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

38

# Acute Diarrhea

MICHEL DRANCOURT

**KEY CONCEPTS**

- Diarrhea can be caused by a wide spectrum of viruses, bacteria and parasites. Multiple infections are common.
- The spectrum of illness ranges from self-limited disease to a potentially deadly situation depending on the pathogen and the host.
- In healthcare-associated diarrhea the cause is typically limited to *Clostridium difficile* and norovirus.
- Acute diarrhea can be diagnosed at the point-of-care by using rapid lateral flow and real-time polymerase chain reaction tests.
- Recently available multiplex tests allow for a rapid syndromic diagnosis.
- Appropriate water networking, environmental surface cleansing and hand hygiene are key to preventing outbreaks.

## Introduction

There is an increasingly recognized array of bacterial, parasitic and viral organisms associated with infection of the intestinal tract which can profoundly disrupt intestinal function with or without causing acute diarrhea. Acute diarrhea is a syndrome that is frequently not differentiated clinically by a specific etiologic agent. The wide spectrum of evolution varies from self-limited disease to death. Death is mainly due to dehydration and acute diarrhea takes the highest toll among children in low- and middle-income countries (LMIC). This chapter examines the viral and bacterial causes of acute diarrhea, clinically defined by three or more loose or watery stools per day or a definite decrease in consistency and increase in frequency based upon an individual baseline lasting for less than 2 weeks. Parasitic infections of the gastrointestinal tract will be presented in Section 6 and diarrhea associated with food poisoning is discussed in Chapter 37. Diarrhea associated with *Clostridium difficile* infection is covered in Chapter 40. When diarrhea lasts for 14 days it can be considered persistent; the term chronic generally refers to diarrhea that lasts for at least one month (see Chapter 39).

## Epidemiology

### PREVALENCE

Acute diarrheal diseases ranked seventh in the causes of mortality in LMIC in the global disease burden series, 2013, with an estimated 1.3 million deaths (2.4 %).[1] Most of these deaths occur in children under the age of 5 years in LMIC and diarrhea remains among the top five causes of all deaths among children younger than age 5 years, as tabulated in 2013.[1] The incidence of acute diarrhea in the general population could be estimated by prospective studies such as those organized in the Food-borne Disease Active Surveillance Network (FoodNet) in the USA. The network observed that 6% of interviewed people reported an acute diarrheal illness during the 4 weeks preceding the interview, that is an annualized rate of 0.72 episodes per person-year. Rates of illness were highest among children younger than 5 years (1.1 episodes per person-year) and were lowest in persons aged ≥65 years (0.32 episodes per person-year).[2] A study in 2000 that estimated the economic burden of both infectious and noninfectious gastrointestinal and liver disease in the USA found that the most prevalent diseases were non-food-borne gastroenteritis (135 million cases per year) and food-borne illness (76 million cases per year).[3] A report from the US Centers for Disease Control and Prevention (CDC) found that food-borne diseases account for approximately 76 million illnesses, 325 000 hospitalizations and 5000 deaths each year in the USA based upon surveillance data from multiple sources.[4] In the Netherlands, the incidence of gastroenteritis was 45 per 100 person-years in a prospective study.[5]

Because some enteric pathogens such as *Vibrio cholerae* are not ubiquitous, some pathogens are seasonal and some pathogens are responsible for epidemics, the prevalence of various pathogens responsible for diarrhea is variable. The bacterial pathogens most frequently found are enteropathogenic clones of *E. coli*, *Shigella* spp., *Salmonella enterica* subsp., *Campylobacter* spp. and *Aeromonas* spp. The most frequently identified causative viruses (outside local epidemics) include rotavirus, caliciviruses (norovirus and sapovirus), astrovirus and enteric adenovirus. Less prevalent viruses include paramyxovirus, morbillivirus, rubivirus and reovirus. The prevalence of norovirus has been recently estimated to be 12% in children under 5 years of age hospitalized for severe diarrhea and 12% of mild and moderate diarrhea cases among patients of all ages.[12] These authors estimated that noroviruses were responsible for up to 200 000 deaths of children <5 years of age in LMIC.[12]

### SURVEILLANCE

Not all enteric pathogens are notifiable, depending on the country. Moreover, a recent study in six US states indicated that multiple steps between onset of food-borne illness and its investigation by a public health agency could take up to 3 weeks.[6]

### SOURCES OF PATHOGENS

Infected persons, animals and the inanimate environment are sources of pathogens. Indeed, diarrhea is a contagious situation where infected persons are the main source of contamination, implying the isolation of the infected person as recalled by the recent outbreak of cholera in Haiti.[7] However, some enteric pathogens are zoonotic and contaminated poorly cooked food is the source of infection, as in the case of enteroinvasive *Escherichia coli* strains and *Campylobacter*[8] and *Listeria monocytogenes*.[9] Contaminated water is less likely to be a source of infection except in circumstances where there is a leak between potable and unpotable water networks. Water-borne outbreaks associated with recreational water (e.g., swimming or wading pools) are another source of acute diarrhea. These are associated most frequently with *Cryptosporidium* (50%) in treated water sources and with toxigenic *E. coli* (25%) and norovirus (25%) in freshwater sources. When there is a direct transmission of water-borne and food-borne pathogens, hands are increasingly recognized as vectors of enteric pathogens.[10]

Travel is increasingly reported as a circumstance for acute diarrhea, including enterotoxigenic *Escherichia coli* (ETEC) infection. *Aeromonas* infections have been traced to aquarium water.[11]

## Pathogenesis and Pathology

Diarrhea reflects an increased water content of the stool, whether due to impaired water absorption or active water secretion by the bowel. In severe infectious diarrhea, the daily volume of stool may exceed 2 liters. Dehydration and loss of potassium (hypokalemia) are two life-threatening consequences of severe diarrhea. Water is mainly absorbed in the small bowel (about 8 liters a day in an adult) and further in the

colon. By the time the initial 8 liters of fluid reaches the ileocecal valve, only about 600 mL remain, representing an efficiency of water absorption of 93%. By the time the remaining 600 mL of fluid reaches the anus, only about 100 mL of fluid remains, generally as formed feces. In the small intestine, water is absorbed by three basic mechanisms: 'neutral' sodium chloride (NaCl) absorption mediated by two coupled systems – one of which exchanges Na/H (cation exchanger), and the other exchanges Cl/$HCO_3$ (anion exchanger); 'electrogenic' sodium absorption where sodium enters the cell via an electrochemical gradient – this electrogenic sodium absorption mechanism is commonly damaged during acute enteric infection; and sodium co-transport whereby sodium absorption is coupled to the absorption of organic solutes such as glucose, many amino acids and peptides. This co-transport mechanism remains intact during most acute diarrheal disorders. It is for this reason that oral rehydration is effective during acute diarrheal illness.

Osmotic diarrhea occurs when an absorbable solute, such as lactose, is not absorbed properly and retains water in the gut lumen. Infections that damage the intestinal epithelial cells either directly (rotavirus) or by a toxin (*Shigella* spp.) cause malabsorption and osmotic diarrhea. Secretory diarrhea results from an active, toxin-mediated secretion of water into the gut lumen. This is observed during cholera, and infection by Shiga-toxin producing *Escherichia coli* and *Shigella* species. Rotavirus also produces a viral enterotoxin, the nonstructural glycoprotein (NSP4). Lastly, diarrhea can result from infection-mediated intestinal inflammation. After ingestion, an enteric organism colonizes the intestinal epithelium by adhering to enterocytes. One of two pathways are generally followed depending upon the offending organism, either mucosal invasion or production of an enterotoxin.

# Clinical Features

## BACTERIAL ENTERITIS

### *Aeromonas Infection*

*Aeromonas* species are inhabitants of aquatic environments worldwide, including rivers and lakes as well as drinking water plants and distribution systems. Also, most pathogenic *Aeromonas* species can be found in meat and dairy products. Some *Aeromonas* isolates encode enterotoxins, including an *alt* gene-encoded heat-labile and an *ast* gene-encoded heat-stable enterotoxin. *Aeromonas* enteric infection may range from, most commonly, an acute watery diarrhea to dysenteric illness. Symptoms may include abdominal cramps (70%), nausea (40%), vomiting (40%) and fever (40%). Infection is usually self-limiting although children may rarely be hospitalized because of dehydration. *Aeromonas caviae* is the most prevalent species. *Aeromonas veronii* can be associated with rare cholera-like illness and dysenteric diarrhea resembling shigellosis with bloody and purulent stools. One-tenth of patients are coinfected with a second enteric pathogen. Intermittent and persistent diarrhea may occur for years after initial infection. *Aeromonas* enteritis can be complicated by the hemolytic uremic syndrome (HUS) and kidney disease.[13]

### *Campylobacter Infection*

*Campylobacter* species are motile, gram-negative, S-shaped, microaerophilic organisms responsible for zoonoses. Not only food animals such as poultry, cattle, sheep and pigs, but also domestic pets are reservoirs for worldwide human infection. Although the incidence is decreasing in the USA, *Campylobacter* species are still responsible for sporadic infections following improper handling of poorly cooked meat. Poultry is a major source of infection.[14] Unpasteurized dairy products and water have been found to be sources for limited outbreaks. The incidence of infection with *Campylobacter* spp. is higher in LMIC than in industrialized nations and travelers to LMIC are at risk of *Campylobacter* infection. The pathogenesis of *Campylobacter* infections is poorly understood. *C. jejuni* and *C. coli* are the most frequently encountered species responsible for diarrhea. Signs and symptoms may vary from asymptomatic infections to include fever, abdominal cramps and diarrhea with or without blood and fecal white blood cells. Although generally self-limiting, relapse with chronic diarrhea is possible as well as extraintestinal infection including bacteremia. *C. jejuni* infection is the most often recognized infection preceding the development of Guillain–Barré syndrome.[15] The mechanisms rely on the cross-reactivity between ganglioside-like motifs present in *C. jejuni* lipopolysaccharide and those of peripheral nerves. Also, this species has been associated with immunoproliferative small intestinal disease.[16] Species other than *C. jejuni* and *C. coli* are increasingly isolated from the stools of patients with diarrhea, including *C. fetus*, mainly isolated from extraintestinal sites, and *C. upsaliensis*. Both species being susceptible to cephalothin, an antibiotic usually incorporated in *C. jejuni*-selective media, their prevalence in stools and diarrhea may be underestimated by culture methods.

*Clostridium difficile* infection is discussed in detail in Chapter 40.

### *Escherichia coli Infection*

*E. coli* organisms are common inhabitants of the intestinal tract of healthy people, yet a limited number of clones are responsible for acute diarrhea and extraintestinal infections. *E. fergusonii* is frequently isolated from stools yet its pathogenic role is non proven, and *E. albertii* is a possible agent of acute diarrhea.[17] There are five groups of *E. coli* organisms associated with acute diarrhea: Shiga toxin-producing *Escherichia coli* (STEC), also named enterohemorrhagic *Escherichia coli* (EHEC); enterotoxigenic *Escherichia coli* (ETEC); enteropathogenic *Escherichia coli* (EPEC); enteroaggregative *Escherichia coli* (EAEC); and enteroinvasive *Escherichia coli* (EIEC). STEC produce one or several Shiga toxins also known as verocytotoxins and are the *E. coli* organisms most frequently associated with acute diarrhea in industrialized countries. These organisms, including various *E. coli* O157 serotypes, are responsible for mild non-bloody and bloody acute diarrhea.[18] Non-O157:H7 STEC are associated with illnesses that differ from those caused by *E. coli* O157:H7. Most notably, they are found later and have a lower proportion of bloody diarrhea than in patients infected with *E. coli* O157:H7.[19] STEC are also responsible for an estimated 80% of HUS cases in about 4% of patients with enteric infection. Ground beef has been the major vehicle of transmission of O157 STEC, although other vehicles contaminated by bovine manure have been reported, including raw milk, sausage, apple cider, and raw vegetables and non-chlorinated water supply. Also, person-to-person transmission is responsible for outbreaks in communities.

ETEC produce heat-labile (LT) and heat-stable (ST) enterotoxins and are a frequent cause of acute diarrhea in LMIC, thus being a frequent cause of travelers' diarrhea. ETEC infection manifests as relatively mild watery diarrhea and abdominal cramps, but without vomiting or fever. EPEC comprise organisms characterized by an adherence factor plasmid and the chromosomal locus of enterocyte effacement. These organisms are responsible for severe infantile diarrhea in LMIC, associated with fever, vomiting and prolonged evolution. Chronic diarrhea may follow EPEC infection and be responsible for malabsorption, weight loss and growth retardation. EIEC are responsible for an infection mimicking shigellosis.

EAEC are responsible, worldwide, for mild enteric infections with non-bloody diarrhea, abdominal pain and mild fever.

### *Salmonella Infection*

The genus *Salmonella* comprises motile enteric bacteria of problematic nomenclature. *Salmonella* comprises two species and the species *Salmonella enterica* comprises five subspecies. The vast majority of human infections are due to strains of *Salmonella enterica* subspecies I, also isolated from warm-blooded animals, while the other *Salmonella* organisms are isolated from the environment and cold-blooded animals. These organisms are further serotyped and serotype generally correlates with the food source of infection. Notably, *Salmonella enterica* serotype Typhi is the agent of typhoid fever. *Salmonella enterica* serotypes Enteritidis and Typhimurium are the most commonly isolated in LMIC.

Non-typhoidal *S. enterica* organisms are responsible for acute diarrhea with fever and abdominal cramps lasting for an average of one

week. Rarely, these organisms are responsible for bacteremia and extraintestinal infections in immunocompromised patients. Contacts with animals and animal foods are the sources of infection with the Enteritidis serotype, being associated with chicken and egg products. Serotype Cholerasuis is adapted to cattle and serotype Dublin is adapted to pigs. The latter serotype harbors virulence traits in common with serotype Typhi, the typhoid fever agent. Typhoid fever is a life-threatening sepsis rarely observed in industrialized countries but still of public health concern in LMIC (see Chapter 115). Humans are the only known reservoir for serotype Typhi, which is therefore transmitted by direct person-to-person contact and through contaminated water and food. A syndrome similar to typhoid fever is due to serotypes Paratyphi A, Paratyphi B and Paratyphi C.

### Shigella Infection

*Shigella dysenteriae*, *Shigella flexneri*, *Shigella boydii* and *Shigella sonnei*[20]are responsible for acute diarrhea. Man is the only known reservoir for *Shigella* spp. and transmission is by direct contact from person-to-person and by contaminated water and food. Sexual transmission has been observed in homosexual males. Most cases in industrialized countries are imported from LMIC. *Shigella* spp. are responsible for bacillary dysentery characterized by acute, bloody diarrhea accompanied by fever and abdominal cramps. Classic dysentery is characterized by scant stools containing mucus, pus and blood. Shigellosis is responsible for rectal and colonic ulcerations that do not develop beyond the lamina propria. Rare cases of sepsis have been observed but *Shigella* spp. are responsible for HUS.

### Tropheryma whipplei Infection

*Tropheryma whipplei* is an Actinobacterium and the etiologic agent of Whipple disease.[21] Besides frequent fecal carriage in children,[22,23] *T. whipplei* has been more recently recognized as an etiologic agent of mild gastroenteritis and diarrhea in children.[24] Indeed, it was not detected in asymptomatic children but its DNA was detected with high bacterial loads in the stools of symptomatic children, followed by disappearance in children recovering from diarrhea, associated with seropositivity.[24] Adults also may present with *T. whipplei* diarrhea and *T. whipplei* must be added to the list of agents responsible for travelers' diarrhea.[25] In adults, however, there is asymptomatic fecal carriage of the micro-organism[26] and although the ultimate sources and precise routes of infection are not elucidated, colonized persons are likely sources of infection by the oro-oral and oro-fecal routes of transmission. Diagnosis relies on home-made real-time polymerase chain reaction (PCR) assays tested on two different specific sequences.[27,28] This approach increases the sensitivity of diagnosis over 16S rRNA gene detection.[29] There is no specific treatment for *T. whipplei* diarrhea.

### Vibrio Infection

*Vibrio* species are found ubiquitously in aquatic environments and more than 70 *Vibrio* spp. are classified as responsible for trauma-related, extraintestinal infections and intestinal infections with diarrhea.[30] *Vibrio cholerae* is the etiologic agent of cholera. This is a motile, gram-negative, facultative anaerobe bacterium which requires a small concentration of sodium for growth. *V. cholerae* is primarily an aquatic inhabitant found in freshwater rivers and lakes as well as in estuarine and maritime environments. In these environments, *V. cholerae* is isolated from both the inanimate environment and from plankton and various bivalves, crabs, shrimp and prawns. A viable-but-not-cultivable state has been described in which regulation may be phage-dependent.[31] *V. cholerae* comprises three major subgroups, *V. cholerae* O1, *V. cholerae* O139 and *V. cholerae* non-O1, widely distributed in tropical and sub-tropical areas, including the Gulf of Mexico for *V. cholerae* O1. *V. cholerae* O1 chromosomes contain virulence cassette and pathogenicity islands, encoding virulence factors such as the pilus responsible for the attachment of *V. cholerae* O1 organisms to the intestinal epithelium, and the cholera enterotoxin responsible for the substantial excretion of electrolytes and water in the intestinal lumen. Two biotypes, designated Classical and El Tor biotypes, can be differentiated on the basis of simple laboratory tests including the hemolysis of sheep erythrocytes, the Voges–Proskauer test and resistance to polymyxin, which are all positive in the El Tor biotype. The first six historical pandemics are thought to be due to the Classical biotype whereas the on-going seventh pandemic since 1961 is due to the El Tor biotype.

*V. cholerae* O1 is the organism responsible for historical pandemics of cholera since 1816, including the current pandemics. Most patients contaminated with *V. cholerae* O1 have an asymptomatic or self-limited diarrhea (>75%), but massive contamination results in severe diarrhea and large volumes of 'rice water stools' and dehydration. Clinical manifestations include loss of skin elasticity, watery eyes, painful muscle cramps and anuria. Dehydration leads to hypovolemic shock and death. Exceptional extraintestinal *V. cholerae* O1 bacteremia infections have been reported.

In 1992, cholera cases due to a new serogroup, *V. cholerae* O139 (Bengal), were reported in India and Bangladesh and spread rapidly throughout Asia. The new serogroup probably resulted from the lateral gene transfer of novel capsule and somatic antigen genes to the El Tor strains. It causes a disease similar to that caused by *V. cholerae* O1 except that adults are more frequently infected.

Some *V. cholerae* isolates do not agglutinate with anti-O1 and anti-O139 antisera and are therefore referred as *V. cholerae* non-O1 isolates. *V. cholerae* non-O1 isolates do not produce the cholera enterotoxin and are responsible for mild watery diarrhea. Unlike *V. cholerae* O1 isolates, *V. cholerae* non-O1 isolates are responsible for extraintestinal infection such as life-threatening sepsis, especially in patients with previous liver disease or hematologic malignancies. *V. cholerae* non-O1 isolates have also been recovered from other anatomical sites.

Other *Vibrio* species are responsible for diarrhea. They include *V. mimicus*, a species phenotypically related to *V. cholerae*, which is responsible for diarrhea after the consumption of raw seafoods; some strains harboring the cholera toxin can produce cholera-like symptoms. In Asia, *V. parahaemolyticus* is the leading cause of food-borne intestinal infections after the consumption of raw fish or shellfish. The species is responsible for watery diarrhea, rarely bloody diarrhea and exceptionally is responsible for severe dehydration and death. A first pandemic clone of *V. parahaemolyticus* serotype O3:K6 emerged in 1996 in Taiwan and then spread throughout Asia to America, Africa and Russia. New serotypes emerged for a few years. *V. vulnificus* is primarily responsible for life-threatening sepsis and secondary skin infection with necrosis; however, it has an intestinal route of entry and is responsible for vomiting, diarrhea and abdominal cramps after the consumption of raw oysters. Three biogroups have been defined in *V. vulnificus*, the vast majority of infections being due to biogroup 1. *V. fluvialis*, *V. furnisii* and *Grimontia* (*Vibrio*) *hollisae* cause sporadic cases of diarrhea worldwide.[32] *V. alginolyticus* is occasionally isolated from stools but there is little evidence for *V. alginolyticus* being actually responsible for intestinal infection and diarrhea.

### Yersinia Infection

Among the numerous members of the *Yersinia* genus, only *Y. enterocolitica* and *Y. pseudotuberculosis* have been associated with digestive tract infection. *Y. enterocolitica*, further divided into two subspecies *enterocolitica* and *paleartica* on the basis of 16S rDNA sequencing,[33] comprises more than 70 serotypes, five of them being associated with human infection. These strains encode for an enterotoxin and some strains harbor a chromosome-borne pathogenicity island which contains the yersiniabactin gene, providing the organisms with iron. *Y. enterocolitica* is primarily an environmental organism isolated from the gastrointestinal tract of numerous animals, most commonly swine, dogs and rodents. Its distribution is mostly in Northern Europe and the northern USA, reflecting its increased growth at cold temperatures. This species is responsible for gastroenteritis associated with the consumption of contaminated water and food, mainly poorly cooked swine meat. The disease spectrum comprises self-limited, acute diarrhea to terminal ileitis and mesenteric lymphadenitis mimicking appendicitis. Prolonged shedding has been observed. Sepsis is an uncommon complication observed in patients with an increased iron

pool, such as thalassemic patients in Western countries,[34] liver disease, cancer and receiving steroid therapy. *Y. enterocolitica* is a prominent cause of bacterial sepsis associated with blood transfusion. Reactive arthritis is an uncommon sequela observed in HLA-B27-positive patients and immunocompromised patients; it is characterized by an asymmetrical involvement of multiple joints, including the sacroiliac joints and the spine.

*Y. pseudotuberculosis* is rarely isolated as a cause of a self-limited acute diarrhea; it has been associated with outbreaks of gastroenteritis after consumption of contaminated fresh fruit and vegetables.[35,36] *Y. pseudotuberculosis* is also responsible for pseudoappendicitis, and reactive arthritis may develop after infection with *Y. pseudotuberculosis* O3.[37]

### Miscellaneous Bacteria

*Arcobacter* are *Campylobacter*-like organisms occasionally isolated from the stools of patients with diarrhea, including *Arcobacter butzleri*[38] and *Arcobacter cryaerophilus* DNA group 1B.[39] Particular culture conditions are required for proper isolation of these fastidious organisms, therefore limiting their detection to a few studies. *Listeria monocytogenes* has only recently been recognized as an agent of acute enteritis, but it has now been associated with several outbreaks.[40] Enteritis typically occurs after ingestion of a large inoculum and is self-limiting after a few days.[41] *Klebsiella oxytoca* is found in the environment but its principal reservoir is the human gastrointestinal tract. *K. oxytoca* has been associated with *C. difficile*-negative antibiotic-associated colitis.[42] *K. oxytoca* organisms cause experimental colitis and exhibit cytotoxicity against HEp-2 cultured cells.[42] Its culture is not routinely performed and requires a specific isolation agar medium. *Laribacter hongkongensis* is a facultative anaerobic gram-negative bacillus that was initially reported as being responsible for acute diarrhea in Asian patients.[43] Case–control study indicated that eating fish and travel were associated with *L. hongkongensis* acute diarrhea.[44] *Dysgonomonas capnocytophagoides* (formerly CDC group DF-3)[45] are *Captocytophaga*-like organisms isolated from the stools of immunocompromised patients.[46–48]

## VIRAL ENTERITIS

### Rotavirus Infections

Rotaviruses are RNA viruses appearing as 70 nm particles with a wheel-like appearance. Based on group-specific antigens of the major viral structural protein VP6, rotaviruses can be classified in six groups A to G. Groups A to C infect humans, the other groups are found in animals. Human rotaviruses are responsible for severe acute diarrhea with dehydration associated with childhood death in low- and middle-income countries. In Europe, children with rotavirus-positive acute gastroenteritis were more likely to have lethargy, fever, vomiting and dehydration, and, therefore, more severe disease than were children with rotavirus-negative acute gastroenteritis. Dehydration was up to 5.5 times more likely in children with rotavirus-positive acute gastroenteritis than in those with rotavirus-negative acute gastroenteritis.[49] Acquisition of rotaviruses is likely from subclinical infection in parents or siblings but rotavirus infection can be a zoonosis. Rotaviruses are resistant in the inanimate environment which may participate as a source of infection, including nosocomial outbreaks. Rotavirus infection is seasonal, with a peak of incidence in winter/spring in temperate countries. Clinical symptoms include acute diarrhea for 2–3 days, fever, vomiting and anorexia. Rapid diagnosis at the point-of-care can be achieved within 15 minutes by using a commercially available lateral-flow assay with parallel detection of adenovirus.

### Calicivirus and Norovirus Infections

The family Caliciviridae includes the genera *Norovirus* and *Sapovirus*, both responsible for enteritis. These RNA viruses appear as <40 nm nonenveloped particles. Noroviruses comprise five genotypes, the genotypes I, II and IV are responsible for human infections, the two other genogroups being animal-associated. Likewise, sapoviruses comprise five genogroups, the genotypes I, II, IV and V are responsible for human infections. These human viruses are highly contagious viruses which resist in the inanimate environment comprising contaminated surfaces, water and food. Outbreaks of norovirus infection are observed in daycare centers where child vomiting can readily contaminate floor and fomites.[50] Accordingly, direct evidence for animals as reservoirs for human infection is still lacking. Noroviruses are the most prevalent cause of nonbacterial acute enteritis worldwide.[51] These viruses cause large outbreaks and provoke incapacitation for a few days; they have therefore been included in the list B of potential bioterrorism agents by the NIAID. Outbreaks mainly occur in institutions including healthcare centers. Cruise ships appear to be an emerging setting for norovirus infection. Also, air flight has been shown to be a circumstance for norovirus diarrhea, for both cabin crew and passengers.[52] The inanimate environment in healthcare centers is also a source for norovirus infection, and the viruses are resistant to routine cleansing and routine alcohol hand hygiene.[53]

The diagnosis can be made within 10 minutes at point-of-care thanks to commercially available immunochromatographic tests.

### Astrovirus Infections

These RNA viruses, which average 30 nm diameter, are mainly responsible for acute diarrhea in children, although outbreaks in military troops and hospitals have also been reported. These worldwide viruses are responsible for 2–10% of pediatric cases of acute diarrhea. Clinical signs and symptoms are nonspecific.[54]

### Enteric Adenovirus Infections

Adenoviruses look like non-enveloped, 100 nm round particles containing DNA and are responsible for human infections. They belong to 51 different serotypes and six subgroups, but only two serotypes Ad40 and Ad41 (subgroup F) have been clearly demonstrated to be agents of acute diarrhea. Clinical characteristics include a higher prevalence in children <4 years of age and a mean duration of disease of 5–10 days, that is longer than that caused by other viruses. Prolonged diarrhea has been observed in immunocompromised patients.[55]

### Miscellaneous Viruses

A few other viruses have been associated with acute diarrhea, yet their role remains to be firmly established. These include coronavirus, a definite agent of diarrhea in animals and seldom visualized by electron microscopy and isolated in culture from the stools of patients with diarrhea. Likewise, torovirus is responsible for acute human gastroenteritis and is responsible for nosocomial cases. Aichi virus, a picornavirus, has been characterized by reverse transcription-PCR during an outbreak of enteritis following the consumption of oysters in Japan.[56] Picobirnaviruses have been detected in stools of animals and humans; their significance remains to be established. Recently, cardiovirus, closely related to Theiler's murine encephalomyelitis virus, has been detected in the stools in 1.2% patients with acute enteritis.[57]

# Prevention

The global mortality from diarrhea declined from approximately 4.6 million annual deaths during the mid-1980s, to 2.4 million deaths in 1990 and to the current estimate of 1.6–2.1 million.[1] The decline is generally attributed to global improvements in sanitation and the use of glucose-electrolyte oral rehydration therapy (ORT) which has dramatically reduced acute mortality from dehydration caused by diarrhea. In contrast to the fortunate decrease of mortality, morbidity remains as high as during the previous century. However, simple, cheap measures could be undertaken to make the incidence fall. A prospective study in India demonstrated that the promotion of hand washing with plain soap reduced by 53% the incidence of acute diarrhea (and of pneumonia and impetigo).[58] In industrialized countries, prevention relies on increased sanitary measures in sources of enteric pathogens such as recreational lakes for fishing and swimming, and swimming pools, as well as better control over fresh foods. A lifelong oral vaccine against rotavirus has been recently licensed after a few previous attempts and its safety and preventive effects have been carefully evaluated.[59] Cost-effectiveness of a vaccine against rotavirus has been evaluated favorably in the Netherlands.[60]

As for travelers, pre-travel prophylaxis relies on vaccines. There is currently only one vaccine available that provides protection against diarrhea caused by *Vibrio cholerae* and ETEC. This vaccine is licensed in only a few Western countries. Protective efficacy against cholera is 85%, while protection against the heat-labile toxin of ETEC reaches 67%. Current studies show a protective effect of up to 43%. Vaccination against cholera and ETEC should be recommended for at-risk travelers, in particular those with high exposure at their travel destination or high personal risks through fluid loss.[61] Typhim Vi is a conjugate vaccine aimed at prevention against typhoid fever; its safety and effectiveness have been favorably evaluated.[62,63] During travel, systematic administration of antibiotics including fluoroquinolones, cyclines and trimethoprim–sulfamethoxazole (co-trimoxazole) is controversial. Prophylaxis may rely on the basic rules of boiling fresh water or drinking bottled water, and cooking foods.

## Diagnosis

There is no recommended serologic test for the microbiologic diagnosis of enteric pathogens, and the laboratory diagnosis of diarrhea relies solely on direct diagnosis. Serologic testing is useful for epidemiologic investigation of *Campylobacter* species infections.[64]

Fresh stools should be collected in a clean container with a tight lid. Alternatively, a transport medium incorporating buffered glycerol in saline can be used. Rectal swab is an alternative specimen in selected situations. It is well established that hospitalized patients who did not enter the hospital with diarrhea are unlikely to develop diarrhea caused by other bacterial agents than *C. difficile*; therefore, stool culture should not be performed in patients hospitalized for more than 72 hours (the three-day rule) and a rapid detection of *C. difficile* toxins should be performed.[65] For routine purposes, testing a single stool specimen has acceptable sensitivity but testing a second specimen is mandatory when the first one had a more than 2-hour delay in transport.[66]

Several techniques have been developed for the point-of-care diagnosis of diarrhea including the rapid (<30 minutes) agglutination-based detection of rotavirus and adenovirus as well as the detection of *C. difficile* toxins. The rapid detection of *C. difficile* toxins A and B should be routinely performed for both out-clinic patients and hospitalized patients. Point-of-care detection of Shiga toxin-producing *Escherichia coli* in children using EIA has not been evaluated favorably.[67] A commercially available *Campylobacter* antigen detection kit has been favorably evaluated.[68] A dipstick test for the rapid detection of *Shigella* is under evaluation.[69]

Multiplex real-time PCR assays are now commercially available for a 1–3-hour diagnosis of bacteria virus and parasites.[70]

Further detection of the causative organism relies on stool examination in the clinical microbiology laboratory. Direct microscopic examination may yield motile bacteria such as *Vibrio* and *Salmonella* species and parasites. Although Gram-staining analysis of stool specimens may not be routinely done, it has demonstrated 66–94% sensitivity and >95% specificity for the rapid detection of *Campylobacter* species.[71]

Culture of stools will focus on frequent pathogens and the systematic query of less frequent bacterial pathogens will be guided by the local epidemiologic situation. Pathogens routinely detected by culture of diarrheal stools include O157 *E. coli*, *Shigella* spp., *S. enterica* serotypes, *C. jejuni* and *C. coli* and *Aeromonas* spp. Enrichment of stools in O157, O111 and O26 serotypes of *E. coli* can be done by using specific, commercially available magnetic beads. Sorbitol MacConkey agar should be used for the isolation of O157 STEC as these organisms do not ferment D-sorbitol, contrary to the vast majority of other *E. coli* strains. *S. enterica* serotypes are better isolated by using an enrichment broth before plating onto selective media. Biochemical identification of *Salmonella* spp. and O (somatic), H (flagellar) and Vi (capsular) antigen serotyping should be performed in order to identify *Salmonella* enteritis Typhi (the typhoid fever agent, being capsular antigen Vi positive) and the most prevalent non-Typhi serotypes. The Vi capsular antigen is occasionally detected in non-Typhi, Dublin and Paratyphi C serotypes. O serotype determination is done by agglutination using pooled antisera while further H serotype determination is done by tube agglutination tests using broth culture and testing the two phases of the flagellar antigens. *Campylobacter* spp. are recovered by using the filtration method in parallel to selective, blood-containing or non-blood containing media and a micro-aerophilic atmosphere. Some *Campylobacter* spp. require 6% hydrogen in atmosphere. A 42 °C incubation temperature allows the growth of *C. jejuni* and *C. coli* but not all *Campylobacter* and *Aeromonas* spp. are recovered using blood agar incorporating 20 μg/mL ampicillin and produce β-hemolytic colonies. Further identification should be done for oxidase-positive and indole-positive colonies. Modified cefsulodin-irgasan-novobiocin agar is also suitable for the isolation of *Aeromonas* species. The interpretation of recovery of *Aeromonas* in stools must be cautious since there is no strong evidence that all *Aeromonas* isolates from stools are responsible for diarrheal infection.[72]

Blood cultures are mandatory for the diagnosis of typhoid fever as well as bacteremia due to non-Typhi serotypes of *Salmonella*.

The systematic search for other enteritis pathogens may depend on local epidemiology, including *Y. enterocolitica*, *Vibrio* spp., *K. oxytoca*, *L. monocytogenes* and *Plesiomonas shigelloides*. Growth of *Y. enterocolitica* from stools is enhanced by incubation of selective media at 35 °C. A pectin agar should be used for the isolation of *Y. enterocolitica* from stools. *V. cholerae* will be visible as very motile, gram-negative slightly curved bacilli cultivated using a TCBS agar after enrichment. Yellow colonies of oxidase-negative bacilli can be confirmed, by 16S rDNA sequencing. In parallel to the search for pathogenic bacteria, the search for viruses should be done using electron microscope observation after negative staining as well as detection of rotavirus. Identification of bacterial colonies is now routinely done by using matrix-assisted laser desorption ionization time-of-flight mass spectrometry.[73]

## Management

Management of acute diarrhea should include the clinical evaluation of the patient, including risk factors for specific etiology and dehydration; rapid diagnosis of viral diarrhea; and treatment, including rehydration, antibiotic treatment and symptomatic treatment. Rehydration is a major therapeutic measure. Oral rehydration has a higher risk of paralytic ileus, but intravenous rehydration exposes patients to risks of intravenous therapy. For every 25 children treated with oral rehydration one will fail and require intravenous rehydration.[74] Rapid diagnosis of viral diarrhea is important in order to avoid unnecessary antibiotic treatment. Because of the absence of any antiviral drug effective against the viruses responsible for acute diarrhea, the management of viral diarrhea comprises the relief of symptoms and rehydration. Most acute diarrhea episodes are self-limiting and do not require antibiotic treatment. Meta-analysis has confirmed that antibiotic treatment is useful to shorten the duration of signs and symptoms in travelers' acute diarrhea.[75] When antibiotics should be prescribed, fluoroquinolones are the drugs of first choice, and one-day treatment is advocated except for *Campylobacter* and *Shigella* infections, which may be treated for three days.[76] In the case of patients returned from countries where fluoroquinolone resistance is prevalent, such as *Campylobacter* spp. in Thailand, azithromycin (500 mg ×1/d) could be used for three days (see also Chapter 37 and Practice Point 11).[77] Antimicrobial therapy for O157 *E. coli* enteritis remains a controversial issue because some studies reported a deleterious effect on the evolution of hemolytic uremic syndrome. The increasing resistance of *S. enterica* Typhi to antibiotics, notably to ciprofloxacin, makes the choice of first-line antibiotic treatment of typhoid fever more problematic (see Chapter 115). The majority of *Y. enterocolitis* gastroenteritis does not require antibiotic treatment, contrary to systemic infection which could be treated using trimethoprim–sulfamethoxazole (no resistant strain reported) or fluoroquinolones, despite the fact that a few resistant strains have been reported.[78]

References available online at expertconsult.com.

## KEY REFERENCES


Al-Abri S., Beeching N., Nye F.: Traveller's diarrhoea. *Lancet Infect Dis* 2005; 5:349-360.

Friedman C.R., Hoekstra R.M., Samuel M., et al., Emerging Infections Program FoodNet Working Group: Risk factors for sporadic *Campylobacter* infection in the United States: a case–control study in FoodNet sites. *Clin Infect Dis* 2004; 38:S285-S296.

Giaquinto C., Van Damme P., Huet F., et al., REVEAL Study Group: Clinical consequences of rotavirus acute gastroenteritis in Europe, 2004–2005: the REVEAL study. *J Infect Dis* 2007; 195:S26-S35.

Global Burden of Disease Study 2013 Collaborators: Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 386(9995):743-800.

Hartling L., Bellemare S., Wiebe N., et al.: Oral versus intravenous rehydration for treating dehydration due to gastroenteritis in children. *Cochrane Database Syst Rev* 2006; (3):CD004390.

Heijne J.C., Teunis P., Morroy G., et al.: Enhanced hygiene measures and norovirus transmission during an outbreak. *Emerg Infect Dis* 2009; 15:24-30.

Heijne J.C., Teunis P., Morroy G., et al.: Enhanced hygiene measures and norovirus transmission during an outbreak. *Emerg Infect Dis* 2009; 15:24-30.

Imhoff B., Morse D., Shiferaw B., et al.: Burden of self-reported acute diarrheal illness in FoodNet surveillance areas, 1998–1999. *Clin Infect Dis* 2004; 38(Suppl. 3):S219-S226.

Piarroux R., Barrais R., Faucher B., et al.: Understanding the cholera epidemic, Haiti. *Emerg Infect Dis* 2011; 17:1161-1168.

## REFERENCES


1. Global Burden of Disease Study 2013 Collaborators: Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 386(9995):743-800.
2. Imhoff B., Morse D., Shiferaw B., et al.: Burden of self-reported acute diarrheal illness in FoodNet surveillance areas, 1998–1999. *Clin Infect Dis* 2004; 38(Suppl. 3): S219-S226.
3. Sandler R.S., Everhart J.E., Donowitz M., et al.: The burden of selected digestive diseases in the United States. *Gastroenterology* 2002; 122:1500-1511.
4. Mead P.S., Slutsker L., Dietz V., et al.: Food-related illness and death in the United States. *Emerg Infect Dis* 1999; 5:607-625.
5. de Wit M.A., Hoogenboom-Verdegaal A.M., Goosen E.S., et al.: A population-based longitudinal study on the incidence and disease burden of gastroenteritis and *Campylobacter* and *Salmonella* infection in four regions of The Netherlands. *Eur J Epidemiol* 2000; 16:713-718.
6. Hedberg C.W., Greenblatt J.F., Matyas B.T., et al.: Timeliness of enteric disease surveillance in 6 US States. *Emerg Infect Dis* 2008; 14(2):311-313.
7. Piarroux R., Barrais R., Faucher B., et al.: Understanding the cholera epidemic, Haiti. *Emerg Infect Dis* 2011; 17:1161-1168.
8. Taylor B.V., Williamson J., Luck J., et al.: Sensitivity and specificity of serology in determining recent acute *Campylobacter* infection. *Intern Med J* 2004; 34:250-258.
9. Fleming D.W., Cochi S.L., MacDonald K.L., et al.: Pasteurized milk as a vehicle of infection in an outbreak of listeriosis. *N Engl J Med* 1985; 312:404-407.
10. Heijne J.C., Teunis P., Morroy G., et al.: Enhanced hygiene measures and norovirus transmission during an outbreak. *Emerg Infect Dis* 2009; 15:24-30.
11. Filler G., Ehrich J.H., Strauch E., et al.: Acute renal failure in an infant associated with cytotoxic *Aeromonas sobria* isolated from patient's stool and from aquarium water as suspected source of infection. *J Clin Microbiol* 2000; 38:469-470.
12. Patel M.M., Widdowson M.A., Glass R.I., et al.: Systematic literature review of role of noroviruses in sporadic gastroenteritis. *Emerg Infect Dis* 2008; 14:1224-1231.
13. Bogdanović R., Cobeljić M., Marković M., et al.: Haemolytic–uraemic syndrome associated with *Aeromonas hydrophila* enterocolitis. *Pediatr Nephrol* 1991; 5:293-295.
14. Friedman C.R., Hoekstra R.M., Samuel M., et al.: Risk factors for sporadic *Campylobacter* infection in the United States: a case–control study in FoodNet sites. *Clin Infect Dis* 2004; 38:S285-S296.
15. Yuki N., Kuwabara S.: Axonal Guillain–Barré syndrome: carbohydrate mimicry and pathophysiology. *J Peripher Nerv Syst* 2007; 12:238-249.
16. Lecuit M., Abachin E., Martin A., et al.: Immunoproliferative small intestinal disease associated with *Campylobacter jejuni*. *N Engl J Med* 2004; 350:239-248.
17. Stock I., Rahman M., Sherwood K.J., et al.: Natural antimicrobial susceptibility patterns and biochemical identification of *Escherichia albertii* and *Hafnia alvei* strains. *Diagn Microbiol Infect Dis* 2005; 51:151-163.
18. Rangel J.M., Sparling P.H., Crowe C., et al.: Epidemiology of *Escherichia coli* O157:H7 outbreaks, United States, 1982–2002. *Emerg Infect Dis* 2005; 11:603-609.
19. Klein E.J., Stapp J.R., Clausen C.R., et al.: Shiga toxin-producing *Escherichia coli* in children with diarrhea: a prospective point-of-care study. *J Pediatr* 2002; 141:172-177.
20. Lan R., Alles M.C., Donohoe K., et al.: Molecular evolutionary relationships of enteroinvasive *Escherichia coli* and *Shigella* spp. *Infect Immun* 2004; 72:5080-5088.
21. Fenollar F., Lagier J.C., Raoult D.: *Tropheryma whipplei* and Whipple's disease. *J Infect* 2014; 69:103-112.
22. Keita A.K., Dubot-Pérès A., Phommasone K., et al.: High prevalence of *Tropheryma whipplei* in Lao kindergarten children. *PLoS Negl Trop Dis* 2015; 9:e0003538.
23. Fenollar F., Trape J.F., Bassene H., et al.: *Tropheryma whipplei* in fecal samples from children, Senegal. *Emerg Infect Dis* 2009; 15:922-924.
24. Raoult D., Fenollar F., Rolain J.M., et al.: *Tropheryma whipplei* in children with gastroenteritis. *Emerg Infect Dis* 2010; 16:776-782.
25. Gautret P., Raoult D.: *Tropheryma whipplei* as a causative agent of travelers' diarrhea: further studies required. Reply to Razavi SM. *Travel Med Infect Dis* 2015; 13(1):114.
26. Fenollar F., Marth T., Lagier J.C., et al.: Sewage workers with low antibody responses may be colonized successively by several *Tropheryma whipplei* strains. *Int J Infect Dis* 2015; 35:51-55.
27. Fenollar F., Fournier P.E., Robert C., et al.: Use of genome selected repeated sequences increases the sensitivity of PCR detection of *Tropheryma whipplei*. *J Clin Microbiol* 2004; 42:401-403.
28. Edouard S., Fenollar F., Raoult D.: The rise of *Tropheryma whipplei*: a 12-year retrospective study of PCR diagnoses in our reference center. *J Clin Microbiol* 2012; 50:3917-3920.
29. Morel A.S., Dubourg G., Prudent E., et al.: Complementarity between targeted real-time specific PCR and conventional broad-range 16S rDNA PCR in the syndrome-driven diagnosis of infectious diseases. *Eur J Clin Microbiol Infect Dis* 2015; 34:561-570.
30. Thompson F.L., Iida T., Swings J.: Biodiversity of vibrios. *Microbiol Mol Biol Rev* 2004; 68:403-431.
31. Alam M., Sultana M., Nair G.B., et al.: Viable but non-culturable *Vibrio cholerae* O1 in biofilms in the aquatic environment and their role in cholera transmission. *Proc Natl Acad Sci USA* 2007; 104:17801-17806.
32. Thompson F.L., Hoste B., Vandemeulebroecke K., et al.: Reclassification of *Vibrio hollisae* as *Grimontia hollisae* gen. nov., comb. nov. *Int J Syst Evol Microbiol* 2003; 53:1615-1617.
33. Neubauer H., Aleksic S., Hensel A., et al.: *Yersinia enterocolitica* 16S rRNA gene types belong to the same genospecies but form three homology groups. *Int J Med Microbiol* 2000; 290:61-64.
34. Vento S., Cainelli F., Cesario F.: Infections and thalassaemia. *Lancet Infect Dis* 2006; 6:226-233.
35. Nuorti J.P., Niskanen T., Hallanvuo S., et al.: A widespread outbreak of *Yersinia pseudotuberculosis* O:3 infection from iceberg lettuce. *J Infect Dis* 2004; 189:766-774.
36. Jalava K., Hakkinen M., Valkonen M., et al.: An outbreak of gastrointestinal illness and erythema nodosum from grated carrots contaminated with *Yersinia pseudotuberculosis*. *J Infect Dis* 2006; 194:1209-1216.
37. Hannu T., Mattila L., Nuorti J.P., et al.: Reactive arthritis after an outbreak of *Yersinia pseudotuberculosis* serotype O:3 infection. *Ann Rheum Dis* 2003; 62:866-869.
38. Vandenberg O., Dediste A., Houf K., et al.: *Arcobacter* species in humans. *Emerg Infect Dis* 2004; 10:1863-1867.
39. Snelling W.J., Matsuda M., Moore J.E., et al.: Under the microscope: *Arcobacter*. *Lett Appl Microbiol* 2006; 42:7-14.
40. Hof H.: *Listeria monocytogenes*: a causative agent of gastroenteritis? *Eur J Clin Microbiol Infect Dis* 2001; 20:369-373.
41. Ooi S.T., Lorber B.: Gastroenteritis due to *Listeria monocytogenes*. *Clin Infect Dis* 2005; 40:1327-1332.
42. Hogenauer C., Langner C., Beubler E., et al.: *Klebsiella oxytoca* as a causative organism of antibiotic-associated hemorrhagic colitis. *N Engl J Med* 2006; 355:2418-2426.
43. Ni X.P., Ren S.H., Sun J.R., et al.: *Laribacter hongkongensis* isolated from a patient with community-acquired gastroenteritis in Hangzhou City. *J Clin Microbiol* 2007; 45:255-256.
44. Woo P.C., Lau S.K., Teng J.L., et al.: Association of *Laribacter hongkongensis* in community-acquired gastroenteritis with travel and eating fish: a multicentre case–control study. *Lancet* 2004; 363:1941-1947.
45. Hofstad T., Olsen I., Eribe E.R., et al.: *Dysgonomonas* gen. nov. to accommodate *Dysgonomonas gadei* sp. nov., an organism isolated from a human gall bladder, and *Dysgonomonas capnocytophagoides* (formerly CDC group DF-3). *Int J Syst Evol Microbiol* 2000; 50(Pt 6):2189-2195.
46. Heiner A.M., DiSario J.A., Carroll K., et al.: Dysgonic fermenter-3: a bacterium associated with diarrhea in immunocompromised hosts. *Am J Gastroenterol* 1992; 87:1629-1630.
47. Martinez-Sanchez L., Vasallo E.J., Garcia-Gorrote E., et al.: Clinical isolation of a DF-3 microorganism and review of the literature. *Clin Microbiol Infect* 1998; 4:344-346.
48. Grob R., Zbinden R., Ruef C., et al.: Septicemia caused by dysgonic fermenter 3 in a severely immunocompromised patient and isolation of the same microorganism from a stool specimen. *J Clin Microbiol* 1999; 37:1617-1618.
49. Giaquinto C., Van Damme P., Huet F., et al.: Clinical consequences of rotavirus acute gastroenteritis in Europe, 2004–2005: the REVEAL study. *J Infect Dis* 2007; 195:S26-S35.
50. Fankem S.L., Boone S.A., Gaither M., et al.: Outbreak of norovirus illness in a college summer camp: impact of cleaning on occurrence of norovirus on fomites. *J Environ Health* 2014; 76(8):20-26.
51. Fankhauser R.L., Monroe S.S., Noel J.S., et al.: Epidemiologic and molecular trends of 'Norwalk-like viruses' associated with outbreaks of gastroenteritis in the United States. *J Infect Dis* 2002; 186:1-7.
52. Thornley C.N., Emslie N.A., Sprott T.W., et al.: Recurring norovirus transmission on an airplane. *Clin Infect Dis* 2011; 53:515-520.
53. Heijne J.C., Teunis P., Morroy G., et al.: Enhanced hygiene measures and norovirus transmission during an outbreak. *Emerg Infect Dis* 2009; 15:24-30.
54. Walter J.E., Mitchell D.K.: Astrovirus infection in children. *Curr Opin Infect Dis* 2003; 16:247-253.
55. Schofield K.P., Morris D.J., Bailey A.S., et al.: Gastroenteritis due to adenovirus type 41 in an adult with chronic lymphocytic leukemia. *Clin Infect Dis* 1994; 19:311-312.
56. Yamashita T., Sugiyama M., Tsuzuki H., et al.: Application of a reverse transcription-PCR for identification and differentiation of Aichi virus, a new member of the Picornavirus family associated with gastroenteritis in humans. *J Clin Microbiol* 2000; 38:2955-2961.
57. Chiu C.Y., Greninger A.L., Kanada K., et al.: Identification of cardioviruses related to Theiler's murine encephalomyelitis virus in human infections. *Proc Natl Acad Sci USA* 2008; 105(37):14124-14129.
58. Luby S.P., Agboatwalla M., Feikin D.R., et al.: Effect of handwashing on child health: a randomised controlled trial. *Lancet* 2005; 366:225-233.
59. Dennehy P.H.: Rotavirus vaccines: an overview. *Clin Microbiol Rev* 2008; 21:198-208.
60. Goossens L.M., Standaert B., Hartwig N., et al.: The cost–utility of rotavirus vaccination with Rotarix (RIX4414) in the Netherlands. *Vaccine* 2008; 26:1118-1127.
61. Jelinek T., Kollaritsch H.: Vaccination with Dukoral against travelers' diarrhea (ETEC) and cholera. *Expert Rev Vaccines* 2008; 7:561-567.
62. Mai N.L., Phan V.B., Vo A.H., et al.: Persistent efficacy of Vi conjugate vaccine against typhoid fever in young children. *N Engl J Med* 2003; 349:1390-1391.
63. Marcus L.C., Froeschle J.E., Hill D.R., et al.: Safety of Typhim Vi vaccine in a postmarketing observational study. *J Travel Med* 2007; 14:386-391.
64. Taylor B.V., Williamson J., Luck J., et al.: Sensitivity and specificity of serology in determining recent acute *Campylobacter* infection. *Intern Med J* 2004; 34:250-258.
65. Thomson R.B. Jr: Specimen collection, transport, and processing: bacteriology. In: Murray P.R., Baron E.J., Jorgensen J.H., et al., eds. *Manual of clinical microbiology*. 9th ed. Wasington DC: American Society for Microbiology; 2007:291-333.
66. Valenstein P., Pfaller M., Yungbluth M.: The use and abuse of routine stool microbiology: a College of American Pathologists Q-probes study of 601 institutions. *Arch Pathol Lab Med* 1996; 120:206-211.
67. Klein E.J., Stapp J.R., Clausen C.R., et al.: Shiga toxin-producing *Escherichia coli* in children with diarrhea: a prospective point-of-care study. *J Pediatr* 2002; 141:172-177.
68. Dediste A., Vandenberg O., Vlaes L., et al.: Evaluation of the ProSpecT Microplate Assay for detection of *Campylobacter*: a routine laboratory perspective. *Clin Microbiol Infect* 2003; 9:1085-1090.

69. Nato F., Phalipon A., Nguyen T.L., et al.: Dipstick for rapid diagnosis of *Shigella flexneri* 2a in stool. *PLoS ONE* 2007; 2:e361.
70. Buss S.N., Leber A., Chapin K., et al.: Multicenter evaluation of the BioFire FilmArray gastrointestinal panel for etiologic diagnosis of infectious gastroenteritis. *J Clin Microbiol* 2015; 53(3):915-925.
71. Turgeon D.K., Fritsche T.R.: Laboratory approaches to infectious diarrhea. *Gastroenterol Clin North Am* 2001; 30:693-707.
72. Von Graevenitz A.: The role of *Aeromonas* in diarrhea: a review. *Infection* 2007; 35:59-64.
73. Seng P., Drancourt M., Gouriet F., et al.: Ongoing revolution in bacteriology: routine identification of bacteria by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. *Clin Infect Dis* 2009; 49(4):543-551.
74. Hartling L., Bellemare S., Wiebe N., et al.: Oral versus intravenous rehydration for treating dehydration due to gastroenteritis in children. *Cochrane Database Syst Rev* 2006; (3):CD004390.
75. De Bruyn G., Hahn S., Borwick A.: Antibiotic treatment for travellers' diarrhoea. *Cochrane Database Syst Rev* 2000; (3):CD002242.
76. Al-Abri S., Beeching N., Nye F.: Traveller's diarrhoea. *Lancet Infect Dis* 2005; 5:349-360.
77. Tribble D.R., Sanders J.W., Pang L.W., et al.: Traveler's diarrhea in Thailand: randomized, double-blind trial comparing single-dose and 3-day azithromycin-based regimens with a 3-day levofloxacin regimen. *Clin Infect Dis* 2007; 44:338-346.
78. Capilla S., Ruiz J., Goñi P., et al.: Characterization of the molecular mechanisms of quinolone resistance in *Yersinia enterocolitica* O:3 clinical isolates. *J Antimicrob Chemother* 2004; 53:1068-1071.