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Prevention and Self-Treatment of Traveler's Diarrhea

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INTRODUCTION

In 2004, the United Nations World Tourism Organization estimated that 170 million international travelers visited countries in developing and tropical areas such as Latin America, the Caribbean, the Middle East, South and Southeast Asia, and Africa and that at least 20%, or 34 million, of these travelers arrived from their homes in the industrialized world (168). Between 20% and 50% of such individuals will experience diarrhea as a result of ingesting fecally contaminated water or food (67, 108, 152). In 5% to 10%, symptoms typical of dysentery (fever, chills, and bloody stools) occur (20, 141).

Traveler's diarrhea usually begins within the first week of travel, and without treatment, it usually resolves without sequelae within 3 to 5 days (155). However, symptoms can be severe enough to force a change in travel plans and to result in confinement to bed or, rarely, hospitalization (100, 126). Traveler's diarrhea carries significant economic costs both to the traveling public and to developing countries through loss of tourism income and loss of business investment opportunities caused by the threat of disease. Traveler's diarrhea among military personnel also results in reduced combat readiness, a factor of serious concern to the U.S. military as thousands of personnel are increasingly being deployed in areas of elevated risk of infection (149). However, the impact of traveler's diarrhea can be reduced by education about ways to prevent the illness. Similarly, the severity of this disease can be minimized by prompt and well-informed self-treatment. Health care providers can help considerably in ensuring that travelers have safe and enjoyable trips overseas.

EPIDEMIOLOGY

Destination represents the single most important risk factor for developing traveler's diarrhea. High-risk regions include the developing countries of Latin America, Africa, Asia, and parts of the Middle East, which have reported attack rates for traveler's diarrhea ranging between 20 and 75% (20, 126). Areas of intermediate risk include China, southern Europe, Israel, South Africa, Russia, and several Caribbean islands (especially Haiti and the Dominican Republic); attack rates of 8% to 20% have been recorded among travelers to these regions. Low-risk (<5%) destinations include Canada, the United States, Australia, New Zealand, Japan, northern European countries, and a few Caribbean islands (10).

Season of travel also affects the level of risk. Numerous studies have demonstrated that attack rates of traveler's diarrhea are highest during the summer months and in rainy seasons (20, 80). Since ingestion of contaminated food or drink is the means of acquiring traveler's diarrhea, risk varies according to the attention paid to diet. High-risk foods include uncooked vegetables and unpeeled fresh fruit, raw or undercooked meat or seafood (particularly shellfish), and salads. Safe drinks include bottled carbonated beverages, beer or wine, and boiled or treated water (see "PREVENTION"), while ice, tap water, and unpasteurized milk carry increased risks of infection.

Location also modifies the level of risk: meals eaten in a private home carry lower risk than those eaten in a restaurant (50, 80, 166). The type of travel also influences the likelihood of developing diarrhea: those who participate in "adventure" travel or who go on hiking or camping trips are at increased risk, likely because of hygiene practices and choice of food (100). However, dining in expensive restaurants or luxury hotels does not reduce the risk of traveler's diarrhea to zero; several outbreaks in such establishments have been reported

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(73, 128). Purchasing food from street vendors is especially risky (47).

Although gender has no influence on the incidence of diarrhea in travelers (54), age plays a significant role. Those with the highest incidence include small children and young adults aged 21 to 29 years (10, 29, 135), the latter likely due to a lack of vigilance in avoiding contaminated food combined with a more adventurous lifestyle (80). Diarrhea in the former group is probably secondary to a relative lack of immunity and increased fecal-oral contamination. Individuals with achlorhydria have been shown to be at increased risk of traveler's diarrhea (61, 83), and therefore those on proton pump inhibitors or long-acting H_2 blockers, or those who have had gastrectomies, may be similarly affected: in one study, the use of omeprazole, a proton pump inhibitor, was associated with a 10-fold-increased risk of infection due to *Campylobacter* (121). Although conclusive evidence is lacking, travelers with specific medical conditions may also be at higher risk, especially persons with human immunodeficiency virus and reduced CD4 cell counts, patients receiving cytotoxic chemotherapy, and persons with secretory immunoglobulin A (IgA) deficiency.

Certain host genetic factors have been shown to affect susceptibility to traveler's diarrhea. For example, persons with blood group O are at increased risk of developing severe symptoms when infected with *Vibrio cholerae* O1 (8, 63, 105), although a recent study has suggested that people with this blood group are less likely to be infected with this organism (74). Similarly, individuals with the blood group O phenotype are at increased risk of developing disease due to norovirus, as demonstrated in two independent challenge studies (87, 107). Genetic factors also play a role in susceptibility to traveler's diarrhea due to enteroaggregative *Escherichia coli* (EAEC). In a study of American students staying in Mexico, the likelihood of developing EAEC-associated diarrhea was significantly increased among those with the AA or AT genotype at the −251 position in the promoter region of the interleukin-8 (IL-8) gene, compared to those with the TT genotype (93). This IL-8 polymorphism is also likely to impact the course of infection due to other pathogens that cause traveler's diarrhea, such as enterotoxigenic *E. coli* (ETEC), *Campylobacter jejuni*, and *Salmonella*, *Shigella*, and *Cryptosporidium* species, all of which have been shown to result in increased levels of fecal IL-8 (4, 69, 76, 85).

ETIOLOGY

By far the most important etiologic agents of traveler's diarrhea are bacterial pathogens (Table 1), which have been implicated in more than 80% of cases in several studies (5, 15, 126), including a large survey of more than 30,000 short-term visitors to Jamaica (154). Of the bacteria implicated, ETEC accounts for the majority of infections, although *Shigella* species, *Campylobacter* species, *Salmonella* species, *Aeromonas* species (173), *Plesiomonas shigelloides*, and noncholera vibrios have also been isolated from travelers (10). Enteroinvasive *E. coli* (EIEC) and EAEC are increasingly recognized as possible causes of traveler's diarrhea (3, 92, 147, 172), although in the case of EAEC, not all strains may be pathogenic, and virulence factors are still unidentified (69). Both the destination and the season of travel have been shown to affect the identity of the

TABLE 1. Common enteric pathogens isolated in cases of traveler's diarrhea

Enteric pathogen	% Isolation
Bacteria	50–80
Escherichia coli	
ETEC	20–50
EAEC	?
EIEC	5–15
Campylobacter jejuni	5–30
Salmonella spp.	5–25
Shigella spp.	5–15
Aeromonas spp.	0–10
Plesiomonas shigelloides	0–5
Vibrio spp.	5
Viruses	5–25
Norovirus	0–10
Rotavirus	0–10
Protozoa	<10
Giardia intestinalis	0–10
Entamoeba histolytica	0–10
Cryptosporidium parvum	1–5
Cyclospora cayetanensis	0–5
No pathogen isolated	10–50

predominant causative organism: ETEC is the most common cause of diarrhea in travelers to Latin America (10), whereas *Campylobacter jejuni* is relatively more common in Southeast Asia, particularly Thailand (9). *Vibrio parahaemolyticus* has been isolated particularly in travelers to Southeast Asia (151), whereas *Vibrio cholerae* is a rare causative agent, limited mostly to relief workers visiting areas afflicted by cholera epidemics. *Aeromonas* spp. and *P. shigelloides* have also been associated with travel to Asia (148, 170). Seasonal variation in the incidence of ETEC infection has been documented in semitropical countries such as Morocco (112) and Mexico (47); ETEC is isolated more commonly in the wet summer and fall months and uncommonly during the dry winters, when *Campylobacter* acquires greater importance.

Viruses—most notably norovirus, rotavirus, and enteric adenoviruses—have been isolated from 2 to 27% of returning travelers with diarrhea (20, 122, 135), although their etiologic importance is tempered by the fact that bacterial pathogens, especially in the case of rotavirus, are often concomitantly isolated. Some serologic evidence implicating norovirus as an agent of traveler's diarrhea has been reported: studies of Peace Corps volunteers in both Thailand (44) and Honduras (142) have demonstrated seroconversion following diarrheal episodes. Norovirus has particularly been implicated in outbreaks of traveler's diarrhea in certain situations, especially on cruise ships (16).

Among parasites, *Giardia intestinalis* is an important cause of diarrhea in travelers to the mountainous regions of North America (57) and to St. Petersburg, Russia (13, 95), but has also been isolated in an outbreak of illness among British tourists in a Greek hotel (73) and from 7% of Austrian tourists returning from all parts of the globe (135). *Entamoeba histolytica*, *Cryptosporidium parvum*, and *Cyclospora cayetanensis* are less common causes of diarrhea in travelers (10, 89), although cyclosporiasis should be considered in the case of travelers

returning from Peru and Nepal (81) whereas cryptosporidiosis has been reported with relatively increased frequency in travelers to Russia. Diarrhea caused by parasites is more commonly chronic and is more likely to affect travelers who visit developing countries for prolonged periods: in the study by Reinthaler et al. of returning Austrian tourists, 42% of those with parasitic causes of diarrhea had been abroad for more than 2 months, compared to only 18% of those with bacterial etiologies (135).

Overall, no pathogens are isolated in 10 to 50% of all cases of traveler's diarrhea despite the usual investigations. However, most of these cases either are self-limited or respond to empirical antibiotic treatment.

PATHOPHYSIOLOGY

Virulence factors associated with ETEC include heat-labile toxin (LT), heat-stable toxin (STa), and various colonization factors (CFs) (130). Strains producing only LT, only STa, or both toxins have been isolated from travelers with diarrhea, depending on the country visited, and thus likely represent circulating strains (91, 146). In general, ETEC strains producing STa alone or both STa and LT are associated with more severe symptoms than those producing only LT (131), although this may be related to the low prevalence of CFs in LT-producing ETEC strains (60, 114). The LT is a heterohexamer consisting of one A subunit (A1 and A2 linked by a disulfide bond) and five B subunits, bearing 75% sequence homology with cholera toxin (19, 150). LT binds to the GM1 glycophospholipid receptor on the enterocyte microvillous membrane, which induces configurational changes in the membrane that facilitate entry of the enzymatically active A1 subunit. The A1 subunit functions as an ADP-ribosyltransferase that covalently links ADP ribose to adenylate cyclase, resulting in irreversible enzyme activation and increased intracellular concentrations of cyclic AMP (cAMP) (15). Increased levels of cAMP result in activation of a secretory cascade involving protein kinase C, protein phosphorylation, and the opening of chloride channels in the apical membrane of the enterocyte, predominantly in the crypts, resulting in extrusion of these ions and H_2O into the intestine.

The STa toxin binds to an apical receptor linked to membrane-bound guanylate cyclase G (58), activating guanylate cyclase and thereby increasing intracellular concentrations of cyclic GMP (cGMP). Like cAMP, cGMP results in opening of membrane chloride channels. In addition to affecting enterocyte chloride ion secretion, both LT and STa enterotoxins inhibit sodium and chloride absorption. Furthermore, evidence suggests that in addition to the direct effects that ETEC enterotoxins have on enterocyte electrolyte secretion, interactions with the enteric nervous system (stimulation of sensory afferents in the intestinal wall) also occur, further enhancing the intestinal secretory cascade (56).

The pathogenesis of diarrhea caused by EAEC, on the other hand, is not as clear, although it has been demonstrated that these strains do not secrete heat-stable or heat-labile enterotoxins (117). EAEC colonizes the mucosal surface of the small and large bowel abundantly, mediated by structures referred to as aggregative adherence fimbriae (25, 116, 118). Colonization is followed by mild but significant mucosal damage which is most severe in the large bowel and is likely mediated by entero-

toxins (77). Most EAEC strains express the *Shigella* enterotoxin 1 (ShET1) (26, 75), which may contribute to secretory diarrhea. Additionally, many EAEC strains secrete an autotransporter toxin called Pet, which has been shown to induce a rounding of epithelial cells in culture that is dependent on the presence of functional protease activity (52, 119, 120). Pet induces disruption of the actin cytoskeleton in affected cells, possibly through cleavage of spectrin (171).

The microbial pathogens that cause dysentery express virulence factors that either allow direct invasion of enterocytes or liberate cytotoxins which produce cell death. *Salmonella* spp., *Shigella* spp., and EIEC all express invasion plasmid antigens on their surfaces which disrupt the epithelial cell cytoskeleton, thus allowing formation of endocytotic vesicles which transport the organism into the enterocyte cytoplasm. Subsequent intracellular bacterial multiplication eventually leads to cell lysis, with liberation of cytotoxin extracellularly. The invasion and cytotoxin virulence factors are only part of a cascade of events that produces inflammation in the distal ileum and colon (15).

Viral pathogens such as norovirus and rotavirus produce cytopathic changes in epithelial cells lining the small intestine, resulting in acute villous atrophy. The associated loss of enterocytes has been implicated in the transient decrease in disaccharidase activity and temporary lactose intolerance that has been ascribed to these infections. In contrast to viral causes of traveler's diarrhea, the protozoan pathogen *Entamoeba histolytica* induces enterocyte loss in the colon without directly invading cells; after adhering to the epithelial cell wall via surface lectins, *E. histolytica* releases several cytotoxic molecules such as proteinases and a pore-forming protein which creates high-conductance ion channels in the cell membrane, allowing the rapid influx of calcium and other ions, leading to cell death (15). *E. histolytica* then phagocytoses the dead enterocytes, enabling it to penetrate further into the mucosa, forming the classic "flask-shaped" ulcers.

CLINICAL SYNDROMES

Traveler's diarrhea is usually defined in studies as the passage of at least three unformed stools within a 24-h period, in association with at least one symptom of gastrointestinal disease such as nausea, vomiting, fever, abdominal pain or cramps, tenesmus, fecal urgency, or the passage of bloody or mucoid stools. By convention, it usually refers to disease that develops in a resident of the industrialized world who travels to a developing tropical or semitropical country. Typically, symptoms develop within the first week of travel, and more than 90% of cases occur within the first 2 weeks (155). Between four and five loose or watery stools a day with little to no fever is the norm; without treatment, the diarrhea usually lasts for only 3 to 4 days before resolving spontaneously in most cases (9). Approximately 80% of travelers with diarrhea complain of abdominal cramping, 10% to 25% have fever, 20% have vomiting, and between 5% and 10% report having blood or mucus in their stool (20, 141). Traveler's diarrhea can result in significant disruption to an individual's trip: as many as 40% must modify their activities in some way, approximately 20% of persons are bed bound for 1 or 2 days, and hospitalization is required for 1%, although mortality is rare (5, 9, 100, 126). Although symptoms are short-lived in the majority of cases,

between 8% and 15% of affected travelers are symptomatic for longer than a week, and 2% develop chronic diarrhea that lasts for 1 month or more; such long-lived disease is particularly associated with protozoan causes of infection (32, 152).

Severe diarrhea can result in water and electrolyte losses, leading to significant dehydration, electrolyte imbalances, and even impairment of renal function. Traveler's diarrhea, especially when caused by invasive bacteria such as *Salmonella*, *Shigella*, or *Campylobacter*, may exacerbate inflammatory bowel disease, whereas irritable bowel syndrome has been reported to be a chronic complication in as many as 10% of North Americans who develop diarrhea while traveling in Mexico (123).

PREVENTION

Prevention of traveler's diarrhea falls into four broad categories: immunization, avoidance, nonpharmacological therapy, and antibiotic prophylaxis. For U.S. residents, immunization plays an almost insignificant role in the prevention of diarrhea, since vaccines are not yet commercially available in this country for the vast majority of causative agents, although several are currently under development or in the process of licensure (see "Future Developments"). A live-attenuated oral cholera vaccine (Mutacol, Orochol) has been shown to have protective efficacy as high as 90% when recipients were challenged with *Vibrio cholerae* within 3 months of vaccination (161), whereas an oral combination vaccine consisting of both recombinantly produced cholera toxin B (CTB) subunit and inactivated whole-cell *V. cholerae* O1 (Dukoral) has shown protection against diarrhea due to both *V. cholerae* and ETEC, the latter presumably because of the significant homology between LT and CTB. In a large, placebo-controlled trial of Dukoral administered to Finnish travelers to Morocco, protection against diarrhea caused by ETEC was 52%, whereas protective efficacy against ETEC and any other pathogen was 71% (127); this finding was confirmed in another trial with travelers to Mexico, in which the vaccine conferred 50% protective efficacy against all ETEC strains (139, 159).

Both the live-attenuated and CTB/whole-cell cholera vaccines have received regulatory approval in Canada and in Europe; however, neither has been approved for marketing in the United States. Furthermore, cholera is a very uncommon cause of traveler's diarrhea, and vaccination should be considered only for high-risk individuals such as those involved in relief efforts during cholera epidemics. Similarly, *Salmonella enterica* serovar Typhi is an uncommon cause of traveler's diarrhea, although infection with this organism can cause serious illness. Since effective oral (Ty21a) and injectable (Vi) vaccines targeting this pathogen are available, they should be offered to those who will be at high risk of ingesting contaminated food or drink, such as those traveling in rural areas of developing countries for extended periods.

Dietary Counseling

Avoidance of high-risk foods and drink is an oft-cited means of reducing the risk of traveler's diarrhea, although there is little direct evidence that such behavior modification actually reduces disease incidence (17, 80, 103, 111, 129, 155). Studies assessing the relationship between the level of care taken in

TABLE 2. Drugs used for chemoprophylaxis of traveler's diarrhea

Drug	Recommended dose[a]	Adverse effects[b]
Bismuth subsalicylate[c]	2 tabs (262 mg/tab) or 30 ml QID (with meals and QHS)	Darkening of tongue and stools, mild tinnitus
Fluoroquinolones[d]		
Norfloxacin	400 mg QD	Infrequently GI
Ofloxacin	300 mg QD	disturbance, CNS
Ciprofloxacin	500 mg QD	effects, skin rash; avoid
Levofloxacin	500 mg QD	in children <9 yr old
Rifaximin[e]	200 mg BID	GI disturbance, headache

[a] tab, tablet; QID, four times a day; QHS, nightly at bedtime; QD, once a day; BID, twice a day.
[b] GI, gastrointestinal; CNS, central nervous system.
[c] See references 36 and 156.
[d] See reference 134.
[e] See reference 42.

what is eaten and the risk of traveler's diarrhea have yielded conflicting results; furthermore, it is often difficult to assess the effect of dietary counseling, since most studies are retrospective and are thus influenced by recall bias (144).

Nevertheless, because of the simplicity of this risk modification, those seeking pretravel advice should be counseled to drink only "safe" beverages, such as those that have been boiled, bottled, or carbonated. Water should be boiled vigorously for at least 1 min before consuming, which will kill most pathogens. Care should be taken when one is traveling at altitudes higher than 6,562 feet (2,000 m) to boil water for at least 3 min due to the lower atmospheric pressure. Adding either tincture of iodine (5 drops/qt) or tetraglycine hydroperiodide tablets, or using iodinizing filters, is also an effective means of purifying water, although protozoan cysts are often halide resistant; any of these items can be purchased in travel stores or pharmacies and should be used as directed by the manufacturer. While many people take pains to avoid drinking unsafe water while in developing countries, ice cubes are often overlooked, despite the fact that freezing does not kill most microorganisms. Carbonation of water kills enteropathogenic bacteria by reducing the pH; noncarbonated bottled water has been implicated in outbreaks of diarrhea in both Mexico and Portugal (11, 64). Travelers should take care to verify the seals of bottles, since filling discarded bottles with tap water and reselling them is a frequent occurrence in developing countries (53).

Fruit, including tomatoes, should be peeled, unless it has been washed thoroughly in "safe" water. Although the rind is not eaten, watermelons still carry some risk, since they may be injected with water to increase their weight and therefore their price. Salads and raw vegetables should be avoided, and only thoroughly and recently cooked meats or fish should be eaten. Leftovers and condiments in open bottles, as well as food from street vendors, have consistently been shown to carry an increased risk of contamination with organisms that cause traveler's diarrhea (2).

Nonantibiotic Options

Several nonantibiotic agents have been studied for the prevention of traveler's diarrhea (Table 2). The most effective of these is bismuth subsalicylate (BSS; Pepto-Bismol), which has

been shown to have mild antimicrobial activity as well as anti-secretory and anti-inflammatory properties (23, 46, 55, 59, 65, 110, 115). After ingestion, BSS undergoes acid hydrolysis in the gastrointestinal tract, resulting in the generation of numerous bismuth moieties in addition to free salicylate (30). Whereas the antimicrobial effects of BSS derive from the bismuth moieties (23, 110), the antisecretory and anti-inflammatory properties are likely due to the antiprostaglandin and ion channel-inhibitory effects of free salicylate (46, 55, 59, 115). When taken in the form of two 262-mg tablets four times a day with food, BSS decreased attack rates of traveler's diarrhea from 40% to 14% compared to the placebo; twice-daily dosing was less effective (36, 156).

BSS should be avoided by children under the age of 3 years and by persons allergic to salicylates, and caution is advised for patients taking other salicylate-containing medications or anticoagulants, as well as for individuals with gout or chronic renal insufficiency. Side effects are minimal at recommended doses if BSS is taken for short periods (i.e., less than 3 weeks), although BSS may produce tinnitus as well as a blackening of the stool (thus creating diagnostic confusion with melena should diarrhea develop) and tongue, although rinsing the mouth after ingestion can minimize this particular side effect. Lastly, BSS may interfere with the absorption of doxycycline—commonly prescribed for antimalarial prophylaxis—and certain other medications (49).

Lactobacillus preparations have also been used for the prevention of traveler's diarrhea, in the hope of interfering with the colonization of the gastrointestinal tract by pathogenic organisms. However, their effectiveness has been limited, with reported protective efficacy ranging from zero to 47% (78, 124, 143).

Antibiotics

Several antibiotics have been shown to be highly effective in the prevention of traveler's diarrhea, with protection levels between 80% and 90% reported. Despite this, most experts agree that antibiotic prophylaxis should be given only for short courses and only under special circumstances (67, 158). Individuals for whom antibiotic prophylaxis might be considered include those who are at increased risk of developing severe or complicated disease, such as the immunocompromised, those with inflammatory bowel disease, insulin-dependent diabetics, and those taking diuretics (who are therefore more susceptible to dehydration). Prophylaxis may also be offered to those with increased susceptibility to traveler's diarrhea because of achlorhydria, having had a gastrectomy, or taking a proton pump inhibitor. Arguments have been advanced to offer antibiotic prophylaxis to those who undertake "critical travel," such as diplomats or business travelers, for whom even a short-lived illness may not be acceptable.

When used as prophylaxis, antibiotics should be taken daily as a single dose while in an area of risk and continued for 1 to 2 days after leaving. Early studies using either doxycycline (138, 142) or trimethoprim-sulfamethoxazole (TMP-SMX) (37) showed that they were effective in preventing traveler's diarrhea in many parts of the world; however, widespread resistance to both of these agents has subsequently developed (79), thus limiting their usefulness.

The fluoroquinolones, such as ciprofloxacin, ofloxacin, norfloxacin, and levofloxacin, have been shown to be highly effective in the prevention of diarrhea in travelers (Table 2). Daily ciprofloxacin given at a dose of 500 mg has been shown to be up to 95% effective in preventing traveler's diarrhea (134). However, as with doxycycline and TMP-SMX, microbial resistance to this agent—particularly with *Campylobacter* species—has been reported with increasing frequency, especially in Southeast Asia: ciprofloxacin resistance among *Campylobacter* species isolated from both native Thais and travelers to Thailand increased from zero in 1991 to 84% in 1995 (79). Although azithromycin has been shown to be an effective treatment for traveler's diarrhea (1, 104) and likely would be effective as a chemoprophylactic drug, this has not been studied and dosing recommendations cannot be made at this time. Use of azithromycin as a treatment for persons developing acute diarrhea while on fluoroquinolone prophylaxis should be considered, especially for travelers to Thailand, where quinolone-resistant *Campylobacter* is common.

Recently, the drug rifaximin has been shown to be effective for the prevention of diarrhea in travelers to Mexico (42). This semisynthetic rifamycin derivative, although only recently approved in the United States for the treatment of uncomplicated traveler's diarrhea, has been licensed for this indication in several European countries since the 1980s. When administered orally, rifaximin remains active in the gastrointestinal tract and less than 0.4% is systemically absorbed (28, 62). In vitro antibacterial activity has been shown against most of the gram-negative enteric pathogens, in addition to gram-positive rods and anaerobic bacteria (84). In the prophylaxis study reported recently, adult travelers to Guadalajara, Mexico, who took rifaximin daily for 2 weeks reported 72% and 77% protection against traveler's diarrhea and antibiotic-treated traveler's diarrhea, respectively, with minimal side effects (42). Previous studies, as well as the current study, have demonstrated that ETEC is the predominant etiology of traveler's diarrhea in this region. Therefore, further trials must be conducted in areas where etiologic agents other than ETEC predominate before this antibiotic can be generally recommended to travelers. Poorly absorbed antibiotics such as rifaximin have potential advantages over absorbed drugs such as the fluoroquinolones in terms of fewer systemic side effects, improved safety for children and pregnant women (although these have not yet been studied and therefore cannot be recommended), and "sparing" of systemically absorbed antibiotics used for other infections in terms of development of antimicrobial resistance.

Given the existence of a relatively unabsorbed antibiotic with few side effects, the option of offering universal prophylaxis to all travelers has been raised. However, several arguments can be made against universal prophylaxis—whether it be with an absorbed or an unabsorbed antibiotic—including the cost of providing prophylaxis to tens of millions of travelers annually to prevent what in most cases is a relatively mild disease, the risk that development of antimicrobial resistance will be accelerated, and the fact that effective self-treatment can be provided that generally limits the duration of symptoms to a few hours (31, 66).

Furthermore, if chemoprophylaxis is taken, it should remain short-term (generally defined as less than 3 weeks), for a num-

TABLE 3. Drugs used for treatment of traveler's diarrhea

Drug	Recommended dose[a]	Adverse effects[b]
Loperamide[c]	4 mg STAT, then 2 mg after each loose stool; max, 16 mg/day	Abdominal cramping, rarely dizziness, dry mouth, skin rash; do not use with high fever or bloody stools or for longer than 48 h
Bismuth subsalicylate[d]	2 tabs (262 mg/tab) or 30 ml Q30 min; max, 8 doses/day	Darkening of tongue and stools, mild tinnitus
Fluoroquinolones[e]		
Norfloxacin	400 mg BID × 1–3 days	Infrequently GI
Ofloxacin	300 mg BID × 1–3 days	disturbance, CNS
Ciprofloxacin	500 mg BID × 1–3 days	effects, skin rash; avoid
Levofloxacin	500 mg QD × 1–3 days	in children <9 yr old
Azithromycin[f]	500 mg QD × 3 days	GI disturbance, drug interactions
Rifaximin[g]	200 mg TID × 3 days or 400 mg BID × 3 days	GI disturbance, headache

[a] STAT, immediately; max, maximum; tab, tablet; Q30 min, every 30 min; BID, twice a day; QD, once a day; TID, three times a day.
[b] GI, gastrointestinal; CNS, central nervous system.
[c] See references 94 and 169.
[d] See references 38 and 39.
[e] See references 48, 51, 113, 157, and 165.
[f] See reference 104.
[g] See references 35, 41, 88, and 153.

ber of reasons. First, antibiotic prophylaxis engenders a false sense of security in the traveler who might otherwise use more caution in what is eaten. The development of antibiotic-resistant pathogens, severe reactions such as Stevens-Johnson syndrome or anaphylaxis (136), candida vaginitis (37), *Clostridium difficile*-associated diarrhea, and photosensitivity reactions are all potential disadvantages of the use of chemoprophylaxis.

SELF-TREATMENT

For individuals seen in the pretravel period, counseling should focus on safe beverage and food selection. Chemoprophylaxis with either bismuth subsalicylate or antibiotics should be contemplated only in special situations such as those outlined above and is generally discouraged (67, 158). In most cases, prompt self-treatment using a combination of an antimotility agent (usually loperamide) and an antibiotic (usually either a fluoroquinolone or rifaximin)—both of which can be obtained prior to departure and carried unrefrigerated while traveling—is the preferred alternative (Table 3). Travelers should be advised of the dangers of purchasing drugs to treat diarrhea while traveling abroad, especially in developing countries. Such drugs may contain agents such as the antibiotic chloramphenicol, which may induce aplastic anemia, or iodochlorhydroxyquin (EnteroVioform), which can cause serious neurologic damage and optic atrophy (137); both of these medications have been banned in the United States.

Fluid and Electrolytes

In most cases, traveler's diarrhea is neither life threatening nor severe. Treatment, therefore, is directed at minimizing the symptoms and duration of illness. The first goal of therapy is the prevention and treatment of dehydration, which can be of special concern for children, pregnant women, and the elderly.

Travelers with mild diarrhea that does not interfere with activity can readily replace fluid and electrolyte losses with a combination of salted crackers, carbonated noncaffeinated beverages, canned fruit juices, purified water, and clear salty soups. Dairy products may worsen symptoms, and caffeine may increase gastrointestinal fluid secretion, thereby intensifying fluid losses.

Severe diarrhea, especially in infants and pregnant women, requires careful fluid replacement. Commercial packets of oral rehydration salts containing both glucose (or complex sugars) and sodium chloride are readily available in pharmacies and can be purchased prior to travel. It is important to reconstitute them with purified water in the quantities indicated by the packet's manufacturer and to adjust administered volumes according to weight (CDC website, http://www2.ncid.cdc.gov /travel/yb/utils/ybGet.asp?section=children&obj=children_gen _info.htm&cssNav=browseoyb). Oral rehydration solution promotes the absorption of both sodium and water in the small intestine by the active transport of glucose, to which the absorption of sodium is coupled. Rehydration packets containing complex sugars ("rice based") may have a greater effect on reducing fluid losses than those that are glucose based, since glucose itself may paradoxically increase the output of diarrhea fluid (18). If oral rehydration salts are unavailable, a less ideal substitute can be prepared by adding one teaspoon of table salt and eight teaspoons of sugar to one liter of purified water.

Food

During the acute phase of the illness, a diet consisting of complex carbohydrates such as rice, bread, potatoes, bananas, and crackers is prudent, although a recent study reported that restriction of diet during concomitant treatment with an antibiotic did not impact either the duration or the severity of symptoms (86). As soon as the diarrhea begins to resolve, the diet can be quickly advanced as tolerated.

Symptomatic Therapy

Although replacement of fluid losses forms the cornerstone of treatment of traveler's diarrhea, it does not by itself completely relieve the symptoms of this illness. Self-treatment of traveler's diarrhea with antimotility agents and antibiotics has become the standard advice given in most travel clinics in North America. Individuals can take both of these agents with them when they travel, so as to begin treatment as soon as symptoms occur.

Loperamide (Imodium) remains the antimotility agent of choice for traveler's diarrhea. In addition to its antiperistaltic effect, it has also been shown to increase the intestinal absorption of fluid and electrolytes (70). When used as sole therapy, loperamide provides relief for mild to moderate diarrhea (up to five loose stools per day with or without mild cramping pain), in comparison to either a placebo or bismuth subsalicylate (94, 169). Diphenoxylate plus atropine (Lomotil) is another readily available antimotility agent but is less effective than loperamide and may even prolong symptoms, as has been reported with infection secondary to *Shigella* (33). In addition, atropine has a higher incidence of side effects, including uri-

nary retention (especially in elderly men) and central nervous system toxicity, and may be addictive.

Antimotility agents are contraindicated for children under the age of 2 years because of the increased risk of adverse effects, especially narcotic intoxication with loperamide (12). In addition, they should be avoided if there is evidence of dysentery as manifested by symptoms such as high fever or bloody diarrhea, because of the possibility that they may delay clearance of invasive enteropathogens and hence prolong the course of disease.

As previously mentioned, BSS is another nonantibiotic antidiarrheal agent that has antisecretory, anti-inflammatory, and antimicrobial properties and that reduces the number of unformed stools passed and the duration of diarrhea by approximately 50% (23, 46, 55, 59, 65, 110, 115). However, it is less effective than loperamide and has several negative properties that preclude its use as treatment, including large required doses (1 oz or one tablet every 30 min for up to eight doses), delayed onset of action (up to 4 h), possible interference with the absorption of other medications such as doxycycline that may be used as malaria chemoprophylaxis, and potential adverse effects such as tinnitus (38, 39).

It should be noted that although both antimotility agents and BSS alleviate symptoms, they do not effectively treat the underlying infectious causes of the diarrhea, and that relapse of symptoms following cessation of use has been reported (94).

Antimicrobial Therapy

Antibiotic therapy is recommended either with or without loperamide for travelers with moderate to severe symptoms (three or more unformed stools during an 8-h period, particularly if associated with nausea, vomiting, abdominal cramping, fever, or bloody stools). Antimicrobials reduce the duration of diarrhea from 50 to 95 h if untreated to 16 to 30 h, as well as reducing related symptoms such as abdominal cramping and time spent incapacitated (27, 34, 40).

The choice of which antibiotic to carry when traveling has changed since the subject of traveler's diarrhea was first studied. Until recently, TMP-SMX was the drug of choice for the treatment of traveler's diarrhea; however, ubiquitous drug resistance of ETEC and salmonellae to this drug now renders it less effective (79). Moreover, it is inactive against *C. jejuni*, which, as already mentioned, is an important etiologic agent of traveler's diarrhea in Southeast Asia. The only instance in which TMP-SMX might be useful would be in areas where *Cyclospora* is a significant cause of diarrhea, such as Nepal during the summer months. Even then, it should be used only in cases where treatment with a fluoroquinolone and an antimicrobial active against *Giardia* (such as metronidazole or tinidazole) has failed.

Fluoroquinolones such as ciprofloxacin, norfloxacin, ofloxacin, and levofloxacin have until recently been the drugs of choice for the empirical treatment of traveler's diarrhea in adults (31, 45). Either alone or in combination with loperamide, they have been shown to reduce the duration of diarrhea by more than 50% compared to placebo (48, 51, 113, 157, 165). Not only are they safe and well tolerated fluoroquinolones maintain high concentrations in the stool, which may theoretically limit invasive disease. Disadvantages of their use

include drug interactions, such as those with warfarin and anticonvulsants, and the recent emergence of drug resistance, especially among *Campylobacter* isolates from Thailand (79).

In instances where the use of a fluoroquinolone is appropriate, a 3-day course is usually effective (34). Single-dose therapy has been studied and been shown to be adequate in most cases (68, 140); however, for bacteria such as *Campylobacter* and *Shigella dysenteriae*, concerns have been raised that single-dose therapy may be inadequate (5, 98). As a rule of thumb, if evidence of invasive disease exists, such as high fever, chills, or bloody diarrhea, a 3-day course of treatment should be taken.

In areas where fluoroquinolone-resistant *C. jejuni* has been found, azithromycin may be an effective option: in a study comparing azithromycin (500 mg) with ciprofloxacin (500 mg) daily for 3 days for treatment of acute diarrhea in U.S. military personnel in Thailand, azithromycin was shown to be superior in decreasing the duration of excretion of *Campylobacter* and was as effective as ciprofloxacin in decreasing the duration of symptoms (104). Single-dose azithromycin (1,000 mg) has also been shown to be equivalent to single-dose ciprofloxacin (500 mg) for the treatment of traveler's diarrhea in adults visiting Mexico, although microbial eradication rates were nonsignificantly lower with azithromycin than with ciprofloxacin (1). Azithromycin may also be the treatment of choice for children between the ages of 2 and 8 years and for pregnant women, in which cases the use of fluoroquinolones is contraindicated. The treatment of traveler's diarrhea in children under the age of 2 years is usually recommended to be oral rehydration alone.

The drug rifaximin has recently been shown to be an effective chemotherapeutic agent for traveler's diarrhea. Four major studies assessing the efficacy of rifaximin in the treatment of traveler's diarrhea have been conducted in Mexico, Guatemala, Kenya, and Jamaica (35, 41, 88, 153). Compared to placebo, administration of either 200 mg or 400 mg three times daily was associated with improvement in the duration of diarrhea (88, 153), whereas equivalency with ciprofloxacin and superiority to TMP-SMX have also been shown. However, these studies have been conducted primarily with individuals without dysentery, so treatment with rifaximin should be limited to those without fever, bloody stool, or systemic toxicity.

APPROACH TO SELF-TREATMENT

In most cases, travelers to developing countries should bring loperamide and an antibiotic to use for empirical self-treatment should they develop diarrhea. Mild diarrhea (up to three loose bowel movements a day) can be self-treated with oral rehydration and loperamide. If symptoms worsen or do not improve after 24 h, treatment with an antibiotic should be initiated. Traveler's diarrhea that is associated with more severe symptoms warrants immediate treatment with both loperamide and an antibiotic. Loperamide, however, should be avoided in cases of dysentery as evidenced by symptoms such as high fever, chills, and/or bloody diarrhea.

Until recently, the preferred antibiotic class for self-treatment of traveler's diarrhea has been the fluoroquinolones, although the exact choice should be decided by a host of factors, such as the traveler's itinerary, age, pregnancy status, and drug allergies; potential drug interactions; and whether or not chemoprophylaxis against traveler's diarrhea or malaria

will also be taken. However, the unabsorbed antibiotic rifaximin should now also be considered a potential agent for self-treatment, especially for travelers going to areas where ETEC is the predominant etiologic organism, such as Mexico. The addition of rifaximin to the armamentarium of chemoprophylactic agents for traveler's diarrhea carries several advantages, namely, the low rate of side effects and the public health benefit of sparing systemically absorbed antibiotics such as the fluoroquinolones for treatment of other, life-threatening bacterial infections, thereby delaying the development of antimicrobial resistance to these agents. Furthermore, recent evidence that irritable bowel syndrome may be a sequela of traveler's diarrhea (123) has prompted some experts to suggest this agent as a potential universal chemoprophylactic agent to prevent this outcome, although further studies to confirm this finding are needed (29, 43).

If possible, medical advice should be sought if symptoms do not diminish after initial treatment, especially in cases of persistently high fever with chills, blood and mucus in the stool, and frequent vomiting that prevents adequate fluid replacement. However, in certain cases, provision of second- or third-line antibiotics to travelers, for self-treatment of persistent diarrhea after initial treatment, may be considered in lieu of advice to automatically seek medical evaluation. This may be of special concern for travelers to Thailand, where initial treatment with a fluoroquinolone may fail secondary to infection with drug-resistant *Campylobacter*; in these cases, azithromycin would be the second-line agent of choice. Also, for those travelers departing on trips of significant duration, provision of metronidazole (or tinidazole) as a third-line agent may be appropriate, to treat infections secondary to *G. intestinalis* or *E. histolytica* infection.

Almost 3% of travelers to developing countries will develop diarrhea that persists for longer than 2 weeks despite standard antimicrobial treatment. Infection with antibiotic-resistant bacteria may account for this, although illness due to parasites such as *G. intestinalis*, *C. parvum*, and *C. cayetanensis* is also a possibility. Possible noninfectious etiologies include inflammatory bowel disease, disaccharidase deficiency, irritable bowel syndrome, and bowel carcinoma. Wherever possible, chronic symptoms should be investigated by a health care professional; if still traveling, individuals can often obtain the names of competent English-speaking physicians from the embassies of the United States, Canada, Australia, New Zealand, or the United Kingdom.

FUTURE DEVELOPMENTS

Given the large health and economic costs related to traveler's diarrhea, more effective prevention strategies are clearly warranted. Development of a broadly protective vaccine against this syndrome would be beneficial; unfortunately, the wide range of organisms that cause traveler's diarrhea greatly complicates development of such a vaccine and makes it unlikely that a single candidate will effectively prevent most cases. Despite this, considerable effort is being undertaken to develop novel vaccines against the more important agents of traveler's diarrhea, including ETEC, *Shigella* spp., *Salmonella enterica* serovar Typhi, and *C. jejuni*.

Given ETEC's place as the most common cause of traveler's

diarrhea, development of a vaccine against this pathogen has been the priority, and several candidate vaccines are currently undergoing clinical testing. The most studied ETEC vaccine currently in development is an oral whole-cell vaccine consisting of five ETEC strains that express the CF CFA/I and the different subcomponents of CFA/II and CFA/IV combined with recombinant CTB. In adult Swedish volunteers, the vaccine induced high levels of IgA against both CTB and the individual CF components (90). Subsequent studies with Egyptian children and adults (72), and with Bangladeshi children (132, 133), have confirmed the vaccine's safety and immunogenicity in these settings where the disease is endemic, although the results of larger efficacy studies are pending.

Other ETEC vaccines under development include recombinant ETEC CF CS6 in combination with LT, delivered transcutaneously by means of a topical patch (71); an oral live-attenuated vaccine (167); and a candidate vaccine consisting of CS6 encapsulated in biodegradable microspheres (96). All three of these candidates have been evaluated in phase 1 studies and have demonstrated promising safety and immunogenicity profiles.

Although less advanced in clinical development, vaccines are also being developed against shigellosis, including *Shigella sonnei* strain WRSS1, consisting of a live, oral candidate vaccine attenuated by a deletion in the *virG* plasmid virulence gene, which has shown good immunogenicity in phase 1 trials in both the United States and Israel (102, 125). A vaccine consisting of a live, attenuated *Shigella flexneri* type 2a strain carrying mutations in the *virG* and aerobactin (*iuc*) virulence genes (97) has shown 50% efficacy in a challenge study conducted with adults in the United States, although this encouraging result was tempered by safety concerns due to fever and diarrhea that was observed at the higher doses (24). Parenteral conjugate vaccines of purified *S. flexneri* type 2a and *S. sonnei* lipopolysaccharide conjugated to recombinant *Pseudomonas aeruginosa* exotoxin A are also being developed (21, 164); in particular, the *S. sonnei* conjugate vaccine has been shown to be 74% efficacious against disease due to this organism when tested in a field trial on Israeli military recruits (22).

Several new attenuated *Salmonella enterica* serovar Typhi strains are under development for use as live oral vaccines; three of these are currently at an advanced stage of clinical testing. CVD908-*htrA* is an *aroC/aroD/htrA* deletion mutant that has been successfully tested in a phase 2 trial (162), whereas the CVD909 derivative of this strain, which constitutively expresses the Vi antigen, has shown improved mucosal immunity to this virulence factor in a phase 1 trial in the United States (163) without compromising safety. The Ty800 strain, a mutant of the wild-type strain Ty2 with deletion of the *phoP/phoQ* virulence regulatory genes, has been shown to stimulate vigorous IgA and serum antibody responses to the lipopolysaccharide O antigen in a phase 1 trial (82). A third live, oral attenuated, single-dose typhoid vaccine consists of the M01ZH09 strain, carrying the targeted mutation of a structural protein (SsaV) of *Salmonella* pathogenicity island-2, a virulence factor that allows *Salmonella* species to inject bacterial effector components into host cells, allowing them to escape being killed by oxidative burst. M01ZH09 has shown acceptable safety and excellent immunogenicity in preliminary human trials (99), although results from field trials are pending.

Finally, the currently licensed polysaccharide Vi vaccine has been conjugated to a nontoxic recombinant *P. aeruginosa* exotoxin A carrier in an effort to improve its immunogenicity, particularly in young children (101, 160). A randomized, controlled trial of 2 doses of the conjugate vaccine given to 12,000 Vietnamese children of 2 to 5 years of age resulted in 91.5% protective efficacy after 27 months of active surveillance, which remained at 89% protection after an additional 19 months of passive case detection (106, 109).

A prototype oral whole-cell killed *C. jejuni* vaccine administered with ETEC LT as a mucosal adjuvant has been developed (7); however, immunity to *Campylobacter* appears to be strain specific and complex, and the antigens conferring immunity have not yet been adequately elucidated, which has hampered vaccine development (145). Furthermore, there is concern that whole-cell vaccines against this pathogen may induce the Guillain-Barre syndrome, as the exact mechanism of *Camplyobacter*-related Guillain-Barre syndrome remains uncertain.

In addition to vaccines, another area of research includes an effort to better assess the value of personal hygiene precautions in preventing traveler's diarrhea, in order to guide travelers in their choice of food and drink while abroad (144). Besides further research, improvements in the public health infrastructure in tropical and developing countries will likely lead to benefits not only to local populations but also to visitors (14). Hotels and restaurants can also play a role in reducing the risk of their guests' developing traveler's diarrhea by instituting educational programs that improve the culinary hygiene of their workers, which has been shown to reduce the incidence of traveler's diarrhea in Jamaica (6). Together, these efforts will hopefully reduce the enormous morbidity related to traveler's diarrhea, which would otherwise continue to increase as a global health problem due to ever-increasing international travel—for both leisure and business—that is the reality of today's world.

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