (poultry), *Campylobacter* (poultry), *Yersinia* (pork, chitterlings), *S. aureus* (poultry), and *Trichinella* spp. (pork, wild game meat)
Consumption of fruits or unpasteurized fruit juices, vegetables, leafy greens, and sprouts	STEC, nontyphoidal *Salmonella*, *Cyclospora*, *Cryptosporidium*, norovirus, hepatitis A, and *Listeria monocytogenes*
Consumption of undercooked eggs	*Salmonella*, *Shigella* (egg salad)
Consumption of raw shellfish	*Vibrio* species, norovirus, hepatitis A, *Plesiomonas*
EXPOSURE OR CONTACT	
Swimming in or drinking untreated fresh water	*Campylobacter*, *Cryptosporidium*, *Giardia*, *Shigella*, *Salmonella*, STEC, *Plesiomonas shigelloides*
Swimming in recreational water facility with treated water	*Cryptosporidium* and other potentially waterborne pathogens when disinfectant concentrations are inadequately maintained
Healthcare, long-term care, prison exposure, or employment	Norovirus, *Clostridium difficile*, *Shigella*, *Cryptosporidium*, *Giardia*, STEC, rotavirus
Childcare center attendance or employment	Rotavirus, *Cryptosporidium*, *Giardia*, *Shigella*, STEC
Recent antimicrobial therapy	*C. difficile*, multidrug-resistant *Salmonella*
Travel to resource-challenged countries	*Escherichia coli* (enteroaggregative, enterotoxigenic, enteroinvasive), *Shigella*, typhi and nontyphoidal *Salmonella*, *Campylobacter*, *Vibrio cholerae*, *Entamoeba histolytica*, *Giardia*, *Blastocystis*, *Cyclospora*, *Cystoisospora*, *Cryptosporidium*
Exposure to house pets with diarrhea	*Campylobacter*, *Yersinia*
Exposure to pig feces in certain parts of the world	*Balantidium coli*
Contact with young poultry or reptiles	Nontyphoidal *Salmonella*
Visiting a farm or petting zoo	STEC, *Cryptosporidium*, *Campylobacter*
EXPOSURE OR CONDITION	
Age group	Rotavirus (6-18 mo of age), nontyphoidal *Salmonella* (infants from birth to 3 mo of age and adults >50 yr with a history of atherosclerosis), *Shigella* (1-7 yr of age), *Campylobacter* (young adults)
Underlying immunocompromising condition	Nontyphoidal *Salmonella*, *Cryptosporidium*, *Campylobacter*, *Shigella*, *Yersinia*
Hemochromatosis or hemoglobinopathy	*Y. enterocolitica*, *Salmonella*
AIDS, immunosuppressive therapies	*Cryptosporidium*, *Cyclospora*, *Cystoisospora*, microsporidia, *Mycobacterium avium*–intercellulare complex, cytomegalovirus
Anal-genital, oral-anal, or digital-anal contact	*Shigella*, *Salmonella*, *Campylobacter*, *E. histolytica*, *Giardia lamblia*, *Cryptosporidium*

ETEC, enterotoxigenic *Escherichia coli*; *STEC*, Shiga toxin–producing *Escherichia coli*.
From Shane AL, Mody RK, Crump JA, et al: 2017 Infectious Diseases Society for America clinical practice guidelines for the diagnosis and management of infectious diarrhea, *Clin Infect Dis* 65(12):e45–80, 2017 (Table 2, p. e48).

Table 366.6 Foodborne Noninfectious Illnesses

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Antimony	5 min-8 hr usually <1 hr	Vomiting, metallic taste	Usually self-limited	Metallic container	Identification of metal in beverage or food	Supportive care
Arsenic	Few hours	Vomiting, colic, diarrhea	Several days	Contaminated food	Urine Can cause eosinophilia	Gastric lavage, BAL (dimercaprol)
Cadmium	5 min-8 hr usually <1 hr	Nausea, vomiting, myalgia, increase in salivation, stomach pain	Usually self-limited	Seafood, oysters, clams, lobster, grains, peanuts	Identification of metal in food	Supportive care
Ciguatera fish poisoning (ciguatera toxin)	2-6 hr 3 hr 2-5 days	GI: abdominal pain, nausea, vomiting, diarrhea Neurologic: paresthesias, reversal of hot or cold, pain, weakness Cardiovascular: bradycardia, hypotension, increase in T-wave abnormalities	Days to weeks to months	A variety of large reef fish: grouper, red snapper, amberjack, and barracuda (most common)	Radioassay for toxin in fish or a consistent history	Supportive care, IV mannitol Children more vulnerable
Copper	5 min-8 hr usually <1 hr	Nausea, vomiting, blue or green vomitus	Usually self-limited	Metallic container	Identification of metal in beverage or food	Supportive care
Mercury	1 wk or longer	Numbness, weakness of legs, spastic paralysis, impaired vision, blindness, coma Pregnant women and the developing fetus are especially vulnerable	May be protracted	Fish exposed to organic mercury, grains treated with mercury fungicides	Analysis of blood, hair	Supportive care
Mushroom toxins, short-acting (muscimol, muscarine, psilocybin, *Coprinus atramentaria*, ibotenic acid)	<2 hr	Vomiting, diarrhea, confusion, visual disturbance, salivation, diaphoresis, hallucinations, disulfiram-like reaction, confusion, visual disturbance	Self-limited	Wild mushrooms (cooking might not destroy these toxins)	Typical syndrome and mushroom identified or demonstration of the toxin	Supportive care
Mushroom toxins, long-acting (amanitin)	4-8 hr diarrhea; 24-48 hr liver failure	Diarrhea, abdominal cramps, leading to hepatic and renal failure	Often fatal	Mushrooms	Typical syndrome and mushroom identified and/or demonstration of the toxin	Supportive care, life-threatening, may need life support
Nitrite poisoning	1-2 hr	Nausea, vomiting, cyanosis, headache, dizziness, weakness, loss of consciousness, chocolate-brown blood	Usually self-limited	Cured meats, any contaminated foods, spinach exposed to excessive nitrification	Analysis of the food, blood	Supportive care, methylene blue
Pesticides (organophosphates or carbamates)	Few minutes to few hours	Nausea, vomiting, abdominal cramps, diarrhea, headache, nervousness, blurred vision, twitching, convulsions, salivation, meiosis	Usually self-limited	Any contaminated food	Analysis of the food, blood	Atropine; 2-PAM (pralidoxime) is used when atropine is not able to control symptoms; rarely necessary in carbamate poisoning

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Puffer fish (tetrodotoxin)	<30 min	Paresthesias, vomiting, diarrhea, abdominal pain, ascending paralysis, respiratory failure	Death usually in 4-6 hr	Puffer fish	Detection of tetrodotoxin in fish	Life-threatening, may need respiratory support
Scombroid (histamine)	1 min-3 hr	Flushing, rash, burning sensation of skin, mouth and throat, dizziness, urticaria, paresthesias	3-6 hr	Fish: bluefin, tuna, skipjack, mackerel, marlin, escolar, and mahi	Demonstration of histamine in food or clinical diagnosis	Supportive care, antihistamines
Shellfish toxins (diarrheic, neurotoxic, amnesic)	Diarrheic shellfish poisoning: 30 min-2 hr	Nausea, vomiting, diarrhea, and abdominal pain accompanied by chills, headache, and fever	Hours to 2-3 days	A variety of shellfish, primarily mussels, oysters, scallops, and shellfish from the Florida coast and the Gulf of Mexico	Detection of the toxin in shellfish; high-pressure liquid chromatography	Supportive care, generally self-limiting
	Neurotoxic shellfish poisoning: few minutes to hours	Tingling and numbness of lips, tongue, and throat, muscular aches, dizziness, reversal of the sensations of hot and cold, diarrhea, and vomiting				
	Amnesic shellfish poisoning: 24-48 hr	Vomiting, diarrhea, abdominal pain and neurologic problems such as confusion, memory loss, disorientation, seizure, coma				Elderly are especially sensitive to amnesic shellfish poisoning
Shellfish toxins (paralytic shellfish poisoning)	30 min-3 hr	Diarrhea, nausea, vomiting leading to paresthesias of mouth and lips, weakness, dysphasia, dysphonia, respiratory paralysis	Days	Scallops, mussels, clams, cockles	Detection of toxin in food or water where fish are located; high-pressure liquid chromatography	Life-threatening, may need respiratory support
Sodium fluoride	Few minutes to 2 hr	Salty or soapy taste, numbness of mouth, vomiting, diarrhea, dilated pupils, spasms, pallor, shock, collapse	Usually self-limited	Dry foods (e.g., dry milk, flour, baking powder, cake mixes) contaminated with NaF-containing insecticides and rodenticides	Testing of vomitus or gastric washings Analysis of the food	Supportive care
Thallium	Few hours	Nausea, vomiting, diarrhea, painful paresthesias, motor polyneuropathy, hair loss	Several days	Contaminated food	Urine, hair	Supportive care
Tin	5 min-8 hr usually <1 hr	Nausea, vomiting, diarrhea	Usually self-limited	Metallic container	Analysis of the food	Supportive care
Vomitoxin	Few minutes to 3 hr	Nausea, headache, abdominal pain, vomiting	Usually self-limited	Grains such as wheat, corn, barley	Analysis of the food	Supportive care
Zinc	Few hours	Stomach cramps, nausea, vomiting, diarrhea, myalgias	Usually self-limited	Metallic container	Analysis of the food, blood and feces, saliva or urine	Supportive care

BAL, bronchoalveolar lavage; *GI*, gastrointestinal.

From Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, *MMWR* 53(RR-4):1–33, 2004.

person-to-person contact are most often caused by norovirus and *Shigella* species; other pathogens include NTS, rotavirus, *Giardia*, *Cryptosporidium*, *C. difficile,* and *C. jejuni.*

Nosocomial Diarrhea. *C. difficile* is the most common cause of healthcare-associated infection in the United States. Severe disease occurs most often in those with predisposing conditions (e.g., recent antibiotics, gastric acid suppression, immunosuppression, gastrointestinal comorbidities). In contrast to adults, rates of colostomy and in-hospital mortality have not increased in children despite increasing rates of community and hospital-acquired *C. difficile* infection, suggesting that *C. difficile* may be less pathogenic in children. Moreover, high rates of asymptomatic carriage (and presence of toxin) among children younger than 2 yr creates diagnostic uncertainty, so testing and treatment should be reserved for those with supporting clinical evidence (see Table 366.2).

Zoonotic Transmission. Many diarrheal pathogens are acquired from animal reservoirs (see Tables 366.1 to 366.3, 366.5). The ability of NTS to undergo transovarian passage in hens allows infection of intact grade A pasteurized eggs, a source of multiple large outbreaks. Although *Campylobacter* is prevalent in poultry, its lower outbreak potential has been attributed to its lack of transovarian spread in hens and stringent growth requirements, which limit its ability to replicate in foods. On the other hand, *Campylobacter* has an extensive reservoir in domestic and wild animals and remains a major cause of sporadic bacterial foodborne disease in industrialized countries, usually from consumption of contaminated chicken, meat, beef, and milk. Its ubiquitous animal reservoir also has resulted in widespread contamination of surface waters, resulting in diarrhea among hikers and campers who drink from streams, ponds, and lakes in wilderness areas. The predilection for STEC to asymptomatically colonize the intestines of ruminant animals explains why unpasteurized dairy products, fruits harvested from fields where cattle graze, and undercooked hamburger are common vehicles. The major animal reservoir for *Yersinia* is pigs, so ingestion of raw or undercooked pork products is an important risk factor. Pets can be the source of NTS (asymptomatic young birds, amphibians, and reptiles), *Campylobacter*, and *Yersinia* (puppies and kittens that are usually ill with diarrhea).

Seasonality. Seasonality provides a clue to implicate specific pathogens, although patterns may differ in tropical and temperate climates. Rotavirus and norovirus peak in cool seasons, whereas enteric adenovirus infections occur throughout the year, with some increase in summer. *Salmonella, Shigella,* and *Campylobacter* favor warm weather, whereas the tendency for *Yersinia* to tolerate cold manifests as a winter seasonality, with higher prevalence in northern countries, and ability to survive in contaminated blood products during refrigeration.

EPIDEMIOLOGY IN LOW- AND MIDDLE-INCOME COUNTRIES

The Global Enteric Multicenter Study (GEMS) evaluated children younger than 5 yr living in 7 low-income countries in sub-Saharan Africa and South Asia and seeking healthcare for moderate-to-severe diarrhea (Fig. 366.1). Although a broad array of pathogens were identified, most episodes of moderate-to-severe diarrhea were attributed to 4 pathogens: rotavirus, *Cryptosporidium, Shigella*, and ETEC producing heat-stable toxin (ST) either alone or in combination with heat-labile toxin (LT), herein termed ST-ETEC, and, to less extent, adenovirus 40 and 41. On the other hand, several etiologic agents that are common causes of AGE in high-resource settings are notable for their low frequency in resource-limited settings: NTS, STEC, norovirus, and *C. difficile* toxin. The 3 agents associated with most deaths among children under 5 yr are rotavirus (29%), *Cryptosporidium* (12%), and *Shigella* (11%). The Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development Project (MAL-ED) was a study of less severe, community-based diarrhea. Viral causes predominated (36.4% of the overall incidence), but *Shigella* had the single highest attributable incidence (26.1 attributable episodes per 100 child-years).

Host Risk Factors

Most pathogens show an age predilection. The incidence of rotavirus and NTS are highest in infancy. Endemic shigellosis peaks in 1-4 yr olds, whereas *Campylobacter* and *Cryptosporidium* show a bimodal distribution with the greatest number of reported cases in infants and young children a secondary peak in adolescents and young adults. Pandemic *V. cholerae* and *S. dysenteriae* type 1 produce high attack rates and mortality in all age groups and often afflict displaced persons in emergency settings. Some agents (e.g., NTS, *Shigella, Campylobacter, Yersinia*, and *Cryptosporidium*) are more frequent and more severe when the host is immunocompromised or malnourished.

Additional risks factors for AGE include immunodeficiency, measles, malnutrition, and lack of exclusive or predominant breastfeeding. Malnutrition increases the risk of diarrhea and associated mortality, and moderate to severe stunting increases the odds of diarrhea-associated mortality. The fraction of such infectious diarrhea deaths that are attributable to nutritional deficiencies varies with the prevalence of deficiencies; the highest attributable fractions are in sub-Saharan Africa, South Asia, and Andean Latin America. The risks are particularly high with malnutrition, particularly when associated with micronutrient deficiency. Vitamin A deficiency accounts for 157,000 deaths from diarrhea, measles, and malaria. Zinc deficiency is estimated to cause 116,000 deaths from diarrhea and pneumonia. Table 366.7 summarizes some of the key risk factors associated with childhood diarrhea globally, especially in the presence of micronutrient deficiency.

PATHOGENESIS OF INFECTIOUS DIARRHEA

Intrinsic properties of the organism help to define the mode of transmission and incubation period (Table 366.8). Enteropathogens that are infectious in small inocula (*Shigella,* STEC, norovirus, rotavirus, *G. intestinalis, Cryptosporidium* spp., *C. difficile, E. histolytica*) are readily transmitted by person-to-person contact via the fecal-oral route. Pathogens with larger infectious doses, such as cholera, NTS, ETEC, and *Campylobacter*, generally require food or water vehicles (see Tables 366.1 to 366.3). Pathogens that produce preformed toxins (*S. aureus, B. cereus* emetic toxin) have shorter incubation periods (1-6 hr) compared with 8-16 hr for those that must elaborate enterotoxins in situ (e.g., *C. perfringens* and *B. cereus enterotoxin*). Incubation periods of 1-5 days are seen with pathogens that attach to the epithelium and elaborate enterotoxins (e.g., *V. cholerae*, ETEC) or cytotoxins (e.g., *S. dysenteriae* type 1 and STEC) or those that invade and disrupt the intestinal epithelium (*Shigella*, NTS, *Campylobacter*, and *Yersinia*). The requirement for protozoa to progress through a life cycle to trigger pathogenic processes results in a more extended incubation period. Other properties affecting transmissibility are bioavailability as conferred by a copious and/or prolonged fecal shedding, extended infectivity in the environment, and resistance to disinfection (all exhibited by norovirus and *Cryptosporidium*), or a large environmental or animal reservoir (e.g., *Campylobacter*). The ability to circumvent immune surveillance by frequent antigenic changes resulting from recombinational events (e.g., norovirus) or a large serotype diversity (e.g., *Shigella*) maintains a susceptible host population.

Viral AGE causes a cytolytic infection of the small intestinal villus tips resulting in decreased absorption of water, disaccharide malabsorption, inflammation, and cytokine activation. The rotavirus protein NSP4 acts as a viral enterotoxin that produces secretory diarrhea. In addition, rotavirus activates the enteric nervous system causing decreased gastric emptying and increased intestinal mobility. There is a genetic susceptibility to both rotavirus and norovirus infection that is mediated by histo-blood group antigens on the epithelial cell surface and in mucus secretions (Fig. 366.2).

Pathogens primarily manifesting as secretory diarrhea attach to the surface of the epithelium and stimulate secretion of water and electrolytes by activating adenylate cyclase and raising intracellular cAMP (*V. cholerae* and heat- LT–producing ETEC) and/or cGMP (ETEC producing heat-ST) (Figs. 366.3 and 366.4). The diarrheagenic phenotype of *C. difficile* is attributed to production of toxins A (an enterotoxin) and B (an enterotoxin and cytotoxin). The epidemic hypervirulent NAP1 *C. difficile* also makes binary toxin, which may enhance colonization and augment toxin production.

Shigella, NTS, *Campylobacter*, and *Yersinia* all possess an invasive phenotype and elicit diarrhea by a variety of mechanisms that generally involves elicitation of inflammatory cytokines with or without associated toxin production (Fig. 366.5). The pathogenesis of *Shigella*, the most

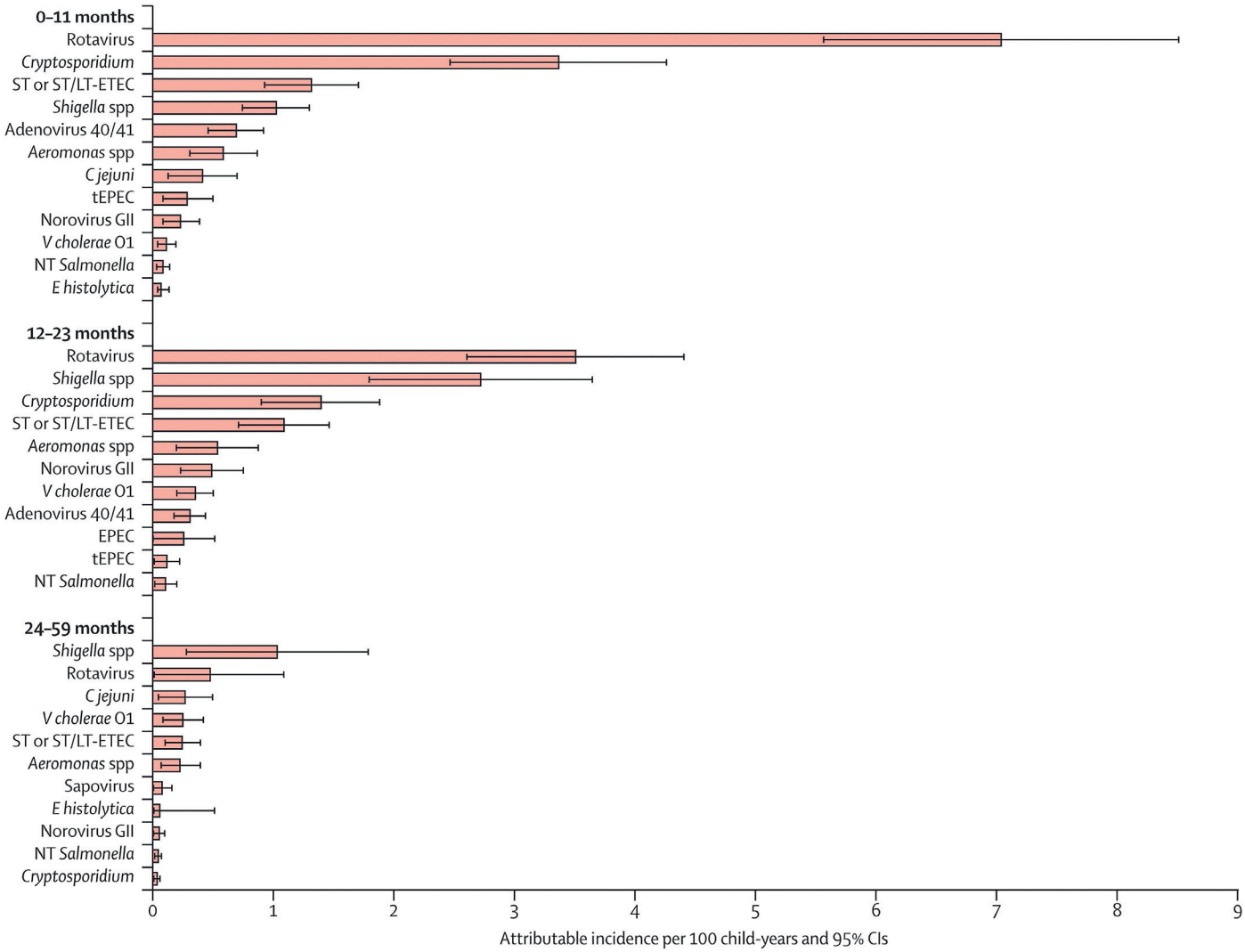

Fig. 366.1 Attributable incidence of pathogen-specific moderate-to-severe diarrhea per 100 child-yr by age stratum, all sites combined. The *bars* show the incidence rates, and the *error bars* show the 95% confidence intervals. *EPEC*, enteropathogenic; *ETEC*, enterotoxigenic; *LT*, labile toxin; *NT*, Nontyphoidal; *ST*, stable toxin. *(Modified from Kotloff KL, Nataro JP, Blackwelder WC, et al: Burden and aetiology of diarrhoeal disease in infants and young children in developing countries [the Global Enteric Multicenter Study, GEMS]: a prospective, case-control study,* Lancet *382[9888]:209–222, 2013, Fig. 4.)*

common cause of bacillary dysentery, has been characterized in greatest detail. Following invasion, *Shigella* induces extensive destruction and inflammation of the intestinal epithelium producing ulcers and microabscesses that manifest with diarrheal stools containing blood and pus. Production of enterotoxins contributes to secretory diarrhea, which can be seen early in shigellosis or as the sole manifestation. A single serotype of *Shigella*, *S. dysenteriae* type 1, elaborates the Shiga toxin which increases the severity of illness and is responsible for development of hemolytic uremic syndrome (HUS).

Cryptosporidia sporozoites released from ingested cysts penetrate intestinal epithelial cells and develop into trophozoites within the intracellular, but extracytoplasmic, environment. After undergoing asexual multiplication and sexual development, they are released in the colon as infectious oocysts capable of causing autoinfection. Host factors, in particular T-cell function, play a critical role in disease severity. *Cyclospora* cysts are not infectious in freshly passed stools but must sporulate in the environment for 1-2 wk to become infectious; they are usually transmitted in contaminated produce and water (see Table 366.4).

CLINICAL MANIFESTATION OF DIARRHEA

General Findings. Diarrhea is usually defined as the passage of 3 or more abnormally loose or liquid stools per day. Frequent passage of formed stools is not diarrhea, nor is the passing of loose, pasty stools by breastfed babies. Clinical clues to the possible etiology of gastroenteritis are noted in Table 366.9.

In the past, many guidelines divided patients into subgroups for mild (3–5%), moderate (6–9%), and severe (≥10%) dehydration. However, it is difficult to distinguish between mild and moderate dehydration based on clinical signs alone. Therefore most guidelines now combine mild and moderate dehydration and simply use none, some, and severe dehydration. The individual signs that best predict dehydration are prolonged capillary refill time >2 sec, abnormal skin turgor, hyperpnea (deep, rapid breathing suggesting acidosis), dry mucous membranes, absent tears, and general appearance (including activity level and thirst). As the number of signs increases, so does the likelihood of dehydration. Tachycardia, altered level of consciousness, and cold extremities with or without hypotension suggest severe dehydration.

Viral Diarrhea. Symptoms of rotavirus AGE usually begin with vomiting followed by frequent passage of watery nonbloody stools, associated with fever in about half the cases (see Table 366.1). The diarrhea lacks fecal leukocytes, but stools from 20% of cases contain mucus. Recovery with complete resolution of symptoms generally occurs within 7 days. Although disaccharide malabsorption is found in 10–20% of episodes, it is rarely clinically significant.

Other viral agents elicit similar symptoms and cannot be distinguished from rotavirus based on clinical findings. In an outbreak setting, the

Table 366.7 Proven Risk Factors With Direct Biologic Links to Diarrhea: Relative Risks or Odds Ratios and 95% Confidence Intervals

	DIARRHEAL MORBIDITY	DIARRHEAL MORTALITY
No breastfeeding (0-5 mo)	RR = 2.7 (1.7-4.1) compared with exclusive breastfeeding	RR = 10.5 (2.8-39.6) compared with exclusive breastfeeding
No breastfeeding (6-23 mo)	RR = 1.3 (1.1-1.6) compared with any breastfeeding	RR = 2.2 (1.1-4.2) compared with any breastfeeding
Underweight	(compared with ≥2 WAZ)	(compared with ≥1 WAZ)
–2 to ≤1 WAZ		OR = 2.1 (1.6-2.7)
–3 to ≤2 WAZ	RR = 1.2 (1.1-1.4)	OR = 3.4 (2.7-4.4)
≤3 WAZ		OR = 9.5 (5.5-16.5)
Stunted		
–2 to ≤1 HAZ		OR = 1.2 (0.9-1.7)
–3 to ≤2 HAZ		OR = 1.6 (1.1-2.5)
<–3 HAZ		OR = 4.6 (2.7-14.7)
Wasted		
–2 to ≤1 WHZ		OR = 1.2 (0.7-1.9)
–3 to ≤2 WHZ		OR = 2.9 (1.8-4.5)
≤3 WHZ		OR = 6.3 (2.7-14.7)
Vitamin A deficiency (vs. not deficient)		RR = 1.5 (1.3-1.8)
Zinc deficiency (vs. not deficient)	RR = 1.2 (1.1-1.2)	RR = 1.2 (1.0-1.6)

HAZ, height-for-age Z-score; *OR,* odds ratio; *RR,* relative risk; *WAZ,* weight-for-age Z score; *WHZ,* weight-for-height Z-score.
Modified from Walker CL, Rudan I, Liu L, et al: Global burden of childhood pneumonia and diarrhoea, *Lancet* 381:1405–1416, 2013.

Table 366.8 Comparison of 3 General Pathogenic Mechanisms of Enteric Infection

	TYPE OF INFECTION		
PARAMETER	**I**	**II**	**III**
Mechanism	Noninflammatory (enterotoxin or adherence/superficial invasion)	Inflammatory, epithelial destruction (invasion, cytotoxin)	Penetrating
Location	Proximal small bowel	Colon	Distal small bowel
Illness	Watery diarrhea	Dysentery	Enteric fever
Stool examination	No fecal leukocytes Mild or no ↑ lactoferrin	Fecal polymorphonuclear leukocytes ↑↑ Lactoferrin	Fecal mononuclear leukocytes
Examples	*Vibrio cholerae* ETEC *Clostridium perfringens* *Bacillus cereus* *Staphylococcus aureus* Also†: *Giardia intestinalis* *Rotavirus* Noroviruses *Cryptosporidium* spp. EPEC, EAEC *Cyclospora cayetanensis*	*Shigella* EIEC STEC NTS *Vibrio parahaemolyticus* *Clostridium difficile* *Campylobacter jejuni* *Entamoeba histolytica**	*Yersinia enterocolitica* *Salmonella* Typhi, *S.* Paratyphi, and occasionally NTS, *Campylobacter,* and *Yersinia*

*Although amebic dysentery involves tissue inflammation, the leukocytes are characteristically pyknotic or absent, having been destroyed by the virulent amebae.
†Although not typically enterotoxic, these pathogens alter bowel physiology via adherence, superficial cell entry, cytokine induction, or toxins that inhibit cell function.
EAEC, enteroaggregative *E. coli;* EIEC, enteroinvasive *E. coli;* EPEC, enteropathogenic *Escherichia coli;* ETEC, enterotoxigenic *Escherichia coli*; *NTS,* nontyphoidal *Salmonella; STEC,* Shiga toxin–producing *Escherichia coli.*
Modified from Mandell GL, Bennett JE, Dolin R, editors: *Principles and practices of infectious diseases,* ed 7, Philadelphia, 2010, Churchill Livingstone.

pattern of a brief incubation period (12-48 hr), short duration of illness, and clustering of cases is shared by caliciviruses and preformed bacterial toxin. However, unlike preformed toxins, caliciviruses cause secondary infections, which confirm the contagious nature of the outbreak. Diarrheal illnesses caused by enteric adenovirus infections tend to be more prolonged than rotavirus (7 to 10 days), whereas astroviruses cause a shorter course (~5 days) usually without significant vomiting.

Bacterial Diarrhea. Although there is considerable overlap, fever >40°C, overt fecal blood, abdominal pain, no vomiting before diarrhea onset, and high stool frequency (>10 per day) are more common with bacterial pathogens (see Tables 366.2 and 366.9). Although high fever

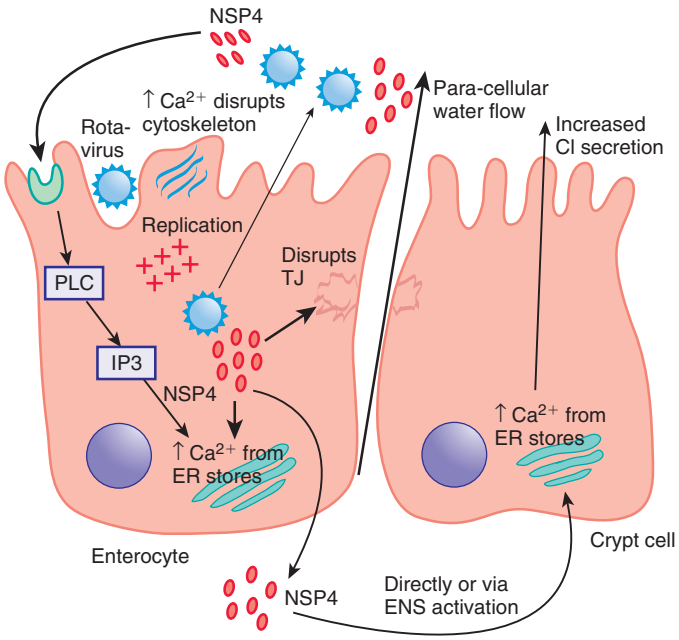

Fig. 366.2 Pathogenesis of rotavirus infection and diarrhea. *ENS,* Enteric nervous system; *ER,* endoplasmic reticulum; *NSP4,* non-structural protein 4; *PLC,* phospholipase C; *TJ,* tight junction. *(Modified from Ramig RF: Pathogenesis of intestinal and systemic rotavirus infection,* J Virol *78:10213–10220, 2004.)*

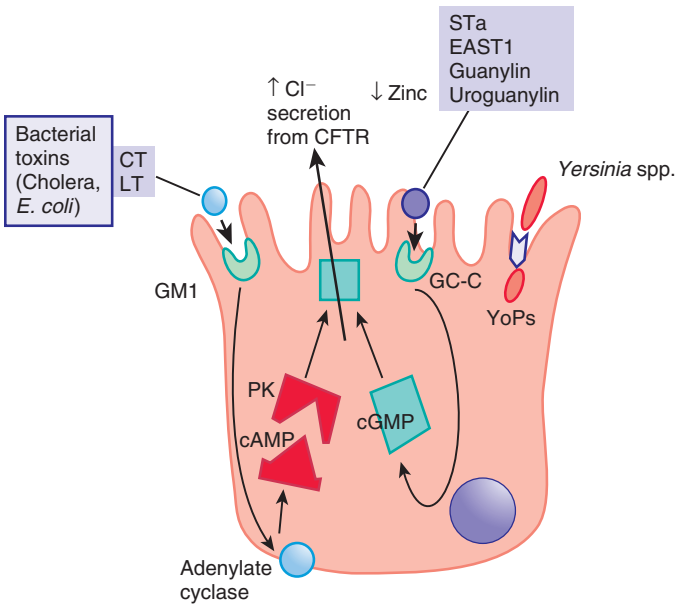

Fig. 366.3 Mechanism of secretory and penetrating diarrhea. *cAMP,* Cyclic adenosine monophosphate; *CFTR,* cystic fibrosis transmembrane conductance regulator through which chloride is secreted; *cGMP,* cyclic guanosine monophosphate; *YoPs, Yersinia* outer proteins that alter host cell functions to promote disease; *CT,* cholera toxin; *EAST 1,* enteroaggregative *E. coli* ST; *GC-C,* guanylate cyclase, the transmembrane receptor for STa and other toxins; *GM1,* a ganglioside containing one sialic acid residue that serves as the receptor for CT and LT; *LT,* heat labile toxin; *PK,* protein kinase; *STa,* heat stable toxin a. *(Modified from Thapar M, Sanderson IR: Diarrhoea in children: an interface between developing and developed countries,* Lancet *363:641–653, 2004; and Montes M, DuPont HL: Enteritis, enterocolitis and infectious diarrhea syndromes. In Cohen J, Powderly WG, Opal SM, et al, editors:* Infectious diseases, *ed 2, London, 2004, Mosby, pp. 31–52.)*

and overt fecal blood are often absent in bacterial enteritis, when present, there is a high probability of a bacterial etiology. The classical bacterial agents, NTS, *Shigella, Campylobacter,* and *Yersinia,* present with 1 of 5 syndromes.

1. Acute diarrhea, the most common presentation, may be accompanied by fever and vomiting. Clinically silent bacteremia associated with uncomplicated NTS AGE can be seen among otherwise healthy children younger than 2 yr living in industrialized countries.
2. Bloody diarrhea or frank dysentery is classically caused by *Shigella*. Watery diarrhea typically precedes dysentery and is often the sole clinical manifestation of mild infection. Progression to dysentery indicates colitis and may occur within hours to days. Patients with severe infection may pass more than 20 dysenteric stools in 1 day. Dysenteric illnesses due to *Campylobacter* have been confused with inflammatory bowel disease.
3. Invasive, nonfocal disease (**enteric fever**) is a febrile illness associated with bacteremia without localized infection. Diarrhea may be minimal or absent. Although classically the result of *S.* Typhi or Paratyphi A and B, enteric fever can result from systemic spread of the classical bacterial enteropathogens. Although enteric fever caused by *S.* Typhi or Paratyphi A and B primarily affect preschool and school-age children in endemic countries, other bacterial enteropathogens most often cause disease in infants (particularly <3 mo), the immunocompromised, and children with malnutrition. Additional risk factors include hemolytic anemia and intravascular lesions for NTS, and iron overload, cirrhosis, and chelation therapy for *Yersinia* sepsis. The distinct clones of NTS that have arisen in sub-Saharan Africa described earlier are causing enteric fever–type illnesses often in the absence of AGE. *Shigella* sepsis is rare and is seen most often in malnourished and immunocompromised hosts.
4. Extraintestinal invasive infections can result from either local invasion or bacteremic spread (Table 366.10). Examples of local invasion include mesenteric adenitis, appendicitis, and rarely cholecystitis, mesenteric venous thrombosis, pancreatitis, hepatic, or splenic abscess. Bacteremic spread may result in pneumonia, osteomyelitis, meningitis (3 conditions seen most commonly with NTS), abscesses, cellulitis, septic arthritis, and endocarditis. *Shigella* can cause noninvasive contiguous infections such as vaginitis and urinary tract infections.
5. Vertical transmission of *Shigella*, NTS, and *Campylobacter* can produce perinatal infection resulting in a spectrum of illness from isolated diarrhea or hematochezia to fulminant neonatal sepsis. One species of *Campylobacter, C. fetus,* is particularly virulent in pregnant women and can result in chorioamnionitis, abortion, and neonatal sepsis and meningitis.

Crampy abdominal pain and nonbloody diarrhea are the first symptoms of STEC infection, sometimes with vomiting. Within several days, diarrhea becomes bloody and abdominal pain worsens. Bloody diarrhea lasts between 1 and 22 days (median 4 days). In contrast to dysentery, the stools associated with STEC hemorrhagic colitis are large volume and rarely accompanied by high fever. ETEC produce a secretory watery diarrhea that affects infants and young children in developing countries and is the major causative agents of travelers' diarrhea, accounting for about half of all episodes in some studies. EPEC remains a leading cause of persistent diarrhea associated with malnutrition among infants from developing countries. EIEC, which are genetically, biochemically, and clinically nearly identical to *Shigella*, causes rare foodborne outbreaks in industrialized countries. EAEC has been associated with persistent diarrhea in immunocompromised persons and sporadic diarrhea in infants in countries with varying levels of economic development; however, some other studies have not found an association with disease.

C. difficile toxin is associated with several clinical syndromes. The most common is mild to moderate watery diarrhea, low-grade fever, and mild abdominal pain. Occasionally, the illness will progress to full-blown *pseudomembranous colitis* characterized by diarrhea, abdominal cramps, and fever. The colonic mucosa contains 2-5 mm raised, yellowish plaques. Fatal cases are associated with toxic megacolon, systemic toxicity, and multisystem organ failure, possibly related to systemic absorption of toxin. A vomiting illness is associated with

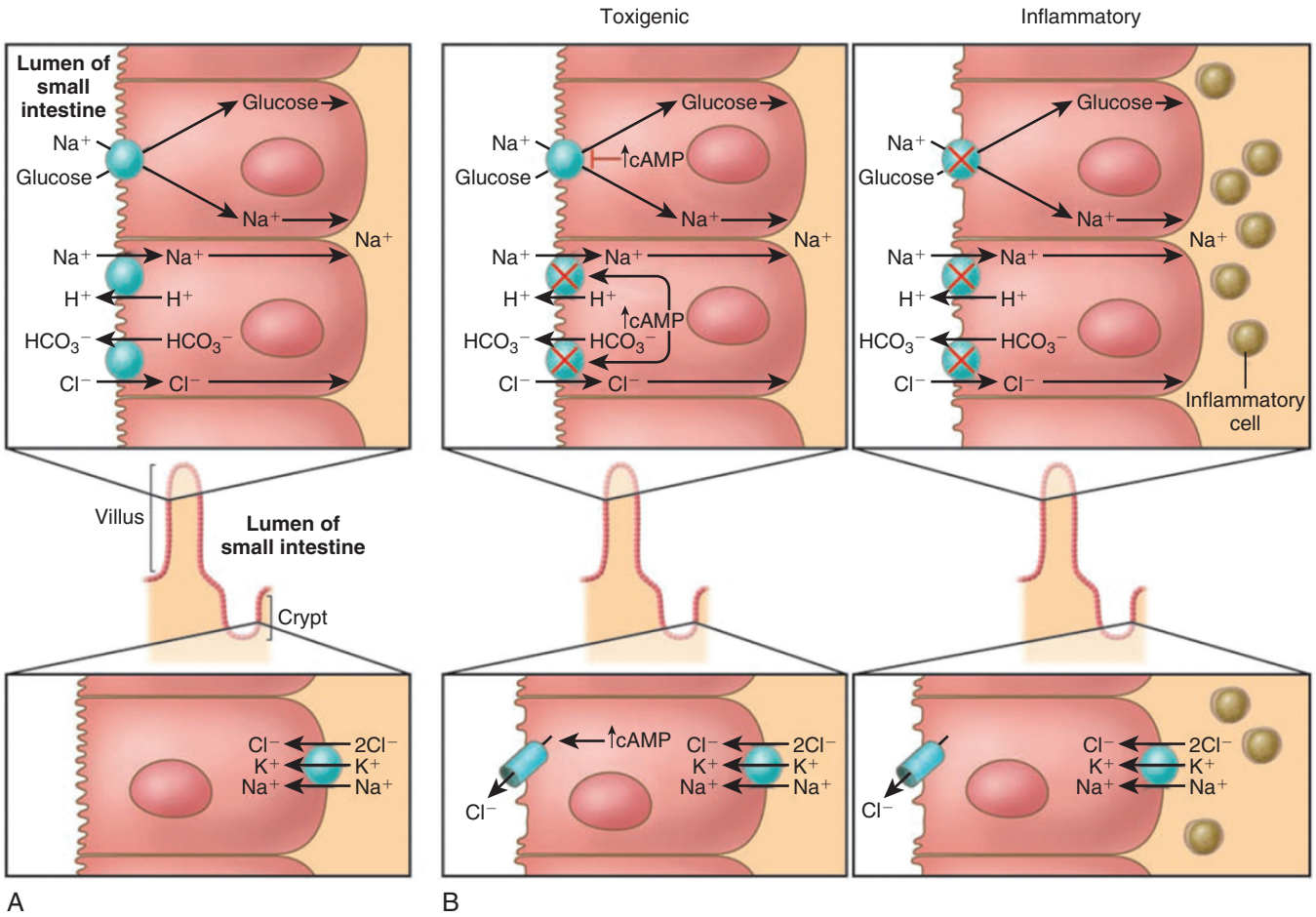

Fig. 366.4 Movement of Na^+ and Cl^- in the small intestine. **A,** Movement in normal subjects. Na^+ is absorbed by 2 different mechanisms in absorptive cells from villi: glucose-stimulated absorption and electroneutral absorption (which represents the coupling of Na^+/H^+ and Cl^-/HCO_3^- exchanges). **B,** Movement during diarrhea caused by a toxin and inflammation. *(From Petri WA, Miller M, Binder HJ, et al: Enteric infections, diarrhea and their impact on function and development,* J Clin Invest *118:1277–1290, 2008.)*

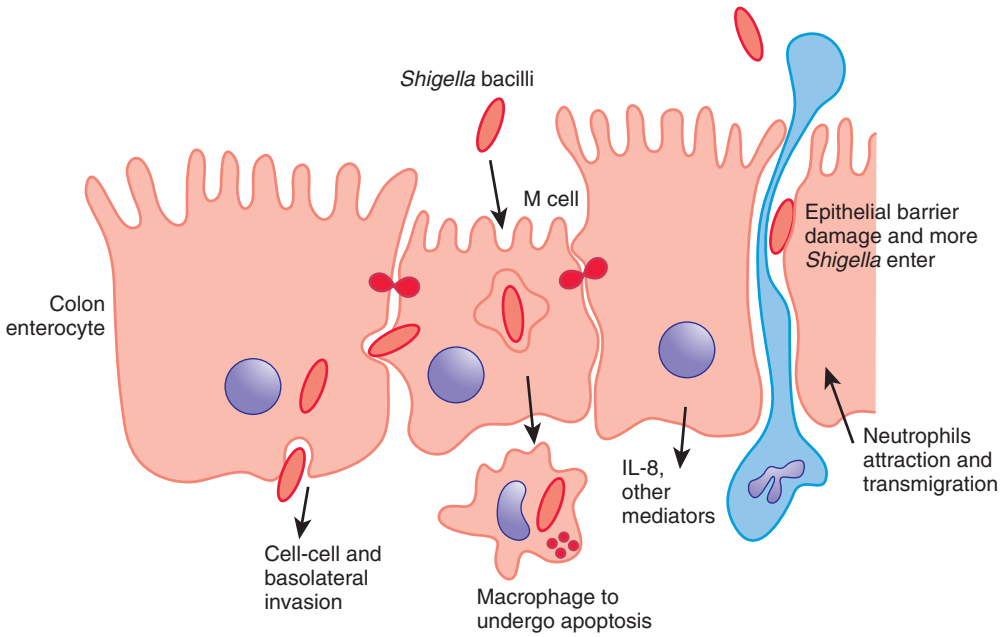

Fig. 366.5 Pathogenesis of shigella infection and diarrhea. *IL-8,* interleukin-8. *(Modified from Opal SM, Keusch GT: Host responses to infection. In Cohen J, Powderly WG, Opal SM, et al, editors:* Infectious diseases, *ed 2, London, 2004, Mosby, pp. 31–52.)*

Table 366.9 Clinical Presentations Suggestive of Infectious Diarrhea Etiologies

FINDING	LIKELY PATHOGENS
Persistent or chronic diarrhea	*Cryptosporidium* spp., *Giardia lamblia*, *Cyclospora cayetanensis*, *Entamoeba histolytica*, non-typhoidal *Salmonella*, *Yersinia*, and *Campylobacter* spp.
Visible blood in stool	STEC, *Shigella*, *Salmonella*, *Campylobacter*, *Entamoeba histolytica*, noncholera *Vibrio parahaemolyticus*, *Yersinia*, *Balantidium coli*, and *Aeromonas*
Fever	Not highly discriminatory—viral, bacterial, and parasitic infections can cause fever. In general, higher temperatures are suggestive of bacterial etiology or *E. histolytica*. Patients infected with STEC usually are not febrile at time of presentation
Abdominal pain	STEC, *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, noncholera *Vibrio* species, *Clostridium difficile*
Severe abdominal pain, often grossly bloody stools (occasionally nonbloody), and minimal or no fever	STEC, *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia enterocolitica*
Persistent abdominal pain and fever	*Y. enterocolitica and Y. pseudotuberculosis*; may mimic appendicitis
Nausea and vomiting lasting ≤24 hr	Ingestion of *Staphylococcus aureus* enterotoxin or *Bacillus cereus* (short-incubation emetic syndrome)
Diarrhea and abdominal cramping lasting 1-2 days	Ingestion of *Clostridium perfringens* or *Bacillus cereus* (long-incubation emetic syndrome)
Vomiting and nonbloody diarrhea	Norovirus (low-grade fever usually present during the first 24 hr in 40% of infections); diarrhea usually lasts 2-3 days or less; other viral diarrheas (e.g., rotavirus, enteric adenovirus, sapovirus, astrovirus) usually last 3-8 days.
Chronic watery diarrhea, often lasting a year or more	Brainerd diarrhea (epidemic secretory diarrhea, etiologic agent has not been identified); postinfectious irritable bowel syndrome

STEC, Shiga toxin–producing *Escherichia coli.*

From Shane AL, Mody RK, Crump JA, et al: 2017 Infectious Diseases Society for America clinical practice guidelines for the diagnosis and management of infectious diarrhea, *Clin Infect Dis* 65(12):e45–80, 2017 (Table 3, p. e54).

Table 366.10 Intestinal and Extraintestinal Complications of Enteric Infections

COMPLICATION	ASSOCIATED ENTERIC PATHOGEN(S)
INTESTINAL COMPLICATIONS	
Persistent diarrhea	All causes
Recurrent diarrhea (usually immunocompromised persons)	*Salmonella, Shigella, Yersinia, Campylobacter, Clostridium difficile, Entamoeba histolytica, Cryptosporidium, Giardia*
Toxic megacolon	*Shigella*, *C. difficile*, *E. histolytica*
Intestinal perforation	*Shigella*, *Yersinia*, *C. difficile*, *E. histolytica*
Rectal prolapse	*Shigella*, STEC, *C. difficile*
Enteritis necroticans–jejunal hemorrhagic necrosis	*Clostridium perfringens* type C beta toxin
EXTRAINTESTINAL COMPLICATIONS	
Dehydration, metabolic abnormalities, malnutrition, micronutrient deficiency	All causes
Bacteremia with systemic spread of bacterial pathogens, including endocarditis, osteomyelitis, meningitis, pneumonia, hepatitis, peritonitis, chorioamnionitis, soft tissue infection, and septic thrombophlebitis	Nontyphoidal *Salmonella, Shigella, Yersinia, Campylobacter*
Local spread (e.g., vulvovaginitis and urinary tract infection)	*Shigella*
Pseudoappendicitis	*Yersinia, Campylobacter* (occasionally)
Exudative pharyngitis, cervical adenopathy	*Yersinia*
Rhabdomyolysis and hepatic necrosis	*Bacillus cereus* emetic toxin
POSTINFECTIOUS COMPLICATIONS	
Reactive arthritis	*Salmonella, Shigella, Yersinia, Campylobacter, Cryptosporidium, C. difficile*
Guillain-Barré syndrome	*Campylobacter*
Hemolytic uremic syndrome	STEC, *Shigella dysenteriae* 1
Glomerulonephritis, myocarditis, pericarditis	*Shigella, Campylobacter, Yersinia*
Immunoglobulin A (IgA) nephropathy	*Campylobacter*
Erythema nodosum	*Yersinia, Campylobacter, Salmonella*
Hemolytic anemia	*Campylobacter, Yersinia*
Intestinal perforation	*Salmonella, Shigella, Campylobacter, Yersinia, Entamoeba histolytica*
Osteomyelitis, meningitis, aortitis	*Salmonella, Yersinia, Listeria*

STEC, Shiga toxin–producing *Escherichia coli.*

From Centers for Disease Control and Prevention: Managing acute gastroenteritis among children, *MMWR Recomm Rep* 53:1–33, 2004.

S. aureus and *B. cereus* emetic toxin, while diarrhea is the major manifestation of *C. perfringens* and *B. cereus* enterotoxins.

Protozoal Diarrhea. Illnesses due to intestinal protozoa tend to be more prolonged, sometimes for 2 wk or more, but usually self-limited in the otherwise healthy host (see Table 366.3). In general, the duration and severity of *Cryptosporidium* diarrhea is strongly influenced by the immune and nutritional status of the host. A protozoal etiology should be suspected when there is a prolonged diarrheal illness characterized by episodes of sometimes-explosive diarrhea with nausea, abdominal cramps, and abdominal bloating. The stools are usually watery but can be greasy and foul smelling due to concomitant malabsorption of fats, which is more likely to occur if the parasite load is high. Occasionally diarrhea may alternate with constipation.

In addition to diarrhea, *E. histolytica* causes a range of other syndromes. Amebic dysentery is characterized by bloody or mucoid diarrhea, which may be profuse and lead to dehydration or electrolyte imbalances. Hepatic amebiasis is limited to abscess formation in the liver, which may occur with or without intestinal disease.

INTESTINAL AND EXTRAINTESTINAL COMPLICATIONS

The major complications from diarrhea from any cause are dehydration, electrolyte, or acid-base derangements, which can be life-threatening (see Table 366.10). Avoiding delays in diagnosis and treatment, and appropriate supportive care using either oral, enteral, or intravenous hydration can prevent or treat most of these conditions. Children who experience frequent episodes of acute diarrhea or prolonged or persistent episodes (seen especially in low resource settings) are at risk for poor growth and nutrition and complications such as secondary infections and micronutrient deficiencies (iron, zinc, vitamin A). Ensuring continued nutritional support during diarrheal episodes is important because prolonged limitation of the diet may extend diarrheal symptoms. Reestablishing a normal diet generally restores villous anatomy and function with resolution of loose stools.

Viral AGE illnesses are usually self-limited and resolve after several days. Rarely, **intussusception** is triggered by lymphoid hyperplasia associated with viral AGE. Complications of bacterial AGE may be the result of local or systemic spread of the organism; in malnourished children and HIV-infected populations, associated **bacteremia** is well-recognized. Toxic megacolon, intestinal perforation, and rectal prolapse can occur, particularly in association with *Shigella* in developing countries and *C. difficile*. The most dreaded complication of pediatric diarrhea in the United States is **HUS**, the leading cause of acquired renal failure in children, developing in 5–10% of patients infected with STEC. It is usually diagnosed 2-14 days after the onset of diarrhea. HUS is unlikely to occur once diarrhea has remained resolved for 2 or 3 days with no evidence of hemolysis. Risk factors include age 6 mo to 4 yr, bloody diarrhea, fever, elevated leukocyte count, and treatment with antibiotics and antimotility agents. Two-thirds of patients no longer excrete the organism at the time they develop HUS (Chapter 538.5).

Pseudoappendicitis secondary to mesenteric adenitis is a notable complication of *Yersinia*, and sometimes *Campylobacter*. Older children and adolescents are most often affected. It typically presents with fever and abdominal pain with tenderness localized to the right lower quadrant, with or without diarrhea, and can be confused with appendicitis. CT scan or sonogram may be helpful to distinguish true appendicitis.

Immune-mediated complications that are thought to result from immunologic cross reactivity between bacterial antigens and host tissues are more often seen in adults than children. These include reactive arthritis following infection with the classical bacterial enteropathogens and Guillain-Barré syndrome following *Campylobacter* infection.

Protozoan illnesses, when persistent, can lead to poor weight gain in the young and immunocompromised individuals, weight loss, malnutrition, or vitamin deficiencies. Infection with *Entamoeba* can cause severe ulcerating colitis, colonic dilation, and perforation. The parasite may spread systemically, most commonly causing liver abscesses. In high-risk settings, it is critical to exclude *Entamoeba* infection and tuberculosis before initiating corticosteroids for presumed ulcerative colitis.

Table 366.11 Differential Diagnosis of Acute Dysentery and Inflammatory Enterocolitis

SPECIFIC INFECTIOUS PROCESSES
• Bacillary dysentery *(Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Shigella boydii; invasive Escherichia coli)*
• Campylobacteriosis *(Campylobacter jejuni)*
• Amebic dysentery *(Entamoeba histolytica)*
• Ciliary dysentery *(Balantidium coli)*
• Bilharzial dysentery *(Schistosoma japonicum, Schistosoma mansoni)*
• Other parasitic infections *(Trichinella spiralis)*
• Vibriosis *(Vibrio parahaemolyticus)*
• Salmonellosis *(Salmonella typhimurium)*
• Typhoid fever *(Salmonella typhi)*
• Enteric fever *(Salmonella choleraesuis, Salmonella paratyphi)*
• Yersiniosis *(Yersinia enterocolitica)*
• Spirillar dysentery *(Spirillum spp.)*
PROCTITIS
• Gonococcal *(Neisseria gonorrhoeae)*
• Herpetic (herpes simplex virus)
• Chlamydial *(Chlamydia trachomatis)*
• Syphilitic *(Treponema pallidum)*
OTHER SYNDROMES
• Necrotizing enterocolitis of the newborn
• Enteritis necroticans
• Pseudomembranous enterocolitis *(Clostridium difficile)*
• Typhlitis
CHRONIC INFLAMMATORY PROCESSES
• Enteropathogenic and enteroaggregative *E. coli*
• Gastrointestinal tuberculosis
• Gastrointestinal mycosis
• Parasitic enteritis
SYNDROMES WITHOUT KNOWN INFECTIOUS CAUSE
• Idiopathic ulcerative colitis
• Celiac disease
• Crohn disease
• Radiation enteritis
• Ischemic colitis
• Immune deficiency including HIV infection
• Allergic enteritis

From Mandell GL, Bennett JE, Dolin R, editors: *Principles and practices of infectious diseases*, ed 7, Philadelphia, 2010, Churchill Livingstone.

DIFFERENTIAL DIAGNOSIS

The physician should also consider noninfectious diseases that can present with bright red blood per rectum or hematochezia (Table 366.11). In an infant or young child without systemic symptoms, these may include anal fissures, intermittent intussusception, juvenile polyps, and Meckel diverticulum. Necrotizing enterocolitis can cause lower gastrointestinal bleeding in infants, especially premature neonates. Inflammatory bowel disease should be considered in older children. Examples of noninfectious causes of nonbloody diarrhea include congenital secretory diarrheas, endocrine disorders (hyperthyroidism), neoplasms, food intolerance, and medications (particularly antibiotics). Noninfectious causes of chronic or relapsing diarrhea include cystic fibrosis, celiac disease, milk protein intolerance, and congenital or acquired disaccharidase deficiency. Significant abdominal pain should raise suspicion of other infectious processes in the abdomen such as appendicitis and pelvic inflammatory disease. Prominent vomiting with or without abdominal pain can be a manifestation of pyloric stenosis, intestinal obstruction, pancreatitis, appendicitis, and cholecystitis.

Clinical Evaluation of Diarrhea

In the initial evaluation of all patients with AGE, the physician should focus on the patient's hydration status and electrolyte balance, as well as evidence of sepsis or invasive bacterial infection, which could complicate bacterial AGE (Fig. 366.6). Once the patient is stabilized,

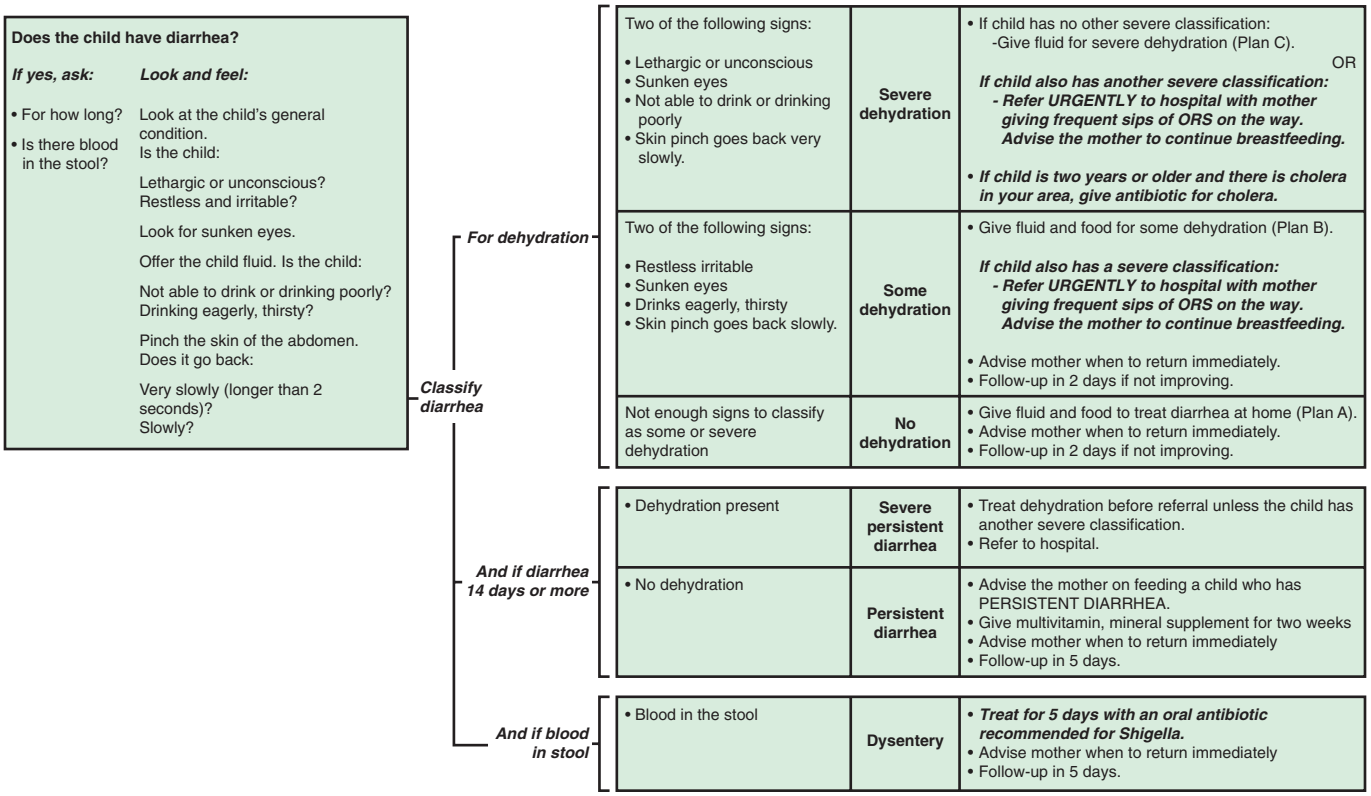

Fig. 366.6 Integrated Management of Childhood Illnesses protocol for the recognition and management of diarrhea in developing countries. *ORS,* oral rehydration solution.

Table 366.12 Clinical Signs Associated With Dehydration

SYMPTOM	MINIMAL OR NO DEHYDRATION	SOME DEHYDRATION	SEVERE DEHYDRATION
Mental status	Well; alert	Normal, fatigued or restless, irritable	Apathetic, lethargic, unconscious
Thirst	Drinks normally; might refuse liquids	Thirsty; eager to drink	Drinks poorly; unable to drink
Heart rate	Normal	Normal to increased	Tachycardia, with bradycardia in most severe cases
Quality of pulses	Normal	Normal to decreased	Weak, thready, or impalpable
Breathing	Normal	Normal; fast	Deep
Eyes	Normal	Slightly sunken	Deeply sunken
Tears	Present	Decreased	Absent
Mouth and tongue	Moist	Dry	Parched
Skinfold	Instant recoil	Recoil in <2 sec	Recoil in >2 sec
Capillary refill	Normal	Prolonged	Prolonged; minimal
Extremities	Warm	Cool	Cold; mottled; cyanotic
Urine output	Normal to decreased	Decreased	Minimal

Modified from Duggan C, Santosham M, Glass RI: The management of acute diarrhea in children: oral rehydration, maintenance, and nutritional therapy, *MMWR Recomm Rep* 41(RR-16):1–20, 1992; and World Health Organization: *The treatment of diarrhoea: a manual for physicians and other senior health workers,* Geneva, 1995, World Health Organization; and Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, *MMWR* 53(RR-4):1–33, 2004.

the history and physical examination can focus on detecting risk factors and exposures, as well as the clinical features that may suggest specific etiologic agents (see Tables 366.5 and 366.6).

Important elements of the medical history include the duration of diarrhea and a description of stools (frequency, amount, presence of blood or mucus), fever (duration, magnitude), vomiting (onset, amount and frequency), and the amount and type of solid and liquid oral intake. Clinical signs of dehydration should be evaluated (Table 366.12): urine output (number of wet diapers per day and time since the last urination), whether eyes appear sunken, whether the child is active, whether the child drinks vigorously, and the date and value of the most recent weight measurement. A documented weight loss can be used to calculate the fluid deficit. The past medical history should identify comorbidities that might increase the risk or severity of AGE.

Certain physical signs are best assessed before approaching the child directly, so he/she remains calm, including general appearance (activity, response to stimulation) and respiratory patterns. Skin turgor is assessed by pinching a small skin fold on the lateral abdominal wall at the level of the umbilicus. If the fold does not promptly return to normal after release, the recoil time is quantified as delayed slightly or ≥2 sec. Excess

subcutaneous tissue and hypernatremia may produce a false negative test and malnutrition can prolong the recoil time. To measure capillary refill time, the palmar surface of the child's distal fingertip is pressed until blanching occurs, with the child's arm at heart level. The time elapsed until restoration of normal color after release usually exceeds 2 sec in the presence of dehydration. Mucous membrane moisture level, presence of tears, and extremity temperature should be assessed.

Laboratory Diagnosis

Most cases of AGE do not require diagnostic laboratory testing. Stool specimens could be examined for mucus, blood, neutrophils or fecal lactoferrin, a neutrophil product. The finding of more than 5 leukocytes per high-power field or a positive lactoferrin assay in an infant not breastfeeding suggests an infection with a classical bacterial enteropathogen; patients infected with STEC and *E. histolytica* usually have negative tests.

Laboratory diagnosis of viral AGE may be helpful when an outbreak is suspected, cases are linked to a suspected outbreak, or when cohorting of patients is considered to limit the spread of infection. The preferred method of testing norovirus is real-time reverse transcription quantitative polymerase chain reaction (RT-qPCR), available at most public health and virology laboratories. Commercial tests are available for the diagnosis of rotavirus and enteric adenoviruses but not for astrovirus in the United States (see Table 366.1).

Stool cultures for detection of bacterial agents are costly, so requests should be restricted to patients with clinical features predictive of bacterial AGE, have moderate or severe disease, are immunocompromised, in outbreaks with suspected hemolytic-uremic syndrome, or have a highly suggestive epidemiologic history. To optimize recovery of pathogens, stool specimens for culture need to be transported and plated quickly; if the latter is not quickly available, specimens might need to be transported in special transport media. If the child has not passed a stool and antibiotics will be administered, a rectal swab should be collected promptly. After dipping the cotton tip into the medium that will be used for transport, it is gently inserted into the child's rectum and rotated 360 degrees. A properly collected rectal swab is stained or covered with fecal material. Standard stool culture methods performed in clinical microbiology laboratories recover *Shigella* and *Salmonella* species. If *Campylobacter*, *Yersinia*, or *Vibrio* species are suspected, the laboratory should be notified unless media are routinely used for their detection. All bloody stools should also be inoculated into media specific for detection of *E. coli* 0157:H7 or directly tested for the presence of Shiga-like toxin (or both). Except for *C. difficile*, nosocomial acquisition of a bacterial enteric pathogen is very unlikely. Hence stool microbiologic assays are generally not indicated for patients in whom diarrhea develops more than 3 days after admission unless the patient is immunocompromised or to investigate a hospital outbreak (see Table 366.2). Stool can also be tested for bacterial pathogens by nucleic acid amplification test (NAAT); if the NAAT is positive, the sample should automatically be cultured to determine antimicrobial sensitivities.

For children older than 2 yr who have recently received antibiotics or have other risk factors, evaluation for *C. difficile* infection may be appropriate. The cytotoxin assay detects toxin B, but testing for toxin A is also available in some laboratories; however, this test is laborious. Several tests are commercially available to detect toxin-producing *C. difficile* in stool, including enzyme immunoassays for toxins A and B, cell culture cytotoxicity assay, and PCR. The sensitivities of cell culture and PCR are superior to that of immunoassay. Testing for *C. difficile* toxin in children younger than 2 yr is discouraged because the organism and its toxins are commonly detected in asymptomatic infants (see Table 366.2).

Evaluation for intestinal protozoa that cause diarrhea is usually indicated in patients who recently traveled to an endemic area, have contact with untreated water, and manifest suggestive symptoms. The most commonly used method is direct microscopy of stool for cysts and trophozoites. However, this approach is time consuming and lacks sensitivity, in part because shedding can be intermittent. Analyzing 3 specimens from separate days is optimal, and fecal concentration techniques provide some benefit. The sensitivity and specificity of microscopy are substantially improved using immunofluorescence antibodies that are commercially available for visualization of *Cryptosporidium* and *Giardia* cysts. In addition, enzyme immunoassays are available for *Cryptosporidium, Giardia,* and *Entamoeba* that are more sensitive and specific than direct microscopy and provide a useful diagnostic tool (not all commercial kits distinguish between pathogenic *E. histolytica* and nonpathogenic *E. dispar*). Molecular methods (NAAT) are also available.

Several culture-independent *rapid multiplex molecular panels* for detection of viral, bacterial, and protozoal gastrointestinal pathogens directly from stool samples are FDA approved, including xTag GPP (14 pathogens), Verigene EP (9 pathogens), and the FirmArray GI (22 pathogens). These methods offer several advantages over conventional diagnostics, including reduced sample volume requirements, broad coverage without the need to select specific tests, enhanced ability to detect coinfections, increased sensitivity, and rapid turnaround. However, their use is controversial because the available tests do not provide strain specificity or antimicrobial susceptibility testing to assist with outbreak detection and treatment decisions.

Most episodes of diarrheal dehydration are isonatremic and do not warrant serum electrolyte measurements. Electrolyte measurements are most useful in children with severe dehydration, when intravenous fluids are administered, when there is a history of frequent watery stools, yet the skin pinch feels doughy without delayed recoil, which suggests hypernatremia, or when inappropriate rehydration fluids have been administered at home. A suspicion for HUS prompts a complete blood count with review of the peripheral smear, platelets, serum electrolytes, and renal function tests. Patients with shigellosis can demonstrate bandemia or even a leukemoid reaction. Blood culture should be obtained if there is concern for systemic bacterial infection. This includes infants and children with fever and/or blood in the stool who are younger than 3 mo, are immunocompromised, or have hemolytic anemia or other risk factors. If diarrhea persists with no cause identified, endoscopic evaluation may be indicated. Biopsy specimens help in diagnosing inflammatory bowel disease or identifying infecting agents that may mimic it. A sweat test is warranted if cystic fibrosis is suspected.

TREATMENT

The broad principles of management of AGE in children include rehydration and maintenance ORS plus replacement of continued losses in diarrheal stools and vomitus after rehydration, continued breastfeeding, and refeeding with an age-appropriate, unrestricted diet as soon as dehydration is corrected. Zinc supplementation is recommended for children in developing countries.

Hydration

Children, especially infants, are more susceptible than adults to dehydration because of the greater basal fluid and electrolyte requirements per kilogram and because they are dependent on others to meet these demands (Table 366.13). *Dehydration must be evaluated rapidly and corrected in 4-6 hr according to the degree of dehydration and estimated daily requirements.* When there is emesis, small volumes of ORS can be given initially by a dropper, teaspoon, or syringe, beginning with as little as 5 mL at a time. The volume is increased as tolerated. The low-osmolality World Health Organization (WHO) ORS containing 75 mEq of sodium, 64 mEq of chloride, 20 mEq of potassium, and 75 mmol of glucose per liter, with total osmolarity of 245 mOsm/L, is now the global standard of care and more effective than home fluids. Soda beverages, fruit juices, tea, and other home fluids are not suitable for rehydration or maintenance therapy because they have inappropriately high glucose concentration and osmolalities and low sodium concentrations. Tables 366.12 and 366.13 outline a clinical evaluation plan and management strategy for children with moderate to severe diarrhea. Replacement for emesis or stool losses is noted in Table 366.13. Oral rehydration can also be given by a nasogastric tube if needed; this is not the usual route.

A small minority of children, including those with severe dehydration or unable to tolerate oral fluids, require initial intravenous rehydration, but oral rehydration is the preferred mode of rehydration and replacement of ongoing losses. Signs of severe dehydration that might necessitate intravenous resuscitation are shown in Table 366.13. Limitations to ORS include shock, decreased level of consciousness, an ileus, intussusception, carbohydrate intolerance (rare), severe emesis, and high stool output (>10 mL/kg/hr).

Table 366.13 Fluid and Nutritional Management of Diarrhea

DEGREE OF DEHYDRATION*	REHYDRATION THERAPY	REPLACEMENT OF LOSSES DURING MAINTENANCE†
Some dehydration	Infants‡ and children: ORS, 50-100 mL/kg over 3-4 hr. Continue breast feeding. After 4 hr, give food every 3-4 hr for children who normally receive solid foods.	Infants and children: <10 kg body weight: 50-100 mL ORS for each diarrheal stool or vomiting episode, up to ~500 mL/day >10 kg body weight: 100-200 mL ORS for each diarrheal stool or vomiting episode; up to ~1 L/day Replace losses as above as long as diarrhea or vomiting continues
Severe dehydration	Malnourished infants may benefit from smaller-volume, frequent boluses of 10 mL/kg body weight due to reduced capacity to increase cardiac output with larger volume resuscitation. Infants (<12 months) and children (12 mo to 5 yr) without malnutrition: Give 20-30 mL/kg boluses of intravenous isotonic crystalloid solution (e.g., normal saline solution) over 30-60 min. Repeat boluses as necessary to restore adequate perfusion. Then give 70 mL/kg over 2.5-5 hr. (Note the slower infusion times are for infants.) Reassess the infant or child frequently and adjust infusion rate if needed. Switch to ORS, breast milk, and feed as described for some dehydration, when the child can drink, perfusion is adequate, and mental status is normal. Adjust electrolytes and administer dextrose based on chemistry values.	Infants and children: <10 kg body weight: 50-100 mL ORS for each diarrheal stool or vomiting episode, up to ~500 mL/day >10 kg body weight: 100-200 mL ORS for each diarrheal stool or vomiting episode; up to ~1 L/day Adolescents and adults: Ad libitum, up to ~2 L/day Replace losses as above as long as diarrhea or vomiting continue. If unable to drink, administer either through a nasogastric tube or give 5% dextrose 0.25 normal saline solution with 20 mEq/L potassium chloride intravenously.

*A variety of scales are available to grade the severity of dehydration in young children, but no single, standard, validated method exists. Note that signs of dehydration may be masked when a child is hypernatremic. The World Health Organization defines some dehydration as the presence of two or more of the following signs: restlessness/irritability, sunken eyes, drinks eagerly, thirsty, and skin pinch goes back slowly. Severe dehydration is defined as two or more of the following signs: lethargy/unconsciousness, sunken eyes, unable to drink/drinks poorly, and skin pinch goes back very slowly (>2 sec).

†After rehydration is complete, maintenance fluids should be resumed along with an age-appropriate normal diet offered every 3-4 hr. Children previously receiving a lactose-containing formula can tolerate the same product in most instances. Diluted formula does not appear to confer any benefit.

‡Breastfed infants should continue nursing throughout the illness.

Low-osmolarity ORS can be given to all age groups, with any cause of diarrhea. It is safe in the presence of hypernatremia, as well as hyponatremia (except when edema is present). Some commercially available formulations that can be used as ORS include Pedialyte Liters (Abbott Nutrition), CeraLyte (Cero Products), and Enfalac Lytren (Mead Johnson). Popular beverages that should not be used for rehydration include apple juice, Gatorade, and commercial soft drinks.

ORS, oral rehydration solution.

Modified from Centers for Disease Control and Prevention: Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep* 52(RR-16):1–16, 2003; and World Health Organization. Pocket book of hospital care for children: Guidelines for the management of common childhood illnesses, ed 2 (http://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/).

Enteral Feeding and Diet Selection

Continued breastfeeding and refeeding with an age-appropriate, unrestricted diet as soon as dehydration is improving or resolved aids in recovery from the episode. Foods with complex carbohydrates (rice, wheat, potatoes, bread, and cereals), fresh fruits, lean meats, yogurt, and vegetables should be reintroduced while ORS is given to replace ongoing losses from emesis or stools and for maintenance. Fatty foods or foods high in simple sugars (juices, carbonated sodas) should be avoided. The usual energy density of any diet used for the therapy of diarrhea should be around 1 kcal/g, aiming to provide an energy intake of a minimum of 100 kcal/kg/day and a protein intake of 2-3 g/kg/day. In selected circumstances when adequate intake of energy-dense food is problematic, the addition of amylase to the diet through germination techniques can also be helpful.

If the normal diet includes infant formula, it should not be diluted, or changed to a lactose-free preparation unless lactose malabsorption is evident. With the exception of acute lactose intolerance in a small subgroup, most children with diarrhea are able to tolerate milk and lactose-containing diets. *Withdrawal of milk and replacement with specialized lactose-free formulations are unnecessary.* Although children with persistent diarrhea are not lactose intolerant, administration of a lactose load exceeding 5 g/kg/day may be associated with higher purging rates and treatment failure. Alternative strategies for reducing the lactose load while feeding malnourished children who have prolonged diarrhea include addition of milk to cereals and replacement of milk with fermented milk products such as yogurt.

Rarely, when dietary intolerance precludes the administration of cow's milk–based formulations or whole milk, it may be necessary to administer specialized milk-free diets such as a comminuted or blenderized chicken-based diet or an elemental formulation. Although effective in some settings, the latter are unaffordable in most developing countries. In addition to rice-lentil formulations, the addition of green banana or pectin to the diet has also been shown to be effective in the treatment of persistent diarrhea. Fig. 366.7 gives an algorithm for managing children with prolonged diarrhea in developing countries.

Among children in low- and middle-income countries, where the dual burden of diarrhea and malnutrition is greatest and where access to proprietary formulas and specialized ingredients is limited, the use of locally available age-appropriate foods should be promoted for the majority of acute diarrhea cases. Even among those children for whom lactose avoidance may be necessary, nutritionally complete diets composed of locally available ingredients can be used at least as effectively as commercial preparations or specialized ingredients. These same conclusions may also apply to the dietary management of children with persistent diarrhea, but the evidence remains limited.

Zinc Supplementation

Zinc supplementation in children with diarrhea in developing countries leads to reduced duration and severity of diarrhea and could potentially prevent a large proportion of cases from recurring. Zinc administration for diarrhea management can significantly reduce all-cause mortality by 46% and hospital admission by 23%. In addition to improving diarrhea recovery rates, administration of zinc in community settings leads to increased use of ORS and reduction in the inappropriate use of antimicrobials. All children older than 6 mo of age with acute diarrhea in at-risk areas should receive oral zinc (20 mg/day) in some form for 10-14 days during and continued after diarrhea. The role of zinc in well nourished, zinc replete populations in developed countries is less certain.

Additional Therapies

The use of probiotic nonpathogenic bacteria for prevention and therapy of diarrhea has been successful in some settings, although the evidence does not support a recommendation for their use in all settings. A variety of organisms *(Lactobacillus, Bifidobacterium)* have a good safety record;

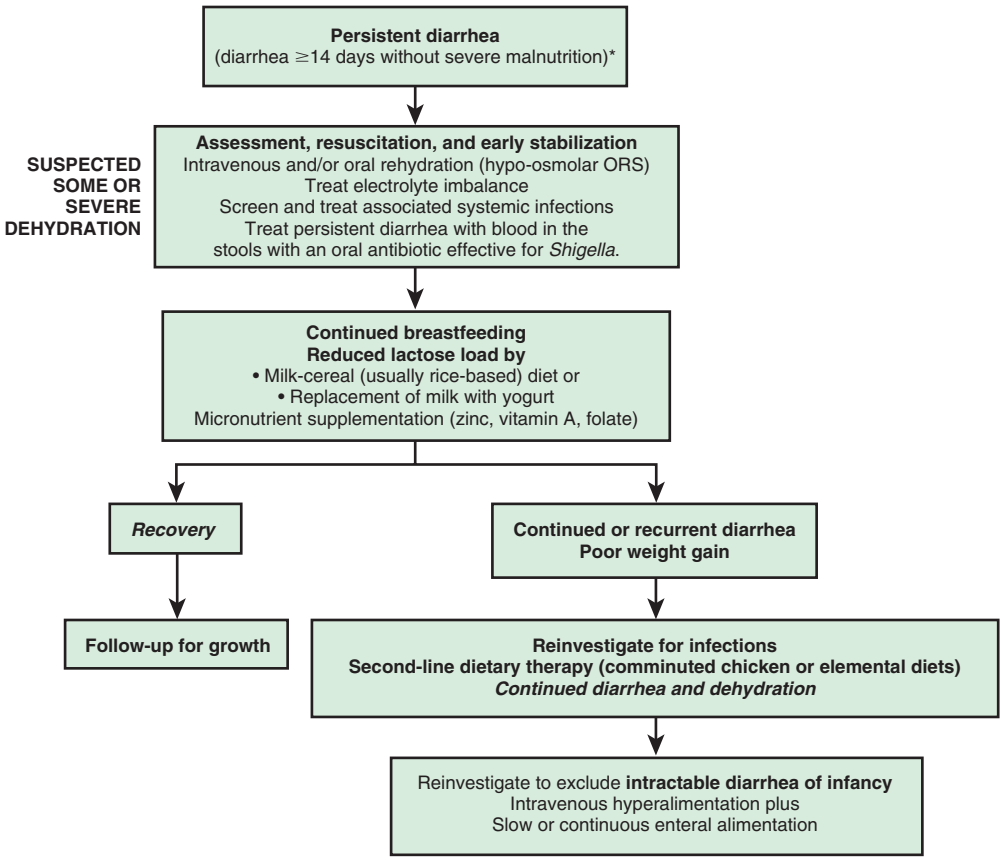

Fig. 366.7 Management of persistent diarrhea. *IV,* intravenous; *NG,* nasogastric tube; *ORS,* oral rehydration solution. *Severely malnourished children require urgent referral for hospitalization and specific treatment.

therapy has not been standardized and the most effective (and safe) organism has not been identified. *Saccharomyces boulardii* is effective in antibiotic-associated and in *C. difficile* diarrhea, and there is some evidence that it might prevent diarrhea in daycare centers. Two large randomized placebo-controlled trials evaluating the efficacy of two *Lactobacillus*-based probiotic formulations failed to reduce a clinical severity score in Canadian infants and preschool children with acute gastroenteritis. *Lactobacillus rhamnosus GG* or a combination probiotic product containing *L. rhamnosus* R0011 and *L. helveticus* R0052 is has shown variable efficacy; reduction is more evident in cases of childhood rotavirus diarrhea.

Ondansetron (oral mucosal absorption preparation) reduces the incidence of emesis, thus permitting more effective oral rehydration and is well-established in emergency management of AGE in high-resource settings, reducing intravenous fluid requirements and hospitalization. Because persistent vomiting can limit ORS, a single sublingual dose of an oral dissolvable tablet of ondansetron (4 mg for children 4-11 yr old and 8 mg for children older than 11 yr [generally 0.2 mg/kg]) may be given. However, most children do not require specific antiemetic therapy; careful ORS is usually sufficient. Antimotility agents (loperamide) are contraindicated in children with dysentery and probably have no role in the management of acute watery diarrhea in otherwise healthy children. Similarly, antiemetic agents, such as the phenothiazines, are of little value and are associated with potentially serious side effects (lethargy, dystonia, malignant hyperpyrexia).

Antibiotic Therapy

Judicious antibiotic therapy for suspected or proven bacterial infections can reduce the duration and severity of illness and prevent complications (Table 366.14). Several factors justify limited use. First, most episodes of AGE are self-limited among otherwise healthy children. Second, the increasing prevalence of antibiotic resistance has prompted restricted use of these drugs. Third, antibiotics may worsen outcome, because some studies have shown that antibiotic therapy of STEC infection increases the risk of HUS and prolongs excretion of NTS without improving clinical outcome. Therefore antibiotics are used primarily to treat severe infections, prevent complications in high-risk hosts, or to limit the spread of infection. Microbiologic (culture) confirmation of the etiology and susceptibility testing should be sought prior to treatment if possible.

Treatment of *C. difficile* infection warrants special consideration. Removal of the offending antibiotic, if possible, is the first step. Antibiotic therapy directed against *C. difficile* should be instituted if the symptoms are severe or persistent. Testing for *C. difficile* is discouraged for children with diarrhea who are <2 yr unless there is strong evidence to implicate *C. difficile* as the etiologic agent. This recommendation is based on the high rates of asymptomatic infection with toxigenic and nontoxigenic strains and the rarity of characteristic clinical manifestations not attributed to other pathogens in this age group. Oral vancomycin and metronidazole for 7-14 days (first line agents) displayed equivalent efficacy in a prospective randomized trial; however, metronidazole is preferred because of lower cost and decreased potential for inducing vancomycin-resistant enterococci. Twenty percent of adults treated for *C. difficile* diarrhea have a relapse, but the frequency in children is not known. The first relapse should be treated with another course of antibiotics based on severity of illness. For recurrent disease, tapering and/or pulsed regimen of oral vancomycin over a 4- to 6-wk period has been proposed. In the absence of ongoing symptoms, a test of cure is not necessary. The role of probiotics in the prevention of *C. difficile*-associated diarrhea in children has not been established. Fecal transplant is being explored to treat persistent or recurrent *C. difficile* colitis. *Fidaxomicin* is an alternate agent approved for patients ≥18 yr of age; it is recommended for the initial episode (severe and nonsevere) and recurrences. The adult dose is 200 mg BID for 10 days by mouth. *Bezlotoxumab,* a monoclonal antibody against *C. difficile* toxins A and B, has been shown to reduce the recurrence rate.

Antibiotic therapy for parasitic infections is shown in Table 366.14.

Table 366.14 Antibiotic Therapy for Infectious Diarrhea

ORGANISM	INDICATION FOR THERAPY	DOSAGE AND DURATION OF TREATMENT
Shigella spp.	In high-income countries, judicious treatment is recommended to curtail growing antibiotic resistance because most shigellosis is self-limited. Treatment should be reserved for moderate to severe disease (require hospitalization, have systemic disease or complications), immunocompromised, or to prevent or mitigate outbreaks in certain settings (e.g., childcare or food handling). Also consider treating patients with significant discomfort, intestinal comorbidities, institutional settings, or household exposure to high-risk individuals. WHO recommends empiric antibiotics for all children in developing countries with dysentery assuming that most cases are caused by *Shigella*.	*First line:* • Ciprofloxacin* 15 mg/kg/day PO bid × 3 days; OR • Ceftriaxone 50-100 mg/kg/day IV or IM, qd × 3 days for severe illness requiring parenteral therapy; OR • Azithromycin* 12 mg/kg once on 1st day, then 6 mg/kg once daily on days 2 through 4 (total course: 4 days) *Second line:* • Cefixime 8 mg/kg once daily for 3 days; OR • Trimethoprim-sulfamethoxazole 4 mg/kg/day of TMP and 20 mg/kg/day SMX twice a day for 5 days (if susceptibility known or likely based on local data)
ETEC	Watery diarrhea in a traveler returning from an endemic area that interferes with planned activities or is persistent.	*First line:* • Azithromycin* 12 mg/kg once on first day, then 6 mg/kg once daily on days 2 and 3 (total course: 3 days) *Second line:* • Ciprofloxacin* 15 mg/kg/day PO bid × 3 days
STEC	Avoid antimicrobials and anti-motility drugs	
Salmonella, non-typhoidal	Antibiotics for uncomplicated gastroenteritis in normal host are ineffective and may prolong excretion and are not recommended Treatment should be reserved for infection in infants younger than 3 mo, and patients with immunocompromise, malignancy, chronic GI disease, severe colitis hemolytic anemia, or HIV infection. Most strains are resistant to multiple antibiotics	See treatment of *Shigella*. Patients without bacteremia can be treated orally for 5-7 days. Patients with bacteremia (proven or until blood culture results are available in a high-risk host) should be treated parenterally for 10-14 days. Focal or disseminated invasive infections (e.g., osteomyelitis, meningitis) and bacteremic patients with HIV/AIDS should be treated parenterally for 4-6 wk.
Yersinia spp.	Antibiotics are not usually required for diarrhea, which is usually self-limited and clinical benefits of antibiotics are not established. Bacteremia and focal invasive infections should be treated. Deferoxamine therapy should be withheld for severe infections or associated bacteremia	For bacteremia or focal invasive infections, use third generation cephalosporins. Can also consider carbapenem, doxycycline (for children ≥8 yr) plus aminoglycoside, TMP-SMX, or fluoroquinolone at doses recommended for sepsis. Begin IV then switch to oral when clinically stable, for a total course of 2-6 wk.
Campylobacter spp.	Dysentery, moderate and severe gastroenteritis or at risk for severe disease (e.g., elderly, pregnant, or immunocompromised), and bacteremia or focal invasive infection should be treated. Treatment of gastroenteritis appears effective if given within 3 days of onset of illness.	*For gastroenteritis or dysentery:* • Erythromycin PO 40 mg/kg/day divided qid × 5 days; OR • Azithromycin PO 10 mg/kg/day × 3 days *For bacteremia or focal invasive infection:* • Consider parenteral macrolides or carbapenems pending susceptibility results. Fluoroquinolone resistance is >50% in some areas of the world.
Clostridium difficile	Colitis • Discontinue inciting antibiotics if possible; • Infectious disease consult suggested if disease is persistent or recurrent.	*First line (mild-moderate colitis):* • Metronidazole PO 30 mg/kg/day divided tid or qid × 10 days; max 500 mg/dose; OR • Vancomycin PO 40 mg/kg/day divided qid × 10 days, max 125 mg/dose *Second line (severe colitis):* • Vancomycin PO 40 mg/kg/day divided qid × 10 days, max 500 mg/dose; OR • If ileus, give same dose PR as 500 mg/100 mL normal saline by retention enema with or without plus metronidazole IV 30 mg/kg/day divided tid × 10 days; max 500 mg/dose • Fidaxomicin not yet approved for children; see text
Entamoeba histolytica	Treat the following conditions: • Asymptomatic cyst excretors • Mild to moderate intestinal disease • Severe intestinal or extraintestinal disease (including liver abscess)	*Asymptomatic cyst excretors:* • Iodoquinol PO 30-40 mg/kg/day, max 2 g, divided tid × 20 days; OR • Paromomycin PO 25-35 mg/kg/d divided tid × 7 days; *Mild to moderate intestinal disease and severe intestinal or extra-intestinal disease:* • Metronidazole PO 30-40 mg/kg/day divided tid × 7-10 days; OR • Tinidazole PO 50 mg/kg, single dose, max 2 g (for children ≥ 3 yr old) × 3 days, OR 5 days for severe disease EITHER FOLLOWED BY (to prevent relapse) • Iodoquinol PO 30-40 mg/kg/day tid × 20 days; OR • Paromomycin PO 25-35 mg/kg/day tid × 7 days

Continued

Table 366.14 Antibiotic Therapy for Infectious Diarrhea—cont'd

ORGANISM	INDICATION FOR THERAPY	DOSAGE AND DURATION OF TREATMENT
Giardia intestinalis	Persistent symptoms	• Tinidazole PO 50 mg/kg, single dose, max 2 g (for children ≥ 3 yr old); OR • Nitazoxanide PO; OR – Age 1-3 yr: 100 mg bid × 3 days – Age 4-11 yr: 200 mg bid × 3 days – Age over 11 yr: 500 mg bid × 3 days • Metronidazole PO 30-40 mg/kg/day divided tid × 7 days (max 250 mg per dose)
Cryptosporidium spp.	Treat immunocompromised and HIV-infected hosts, although efficacy is equivocal Treatment may not be needed in normal hosts	*Immunocompetent children:* • Nitazoxanide, as for *Giardia* *Solid organ transplants:* • Nitazoxanide, as for *Giardia*, × ≥14 days; reduce immunosuppression if possible and consider paromomycin combined with azithromycin for severe symptoms or treatment failure *HIV-infected children:* • Combined antiretroviral therapy is the primary treatment • Nitazoxanide, as for *Giardia*, generally for 3-14 days while awaiting CD4 cell recovery; OR • Consider paromomycin alone or combined with azithromycin in severe disease or treatment failure
Cyclospora spp *Isospora belli* (now designated *Cystoisospora belli*).	All symptomatic children	TMP 5 mg/kg/day and SMX 25 mg/kg/day PO bid × 7-10 days (HIV-infected children may need longer courses)
Blastocystis hominis	The significance of *B. hominis* as a cause of disease is controversial, so treatment should be reserved for those with suggestive symptoms and no other pathogen that could be the cause.	• Metronidazole PO 30-40 mg/kg/day divided tid × 7-10 days; OR • Nitazoxanide, as for *Giardia*; OR TMP-SMX as for *Cyclospora*; OR Tinidazole, as for *Giardia*

EIEC, enteroinvasive *Escherichia coli*; *EPEC,* enteropathogenic *E. coli*; *ETEC,* enterotoxigenic *E. coli*; *GI,* gastrointestinal; *IV,* intravenous; *IM,* intramuscular; *max,* maximum; *SMX,* sulfamethoxazole; *TMP,* trimethoprim; *WHO,* World Health Organization.

*Azithromycin and fluoroquinolones should be avoided in patients taking the antimalarial artemether. These drugs can prolong the QT interval on the electrocardiogram and trigger arrhythmias.

PREVENTION

Promotion of Exclusive Breastfeeding and Vitamin A

Exclusive breastfeeding (administration of no other fluids or foods for the first 6 mo of life) protects young infants from diarrheal disease through the promotion of passive immunity and through reduction in the intake of potentially contaminated food and water. In developing countries, exclusive breastfeeding for the first 6 mo of life is widely regarded as one of the most effective interventions to reduce the risk of premature childhood mortality and has the potential to prevent 12% of all deaths of children younger than 5 yr of age. Vitamin A supplementation reduces all-cause childhood mortality by 25% and diarrhea-specific mortality by 30%.

Rotavirus Immunization

Three live oral **rotavirus** vaccines are licensed: the 3-dose pentavalent G1, G2, G3, G4, P[8] human-bovine vaccine (RotaTeq), the 2-dose monovalent human G1P[8] vaccine (ROTARIX), and the 3-dose monovalent human-bovine 116E G6P[11] vaccine (Rotavax). The result has been substantial reductions in rotavirus-associated and all-cause hospitalizations for diarrheal disease in both vaccinated infants (direct protection) and unvaccinated individuals (indirect, or herd protection), as well as reductions in-office visits for less severe rotavirus diarrhea. Reductions in all-cause diarrhea deaths have been demonstrated in some countries.

Programmatic uptake has lagged in low-resource settings where most severe disease and death occurs; however, Gavi, the Vaccine Alliance, has supported introduction of rotavirus vaccine into more than 40 countries to date. Even though vaccine efficacy against severe rotavirus AGE is lower (50–64%) in low- compared with high-resource countries, the number of severe rotavirus AGE prevented per vaccinated child is higher because of the substantially greater baseline rate of severe rotavirus gastroenteritis in developing countries. Vaccine (live virus) associated rotavirus infection has been reported in children with severe combined immunodeficiency disease, but the vaccine has been shown to be safe in HIV-infected populations.

Two licensed, efficacious 2-dose oral inactivated **cholera** vaccines (Dukoral for children 2 yr and older and ShanChol for children 1 yr or older) are available in many countries but currently have no specific indication in endemic and epidemic settings where they could potentially reduce the burden of severe diarrhea and mortality in young children. For travelers, a single-dose live oral cholera vaccine (Vaxchora) was recently licensed for adults in the United States. In addition, 2 forms of typhoid fever vaccine are available: a polysaccharide vaccine delivered intramuscularly that can be administered to children older than 2 yr (Vivotif) and an oral, live attenuated vaccine that can be administered to children over 6 yr of age (Typhim Vi). Conjugate polysaccharide typhoid vaccines that could be used in children younger than 2 yr have recently become available. In 2018, the World Health Organization issued a recommendation for the use of this vaccine in infants and children 6 mo of age or older living in endemic areas, with catch-up vaccination campaigns, if possible, for children up to 15 yr old. The vaccine is not yet available in the United States or Europe.

Improved Water and Sanitary Facilities and Promotion of Personal and Domestic Hygiene

Much of the reduction in diarrhea prevalence in the developed world is the result of improvement in standards of hygiene, sanitation, and water supply. Strikingly, an estimated 88% of all diarrheal deaths worldwide can be attributed to unsafe water, inadequate sanitation, and poor hygiene. Handwashing with soap and safe excreta disposal can reduce the risk of diarrhea by 48% and 36%, respectively, and a 17% reduction is estimated as a result of improvements in water quality.

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366.1 Traveler's Diarrhea

Karen L. Kotloff

Traveler's diarrhea is a common complication of visitors to developing countries and is caused by a variety of pathogens, in part depending on the season and the region visited. It is the most common (28%) travel-associated health problem in children. Traveler's diarrhea can manifest with watery diarrhea or as dysentery. Without treatment, 90% will have resolved within a week and 98% within a month of onset. Some individuals develop more severe or persistent diarrhea and become dehydrated or unwell and may experience complications such as bacteremia and intestinal perforation. Children younger than 2 yr are at higher risk for traveler's diarrhea, as well as more severe disease. According to the FoodNet, the pathogens identified most commonly in travelers in the United States were *Campylobacter* (42%), NTS (32%), and *Shigella* (13%). ETEC and intestinal protozoa (*G. intestinalis* and *E. histolytica*) are also important.

TREATMENT

For infants and children, rehydration, as discussed in Chapter 366, is appropriate, followed by a standard diet. Adolescents and adults should increase their intake of electrolyte-rich fluids. Kaolin-pectin, anticholinergic agents, *Lactobacillus,* and bismuth salicylate are not effective therapies. Loperamide, an antimotility and antisecretory agent, reduces the number of stools in older children with watery diarrhea and improves outcomes when used in combination with antibiotics in traveler's diarrhea. However, loperamide should not be used in febrile or toxic patients with dysentery, in those with bloody diarrhea, and in children younger than 6 yr.

The effectiveness of antibiotics depends on the pathogen and its susceptibility profile. In forming a treatment plan, the potential side effects should be weighed against the treatment need for a short-lasting and self-limiting disease such as traveler's diarrhea. Antibiotics are not recommended for mild diarrhea that is tolerable, is not distressing, and does not interfere with planned activities. When empiric therapy is required abroad, azithromycin is suggested for young children. Fluoroquinolones are recommended for older children and adults and as second line therapy for younger children. Short-duration (3 days) therapy is effective. Travelers should be reminded that diarrhea can be a symptom of other severe diseases, such as malaria. Therefore, if diarrhea persists or additional symptoms such as fever occur, travelers should seek medical advice. For up-to-date information on local pathogens and resistant patterns, see www.cdc.gov/travel.

If the patient has returned home with diarrhea, a microbiologic evaluation can be obtained before initiating antibiotic therapy. Prolonged diarrhea should prompt further investigation into possible parasitic infections or NTS. Prophylactic antibiotics for travelers are not recommended.

PREVENTION

In the pretravel visit, caregivers should be advised about diarrhea prevention, the signs, symptoms, and management of dehydration, and the use of ORS. ORS and age-appropriate antibiotics should be included in a routine health packet. Travelers should drink bottled or canned beverages or boiled water. They should avoid ice, salads, and fruit they did not peel themselves. Food should be eaten hot, if possible. Raw or poorly cooked seafood is a risk, as is eating in a restaurant rather than a private home. Swimming pools and other recreational water sites can also be contaminated.

Chemoprophylaxis is not routinely recommended for previously healthy children or adults. Nonetheless, travelers should bring azithromycin (younger than 16 yr of age) or ciprofloxacin (older than 16 yr of age) and begin antimicrobial therapy if diarrhea develops.

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Keywords
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