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100 Nausea, Vomiting, and Noninflammatory Diarrhea

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SHORT VIEW SUMMARY

Definition
- A disease group consisting of acute and chronic forms of gastroenteritis occurs in both pediatric and adult patients, and these diseases have the unifying characteristic of being predominantly noninflammatory in nature.

Epidemiology
- Noninflammatory gastroenteritides are among the most common infections of humans. As a group, they are second in incidence only to viral upper respiratory infections.
- Most cases of these diseases are not tracked or reported but are estimated to affect tens of millions of people worldwide each year.
- There are baseline endemic and seasonal rates as well as epidemic outbreaks of most forms of these infections.
- The rates of infection as well as etiologic agents vary according to age, climate, and geography. In addition, there are differences in these parameters observed for place of acquisition (e.g., community- vs. health care facility–acquired infections).

Microbiology
- Viruses, including members of the rotavirus, norovirus, adenovirus, and astrovirus genera, are the cause of most cases of noninflammatory gastroenteritis.
- Among the bacterial causes of this syndrome, certain pathogenic strains of *Escherichia coli* and some serotypes of cholera and noncholera *Vibrio* are particularly noteworthy.
- Certain protozoan types of parasites can cause a predominantly noninflammatory type of gastroenteritis and include members of the *Giardia*, *Cryptosporidium*, *Cystoisospora*, and *Cyclospora* genera.
- Although many of the etiologic agents are similar, there are also some important differences between the endemic and epidemic causes of noninflammatory gastroenteritis in developing, newly industrialized, and developed countries. Newborn nursery–associated and nosocomial outbreaks of this syndrome have differences from those cases acquired in the community.
- The number of potential infectious agents is much greater in immunocompromised compared with immunocompetent hosts.

Diagnosis
- The typical clinical syndrome consists of varying degrees of nausea, vomiting, and watery diarrhea, often in combination with fever, myalgias, and arthralgias.
- Most cases of this syndrome are self-limited, and no specific etiology is identified.
- In certain instances, such as epidemic, nosocomial, and foodborne cases, an etiologic agent can be identified by either culture or molecular diagnostic assay.

Therapy
- Adequate replacement of fluids and electrolytes remains the mainstay of all forms of gastroenteritis, including the noninflammatory gastroenteritides discussed in this chapter.
- In most cases of noninflammatory gastroenteritis, specific antimicrobial therapy is not used. However, in more severe or specific forms of this infection, specific antiviral, antibacterial, or antiparasitic treatment may be beneficial.

Prevention
- Adequate sanitation for the local water supply and food processing and distribution systems helps to prevent many forms of endemic, community-acquired noninflammatory gastroenteritis.
- Although there has been tremendous interest in developing effective vaccination or immunization schemes for many of these infectious agents, only vaccines for rotavirus are currently available for general use.

Gastroenteritis is one of the most common infectious disease syndromes, with an estimated 5 billion episodes occurring worldwide each year.[1-3,4-6] More than 1 billion of these infections occur in children younger than 5 years who reside in underdeveloped areas, and these infections result in more than 2 million deaths yearly.[4-6] Although these syndromes cause considerable morbidity and mortality, the majority of episodes of acute gastroenteritis do not involve a recognizable inflammatory process.[7,8] There can be a variety of forms of inflammatory enteritis occurring during summer months in tropical or subtropical areas of the world with poor sanitation. However, even under these circumstances, most cases of gastroenteritis or diarrheal diseases are noninflammatory, suggesting enterotoxic bacterial, viral, or noninvasive parasitic etiologies.[1-3]

EPIDEMIC DIARRHEA IN NEWBORN NURSERIES

Epidemic infantile diarrhea has long been recognized as a potentially serious problem that occurs in newborn nurseries. The mortality rate for epidemics of this disease can reach levels as high as 24% to 50%.[9,10] The unusual susceptibility of newborns to this syndrome may be explained by their unique host status. Most neonates have not acquired a normal intestinal flora or specific immunity. In infants in special care nurseries, this situation is compounded by severe underlying conditions, such as prematurity or congenital cardiac or pulmonary disease. The consequences of diarrhea in the newborn are unusually severe, partially because they have poorly developed homeostatic mechanisms with limited water and electrolyte reserves. Nosocomial transmission often occurs because the newborn nurseries may be crowded with susceptible infants.[11] In addition, delays in recognizing a nursery outbreak may occur because infants may not develop diarrhea until after they have been discharged from the hospital.

The onset of this form of acute gastroenteritis is often insidious, with the development of listlessness, irritability, and poor feeding over a period of 3 to 6 days.[10,12,13] Vomiting and fever are infrequent, and the stools tend to be watery, yellow-green in color, and usually without mucus, pus, or blood. Early signs, such as failure to gain weight or a slight weight loss and abdominal distention, may be subtle. The disease may progress to more severe signs of dehydration and shock with depressed sensorium, drowsiness, coma, sunken eyes, circumoral cyanosis, and grayish discoloration of the skin. Shock without hyperpnea often occurs in this setting despite the development of severe acidosis. Poorly nourished infants may develop severe hypokalemia, hyponatremic dehydration, and/or paradoxic edema. Although this illness can be quite severe during outbreaks, some studies have also reported a milder form of this illness with much lower morbidity and mortality.[14,15]

The typical illness usually lasts 5 to 15 days, but persistence or relapse may occur over the course of several weeks after the initial onset of symptoms. Early and late onset of complications may include otitis media, pneumonia, bacteremia, peritonitis, and renal vein or

KEYWORDS

bacterial overgrowth; cholera; colitis; diarrhea; epidemic; *E. coli*; *Escherichia coli*; gastroenteritis; HIV infection; Norwalk; nosocomial diarrhea; rotavirus; traveler's diarrhea; winter vomiting disease

cerebral sinus thrombosis. Several potentially life-threatening processes may mimic this infantile diarrhea syndrome. So-called parenteral diarrhea refers to the well-recognized but poorly understood tendency for systemic infections or localized infections elsewhere (e.g., otitis, meningitis) to be manifested clinically with diarrhea. Likewise, a strangulated hernia, intussusception, or torsion of an ovary or testis may be manifested by abdominal pain or diarrhea.

Appropriate antibiotic therapy must be tailored to the specific sensitivity pattern of the organism isolated.[14] If systemic infection is suspected, parenteral therapy should be started and should be tailored to the antibiotic sensitivity pattern of the organism isolated. Appropriate preventive measures include formation of cohorts of nursery admissions, avoidance of overcrowding in nurseries, use of individual units and equipment, careful formula preparation, isolation of infants with diarrhea, and careful hand washing by hospital personnel.

Epidemic diarrhea among hospitalized newborns has been commonly associated with certain enteropathogenic serotypes of *Escherichia coli* (EPEC). In many areas, such as South Africa and southern Brazil, EPEC organisms are also among the most common causes of sporadic diarrhea in infants and young children, especially during the summer months.[16-18] Up to 20% of cases of endemic childhood diarrheal illness, even in temperate, more developed areas of the world, such as England and Canada, are also known to be caused by EPEC organisms.[16,17]

The association of a certain strain of *E. coli* with infantile diarrhea was first demonstrated by slide agglutination by Bray and Beavan[19] in 1945 and reported in further detail in 1948. They identified serologically homogeneous *E. coli* organisms in most infants with summer diarrhea (87.5%, compared with 4% of the control subjects); half of the cases were hospital acquired. Varela and associates[20] and Olarte and Varela[21] subsequently found this strain (called *E. coli–gomez* by Varela and associates[20]) in patients with infantile diarrhea in Mexico. A second serotype, initially designated as β to distinguish it from the earlier serotype called α, was described by Giles and Sangster[22] as the cause of an outbreak of infantile gastroenteritis in Aberdeen.

E. coli strains are classified into a large number of serotypes on the basis of three major types of antigens: the "O" or heat-stable somatic antigen (lipopolysaccharide endotoxin), which forms the basis for 169 serogroups; an outer, heat-labile capsular antigen called "K," which may inhibit O agglutination; and, for motile organisms, the "H" or flagellar antigen, which is also heat labile. Three different kinds of K antigens have been identified: L, A, and B. The B type is of importance in the identification of EPEC serotypes. The originally named α and β serotypes of *E. coli* were later found to be associated with several outbreaks of infantile epidemic gastroenteritis and were classified as serotypes O111-B4 and O55-B5, respectively, by Kaufmann and Dupont.[23]

Excluding certain invasive serotypes (see Table 101-2 in Chapter 101), there are 14 classically recognized EPEC *E. coli* serotypes, including O111-K58 (α), O55-K59 (β), O127-K63, O128-K67, O26-B6, O86-K61, O119-K69, O125-K70, O126-K71, O20-B7, and O44-K74 (Table 100-1). Additional serotypes recognized as causes of epidemic infantile diarrhea include O114,[9,24,25] O142,[11,26] and O158.[27] The mechanism by which most EPEC organisms cause disease involves a complex set of attachment and effacement traits, as detailed in Chapter 98. Although most are not invasive and do not produce conventionally recognized heat-labile or heat-stable enterotoxins, these organisms are capable of causing diarrheal disease in human volunteers, from whom the organism can be reisolated and in whom an antibody response can be documented.[12,28]

In addition to EPEC organisms, certain enterohemorrhagic (EHEC) and enterotoxigenic (ETEC) strains of *E. coli* have also been recognized as causes of outbreaks of diarrhea in infants. *E. coli* O157-H7 and other EHEC strains have been associated with a syndrome of hemorrhagic diarrhea with only minimal inflammation and mild severity. Most EHEC organisms secrete a Shiga-like toxin, and certain strains of EHEC have also been associated with outbreaks and sporadic cases of hemorrhagic diarrhea that are more severe and can include a form of the hemolytic-uremic syndrome.[29-33]

Certain serotypes of *E. coli* are identified more often as ETEC isolates than other serotypes (Table 100-2).[34,35] The reason for this association is not entirely clear. These *E. coli* serotypes may be better candidates for developing into ETEC strains because they are permissive recipients for enterotoxin plasmids or possibly are simply better adapted to maintaining these plasmids over time.

Enterotoxigenic serotypes of *E. coli* are not the only strains of bacterial organisms that are recognized as causes of epidemic infantile diarrhea. For example, an outbreak of diarrheal illness was described in which multiple serotypes of different organisms (*E. coli, Klebsiella,* and *Citrobacter*) were found to be transiently enterotoxigenic.[36] This observation suggests the transmission of enterotoxigenic potential between susceptible strains, likely by certain plasmids[37] or by bacteriophages.[38] Another report of sporadic diarrhea among infants and children in Africa showed that several enteric organisms other than *E. coli* may produce an enterotoxin under certain conditions.[39] This finding is relevant to other situations as well, as typified by an outbreak of watery diarrhea occurring on a cruise ship and found to be caused by enterotoxigenic strains of *E. coli*, as well as *Klebsiella* spp. and *Citrobacter* spp.[40] Many other well-known bacterial causes of diarrhea, such as shigellosis[41] and epidemic salmonellosis, may also spread readily in the newborn nursery setting.[42,43] Viral causes of epidemic infantile diarrhea include, but are not limited to, specific types of echoviruses,[44] coxsackieviruses,[45] adenoviruses,[46] and rotaviruses.[47-52] For example, echovirus 18 was isolated from 10 of 12 infants who had watery noninflammatory diarrhea in a nursery for premature infants. The virus was also isolated from two nurses, one of whom was implicated in the spread of the agent to five babies in another ward.[44] Hospital

TABLE 100-1 Enteropathogenic and Enterohemorrhagic *Escherichia coli* Serotypes Classically Recognized in Infantile Diarrhea Outbreaks*

SEROTYPE	DIFCO SEROGROUP	REFERENCES
Class I (EAF-Positive) EPEC		
O55-K59(B5):H⁻/6/7	A	22, 23, 34
O111ab-K58(B4):H⁻/5/12	A	19-21, 23, 34
O127a-K63(B8):H6	A	34
O119-K69(B14)	B	34
O125ac-K70(B15):H21	B	34
O126-K71(B10):H⁻/H2	B	34
O128ab-K67(B12)	B	34
O142		11, 26, 34
O158		27, 34
Class II (EAF-Negative) EPEC		
O44-K74	C	34
O114		9, 22, 23, 25
O86a-K61(B7)	B	34
O157-H7		29-31
O26-B6	A	34

*See also Table 100-2.
EAF, enteroadherence factor probe for focal HEp-2 cell adherence plasmid pMAR2; EPEC, enteropathogenic *E. coli*.

TABLE 100-2 Serotypes of *Escherichia coli* That Appear with Increased Frequency among Enterotoxigenic Isolates

LT *E. coli*	ST *E. coli*
O6-K15:H16	O78-H11, O78-H12
O8-K40:H9, O8-K25:H9	O115-H40
LT + ST *E. coli*	O128-H7
O11-H27	O148-H28
O20-H⁻, O20:H11	O153
O25-K7:H42	O159-H20
O25-K98:H⁻	O166, O167
O27-H7	
O63-H12	
O80, O85, O139	

LT, heat-labile enterotoxin; ST, heat-stable enterotoxin.

acquisition of rotaviruses is common among newborns, and clinical syndromes range from asymptomatic or mild disease to a moderately severe epidemic type of outbreak.[53] In addition to being clearly implicated as a potential cause of epidemic outbreaks of nosocomial neonatal diarrhea,[50-52] rotaviruses can also be the cause of cases of sporadic infantile diarrhea occurring after the neonatal period.

WEANLING DIARRHEA

Weanling diarrhea usually occurs in the second year of life in areas of the world where sanitation is poor and remains a major cause of infant mortality worldwide. The highest attack rate of diarrhea in the community occurs at the time of weaning, usually between 6 and 24 months of age.[10,11,54,55] The increased susceptibility of a recently weaned infant is related to several factors.[56] In developing countries, weaning foods are often prepared under conditions of poor hygiene and are frequently found to be contaminated with large numbers of potential diarrheal pathogens.[57,58] A second contributing factor is the poor nutritional status that may occur with weaning in many parts of the world.[59,60] Finally, cellular and humoral factors passively transferred in human breast milk appear to convey a level of resistance to some of the pathogenic organisms known to cause diarrhea in this age group and setting.[61-65]

Weanling diarrhea manifests clinically as an acute, sporadic, watery diarrheal illness. It occurs with increased frequency in areas of the world with poor sanitation, often peaking in the summer months. In the well-nourished infant, the disease is usually short lived and resolves within 2 to 3 days with adequate hydration.[55,66] Diarrhea in the malnourished child tends to persist or to recur and is often much more severe.

Weanling diarrhea is usually an acute, noninflammatory process and has been most commonly associated with rotaviruses[66-68] and with enterotoxigenic *E. coli*.[39,69,70] A smaller number of cases may be caused by certain *Shigella* spp. Human colostrum contains antibody directed against the heat-labile enterotoxin (LT) of *E. coli*.[61,62] The demonstration that immune bovine colostrum provides passive protection against experimental enterotoxigenic *E. coli* infections in human volunteers further documents the potential protective role of passive antibody in colostrum or milk.[71] The role of enterotoxigenic *E. coli* in causing infantile diarrhea in temperate climates is less clear, and isolation of ETEC serotypes from toddlers and children with diarrhea is uncommon.[72-74] Certain strains of *Klebsiella, Citrobacter,* and *Aeromonas* produce an LT-like toxin and may cause a small percentage of diarrheal disease occurring in toddlers and young children.[75] Diarrhea produced by LT shares the adenylate cyclase–activating mechanism with cholera toxin.[76-80]

DIARRHEA CAUSED BY ROTAVIRUS

The most common cause of severe diarrhea in infants and young children is gastroenteritis caused by rotaviruses (see Chapter 152).[48,49,81-83] Worldwide, rotaviruses cause more than 100 million cases of gastroenteritis and up to 600,000 deaths each year in children younger than 5 years, with most cases occurring in children aged 6 to 24 months.[49,84] Of these rotavirus-induced deaths, more than 80% occur among children residing in the poorest areas of the world. Few deaths in the United States are attributable to rotavirus infection; however, almost every American child has been infected by the age of 5 years, and rotavirus-induced gastroenteritis causes about 400,000 physician encounters, almost 300,000 emergency department visits, and about 75,000 hospitalizations in the United States each year.[85] The annual direct and indirect health care costs associated with rotavirus gastroenteritis are estimated to be about 1 billion dollars for the United States alone.

Although most adults have demonstrable antibody to rotaviruses that may protect against symptomatic disease, children younger than 2 years throughout temperate and tropical climates appear to be highly susceptible to rotavirus diarrhea,[49] which occurs most frequently in the winter or in cooler, dry months[66,67,72,86-92] and occasionally in the summer months.[93] A high level of viral shedding and infection is common among household residents where the index case occurs .The illness is usually mild, without fever, and is often associated with vomiting; however, clinical syndromes range from asymptomatic carriage to severe gastroenteritis with profound dehydration, shock, and even death.* Serious complications of rotavirus gastroenteritis include necrotizing enterocolitis in neonates.[95-97]

Most severe cases of rotavirus gastroenteritis occur in young children residing in underdeveloped and emerging countries.[83,85,95] Even in the United States, however, severe and fatal cases of gastroenteritis caused by rotavirus can occur, especially in more severely immunocompromised children and adults.

The human rotaviruses are nonenveloped RNA viruses of approximately 70 nm, belonging to the Reoviridae family.[85,98-100] Five major serotypes, A through E, have been described for rotavirus strains, with group A strains further subdivided based on the combination of G (the VP7 glycoprotein) and P (the VP4 protease-cleaved protein) types.[81,85,98,99-103] Worldwide, five serotypes (G1 through G4 and G9) predominate.† In the United States, six rotavirus strains are most commonly found (the numbers in brackets indicate the genotype): P1A[8]G1, P1B[4]G2, P1A[8]G3, P1A[8]G4, P1A[8]G4, P1A[8]G9, and P1A[6]G9.[96,100-104a]

Although rotavirus infection is essentially ubiquitous in young children, and subclinical infections remain common in adults, large symptomatic outbreaks of moderately severe diarrhea occur regularly as well. Outbreaks, although geographically distinct, are often caused by the same rotavirus strain. A particular strain, P1B[4]G2, is associated with a more severe form of infection in children than other more common serotypes.[105,106] Such epidemiologic information was important in designing effective rotavirus vaccines for humans.

The clinical diagnosis of rotavirus diarrhea is established with the use of a variety of molecular assays designed to detect virus-specific antigens, antibodies, or nucleic acids in feces of infected patients.[107-110] Rotaviruses can also be cultured directly from stool samples, although this method is time-consuming, expensive, and limited primarily to research-based laboratories.

The major rotavirus-mediated effects on the host intestinal tract include disruption of epithelial cell brush-border enzyme activities, cytotoxic changes, and alteration of the enteral nervous system.[81,82,111-113] Normal columnar epithelium at the villus tips is replaced by irregular cuboidal, cryptlike cells, leading to multiple defects in fluid and electrolyte regulation in the affected intestinal mucosa. The degree of microvillus damage roughly parallels the severity of diarrhea and dehydration that is observed in the patient.[114]

The loss of absorptive villus tip cells may be responsible for the fluid imbalance and nutritional impact of rotaviral infections. Many of these effects are believed to be mediated by a calcium ion–dependent enterotoxin. Certain patients with rotavirus gastroenteritis also exhibit extraintestinal symptoms in association with detectable antigenemia and viremia, supporting a systemic phase to this infection.[115-118]

Therapy for rotavirus gastroenteritis is primarily supportive, directed first at the immediate restoration of fluid balance, by intravenous or oral glucose-electrolyte therapy, and subsequent restoration of the patient's nutritional state to normal. No definitive antiviral therapy is established for rotavirus infection; however, the antiparasitic drug nitazoxanide was shown, in randomized, controlled studies, to shorten the duration of illness in children and adults with symptomatic rotavirus diarrhea.[119,120]

Prevention is the key to controlling the occurrence and escalation of rotavirus epidemics. Reasonable preventive measures include provision of improved sanitation facilities and safe water supplies and efforts to develop protective antibacterial, antitoxic, or antiviral immunity.[121] Because of the great global burden of childhood rotavirus gastroenteritis, significant multinational efforts have been directed toward the development of a safe and effective rotavirus vaccine.

The first rotavirus vaccine approved for use in the United States was the rhesus-human reassortant rotavirus tetravalent vaccine (RRV-TV; Rotashield, Wyeth-Lederle, Madison, NJ). It was approved and released in August 1998 for use in infants. Less than 1 year later, the vaccine was removed from use because of concerns about possible association of vaccine use with cases of intussusception in infants. The significance of the RRV-TV association with intussusception has been extensively examined, although no consensus was reached as to the nature of

*References 48, 66, 67, 81, 85, 94.
†References 81, 85, 98, 99, 101, 104.

the relationship of vaccine use to development of this particular complication.[122,123]

Since the withdrawal of the RRV-TV, two new rotavirus vaccines have become licensed and approved for use in the United States.[85,99,124,125] A live oral pentavalent rotavirus vaccine (PRV; RotaTeq, Merck Vaccines, Whitehouse Station, NJ), comprising bovine-human recombinant strains, was licensed for universal use in infants in 2006.[85,124-126] This vaccine is also approved for use in Europe. It is administered in a three-dose schedule, starting between 6 and 14 weeks of age, and appears to be highly efficacious in preventing primary infection. Prelicensing and postlicensing data suggest no significant increased risk of intestinal intussusception at this time, although surveillance continues.

A monovalent human rotavirus vaccine (HRV; RotaRix, GlaxoSmithKline, London), derived from an attenuated P1A[8]G1 rotavirus strain, was approved for use in the United States in 2008,[85,124-128] having previously been licensed in more than 30 other countries worldwide. HRV is also indicated for universal use in infants; however, this vaccine requires a schedule of only two doses. Efficacy and side effects appear to be similar to those of PRV. There may be a risk of transmission from vaccine recipients to immunocompromised household contacts. Although immunocompromised infants and children are at risk for severe complications from natural rotavirus infection, no efficacy or safety data are available for PRV or HRV in these high-risk populations.[100,129]

ACUTE NAUSEA AND VOMITING (WINTER VOMITING DISEASE)

The syndrome of acute nausea and vomiting, "intestinal flu," "viral gastroenteritis," or "winter vomiting disease" commonly occurs in winter months in temperate climates.[130,131] Although there is some overlap of this syndrome with rotavirus-associated infantile gastroenteritis, rotaviruses appear to be a relatively uncommon cause of winter vomiting disease in older children and adults. The Cleveland family studies of Dingle and co-workers[132] showed that enteritis was second only to upper respiratory infection as a cause of illness in homes. Gastrointestinal illnesses were most common between the ages of 1 and 10 years, when approximately two illnesses occurred per person per year. The peak season for these gastrointestinal illnesses was November through February, with June being the month of lowest frequency. Most illnesses lasted 1 to 3 days; 20% occurred with respiratory symptoms, and 20% involved only diarrhea.

Illnesses tended to occur in one of two patterns: (1) a mild afebrile illness with watery diarrhea or (2) a more severe febrile illness with vomiting, headache, and constitutional symptoms. Although etiologic agents were rarely identified, these two patterns of illness subsequently developed among volunteers who ingested filtrates prepared from the feces of ill patients.[133-135] Studies done in Charlottesville, Virginia, confirmed this pattern of wintertime gastroenteritis, including clustering in families, highest attack rates in children, and absence of identifiable etiologic agents in most cases despite the application of techniques for virologic and enterotoxin studies.[73,74] More recently, certain caliciviruses have been commonly implicated in many epidemic and sporadic cases of winter gastroenteritis.

The Caliciviridae family comprises four genera[136,137]: *Norovirus, Sapovirus, Lagovirus*, and *Vesivirus.* Viruses belonging to *Norovirus* (from *Nor*walk) and *Sapovirus* (from *Sap*poro) genera are now known to be some of the most common and most important causative agents for viral gastroenteritis in humans.[136-140] Noroviruses, in particular, have emerged as major causes of outbreaks of acute viral gastroenteritis, especially in older children and adults (see Chapter 178). Previously, these viruses were often referred to as Norwalk-like viruses. Their individual names were originally derived from the site of origin of each particular outbreak and included Norwalk,[141-143] Hawaii,[144] Snow Mountain,[145] Taunton, and W agents.[146] These noroviruses cause illness throughout the year, and symptoms typically consist of low-grade fever in association with varying combinations of nausea, vomiting, abdominal cramps, and diarrhea.[136-138] Person-to-person spread is common, and secondary attack rates can be high.

These viruses affect the general population worldwide, and illness outbreaks caused by noroviruses have been observed in a wide variety of settings,[147,148] including hospitals,[149] extended-care facilities,[150] child care centers,[151] cruise ships,[152] refugee centers associated with natural disasters (e.g., Hurricane Katrina[153]), and military combat arenas, including Afghanistan[154] and Iraq.[155] Several genotypes are known to infect humans[138,147,148]; in recent years, newly identified variant strains of norovirus genotype GII.4 have caused outbreaks worldwide,[156-158] including areas of the United States, United Kingdom, Europe, New Zealand, and Australia.

TABLE 100-3 Viral Pathogens Causing Gastroenteritis

ESTABLISHED PATHOGENS	LIKELY AND EMERGING PATHOGENS
Adenoviruses (enteric types)	Coronaviruses
Astroviruses	Enteroviruses (various)
Caliciviruses (including noroviruses and sapoviruses)	Picobirnaviruses, picornaviruses
Rotaviruses groups A-C	Pestiviruses
Cytomegalovirus	Toroviruses

Data from references 46-48, 96, 107, 139, 140, 147, 151, 163, 165 and 169.

The pathophysiologic features of winter vomiting disease caused by noroviruses parallels, in several respects, the features mentioned earlier regarding rotaviruses.[136-138,148] Each type is noninflammatory in nature and observed to cause mucosal villus disruption and transient brush-border enzyme deficiencies in the upper portion of the small bowel, without any alteration in adenylate cyclase activity.[101,159,160] The roles of transient enzyme deficiency, malabsorption of xylose and lactose, and the slight increase in the number of bacteria present during the norovirus illness remain unclear.[159,161]

Several other groups of viral pathogens have been identified in endemic and epidemic cases of gastroenteritis (Table 100-3)[48,107,162-164]: (1) other types of caliciviruses with characteristic, "chalice-like" surface hollows (including agents described in the United States, United Kingdom, Europe, and Japan); (2) astroviruses, with a five- or six-pointed starlike surface structure (including Marin County,[165] UK1-5, and Japan agents); and (3) other miscellaneous or less well-characterized viral agents. Other viral agents, including enteroviruses, enteric adenoviruses,[166] human coronaviruses,[167,168] pestiviruses,[169] toroviruses,[170,171] and picobirnaviruses,[172] are becoming better recognized as pathogens in children and adults; more detailed discussions of these agents may be found in Chapters 145, 152, 153, 174, 178, and 179.

More than one third of the outbreaks of nonbacterial gastroenteritis in the United States have been associated with noroviruses.[173,174] Astroviruses have been found to be among the most common causes of viral gastroenteritis in the pediatric age group.[175-178] Infection with astrovirus occasionally occurs in association with other enteric pathogens; in these cases, the illness is more severe and protracted.[177] Nucleic acid–based assays (e.g., reverse-transcriptase polymerase chain reaction [RT-PCR]) of stool specimens are the standard method of detection of these viruses, especially during outbreak investigation. In the typical clinical situation, however, norovirus-specific diagnostic tests are rarely performed because results of this assay do not alter management of the illness.

ACUTE NONINFLAMMATORY DIARRHEA IN ADULTS

In temperate climates, acute noninflammatory diarrhea in adults may be caused by noroviruses[138,142,148,158,179-181] or other less commonly implicated viruses, such as rotaviruses,[100,179,181] adenoviruses, or coxsackieviruses, In addition, several agents of food poisoning, such as *Clostridium perfringens, Bacillus cereus*, and *Staphylococcus aureus*, commonly cause noninflammatory diarrheal syndromes in adults (see Chapter 103).

In adults living in areas of the world with poor sanitation, several other pathogenic agents are known to cause sporadic noninflammatory diarrhea, but none has had as much historical impact or notoriety as that of *Vibrio cholerae,* causing cholera.[182,183] In certain areas in South Asia, cholera is an endemic cause of severe watery diarrhea. With the

increased infection-to-case ratio of El Tor cholera, the seventh pandemic swept most of the continents of the Eastern Hemisphere, including Asia, Africa, and the Mediterranean portions of Europe.[184] Isolated cases have also occurred in the United States.[185,186] Outbreaks have been related to contaminated mineral water[187] and to undercooked shellfish.[188,189] Beginning in Madras, India, in late 1992 and rapidly spreading to Calcutta and Bangladesh in 1993, a new strain of non-O1 *Vibrio cholerae*—O139, called Bengal—is causing epidemic cholera gravis and may represent the beginning of an eighth pandemic.[190-194] Severe, watery diarrhea in a patient residing in, or having recently traveled to, an endemic area should raise the suspicion of cholera. The disease can be so fulminant as to cause hypovolemic shock and death from the outpouring of fluid into the upper portion of the small bowel before the first diarrheal stool occurs.[195] As discussed in detail in Chapter 216, the entire dehydrating syndrome of cholera appears to be related to the activation of intestinal adenylate cyclase by the potent cholera enterotoxin.[76,77,196,197] To make the diagnosis of cholera bacteriologically, stool specimens should be cultured onto thiosulfate citrate bile salts–sucrose agar. Of prime importance in therapy is fluid replacement, accomplished either intravenously with isotonic fluids or orally with glucose-electrolyte solutions.

Patients from whom *V. cholerae* cannot be isolated may have a cholera-like syndrome caused by certain strains of ETEC. In 1956, De and associates[198] demonstrated that *E. coli* isolated from adults and children with this syndrome caused fluid accumulation similar to that seen with *V. cholerae* infection in ligated rabbit ileal loops. In the early 1960s, Trabulsi,[199] working in São Paulo, reported similar findings with "toxigenic" *E. coli.* Since then, a variety of investigators have shown that many cases of "acute undifferentiated diarrhea" in adults were caused by enterotoxigenic *E. coli* strains that usually were not of the classically recognized pathogenic serotypes.[200-203] The toxic material present in the culture filtrate of these *E. coli* strains was demonstrated to be heat labile and nondialyzable. Subsequent studies demonstrated two types of enterotoxin produced by ETEC, namely LT and heat-stable enterotoxin (ST).[204] Like cholera toxin, the *E. coli* LT activates mucosal adenylate cyclase.[60-62] and is antigenically and mechanistically similar to cholera toxin in many ways. In contrast, ST activates guanylate cyclase,[205-207] has an earlier onset of action,[204] has greater tissue specificity,[207] and has a much lower molecular weight than LT.[208] I The role of yet a different type of enterotoxin, STb, which causes secretion in piglets without altering intestinal cyclic adenosine monophosphate or cyclic guanosine monophosphate remains unclear in humans at present.[209-211]

Several studies have shown that ETEC strains producing LT only, ST only, and/or LT plus ST can be associated with episodes of diarrhea in adults (see Table 100-2).[6] Adults living in areas of poor sanitation may often carry LT-producing *E. coli* asymptomatically.[212,213] In contrast, ST-producing *E. coli* strains are significantly associated with diarrheal disease and are less frequently present in asymptomatic control patients living in similar areas. In the United States and other developed countries, however, these particular enterotoxigenic *E. coli* serotypes are an uncommon cause of diarrhea.[72,73]

Another cause of acute, noninflammatory, and self-limited diarrhea is *Cryptosporidium.* The disease cryptosporidiosis occurs most commonly among persons exposed to infected animals, food, drinking or recreational water, or other infected patients.[214-219] Of the more than 20 species of this tiny coccidian intracellular protozoal parasite, two in particular, *Cryptosporidium parvum* and *Cryptosporidium hominis*, appear to cause the majority of clinical disease in humans.[218-222] Cryptosporidiosis is commonly asymptomatic or mild in normal hosts and usually results from waterborne outbreaks, often related to contaminated drinking water or public swimming pools.[218-222] However, this infection can be severe in immunocompromised hosts, especially in individuals with advanced human immunodeficiency virus (HIV) infection.[214,216-219,223,224] Young children in underdeveloped regions of the world also can develop a persistent diarrhea syndrome that can contribute to the development of significant malnutrition.

Cryptosporidium causes a secretory form of diarrhea that can be associated with dysregulated intestinal absorption. In addition to gastroenteritis, biliary infection with cholangitis also has been reported in some patients. The pathogenesis of cryptosporidiosis is incompletely understood; the organism primarily alters villus structure and function.[219,225,226] No specific enterotoxin has been identified. Diagnosis depends on identification of the organism in stool specimens by standard light microscopy, immunofluorescence assays, or nucleic acid–based molecular tests.[222,227-229] In addition to supportive care, the antiparasitic agent nitazoxanide has been shown to be moderately successful in a variety of patients with cryptosporidiosis. Many experts recommend a prolonged trial of nitazoxanide for these patients, even though the data are not conclusive to universally recommend extended duration of therapy.[230,231,232-234] Alternative therapeutic agents for immunosuppressed patients include combinations of paromomycin and azithromycin.

TREATMENT OF ACUTE NONINFLAMMATORY DIARRHEA

Treatment of diarrhea from any cause in adults and children consists primarily of rehydration.[235] If glucose or sucrose accompanies the isotonic fluid taken orally, the coupled absorption of sodium and water is often sufficient to replace fluid loss.[236] Bismuth subsalicylate (Pepto-Bismol) may reduce enterotoxin action,[237] and, if there is no significant febrile or inflammatory process, low doses of antimotility agents may offer some relief with minimal risk. Some studies also suggest that novel analogues of glutamine may be beneficial in reducing the severity and extent of symptoms associated with certain forms of infectious diarrhea.[238] The potential utility of probiotic compounds for the treatment of various forms of diarrhea has also garnered attention. The current data are not sufficient to issue a general recommendation on the use of probiotics for the management of infectious diarrhea, although these agents may provide benefit as an adjunct to standard therapy in selected cases (see Chapter 3).[239-244]

There is an emerging interest in analyzing the roles of various micronutrients in the management of diarrheal disease, especially in young children residing in underdeveloped areas.[244,245] Several agents have been examined, but the strongest support has emerged relating to zinc supplementation. Several randomized, controlled international studies as well as a Cochrane Database Review found a beneficial effect of oral zinc supplementation in the prevention and management of a variety of infectious forms of diarrhea, especially in children (see Chapter 50).[246-249]

DIARRHEA IN HIV-INFECTED PATIENTS

Patients with HIV infection often develop or present with diarrhea. In countries where antiretroviral therapy (ART) is widely available, the incidence of infectious diarrheal episodes among HIV-infected patients has decreased markedly in recent years.[250,251] However, among HIV-infected patients in the United States meeting criteria for acquired immunodeficiency syndrome (AIDS), 30% to 60% present with diarrhea,[211,214,251-257] and this figure can reach 95% in tropical developing areas such as Africa or Haiti.[256] In many patients with advanced HIV infection and immunocompromise, diarrhea becomes prolonged, causes severe malnutrition, predisposes to other types of serious infections, and can be life threatening. In addition, the symptomatic management of chronic diarrhea in such patients poses major difficulties. The importance of the interactions of HIV with the components of intestinal immune system in modulating systemic HIV infection has come to light in recent years.[258,259]

Although some investigators have reported an enteropathy without identifiable infectious pathogens[260,261] or with primary HIV infection of enterochromaffin cells in the bowel mucosal crypts and lamina propria,[262] others have reported one or more enteric pathogens in 55% to 85% of patients with AIDS and diarrhea.[257,263,264] Sexually promiscuous homosexual men often become infected with *Giardia lamblia, Entamoeba histolytica, Campylobacter jejuni, Shigella, Chlamydia trachomatis, Clostridium difficile*, or (with proctitis) *Neisseria gonorrhoeae*, herpes simplex virus, or *Treponema pallidum.*[265] As shown in Table 100-4, the leading agents found in patients with AIDS and diarrhea are cytomegalovirus, *Cryptosporidium*, microsporidia, *E. histolytica, G. lamblia, Salmonella, Campylobacter, Shigella, C. difficile, Vibrio parahaemolyticus*, and *Mycobacterium* spp.[263,264,266-268] *Cyclospora* and *Cystoisospora belli* infections are also potentially treatable causes

TABLE 100-4 Possible Enteric Pathogens in Patients with Acquired Immunodeficiency Syndrome

PATHOGEN	% WITH DIARRHEA (*n* = 181)	% WITH NO DIARRHEA (*n* = 28)
Cytomegalovirus	12-45	15
Cryptosporidium	14-30	0
Microsporidia	7.5-33	0
Entamoeba histolytica	0-15	0
Giardia lamblia	2-15	5
Salmonella spp.	0-15	0
Campylobacter spp.	2-11	8
Shigella spp.	5-10	0
Clostridium difficile toxin	6-7	0
Vibrio parahaemolyticus	4	0
Mycobacterium spp.	2-25	0
Cystoisospora belli	2-6	0
Cyclospora	0-11	0
Blastocystis hominis	2-15	16
Candida albicans	6-53	24
Herpes simplex	5-18	40
Chamydia trachomatis	11	13
Strongyloides	0-6	0
Intestinal spirochetes	11	11
One or more pathogens	55-86	39

Data from references 263-274 and 276-285.

of persistent diarrhea in patients with AIDS, especially in tropical areas such as Haiti.[257,269-271] Even *Pneumocystis jirovecii* infection can occasionally involve the intestinal tract.[272]

Although eradicative treatment may be difficult, most of these patients respond to specific antimicrobial or antiparasitic therapy, emphasizing the need to identify the etiologic agent in these infections whenever possible.[234,235] The antiviral agent ganciclovir often effectively controls intestinal cytomegalovirus infection,[273,274] and most bacterial and parasitic infections can be treated with the expectation of some improvement. *Cryptosporidium*, which infects 3% to 21% of patients with AIDS in the United States, can be found in as many as 50% of patients with AIDS and diarrhea in Africa and Haiti.[214-217,256] *Cryptosporidium-mediated* biliary infection occurs in this patient population as well. Similarly, certain microsporidia organisms, such as *Encephalitozoon intestinalis* or *Enterocytozoon bieneusi*, can cause persistent and severe diarrhea in HIV-infected individuals.

The same acid-fast stain that detects *Cryptosporidium* or *Mycobacterium* in fecal specimens may also reveal *C. belli* and *Cyclospora* in approximately 2% of AIDS patients with diarrhea in the United States and in 15% of those in Africa.[256,257,270,271,275] *Cryptosporidium* and microsporidial infections are associated with villus atrophy, crypt hyperplasia, increased intraepithelial lymphocytes, and D-xylose malabsorption.[266] Nontyphoidal *Salmonella* infections occur with an estimated 20-fold increase in frequency and with increased severity in patients with AIDS.[276-279] Enteric viruses have also emerged as significant potential pathogens associated with diarrhea in HIV-infected individuals. In one study, astrovirus, picobirnavirus, calicivirus, and adenovirus were found in 6% to 12% of HIV-positive patients with diarrhea.[280] Other common enteric infections include esophagitis or stomatitis with *Candida* or herpes simplex virus. In addition, many of the current HIV antiretroviral medications commonly cause diarrhea, often compounding the complexity of the diagnostic workup of the HIV-infected patient with persistent diarrhea.[281,282]

Several practical algorithmic approaches to the diagnosis and management of diarrhea in HIV-infected patients have been published.[253,254,257] These strategies favor the use of early, noninvasive stool studies and practical empirical treatment trials, followed by more invasive tests (e.g., endoscopy with biopsy) for patients with refractory or more severe presentations. ART has decreased the incidence of several important opportunistic infections, including certain causes of gastroenteritis. Of particular note, there has been a dramatic decline in the incidence of tissue-invasive infections caused by cytomegalovirus, including luminal gastrointestinal disease.[274,283,284] The treatment regimens available for many organisms causing infectious gastroenteritis in HIV-infected patients are less than satisfactory, but significant advances continue to be made. In addition to developing more effective treatments, an effort to judiciously adhere to safe food and water guidelines in higher-risk patients can provide significant help in preventing many types of serious enteric infections.[285]

DIARRHEA IN INSTITUTIONS

Institutions provide special host and environmental settings that promote the acquisition of certain enteric pathogens. As with diarrhea in patients with AIDS and traveler's diarrhea, many cases of institution-acquired diarrhea are noninflammatory. However, an increased frequency of *C. difficile*–associated disease (CDAD) should prompt stool immunoasssay or PCR assaying for the presence of *C. difficile* toxins.[286]

Hospitals

Nosocomial diarrhea is among the most common nosocomial outbreaks reported to the Centers for Disease Control and Prevention.[287] However, its frequency is often overlooked, and it has been suggested to be the most common nosocomial infection in some areas.[288] Nosocomial diarrhea appears to be a significant factor predisposing to other nosocomial infections, such as urinary tract infections.[289] Overall rates range from 2.3 to 4.1 illnesses per 100 admissions on pediatric wards[288,290] and from 7.7 per 100 admissions to 41% of adults hospitalized in intensive care units.[288,291]

C. difficile remains the most common, most serious, and most costly infectious cause of nosocomial diarrhea in hospitalized patients.[292-294] In particular, CDAD is an important emerging nosocomial infection worldwide, especially among elderly hospitalized patients and patients occupying beds in surgical wards or intensive care units.[294,295-297] Most sporadic and outbreak cases of CDAD appear to be caused by exposure to contaminated environmental surfaces rather than direct contact with an index case.[298-300]

Other enteric pathogens are occasionally identified in outbreaks of nosocomial diarrhea. *Salmonella*, for example, is a common cause in reported outbreaks of nosocomial gastroenteritis.[287] *Cryptosporidium* may be associated with cases of nosocomial diarrhea involving chronically ill, elderly patients, as well as HIV-infected patients.[301] In young children and in immunocompromised hosts, viral agents (rotaviruses, adenoviruses, coxsackieviruses, and others) are often found.[290,302] In addition, there has been a newfound appreciation for the roles of certain viruses (such as rotaviruses, adenoviruses, coxsackieviruses, and others) as causes of nosocomial diarrhea, especially in neonates, children, and in patients residing in intensive care units.[303-305]

Long-term Care Facilities

Diarrheal illnesses constitute a significant problem in extended-care facilities for elderly persons. A conservative estimate based on passively reported illness rates is that one third of patients in long-term care facilities experience diarrhea each year.[306-308] CDAD remains a common and important cause of diarrhea in these facilities.[309,310] Sporadic cases as well as epidemic outbreaks of CDAD have been reported in many types of long-term care facilities. In other instances, viral causes of gastroenteritis or diarrhea have been identified in certain outbreaks occurring in these settings. The frequency of potentially transmissible enteric pathogens emphasizes the importance of careful hand washing in situations in which hygiene is often difficult.

Daycare Centers

Another special institutional setting in which hygiene is difficult and enteric infections are increasingly appreciated is daycare centers. Numerous outbreaks have been reported in association with viruses, bacteria, or parasites. The most common etiologic agents in infants and children younger than 2 years are the rotaviruses, whereas older toddlers are more likely to acquire *G. lamblia*.[311] Newer diagnostic tests, based on immunoassays and RT-PCR, have been used to detect additional agents, such as astrovirus, in many diarrhea outbreaks in daycare

centers.[312,313] A clinical syndrome of prolonged noninflammatory diarrhea may be associated with *Cryptosporidium* in daycare centers.[314-316] In addition, outbreaks of inflammatory diarrhea caused by enteric pathogens, such as *Shigella, Campylobacter*, and *C. difficile,* have also been reported.[317,318]

TRAVELER'S DIARRHEA (TURISTA)

Whether it "arouses one from bed with a start at 4 AM for a record-breaking race to the bathroom to begin a staccato ballet"[319] or produces the poetry of the psalmist ("I am poured out like water… my heart like wax is melted in the midst of my bowels"[320]), traveler's diarrhea has a major impact each year on the 300 million to 500 million international travelers and probably on the distribution of well over $100 billion in international tourism receipts.[321,322] Tens of millions of people (>10 million from the United States alone) travel from industrialized to developing countries.

Diarrhea is by far the most common and among the most disconcerting illnesses that threaten the traveler.[323-329] Many studies have focused on North Americans and northern Europeans, who appear to be the groups at greatest risk when they travel to Latin America, southern Europe, Africa, or Asia.[330-334] The global nature of the problem and some suggested causal forces are illustrated by its more euphemistic names: Delhi belly, Gyppi tummy, GIs, Rome runs, Greek gallop, Turkey trots, Montezuma's revenge, Aztec two-step, Aden gut, San Franciscitis, Basra belly, la turista, backdoor sprint, summer complaint, coeliac flux, Canary disease, passion, Hong Kong dog, Poona poohs, Casablanca crud, tourist trots, Malta dog, and many more.

Most symptoms of traveler's diarrhea begin 5 to 15 days after arrival, although a range from 3 to 31 days has been noted.[275,317,335-340] The illness is typically manifested by malaise, anorexia, and abdominal cramps, followed by the sudden onset of watery diarrhea. Nausea and vomiting accompany the illness in 10% to 25% of cases. The diarrhea is usually noninflammatory, although a low-grade fever is present in approximately one third of the cases. The duration is usually 1 to 5 days, but up to 50% of patients have an illness that continues 5 to 10 days and sometimes beyond.

The attack rate for traveler's diarrhea varies from 5% to 50%, depending on the destination as well as duration of the trip. In general, it appears that the risk of acquiring turista during travel to a tropical country from a temperate climate for 2 weeks or longer approaches 50%. Destinations with increased risk for acquiring traveler's diarrhea include portions of Africa and Asia (including India) as well as certain areas of Central and South America.[340,341] The attack rate also appears to decrease with age after 25 years, an observation that may reflect different habits and exposures rather than inherent susceptibility.[319,333] Expatriate residents living in certain countries appear to be at some level of persistent risk for diarrhea of infectious causes, for instance, an attack rate of 49% per month observed during the first 2 years of residence in Nepal.[342]

For many years, the etiology of turista was an enigma; only infrequently have parasites or bacteria, such as amebas, *Giardia, Salmonella*, or *Shigella,* been identified, and viral studies have failed to elucidate significant viral causes. The first suggestion that an infectious bacterial process was likely came from the effective reduction in the attack rate achieved by the use of prophylactic antimicrobial agents.[211,335,340,343] Studies by Kean[319] suggested that certain EPEC serotypes might be involved in up to one third of the cases. The involvement of *E. coli* was further confirmed in an outbreak of traveler's diarrhea among British troops in Aden, where *E. coli* O148 was identified in 54% of the British troops with diarrhea.[336]

Later studies demonstrated ETEC in approximately 50% (range, 20% to 75%) of cases of traveler's diarrhea in Latin America, Africa, and Asia (Table 100-5).[317,318] The attack rate ranged from 20% to 100% (median, 52% to 54%) in multiple studies reviewed (see Table 100-5).[341,344,345] *E. coli* ETEC organisms were almost never present before the travel, and such organisms were acquired by only 14 (12.6%) of 111 fellow travelers who did not become ill.[275,338,339] The type of enterotoxin produced by *E. coli* associated with traveler's diarrhea may be the LT type, the ST type, or both (Table 100-6). In some areas, enteroaggregative *E. coli* is a major cause of traveler's diarrhea (see Chapter 220).

A number of other microbial agents have also been indentified in small subsets of patients with traveler's diarrhea. *Salmonella, Shigella, Vibrio,* and *Aeromonas* spp. are present in small numbers of patients with traveler's diarrhea.[344,346] Rotavirus or calicivirus infections have been described in 0% to 36% of cases of traveler's diarrhea but were often found in association with other known bacterial or parasitic pathogens.[347] Noroviruses, in particular, have been implicated in several large outbreaks of gastroenteritis or diarrhea on large cruise ships.[348-350] In many respects, however, cruise ship–associated outbreaks of gastroenteritis share more epidemiologic characteristics with institution-associated gastroenteritis than with the classic form of traveler's diarrhea.

Intestinal protozoa are rare, but important, causes of some cases of traveler's diarrhea. Agents such as *Cryptosporidium parvum, Cyclospora cayetanensis*, and various microsporidia (*Enterocytozoon* and *Encephalitozoon* spp.) should be considered in the workup of subacute or chronic noninflammatory diarrhea in returned international travelers.[351-353] Other protozoal parasites, such as *C. belli* and *Blastocystis hominis*, can be commonly identified in the stools of persons traveling to developing countries. However, it has been difficult to ascertain whether these organisms actually cause disease in this population or

TABLE 100-5 Etiology of Traveler's Diarrhea

CHARACTERISTIC	LATIN AMERICA	AFRICA	ASIA
Duration of stay (days)	21 (2-42)	28 (28-35)	(28-42)
Attack rate (%)	52 (21-100)	54 (36-62)	(39-57)
Organism (%)			
Enterotoxigenic *Escherichia coli*	46 (28-72)	36 (31-75)	(20-34)
Shigella	0 (0-30)	0 (0-15)	(4-7)
Salmonella	—	0 (0-0)	(11-15)
Campylobacter jejuni	—	—	(2-15)
Vibrio parahaemolyticus	—	—	(1-13)
Rotavirus	23 (0-36)	0 (0-0)	—

*Values shown are the median (and range) from multiple studies.[322,345,346,386,397]

TABLE 100-6 Frequency of Enterotoxigenic *Escherichia coli* in Association with Traveler's Diarrhea in Latin America, Africa, and Asia

	REPORTED FREQUENCY (%)				
FEATURE	Gastroenterologists in Mexico[337]	Peace Corps Volunteers in Kenya[338]	Yale Glee Club in Latin America[339]	Japanese Travelers Returning to Tokyo from India, Southeast Asia, Orient[344]	Total
Illness attack rate	49% in 16 days	69% in 5 wk	74% in 1 mo	—	
Type of enterotoxin					
LT only	16	33	25	4.8	21
LT and ST	16	15	12.5	11.8	38
ST only	9.8	2	19	13.6	41
% of ill patients with ETEC	41 (21/51 cases)	52 (14/27 cases)	56 (9/16 cases)	32 (270/843 cases)	33.5

ETEC, enterotoxigenic *E. coli;* LT, heat-labile; ST, heat-stable.

are merely commensal.[354-356] Cholera is rarely a problem for U.S. travelers.[333,357] A subset of patients have persistent diarrhea for which no infectious agent can be implicated. Chronic idiopathic diarrhea, referred to as Brainerd diarrhea, has been reported to occur in a few small travel-related outbreaks.[358-361]

In contrast to the frequent identification of potential etiologic agents among travelers to tropical areas who develop diarrhea, travelers to more developed countries often develop a mild syndrome of diarrhea for which no infectious cause can be identified.[362] Travelers to certain areas, such as Russia and national parks in the United States, may be especially susceptible to development of the more insidious watery diarrhea seen with giardiasis or cryptosporidiosis.[363-366] Strongyloidiasis may also be acquired in tropical areas and may cause noninflammatory diarrhea, abdominal pain, and eosinophilia.[367]

Several other potentially serious infections manifested initially by diarrhea or abdominal pain may be acquired by travelers. Malaria may be manifested initially as "gastroenteritis" with nausea, vomiting, diarrhea, or abdominal pain in 30% to 50% of cases.[368] The physician should also remember to consider typhoid fever and other infections that may be manifested with a "typhoidal pattern," including plague, melioidosis, typhus, and arboviral hemorrhagic fevers.[368,369]

The desire to control the bothersome problem of diarrhea in travelers has led to a variety of medications used for management.[319] Commonly used remedies, such as diphenoxylate-atropine (Lomotil) and kaolin-pectin suspension, were found to have little or no efficacy in most studies.[370] Lomotil and other antimotility agents may actually worsen the illness in inflammatory processes such as shigellosis.[371] Bismuth subsalicylate was shown to inhibit enterotoxin activity in experimental animal models,[303] and it has been recommended for symptomatic therapy as well as prophylaxis.[371-373] As in any type of diarrheal illness, the mainstay of therapy continues to be adequate hydration with an oral glucose- or sucrose-electrolyte solution.

Prevention of traveler's diarrhea should be directed toward reducing the consumption of infectious agents in food and water. Foods that are handled but not cooked (e.g., salads, raw vegetables, etc.) are high-risk foods.[323-325,374] Bottled, noncarbonated water cannot be considered safe because outbreaks of cholera[187] have been traced to bottled water, and typhoid fever[375,376] to other bottled beverages. Care in eating and drinking may reduce one's risk, even in highly endemic areas, to less than 15%.[374,377,378]

The efficacy of prophylactic antimicrobial agents has been documented in several studies.[335,340,379-381] The increased risk of acquiring a more severe infection (e.g., salmonellosis),[382] the risk of drug side effects (e.g., photosensitivity in the tropics), and the emergence of drug-resistant organisms should preclude the widespread use of antibiotic prophylaxis at this time. Because treatment regimens that combine loperamide with an antibiotic are rapidly effective in controlling traveler's diarrhea (<10 hours), most experts consider prophylactic therapy only for travelers with special issues, such as those with a high risk of infection and those for whom it is important to remain disease-free during the trip.[383,384]

Empirical self-treatment of traveler's diarrhea with a fluoroquinolone, such as ciprofloxacin or levofloxacin for 1 to 3 days, can significantly reduce the duration and severity of the disease[323-325,344,385-387] (see Chapters 323 and 324). Fluoroquinolone drugs are contraindicated in pregnant women[323-325,384,386] and in children younger than 16 years. Therapy with trimethoprim-sulfamethoxazole has traditionally been suggested for children, but, because of resistance, most experts currently recommend the use of a macrolide, such as azithromycin.[323-325,388] In addition, the emergence of fluoroquinolone-resistant strains of various *Campylobacter* spp. is of special concern for travelers to many areas of the world, most notably Thailand and other parts of Southeast Asia.[389-392] Therefore, because of emerging resistance issues and recent U.S. Food and Drug Administration "black box" warnings for arthropathy associated with fluoroquinolones,[393] consideration should be given to recommending azithromycin as a first choice for empirical self-treatment of traveler's diarrhea in many individuals. A nonabsorbable relative of rifampin, known as rifaximin, is useful for treatment of less severe cases of traveler's diarrhea in the absence of fever because it is not effective for the treatment of diarrhea caused by agents such as *Salmonella*, *Shigella*, and *Campylobacter*.

DIFFERENTIAL DIAGNOSIS OF ACUTE NONINFLAMMATORY DIARRHEA

Acute noninflammatory diarrhea may be a consequence of several noninfectious processes. As with agents that effect an osmotic diuresis, nonabsorbable agents such as sorbitol may cause diarrhea if consumed in excess. Ipecac fluid extract, used by mistake instead of ipecac syrup, can cause watery diarrhea instead of vomiting. Heavy metal poisoning (with arsenic, tin, iron, cadmium, mercury, or lead) is often associated with diarrhea, probably as a result of toxic effects on the rapidly growing mucosal epithelium.

Endocrine causes of diarrhea that may share the adenylate cyclase–activating mechanism with enterotoxins include non–beta-islet cell tumors, medullary carcinoma of the thyroid, carcinoid tumors, and others that are associated with increased serum levels of prostaglandins or vasoactive intestinal polypeptide.[394] Patients with thyrotoxicosis or adrenal or parathyroid insufficiency may have diarrhea. Congenital and acquired enzyme deficiencies include lactase deficiency and pancreatic or biliary insufficiency, in which inadequately degraded or absorbed nutrients may promote an osmotic diarrhea. A child who has diarrhea and edema, hypertension, or petechiae should be suspected of having hemolytic-uremic syndrome with or without enterohemorrhagic *E. coli* O157-H7. Patients with dermatitis herpetiformis may also have diarrhea that may respond to sulfone or sulfapyridine therapy or to a gluten-free diet.

CHRONIC NONINFLAMMATORY DIARRHEA

Syndromes of chronic noninflammatory diarrhea of infectious etiology include giardiasis, tropical spruelike syndromes, syndromes of bacterial "overgrowth," and *Cryptosporidium* or *C. belli* infection (especially in immunocompromised hosts).[256,262,287,395,396] The patient with weight loss, malaise, and watery or fatty stools should be suspected of having giardiasis or some other cause of a malabsorption syndrome. This syndrome may also be associated with hypocalcemia, with iron or folate deficiency anemia, or with deficiency of vitamin D, vitamin K, or protein.

Giardiasis is endemic throughout most of the United States and much of the world but still may often go undiagnosed for weeks of illness.[218,220,397-399] Spread of disease is through water or food during outbreaks and by direct person-to-person contact. Clinical syndromes range in severity from asymptomatic infection to severe, persistent diarrhea associated with anorexia, weight loss, and malnutrition.[218] Effective diagnosis often requires testing multiple stool samples or occasionally using a small bowel aspirate or "string" sample (Enterotest; Hedeco, Palo Alto, CA). Current immunoassays have markedly improved the sensitivity of stool analysis.[218,220] Recommended therapy classically included metronidazole, with a reported 70% cure rate.[396] Two somewhat newer agents, tinidazole and nitazoxanide, have shown improved efficacy for treatment and are associated with far fewer side effects than standard courses of metronidazole.[218,231,400] We generally use nitazoxanide as initial therapy in most symptomatic cases of giardiasis.

Other infectious agents of chronic noninflammatory diarrhea include *Cryptosporidium, C. belli,* and *Cyclospora.* Each of these agents can be identified by standard stool analyses using ova and parasite testing combined with specific immunoassay as needed. Of note, *Cyclospora* was identified as the etiologic agent causing a large, multistate outbreak of gastroenteritis in 2013 in the United States. Reasonable efficacy is achieved using trimethoprim-sulfamethoxazole for therapy of *Cyclospora* infection.[256,262,397]

BACTERIAL OVERGROWTH SYNDROMES

Many syndromes have been described in which impaired absorption was attributed to abnormal bacterial colonization in the upper segment of the small bowel.[398] Whether these organisms are virulent pathogens or simply part of the normal colonic flora abnormally distributed is unclear at present.

Normally, the upper portion of the small bowel is relatively sparsely populated, with fewer than 10^5 organisms/mL; these are predominantly

facultative gram-positive organisms (diphtheroids, streptococci, and lactobacilli).[401] The organisms most often incriminated in bacterial overgrowth syndromes in the small bowel are aerobic enteric coliforms (members of the family Enterobacteriaceae), anaerobic gram-negative fecal flora (*Bacteroides* and other genera), and miscellaneous other organisms, such as *Plesiomonas shigelloides*.[402]

Bacterial colonization in the upper part of the small bowel may be associated with malabsorption or chronic diarrhea in the absence of significant histopathologic changes. Small bowel overgrowth is usually associated with a predisposing bowel abnormality, such as achlorhydria (from gastritis, pernicious anemia, or gastric surgery), blind-loop syndromes, cholangitis, impaired motility (scleroderma, diabetic neuropathy, vagotomy), surgery, strictures, diverticula, or radiation damage.[403,404] Malnutrition, especially with protein, folate, or vitamin B_{12} deficiency, may also render the bowel more susceptible to microbial colonization and injury.[401,405] An episode of acute infectious diarrhea may provide the initiating event in the establishment of small bowel colonization and chronic diarrhea.[401,406,407] Lindenbaum and colleagues[408] described spruelike morphologic changes in the upper portion of the small bowel in association with increased numbers of bacteria and malabsorption among Peace Corps volunteers living in Pakistan.

The mechanism by which fecal flora in the small bowel causes malabsorption may involve bacterial binding (e.g., vitamin B_{12}) or utilization (e.g., carbohydrates) of nutrients, deconjugation of bile salts by bacteria such as enterococci and anaerobes,[409] or the toxic effects of bacterial products such as fatty acids or amines.[401] *E. coli* organisms that lack other recognized virulence traits but colonize the bowel were shown to cause prolonged diarrhea in a rabbit model,[410] with an associated impairment in water and electrolyte absorption as well as disaccharidase activity.[411]

The approach to the patient with suspected bacterial overgrowth as a cause of malabsorption or chronic diarrhea should include quantitative aerobic and anaerobic cultures of the upper small bowel contents, obtained by intubation or string passage. Because the critical number of organisms appears to be approximately 10^5/mL, semiquantitative estimates from a Gram stain (analogous to the urine Gram stain) may also prove to be of value. In addition, the ^{14}C–glycocholic acid breath test for bacterial deconjugation of bile salts has been shown to be helpful for diagnosis in some patients.[412]

Patients with diarrhea or malabsorption and bacterial overgrowth are potential candidates for antibiotic therapy, especially if a predisposing condition, such as achlorhydria, scleroderma, or diabetes, is present. Depending on the results of quantitative cultures of upper small bowel aspirates, therapy may need to be directed against anaerobes as well as aerobic coliform organisms.[401,406]

OTHER BACTERIAL OVERGROWTH SYNDROMES

Noninfectious causes should also be considered in the differential diagnosis of chronic noninflammatory diarrhea. Examples include congenital deficiency syndromes and food allergies, certain neoplastic and endocrine processes, and less well-understood functional disorders. Causative disorders to be considered in the first two categories are milk allergies, disaccharidase deficiencies, gluten enteropathy, acrodermatitis enteropathica, β-lipoprotein deficiency, familial hyperchloremic alkalosis (congenital "chloridorrhea"), Leiner's disease, and Wiskott-Aldrich syndrome. Neoplastic and endocrine causes of diarrhea include carcinoid tumors, Werner's syndrome (multiple endocrine adenomatosis), Zollinger-Ellison syndrome (gastrinoma), "pancreatic cholera" syndromes, medullary carcinoma of the thyroid, and thyrotoxicosis. Patients with partial mechanical bowel obstruction or pellagra may also have chronic diarrhea. Milder forms of inflammatory bowel disease as well as irritable bowel disease can also be associated with a variety of types of chronic diarrhea. Although a thorough search for an infectious cause of any form of chronic diarrhea is usually warranted, most often the specific diagnosis of one of these etiologies usually requires referral to gastroenterologist.

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