CHAPTER 8

Traveler's Diarrhea: Prevention and Self-Treatment

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Traveler's diarrhea is a common malady affecting up to 60% of international travelers during a 2-week trip. Areas of the world can be divided into high, intermediate, and low risk for acquiring traveler's diarrhea (**Fig. 8.1**). Lowering risk from high to intermediate speaks to excellent efforts by many countries to improve their food and beverage hygiene. However, in the preparation of travelers for self-treatment or prophylaxis of traveler's diarrhea, intermediate risk is managed practically as if the risk were high. Traveler's diarrhea is usually a self-limited illness consisting of 4-6 days of loose stools, sometimes accompanied by low-grade fever, nausea, abdominal cramping, headache, and/or general malaise. Up to 25% of sufferers will alter their activities, 15% will be confined to bed, and 1% will be hospitalized.

Classic traveler's diarrhea occurs when immunologically naïve persons move from industrialized nations to developing areas of the world. Travelers moving in the opposite direction experience far less illness. While travelers might experience gastrointestinal (GI) upset after exposure to new foods and spices, classic traveler's diarrhea is caused by microorganisms contaminating food and, to a much lesser extent, beverages. Other risk factors have been elucidated, but most are either inherent to the chosen itinerary or are host factors that are not amenable to modification (**Table 8.1**).

Enteropathogens associated with traveler's diarrhea include bacteria, viruses, and parasites. A majority of cases of the syndrome are caused by bacteria, which explains the success of antibiotics in treatment and prevention. Pre-travel vaccinations against enteropathogens can protect against typhoid (a rare cause of traveler's diarrhea), cholera (rare among tourists and business travelers), and hepatitis A (not classically included as a cause of traveler's diarrhea, since it does not always cause loose stools). A degree of cross protection against common enterotoxigenic *Escherichia coli* can be achieved with oral cholera vaccine; however, protection is modest, requires two doses completed prior to travel, and does not provide enough protection against other causes of traveler's diarrhea to obviate preparing the traveler for self-treatment and prophylaxis. The immune protection afforded by vaccination and natural protective mechanisms of the GI tract (mainly gastric acidity) can be overwhelmed by the ingestion of heavily contaminated food or water. Some pathogens such as *Shigella* can cause disease after ingestion of a relatively low infectious inoculum.

Common-sense food and water precautions during travel should guard against contracting traveler's diarrhea. However, contamination is ubiquitous in developing countries, and many travelers simply do not exercise the stringent precautions required to prevent disease. Despite efforts in travel medicine clinics to educate clientele about food and water hygiene, risk remains high among most travelers to high-risk areas of the world. For this reason a primary goal during a pre-travel clinic visit is to prepare the traveler for self-treatment and sometimes to prescribe chemoprophylaxis.

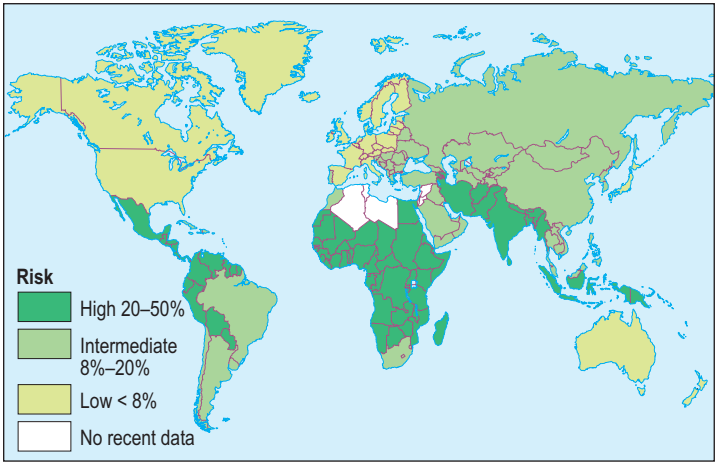

Fig. 8.1 Worldwide risks for traveler's diarrhea. (With permission of Steffen, R., Hill, D.R., DuPont, H.L., 2015. Traveler's diarrhea: a clinical review. JAMA 313, 71–80.)

TABLE 8.1 Risk Factors for Traveler's Diarrhea

Risk Factor	Comments
Age	Highest in infants and young adults
Source of food and water	Quality may depend on type of travel, adherence to dietary precautions
Type of travel	Adventurous travelers, prolonged stays
Decreased gastric acidity	Acid-reducing medications, achlorhydria, hypochlorhydria, gastrectomy
Immune deficiency	HIV infection with low CD4 count; IgA deficiency
Blood group O	Increased risk of severe disease with *Vibrio cholerae* El Tor

HIV, Human immunodeficiency disease; *IgA,* immunoglobulin A.

ETIOLOGY

Bacteria are responsible for the majority of cases of traveler's diarrhea, with viruses and parasites accounting for significantly lower numbers; however, the ratios depend somewhat on the geographic region, time of year, and presence of local outbreaks (e.g., norovirus and diarrhea aboard a cruise ship). In many cases of traveler's diarrhea, no etiologic agent can be identified unless a research laboratory is engaged. While clinical presentation does not usually predict the pathogen that will be isolated, occasionally, bloody or mucoid stools and high fever signal dysentery caused by one of the invasive pathogens.

Enterotoxigenic strains of *E. coli* (ETEC) bacteria are the most common identifiable cause of acute diarrhea in travelers visiting developing and tropical countries, with the exception of Southeast Asia, where *Campylobacter* is the most prevalent organism, followed closely by ETEC. The heat-labile toxin of ETEC is similar to cholera toxin; it causes prolonged secretion of isotonic fluid containing high amounts of bicarbonate and potassium throughout all segments of the small bowel via stimulation of adenylate cyclase. Oral cholera vaccine elicits antibodies to the B subunit of cholera toxin that cross-react with the heat-labile toxin of ETEC, and this is the basis for the vaccine's partial protection against traveler's diarrhea.

The heat-stable toxin alters fluid transport via stimulation of guanylate cyclase in the jejunum and ileum only. Many ETEC strains produce both toxins.

Campylobacter species, mostly *C. jejuni*, are common etiologic agents of traveler's diarrhea, especially in Southeast Asia, but are less frequently isolated in many other regions of the world. Seasonal variance occurs in rates of *Campylobacter* infections: peak incidence in the United States or United Kingdom occurs in the summer or spring, whereas in North Africa it peaks during the drier winter months.

Other bacterial enteric pathogens less frequently isolated in cases of traveler's diarrhea include species of *Salmonella*, *Shigella*, *Aeromonas*, *Plesiomonas shigelloides*, *Vibrio cholerae*, *V. parahaemolyticus*, *V. vulnificus*, and *Yersinia enterocolitica*.

Norovirus, implicated in outbreaks of food-borne gastroenteritis, is a common cause of gastroenteritis in adults and accounts for as high as 10-15% of the cases of traveler's diarrhea in some studies. Rotavirus is less common among adult travelers. Infections with hepatitis A virus or hepatitis E virus can account for some cases of traveler's diarrhea.

The parasites causing acute diarrhea in travelers are usually protozoans, including *Giardia lamblia*, *Cryptosporidium* sp., *Cyclospora cayetanensis*, *Entamoeba histolytica*, *Isospora belli*, and *Dientamoeba fragilis*. Although less common, helminthic infections can also account for diarrhea in travelers.

Food, fish, and shellfish poisoning (Chapters 33 and 34) can also be included among occasional to rare causes of acute diarrhea in travelers.

PREVENTION OF TRAVELER'S DIARRHEA

Potential preventive strategies for traveler's diarrhea include dietary precautions, appropriate immunizations, and chemoprophylactic agents.

Dietary Precautions

Adherence to advice on food and water precautions should logically reduce the risk from all forms of traveler's diarrhea (**Table 8.2**). Most travelers to urban destinations and tourist attractions do not need to learn techniques for water purification (Chapter 7); clean, bottled water is readily available for most travelers around the world. However, adherence to principles of food and beverage hygiene is difficult to sustain for most, particularly longer-term or adventurous, travelers. Families with small infants should consider keeping young infants off the ground and maintaining breast feeding during the trip.

Immunizations

Oral cholera vaccines are only modestly effective against ETEC strains and are not readily available worldwide. Vaccines against hepatitis A and typhoid are effective, but these

TABLE 8.2 Ten Tips for Selection of Safe Food and Water

1. Drink purified, bottled water or carbonated beverages.
2. Eat foods that are thoroughly cooked and served piping hot.
3. Eat fruits that have thick skins (they should be peeled at the table by the traveler).
4. Avoid salads made with raw vegetables, especially leafy green vegetables.
5. Do not use ice cubes, even in beverages containing alcohol.
6. Eat and drink dairy products made only from pasteurized milk.
7. Avoid shellfish and raw or undercooked seafood, even if "preserved" or pickled with vinegar or the juice of lemon or lime.
8. Do not buy and eat food sold by street vendors.
9. If canned beverages are cooled by submersion of the can in a bucket of ice water or in a stream, dry off the outside of the container before drinking the contents.
10. Use purified water for brushing teeth and for taking medications.

TABLE 8.3 Drug Regimens for Prevention of Traveler's Diarrhea

Drug[a]	Adult Dosage	Comments
Bismuth subsalicylate (Pepto-Bismol)	2 tablets, or 60 mL liquid suspension, orally, four times a day	Less effective than antibiotic prophylaxis; contraindicated in people allergic to aspirin, taking other salicylate-containing drugs, or who are pregnant. Not recommended for children.
Fluoroquinolone[b] Ciprofloxacin 500 mg Norfloxacin 400 mg Ofloxacin 200 mg Levofloxacin 500 mg	1 tablet once daily	Contraindicated in pregnancy and in people allergic to quinolones; beware of drug interaction with theophylline and caffeine.
Rifaximin 200 mg	1-2 tablets daily	Only 0.4% absorbed. Should be safe in pregnancy (not studied). Where *Campylobacter* is prevalent, 2 tablets daily is preferred owing to high MICs of the organism (not studied)

[a]Both trimethoprim-sulfamethoxazole and doxycycline showed benefit in prophylaxis in old studies; rising resistance among enteropathogens around the world has now rendered these drugs passé.
[b]All fluoroquinolones should work equally well.
MIC, Minimum inhibitory concentration.

pathogens account for very few cases of traveler's diarrhea. No vaccines are currently available to prevent the many remaining causes of traveler's diarrhea.

Chemoprophylaxis

Medications that can be used to prevent traveler's diarrhea are shown in **Table 8.3**.

Bismuth Subsalicylate

A daily regimen of bismuth subsalicylate (Pepto-Bismol®), taken as two tablets chewed four times a day for up to 3 weeks, affords about 65% protection against traveler's diarrhea. As a prophylactic agent it is relatively expensive and is not available worldwide.

Mechanisms of action of bismuth subsalicylate include antibacterial, antisecretory, and toxin-adsorptive effects. Adverse effects can include black-colored tongue and stools, constipation, and tinnitus. While bismuth subsalicylate has relatively low toxicity, it should be used with caution in those who are already taking salicylate and in patients with salicylate sensitivity, bleeding disorders, impaired renal function, or peptic ulcer disease. Bismuth subsalicylate is not recommended for children owing to the risk of Reye syndrome.

Antibiotic Prophylaxis

Most prophylactic antibiotic regimens involve taking a single daily dose throughout the trip. Taking an antibiotic for prevention of traveler's diarrhea is controversial. Fully informed travelers might prefer chemoprophylaxis after they weigh the risks and benefits of taking preventative antibiotics compared with waiting until the onset of symptoms and initiating a course of effective self-treatment. Certain travelers (business travelers, politicians, athletes, or honeymooners) taking short, critically important trips (where even a single day of illness might seriously ruin the purpose of the trip) might be offered antibiotic prophylaxis. Defining criticality of a trip is probably best left to the informed traveler. In addition, prophylactic antibiotics may be prudent in travelers with inflammatory bowel disease, brittle diabetes, acquired immune deficiency syndrome, or chronic renal impairment.

Effectiveness of antibiotic prophylaxis depends on the spectrum of activity of the antibiotic used relative to the antibiotic-resistance patterns among the local bacterial enteropathogens. Daily doses of doxycycline, trimethoprim-sulfamethoxazole (TMP/SMX),

fluoroquinolones (norfloxacin, ciprofloxacin, and ofloxacin), and rifaximin have been shown to be successful in diarrhea prevention studies. However, in most of the developing world widespread resistance to doxycycline and TMP/SMX exists among enteric pathogens, so these agents can no longer be recommended. Fluoroquinolone resistance is increasingly reported, especially for *Campylobacter* spp. and *Shigella* spp. in Southeast Asian countries such as Thailand, and limits the utility of fluoroquinolones as preventive agents.

The non-absorbed agent rifaximin prevents diarrhea. The agent is well tolerated, has uses in multiple enteric diseases, and has a strong safety record when used chronically in the prevention of hepatic encephalopathy. While it performs poorly in the treatment of invasive pathogens, it can prevent disease by invasive pathogens. It is arguably best positioned as a preventative agent. Azithromycin is commonly recommended for empiric treatment in areas with high levels of fluoroquinolone resistance, but it is not recommended for prophylaxis. The doses of drugs that can be recommended for prevention of diarrhea are shown in **Table 8.4**.

Arguments against the use of antibiotic prophylaxis include altering normal enteric flora and possibly rendering the host more susceptible to infection. Risk of allergic reactions is also a consideration. For instance, fluoroquinolone antibiotics can cause GI upset, rash, and drug interactions and might predispose to *Clostridium difficile* overgrowth. For most travelers, carrying an antibiotic for self-treatment of traveler's diarrhea is the primary approach to management, and antibiotic prophylaxis is a secondary approach.

Probiotics

Several studies have examined the use of probiotics in the prevention of acute diarrhea. A meta-analysis of the available data from 34 masked, randomized, placebo-controlled trials suggests that probiotics reduced the risk of traveler's diarrhea by a meager 8% (95% CI–6–21%). The protective effect did not vary significantly among probiotic strains used alone or in combinations of two or more strains. Probiotics are popular among some travelers, and they are safe, but they cannot be recommended as a substitute for antibiotics in the prevention of traveler's diarrhea.

EMPIRIC SELF-TREATMENT

The majority of travelers will do well if they are instructed to follow the guidelines for safe food and water selection and if they carry a supply of appropriate medications for empiric self-treatment. Treatment of traveler's diarrhea consists of (1) oral rehydration, (2) symptomatic treatment, and (3) empiric antibiotic treatment. As a rule the traveler developing diarrhea within days of return from a developing country can be advised simply to take the medications already prescribed for self-treatment. A trip to the doctor or a costly laboratory work-up can usually be avoided.

Oral Rehydration

Dehydration due to abnormal losses of body fluids through watery diarrhea can accentuate the general feeling of misery. A wide variety of liquids can be used for oral rehydration, including mineral water, canned juices, carbonated caffeine-free beverages, bouillon, Gatorade®, etc. In the event of severe dehydrating diarrhea, many commonly available liquids contain excess sugar and insufficient electrolytes for optimal replacement. Commercially formulated preparations for oral rehydration solution (ORS) can be purchased premixed and in powdered form convenient for mixing in clean water. For the vast majority of travelers, concocting their own ORS is logistically impossible. Furthermore, most traveler's diarrhea, even presenting with severe symptoms, is simply not dehydrating if treated early with an antibiotic plus loperamide regimen (see below). Loperamide has both antimotility and antisecretory properties. The pathogen of leading concern for the possibility of developing dehydration is ETEC, owing to its secretory toxin production. However, unlike cholera toxin, ETEC toxin is not bound irreversibly to the gut, so once an antibiotic kills the organism the secretory effect of the toxin abates in a matter of hours.

TABLE 8.4 Drugs for Self-Treatment of Traveler's Diarrhea in Adults

Drug	Adult Dosage	Comments[a]
Symptomatic medications		
Bismuth subsalicylate (Pepto-Bismol)	30 mL (or 2 tabs) q30 min × 8 doses	The maximum recommended dose is 240 mL/day (16 tablets).
Loperamide (Imodium®)	Take 2 caplets (2 mg each) for first dose; then 1 after each loose stool; do not exceed 8 caplets (16 mg) in 24 h	Antiperistaltic drug; use with caution in dysentery; sold over the counter.
Antibiotics		
Trimethoprim/ sulfamethoxazole (Bactrim®, Septra®)[b]	160-mg/800-mg tab (1 double-strength tab) every 12 hours for 3 days	Do not use in sulfa-allergic patients; less effective against traveler's diarrhea in many areas of the world due to drug-resistance; drug of choice for *Cyclospora* (treat for 7 days).
Norfloxacin (Noroxin®)	400-mg tablet every 12 hours for 3 days	Do not use in pregnancy or in children <18 years old.
Ciprofloxacin (Cipro®)	500-mg tablet every 12 hours for 3 days, or 750-mg tablet once[c]	Do not use in pregnancy or in children <18 years old.
Levofloxacin (Levaquin®)	500-mg tablet once or every 24 hours for 3 days	Do not use in pregnancy or in children <18 years old. Continue therapy for 3 days if inadequate response after first dose or if fever or bloody stool is present.
Azithromycin (Zithromax®)	1 g as a single oral dose or 500 mg once daily for 3 days[b]; 500 mg or 1 g as a single dose[c]	Drug of choice for quinolone-resistant *Campylobacter* strains; use for traveler's diarrhea in persons unable to use fluoroquinolones.
Rifaximin (Xifaxan®)	200-mg tablet three times a day for 3 days	Effective drug treatment for ETEC or pathogen-negative TD; poorly absorbed following an oral dose. Do not use for invasive pathogens.

[a]See Chapter 12 for pediatric guidelines for treatment of diarrhea.
[b]This drug has been studied at both doses for treatment of *Campylobacter*.
[c]Doses for traveler's diarrhea when *Campylobacter* is not prevalent.

Symptomatic Treatment

Regardless of specific etiology, most people will feel better if symptomatic relief from frequent stools and abdominal cramps can be obtained.

Bismuth subsalicylate taken in treatment doses (**Table 8.4**) can reduce the number of stools and is a reasonable choice for initial treatment of mild diarrhea in adults. However, travelers must be warned that they should not take doses of antibiotics (e.g., doxycycline and fluoroquinolones) and bismuth subsalicylate or any product containing bivalent cations at the same time, because of decreased absorption of the antibiotic. If diarrhea develops while using bismuth subsalicylate prophylaxis or if a treatment dose of bismuth subsalicylate was taken but is not giving adequate relief, an oral dose of antibiotic should be delayed by several hours.

Loperamide (Imodium®) is useful for obtaining rapid symptomatic relief from frequent bowel movements and abdominal cramps. Loperamide has an antiperistaltic effect on the intestines, which slows intestinal transit and delays excretion, as well as an antisecretory effect. Studies have shown beneficial results using loperamide and antibiotics in combination for traveler's diarrhea, including dysentery. Using loperamide alone in nondysenteric disease was effective in the majority of patients, but 17% opted to take an antibiotic for better relief. Antimotility agents, including loperamide, should not be given without a concurrent antibiotic in patients with dysentery. Loperamide is not usually recommended in young children due to the risk of side effects such as respiratory depression, drowsiness, and ileus, although in those observations the agent had often been given in too high doses or was continued well beyond the recommended duration of use. Because Lomotil® (the combination of diphenoxylate HCl and atropine sulfate) is habit forming and is no more effective than safer loperamide, it is no longer recommended.

The clay-based products such as attapulgite or kaolin (Kaopectate®) bind water in the colon. In studies these products caused a slightly firmer stool but did not impact the frequency of diarrhea.

Empiric Antibiotic Treatment

Several studies have shown that if self-treatment with loperamide plus one of the antibiotics is started shortly after the onset of nondysenteric traveler's diarrhea, relief can be obtained by many patients within 24 hours. The benefits of antibiotic plus loperamide cannot be predicted by the severity of the onset of diarrhea. A proportion of those treated will benefit from the loperamide regardless of the severity of presentation. Choice of an antibiotic will be dictated by several factors, including the resistance profile of the enteric pathogens likely to be encountered at the destination, age of the traveler, and any underlying medical illnesses.

Any illness that is characterized by high fever (>102° F), severe abdominal pain, or the passage of grossly bloody stools (dysentery) mandates treatment with an antibiotic, and oral rehydration might also be indicated. While loperamide actually benefited patients with dysenteric shigellosis when combined with ciprofloxacin, many experts prefer not to use loperamide when treating overt dysentery. Seeking medical attention at the onset of severe disease in many locations of the developing world will too often result in unnecessary hospitalization and administration of intravenous fluids. Starting an antibiotic (with or without loperamide) early in the course of severe disease often suffices to afford adequate relief and an excellent outcome. If relief of severe disease is not realized within a day or two or if dehydration develops despite self-treatment, medical help should be sought.

If diarrhea is caused by a virus, loperamide will be beneficial, but a course of antibiotic self-therapy is unlikely to influence the outcome. If diarrhea is caused by a resistant bacterial agent or by a parasite, illness might persist beyond the empiric treatment regimen, and the traveler should seek medical consultation.

Fluoroquinolone Antibiotics

The fluoroquinolone antibiotics (e.g., norfloxacin, ofloxacin, levofloxacin, and ciprofloxacin) are active against the majority of bacteria commonly implicated in traveler's diarrhea in many parts of the world. Although the fluoroquinolones are generally accepted as one of the antibiotics of choice for empiric treatment of traveler's diarrhea in adults, growing resistance to this class of antibiotics among *Campylobacter* spp. in some Southeast Asian countries poses a significant challenge to its usefulness for empiric treatment of traveler's diarrhea. In Thailand, for instance, the rate of fluoroquinolone resistance of *Campylobacter jejuni* is extremely high.

Azithromycin

Azithromycin is highly efficacious as a treatment for traveler's diarrhea, including in areas where *Campylobacter* spp. have developed fluoroquinolone resistance. In a study comparing

azithromycin (500 mg) or ciprofloxacin (500 mg) daily for 3 days for the treatment of acute diarrhea among US military personnel in Thailand, azithromycin was superior to ciprofloxacin in decreasing the excretion of *Campylobacter* and as effective as ciprofloxacin in shortening the duration of illness. In another study in Thailand, treatment with a single 1-g dose of azithromycin was significantly more efficacious (96% cure rate) compared with a 3-day regimen of azithromycin at 500 mg daily (85% cure rate) and a 3-day regimen of levofloxacin at 500 mg daily (71% cure rate). In a study conducted among adult travelers in Mexico (where ETEC is prevalent and *Campylobacter* is uncommon), azithromycin given as a single oral dose (1 g) was comparable with levofloxacin (500 mg) for the treatment of traveler's diarrhea, with >90% cure rates in both regimens. When *Campylobacter* is not a concern, azithromycin, in combination with loperamide, can be given as a single 500-mg dose with beneficial results comparable to the use of higher doses.

Rifaximin

Rifaximin, a semisynthetic derivative of rifamycin, is a poorly absorbed antibiotic that is approved for the treatment of traveler's diarrhea in persons 12 years of age and older at a dose of 200 mg three times a day for 3 days. Rifaximin is not recommended for treatment of diarrhea accompanied by fever or blood in the stool, as it shows inadequate efficacy in the treatment of diarrhea due to invasive enteropathogens. In a recent study comparing treatment of traveler's diarrhea (where ETEC was the prevalent pathogen) with rifaximin alone (200 mg three times daily for 3 days), loperamide alone (4 mg initially followed by 2 mg after each unformed stool), or a combination of both drugs using the same dosing regimen, rifaximin-loperamide therapy provided rapid symptomatic improvement compared with either agent alone. The problem with recommending rifaximin plus loperamide as preferred initial empiric therapy is that travelers might need to be armed additionally with an agent predictably active against invasive pathogens in the event rifaximin fails to afford adequate relief.

SPECIAL CONSIDERATIONS

People stricken with diarrhea who are unable to tolerate oral rehydration owing to severe nausea and vomiting may need medical attention and intravenous fluids in a hospital. In particular, this may be the case in hot climates, where insensible water loss is greater and where heat stroke may be a danger.

People taking diuretics need to be especially cautious in the face of severe, watery diarrhea and probably should stop the diuretic during the acute diarrheal illness. In the event of severe diarrhea lasting >1 or 2 days, such people should seek medical attention for a blood pressure check, an examination of the heart and lungs, and a serum potassium check.

In the case of many pathogens, the likelihood of developing diarrhea is inoculum dependent. People with decreased gastric acidity due to achlorhydria, gastric resection, frequent antacids, or medication with H_2 blocking agents or proton pump inhibitors may be more susceptible to illness and therefore may be in special need of pre-travel medical counseling on preventive measures for traveler's diarrhea.

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