REVIEW ARTICLE

Current management of acute diarrheal infections in adults

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KEY WORDS

acute gastroenteritis, culture-independent testing, diagnostics, diarrhea, traveler's diarrhea

ABSTRACT

New guidelines on the management of acute diarrhea in adults were promulgated in 2016. The aim of this review was to provide an overview of the context of acute diarrhea and how to generally approach a patient; to present some new areas in the field concerning diagnostics, particularly culture-independent testing, as well as some of the risks and benefits of treatment; and to discuss prevention, particularly in the traveler's diarrhea setting.

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Introduction Acute diarrhea is usually defined as the passage of a greater number of stools of looser form compared with normal diarrhea lasting less than 14 days, or as an abrupt onset of the passage of 3 or more loose or liquid stools above baseline within 24 hours.[1] Acute diarrhea of infectious etiology, often referred to as gastroenteritis, is typically associated with clinical signs and symptoms including nausea, vomiting, abdominal pain and cramps, bloating, flatulence, fever, passage of bloody stools, tenesmus, and fecal urgency.[1] Acute diarrheal infection represents a frequent cause of outpatient visits and hospitalizations, especially while traveling abroad, and is a major public health issue globally. This review discusses relevant data on acute diarrhea from the United States and Europe, though it is important to note that there is a large amount of data on foodborne illness worldwide.[2] *Clostridioides difficile* (formerly *Clostridium difficile*) (*C. difficile*) infection, the immunocompromised host, and persistent or chronic diarrhea are beyond the scope of this paper (for the current recommendations, see Surawicz et al[3]).

Forces such as climate change, globalization, and centralization of food processing have had impact on the risks of foodborne illness and diarrheal infections and assure that this will remain a major public health challenge for the foreseeable future. In the United States, 1 out of every 6 people gets a foodborne illness every year. The numbers are comparable in Europe, with a greater burden among children. Among foodborne illnesses, there are numerous different pathogens that can cause a variety of clinical syndromes, but most of them cause a diarrheal disease.

In addition to the domestic setting, people who travel are also at particular risk.[4] The World Tourism Organization data have shown a steep rise in world travel. In 2015, over about 1.2 billion people were traveling to and from all countries.[5] Certainly, those coming to Europe are not at risk for bacterial traveler's diarrhea (TD), as opposed to those traveling to many of the lower- or middle--income countries. Based on the World Tourism Organization data on arrivals by location, it can be estimated that there are about 536 million travelers going to risk regions for TD. The incidence varies by destination, ranging between 10% and 40%, which results in 50 to 200 million cases of TD each year. Thus, it is a challenge from a standpoint of both in-country and travelers' acquisition, the latter being a severe problem also within the military setting.

Domestically acquired foodborne illnesses In terms of disease burden, the rates of illness incidence, hospitalizations, and death due to the leading causes of foodborne infection have been estimated.[6] Clearly, norovirus, *Salmonella*, and *Campylobacter* rank particularly high on all of the burden measures (FIGURE 1). The leading cause of hospitalization and death is *Salmonella*, but some other pathogens are also important to consider. Another frequent cause of illness are noroviruses, representing a big fraction of all infections. Viral gastroenteritides, including norovirus, are attributed to approximately 75% of

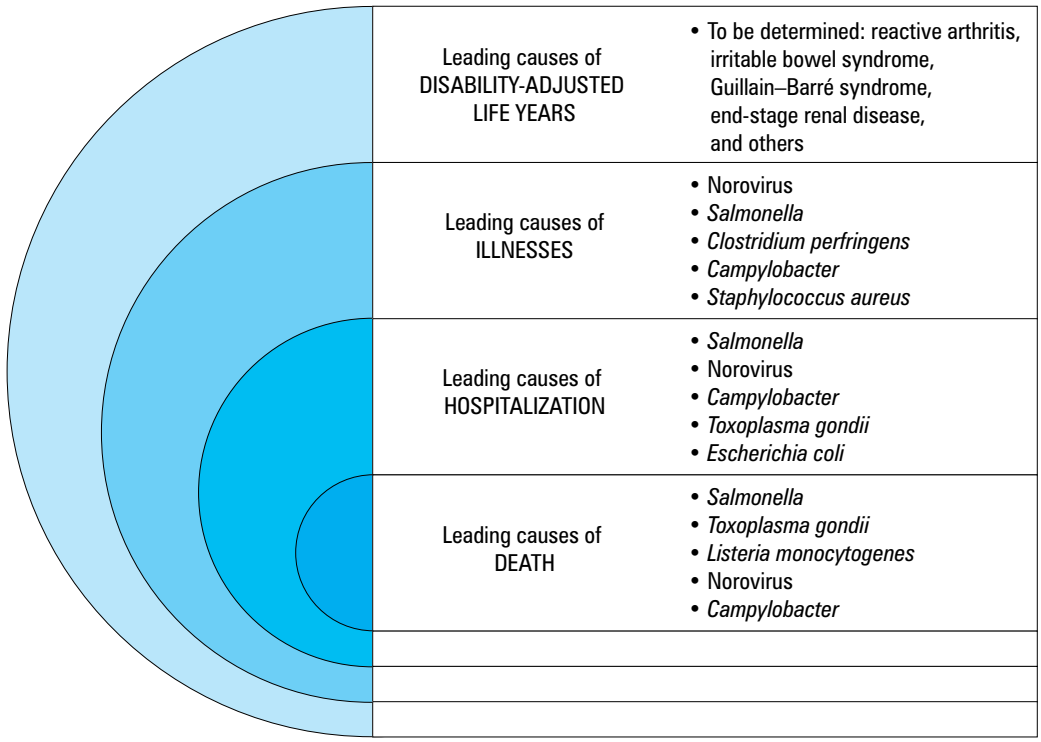

FIGURE 1 Leading causes of illness, hospitalization, and death in the United States (US Centers for Disease Control and Prevention, 2018)

patients with gastroenteritis in the clinical and emergency settings.

Beyond these measures of acute disease burden, epidemiology groups in the United States and Europe have begun to focus on and estimate the disability-adjusted life years (DALYs) related to acute infections but also the chronic health consequences which they may trigger. The association between *Campylobacter* and Guillain–Barré syndrome, the most common and most severe acute paralytic neuropathy, is well described, although fortunately relatively rare.[7] Associations between *Shigella*, *Salmonella*, or *Campylobacter* infections and reactive arthritis, defined as the development of sterile inflammatory arthritis following a remote infection, often in the gastrointestinal or urogenital tract, are well known.[8] However, the bulk of the iceberg of chronic health consequences of foodborne illness are the functional bowel disorders, particularly irritable bowel syndrome. Until now, epidemiology groups and foodborne illness groups have not really accounted for these long-term sequelae, but expansion of research evaluating the full burden of foodborne illness is anticipated. A Danish study from 2014 examined DALYs attributed to *Campylobacter* infection and found that only a fraction of the total DALYs were due to acute diarrhea, whereas the rest were due to the chronic complications of this infection.[9]

Viral gastroenteritis is the most common among in-country foodborne illnesses in Europe, whereas in travelers, bacterial agents are predominant. The latter account for 80% to 90% of cases, and the most common among them is diarrhoeagenic *Escherichia coli* (*E. coli*).

General approach to the adult with acute diarrhea

The general approach to an individual with acute diarrhea, as with any medical patient, is to take a detailed history. Firstly, it is important to establish the duration of symptoms, which helps make treatment and diagnostic choices. Secondly, the characteristics of the stool should be assessed. If it is watery and comes in large volumes, it suggests a secretory cause. On the other hand, if it is bloody and comes in small volumes, it suggests invasive inflammatory causes. Other characteristics to be considered are greasiness and smell. However, while such information can direct towards a potential etiology, it is not pathognomonic. Thirdly, measuring fluid hydration status is fundamental to management. Finally, it is important to consider the potential exposures, that is, what the patient has eaten, where he or she has traveled, and what occupational exposures he or she might have had. The incubation period for some of these illnesses, whether it is a toxin, a virus, or a bacteria, can range from 6 to 96 hours, which can make diagnosis based on exposure history sometimes difficult. Most patients attribute their illness to the dinner that they had the night before, which is not usually the case. Thus, it may be difficult to obtain a relevant food history, but it is advisable to take it nonetheless. This entails also the patient's place of residence, occupation, recent and remote travels, pets, hobbies, and, finally, recent antibiotic use and hospitalization. The latter 2 factors can be informative particularly if *C. difficile* is suspected.

The treatment algorithm is also outlined in the 2016 American College of Gastroenterology guidelines.[1] If an individual has 3 or more unformed stools in 24 hours with a concomitant enteric symptom, it meets the definition of an acute

diarrheal illness. In this case, oral fluid therapy should be introduced in all patients that can be hydrated via this route. It is a common misconception that patients need to be provided with electrolyte solution, that is, oral rehydration salts. This is usually not needed and clean safe water with a small amount of food (glucose) to help a patient absorb the water is sufficient in most cases. If the patient has been vomiting frequently, is severely dehydrated, or has been purging frequently, then replacing electrolytes should be considered. Electrolyte solution in addition to water alone may be considered also in elderly and pediatric patients.

Patients should be stratified into 2 categories: those with watery diarrhea and those with febrile, dysenteric, or bloody diarrhea. A patient with watery diarrhea without severe comorbidities or risk for *C. difficile* infection should be classified as having a mild or moderate illness. Previously, illness severity has been evaluated in terms of a frequentist approach, based on the number of stools and the number of vomiting episodes in a 24-hour period. However, the field is moving towards a patient-reported functional impact or an assessment thereof by a physician or clinician. If the illness is mild, it is not interfering with the individual's activities; if it is moderate, it is impacting the individual's activities; and if it is severe, the patient is not able to go to work or to school due to the illness.

Treatment of mild illness At the first tier, if it is a mild illness, hydration is the cornerstone and loperamide can be used to control stooling. Loperamide, the major antimotility drug used for therapy of acute diarrhea, works chiefly through the reduction of segmental contraction of the gut, which slows the intraluminal movement of fluids and increases absorption.[10] In patients with TD, loperamide was shown to decrease the number of diarrheal stools passed compared with bismuth subsalicylate[11] and to shorten the duration of diarrhea in adults.[12] The recommended therapeutic dose of loperamide for adults with diarrhea is 4 mg initially followed by 2 mg after a loose stool (below 16 mg/d) for up to 48 hours.[1] A typical adverse effect of loperamide use is posttreatment constipation; thus, patients should be advised to wait 1 to 2 hours between doses to avoid overload.

Treatment of moderate to severe illness and febrile diarrhea (not dysentery) With moderate to severe illness, the patient's history should be examined more closely and it should be determined whether the illness is travel- or non–travel-associated. In the case of travel-associated illness, it is known that it is bacterial and predominantly diarrheagenic *E. coli*, for which efficient treatments are available. In the case of non–travel-associated illness, there is a range of possible causes, with viral etiologies being the most common.

The next step is the assessment of fever. If there is no or low-grade fever, loperamide can be considered to help control stooling. In patients with fever of 38.3°C or higher, loperamide can also be used. In this case, the infection is likely to be viral and loperamide may provide some benefit with appropriate follow-up. If the high fever has been present more than 72 hours, a microbiologic assessment should be considered and the indicated treatment should follow.

In patients with acute bacterial diarrhea, antibiotics have been demonstrated to shorten the time from initiation of therapy until the last unformed stool is passed by 1 to 3 days compared with the no-treatment or placebo arms.[13-16] Fluoroquinolones (ciprofloxacin or levofloxacin) have been the primary antibiotics of choice.[14,15,17] However, for instance most *Campylobacter* bacteria are resistant to fluoroquinolones, and the use of macrolides such as azithromycin is recommended for treatment of this type of infection.[18]

A single-dose therapy is preferable as shown in studies demonstrating that once-daily therapy is as effective as a 3-day treatment for TD due to noninvasive pathogens, which comprises most cases,[15,16] with a 3-day therapy recommended for patients presenting with fever or if a single-dose therapy appears ineffective. The recommended regimens (both in a single-dose and 3-day therapy) are as follows: oral ciprofloxacin (750 mg or 500 mg), levofloxacin (500 mg), ofloxacin (400 mg), and azithromycin (1000 mg or 500 mg). In 4 randomized controlled trials (RCTs) that compared the efficacy of azithromycin versus fluoroquinolones in the treatment of TD, no intergroup differences were observed.[13,19-21] A 1000-mg dose of azithromycin can be divided into 2 doses, as it can have some gastric reactogenicity. A single dose of levofloxacin, a single dose of ciprofloxacin, and a 3-day course of rifaximin (200 mg 3 times per day), a nonabsorbable rifamycin-derived antibiotic, are all effective treatments. Rifaximin should not be used if a patient with acute diarrhea is suspected of *Campylobacter*, *Salmonella*, or *Shigella* infection. A recent trial examining azithromycin, levofloxacin, and rifaximin as a single dose demonstrated comparable effectiveness of all 3 treatments.

Nonantibiotic adjunctive therapies In the case of travel-associated mild illness, bismuth subsalicylate products or loperamide can be used to control defecation. In the case of travel-associated moderate illness, antibiotic therapy should be introduced and the guidelines recommend that loperamide should be used as an adjunct to antibiotics. Adsorbent drugs, such as pectin or charcoal that change the form of stools passed, have no effect on the number of stools passed and duration of posttreatment diarrhea. For this reason, such agents are not recommended.[1]

Combination therapy (loperamide plus antibiotics) In 2000, De Bruyn et al[22] examined the odds of clinical cure at 72 hours after therapy initiation in a review of trials comparing the use of any

antibiotic with no antibiotic against a placebo. Normally, a TD episode measured as the time to the last unformed stool lasts from 72 to 120 hours, with an average of 96 hours. The administration of antibiotics shortened the median time to the last unformed stool to 30 hours.

Subsequently, a meta-analysis of newer studies was published, which examined antibiotics with the adjunct loperamide. There were 6 studies that compared antibiotic alone with the same antibiotic regimen combined with loperamide. In this systematic review, the odds of clinical cure was evaluated at 24 hours rather than at 72 hours.[23] All but one study showed a positive treatment effect when loperamide was combined with an antibiotic compared with an antibiotic alone. Time to the last unformed stool dropped from 30 hours with an antibiotic alone to ~12 hours with added loperamide. The study that did not demonstrate any effect of the combined therapy was conducted in Thailand where *Campylobacter* infections are known to predominate and there is widespread resistance to fluoroquinolones.[19]

Treatment of dysentery In the case of dysentery, treatment decisions are based on the following criteria: 1) whether there is no or low-grade fever, and 2) whether there is severe illness with fever and the patient is not associated with the outbreak. In the case of dysentery and no or low-grade fever, Shiga toxin-producing *E. coli* is probable and these infections are being reported more frequently. Clearly, antibiotics should be avoided in these situations. Interestingly, there have been several reports on *E. coli* infections related to specific food items, in particular lettuce and sprouts, in various countries. In July 1995, 40 Montana residents were identified with laboratory-confirmed *E. coli* O157:H7 infection and 52 residents had bloody diarrhea without laboratory confirmation. Thirteen patients were hospitalized, including a single case of hemolytic uremic syndrome.[24] Then there was an outbreak of *E. coli* O157:H7 infections in Connecticut and Illinois during May–June 1996. This infection was associated with consumption of mesclun lettuce from a single producer, and cattle, a known *E. coli* O157:H7 reservoir, were found near the lettuce fields.[25] Another multistate outbreak of *E. coli* O157:H7 infections, diagnosed in 77 patients, occurred in the United States in November–December 2006 in fast food chain restaurants. Fifty-one (66%) patients were hospitalized, and seven (9%) developed nonfatal hemolytic uremic syndrome. This infection was mainly associated with consumption of shredded iceberg lettuce, which was eaten uncooked.[26] In October–November 2011, there was an outbreak of Shiga toxin–producing *E. coli* O157:H7 in 10 states in the United States, associated with romaine lettuce consumption, which identified 58 patients including 6.4% who developed hemolytic uremic syndrome among cases with complete information.[27]

Europe has not been spared by these outbreaks either. There was an outbreak of Shiga toxin–producing *E. coli* in Germany in May, June, and July 2011, which was associated with sprouts as shown by a trace-back investigation of the distributor that supplied restaurants and then producers.[28,29] A total of 3816 cases (including 54 deaths) were reported, predominantly in northern Germany. Twenty-two percent of patients, mainly women (68%) at a median age of 42 years, developed hemolytic uremic syndrome that was diagnosed on average 5 days since the onset of diarrhea. The outbreak strain was typed as an enteroaggregative Shiga toxin–producing *E. coli* O104:H4, producing extended-spectrum β-lactamase.[28] Contaminated sprouted fenugreek seeds were suspected as the primary vehicle of transmission of the EHEC O104:H4 outbreak strain in Germany, with secondary transmission (human to human and human to food).

Such infections are significant because they can cause severe disease and hemolytic uremic syndrome. Certainly, if there is an outbreak reported in the area, clinicians in the region should be aware of this to diagnose and treat patients accordingly. The early diagnosis and appropriate treatment (avoidance of antibiotics) is vital because it has been shown that early detection and fluid expansion reduces the risk of developing hemolytic uremic syndrome and complications.

In the case of severe illness with fever, it should be examined whether it is travel- or non–travel-associated illness. In the case of the latter, laboratory tests should be performed to establish the exact causative agent. A test-and-treat strategy should be considered but depends on the clinical situation, such as whether the practitioner would be able to follow the patient up with rapid test results and provide appropriate therapy, or whether rapid diagnostics are readily available and treatment can be provided appropriately. Alternatively, if diagnostics are not available or the patient cannot be reliably followed, empiric treatment can be considered with azithromycin as the drug of choice: either a single dose or 500 mg once daily for 3 days. This treatment is effective for travel-associated dysentery as well. In all cases, but particularly in moderate to severe illness, a phone call check should be done 24 hours later to make sure that a patient is improving or not significantly worsening.

It is important to note that the 2016 guidelines do not recommend empiric antimicrobial therapy for routine acute diarrhea of infectious origin, except in cases of TD with a high probability of bacterial infection, because community-acquired diarrhea is mostly viral (norovirus, rotavirus, and sapovirus) and is not shortened by antibiotics.[1]

Antibiotic resistance The issue of antibiotic resistance is often discussed in the context of TD or diarrhea in general, both among health care professionals and in the media. Individuals who have traveled overseas have been identified

to be returning to their country of origin with multidrug-resistant organisms in their stool. Some professionals advocate that TD should not be treated or that antibiotic use should be avoided in most cases. In the prospective multicenter COMBAT study, in which 2001 Dutch travelers and 215 nontraveling household members were assessed, the acquisition of extended--spectrum β-lactamase–producing Enterobacteriaceae (ESBL-E) during international travel was investigated.[30] The authors reported that 34.3% of travelers who were ESBL-E negative before travel and had fecal samples tested after return had acquired ESBL-E during international travel. The highest proportion of such positive travelers was detected among those who traveled to southern Asia (75.1%). Of note, antibiotic use during travel (adjusted odds ratio [OR], 2.69; 95% CI, 1.79–4.05), TD that persisted after return (adjusted OR, 2.31; 95% CI, 1.42–3.76), and preexisting chronic bowel disease (adjusted OR, 2.10; 95% CI, 1.13–3.90) were identified as significant predictors of acquisition of ESBL-E during travel. Although colonization after travel lasted on average 30 days, 11.3% of positive patients remained colonized at 12 months. Onward transmission was found in about 8% of household members. This study indicated that acquisition of ESBL-E during and after international travel was substantial and that it could be passed on to close household contacts, though no adverse events due to carriage were noted.[30] It is important to note that travel alone and untreated diarrhea also increase the risk of acquisition, as is antibiotic use for any reason overseas. Diet may be important as vegetarians traveling overseas have been reported to have a higher risk of developing ESBL--E carriage, suggesting a foodborne association with vegetables.

It has been increasingly argued that antibiotics should be avoided because acquisition of multidrug-resistant organisms and the consequence of local and global transmission is an important concern. However, these colonizations have been demonstrated to be transient for most patients and without individual health harm.[30,31] Vading et al[32] suggested that the acquired strains may be less virulent and not of the same type that cause the majority of disease burden associated with nosocomial infections. Certainly, there is a growing concern about antibiotic resistance and its stewardship, and it is often suggested that antibiotics should be strictly reserved for when they are urgently needed. However, the average healthy traveler acquiring ESBL-E is not going to be severely impacted, and there is scarce evidence to suggest that a returning traveler is spreading the disease to the community. Also, transmission usually occurs in the hospital environment, within a iatrogenic transmission dynamic, rather than through individual travelers. Still, a traveler, especially an elderly one, with a urinary tract infection who had come back from travel in the last 6 months should undergo a urine culture test, so that the infection can be appropriately treated. Severely ill patients being hospitalized after travel may also be screened.

The current clinical management balance is that there are clear benefits of treatment of TD and potential consequences of the lack of treatment, or travelers having to seek medical care in a country where other health risks are known to occur. More research is clearly needed in this area to resolve the uncertainty of risks and benefits of TD treatment, and all of the different levels of global and local community as well as individual health need to be considered. It is vital that health care professionals are well informed on this matter in order to have an appropriate conversation with their patients and to take an acceptable course of action.

Postinfectious irritable bowel syndrome In patients with chronic diarrhea and abdominal symptoms following acute infectious diarrhea, postinfectious irritable bowel syndrome (ie, chronic gastrointestinal dysfunction that is not directly mediated by the persistence of an infectious agent) must be considered.[33] Studies of postinfectious irritable bowel syndrome have shown that the longer duration of illness associated with enteric infections and the more severe the illness is, the higher the risk of these postinfectious functional bowel disorders. Thus, it can be hypothesized that if these infections are treated early and effectively, and their severity, invasiveness, and duration are reduced, this frequent complication may possibly also be mitigated, although this has not been confirmed by clinical trials or observational studies.

Diagnostics Conventional diagnostic workup in patients with acute diarrhea involves numerous assays such as bacterial culture, microscopy with and without staining or immunofluorescence, and stool antigen tests for detection of protozoa, as well as electron microscopy or antigen-based tests if viral agents are suspected. To detect bacterial pathogens in a patient with diarrhea, the use of differential culture media is needed and could fail if antibiotics are administered. Culture methods are laborious, and their results are usually available after 2 to 3 days since the specimen collection.[34]

The culture-independent molecular diagnostic methods are increasingly present in clinical practice and such techniques enable a rapid and simultaneous identification of various bacterial, protozoan, and viral pathogens that cause diarrhea.[35] Molecular techniques have some limitations including the need to predefine the particular microbes being sought and lack of discrimination between viable and nonviable organisms, with the risk of detecting low pathogen DNA/RNA amounts in the case of asymptomatic carriage of enteropathogens. A number of multipathogen platforms for enteric infections have been developed. It should be noted that specimens analyzed using culture-independent techniques may

not be compatible with culture due to different collection methods. Moreover, the newer methods may decrease chances of detecting new pathogens causing diarrhea.[36,37]

Although more study is needed on the cost-to-benefit ratio and impact on health outcomes (and antibiotic avoidance), current guidelines recommend the use of stool diagnostic tests in cases of dysentery, moderate to severe disease, and in symptoms that are lasting longer than 7 days.[1] They also recommend that using a culture-independent diagnostic test approved by the Food and Drug Administration or another licensed test in addition to traditional methods may be beneficial.[1] Performing a culture-based test for *Campylobacter*, for instance, can take several days, while culture-independent methods can provide a result in several hours, and the time factor is significant in the decision-making process. Importantly, many public health laboratories or public health systems rely on the culture-based method. The current recommendation is that a culture-independent test is performed in addition to a culture-based test or that the local laboratory test is used.[1] If the result is positive, reflective culture-based tests should be done for public health reporting purposes. In the guidelines, a similar recommendation was included that returning travelers with severe or persistent symptoms should undergo molecular testing, which may help identify a treatable etiology.[38] However, this was an ungraded recommendation because no studies have evaluated whether using these tests improves outcomes.

The interpretation of the results is a further challenge for clinicians. Connor[39] reported a case of a traveler who was spending 3 weeks overseas, in multiple countries, developed several diarrheal illnesses, and was having persistent symptoms on return. He tested positive for diarrheagenic *E. coli*, as well as for viruses and parasites. It was likely that all 3 pathogens were present; however, it remained unclear which was the causative agent. In such a case, a more detailed history is needed to determine the duration and type of diarrhea, and the treatment should be chosen accordingly. It is known that many viruses will continue shedding for approximately 2 months. Thus, it is probable that the patient carried a sapovirus, which can colonize without any symptoms, like several other similar viruses. These tests are undoubtedly helpful, but an in-depth, often complex, interpretation of the results is needed in each individual case.

Prevention Current and future strategies for prevention entail multiple modalities, but the options are still limited.[40] Chemoprophylaxis studies have shown that bismuth subsalicylate, which is not available throughout all of Europe, offers moderate protection. In 1987, an RCT by DuPont et al[41] showed that bismuth subsalicylate could be effective in prophylaxis of TD. Students traveling to Mexico developed diarrhea less frequently when they were randomly assigned to receive 2 tablets (high dose, 2 × 262 mg/tablet) or 1 tablet (low dose, 262 mg/tablet) of bismuth subsalicylate 4 times daily, compared with placebo during 3 weeks. Protection rates were 65% for high-dose and 40% for low-dose bismuth subsalicylate. The medication was well tolerated, with a typical adverse effect of blackening of tongues and stools due to the harmless bismuth sulfide salt. This preventive measure is being reconsidered, given a renewed interest in antibiotic resistance and resulting attempts at preventing infection and avoiding antibiotic use while traveling.

From an antibiotic standpoint, some important older studies on fluoroquinolones have shown a very high level of protection, but the guidelines do not recommend fluoroquinolones due to their dysbiotic effect and the fact that TD can be treated very quickly.[1] In special circumstances, rifaximin is the drug of choice for prophylaxis in travelers who could not tolerate an infection due to comorbidities or other practical reasons (eg, sports figures).[40-44] There is solid evidence to support the use of rifaximin in acute diarrhea. In a study on 210 Americans aged 18 years or older traveling to Mexico (diarrhea-producing *E. coli* as a major pathogen causing TD),[14] participants received rifaximin (200 mg/d, 200 mg twice daily, or 200 mg 3 times daily) or placebo for 2 weeks. TD was observed less frequently in the rifaximin group (14.74% vs 53.70%, respectively), and all rifaximin doses were superior to placebo. In participants without TD, mild diarrhea and moderate and severe intestinal problems, such as pain, cramps, or excessive gas, were significantly less common in patients taking rifaximin. The drug did not increase the risk of adverse events. The authors concluded that "rifaximin prevents travelers' diarrhea with minimal changes in fecal flora, and more liberal chemoprophylaxis against this disease should be considered."[42]

Probiotics are defined as live microorganisms, which have specific features (ie, exhibit nonpathogenic properties), are viable in delivery vehicles, are stable in acid and bile, adhere to target epithelial tissue, persist within the gastrointestinal tract, produce antimicrobial substances, modulate the immune system, and influence metabolic activities.[45] Theoretically, when administered in adequate amounts, probiotics may act through a "colonization resistance" mechanism, by preventing attachment or colonization of microorganisms, in addition to possibly enhancing the immune response and contributing to re-establishment of the normal microflora.[46] Prebiotics are nondigestible food ingredients that can be fermented in the colon and stimulate important colonic microbiota, predominantly bifidobacteria and/or lactobacilli reported to increase resistance to acute infectious diarrhea.[47] The combination of probiotics with prebiotics is termed synbiotics.

Unfortunately, there has been no consistent evidence indicating that probiotics, prebiotics, or their combination provide any significant

protection against TD.[1,48-54] In 2010, a Cochrane systematic review was published, including 63 RCTs and quasi-RCTs comparing probiotics with placebo or no-treatment in patients with acute diarrhea of presumed infectious etiology.[55] Of the 63 trials, 6 were in adult patients in various clinical settings and different endpoints. Since 4 studies with the use of one product, *Enterococcus* LAB SF68, had the same endpoint, namely, diarrhea lasting 4 days or longer, they were analyzed together. The analysis showed that 12.5% of patients in the probiotic arms suffered from prolonged diarrhea compared with 62% of those receiving placebo, which provided a 79% efficacy (relative risk, 0.21; 95% CI, 0.08–0.52) for this outcome with substantial heterogeneity.[55]

Regarding newer studies, evidence remains similarly unconvincing. For example, in an RCT published in 2013, healthy subjects traveling to Mexico were randomized to take 2 capsules of placebo (n = 102) or an oral synbiotic (a combination of 2 probiotics and a prebiotic) called Agri-King Synbiotic beginning 3 days prior to departure, daily while traveling, and for 7 days after return (n = 94).[53] No difference in the incidence of TD was observed (53.9% and 55.3%, respectively), with similar proportions of participants that took antibiotics versus those that did not (35% vs 29%, $P = 0.68$). The study failed to show any reduction in the risk of developing TD while using the prophylactic oral symbiotic.[54]

Further studies with good methodology are needed to evaluate the role of probiotics and prebiotics in prevention of acute diarrhea. Importantly, the guidelines state that the use of probiotics or prebiotics for treatment of acute diarrhea in adults is not recommended, except in cases of postantibiotic-associated illness.[1]

Conclusions Acute diarrhea is a common clinical condition that occurs worldwide and contributes to a substantial burden for public health. Proper clinical management is crucial, and new diagnostic methods are changing the approach to treatment and may offer an opportunity to employ test-to-treat strategies with better outcomes and avoidance of unnecessary antibiotics. Single-dose antibiotics with loperamide for watery TD have shown the greatest effectiveness and are generally well tolerated. Concerns about acquisition of antibiotic-resistant organisms during travel have emerged, and more research is needed on the risks, consequences, and mitigation strategies. Practitioners still remain the frontline of public health and have the important responsibility to identify potential outbreaks of foodborne illness and report them to the local public health authorities so that the disease burden can be minimized. In most cases, acute diarrheal illness in the developed world is viral and does not require antibiotic treatment; however, severe disease, bloody diarrhea, and diarrhea of longer duration should be appropriately diagnosed and treated. Culture-independent diagnostic methods are becoming popular but need to be used as a decision aide rather than a decision maker for treatments, and clinical laboratories should consider the use of reflex culturing to identify potential issues with antibiotic resistance and clinical management.

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