

EDUCATION PRACTICE

Traveling Internationally: Avoiding and Treating Travelers' Diarrhea

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This article has an accompanying continuing medical education activity on page e71. Learning Objectives—At the end of this activity, the learner should be able to identify the causes of travelers' diarrhea and their clinical manifestations, and cite current methods of prophylaxis and treatment.

Clinical Scenario

A 29-year-old woman from the US develops fever (101°F) and passes grossly bloody stools 3 days after arrival in India. She takes 3 days of ciprofloxacin which she brought with her, without benefit. On arrival to her home city in the US she seeks medical attention for 14 days of persistent diarrhea and a 10 pound weight loss. Gastrointestinal workup including esophagogastroduodenoscopy and colonoscopy are normal. Stool samples are negative for *Giardia*, *Cryptosporidium* and *Entamoeba histolytica* by commercial immunoassay. She is given 7 days of metronidazole by her primary physician for the possibility of occult *Giardia* diarrhea with little improvement in her symptoms. By the thirtieth day of her illness, her diarrhea has lessened and the fever is gone. Over the subsequent 6 months a change in stool form and consistency is associated with intermittent but daily abdominal pain and bloating. Her abdominal discomfort is temporarily improved by defecation.

The Problem

Approximately 80% of travelers' diarrhea (TD) is caused by bacterial enteropathogens. The diarrheagenic *Escherichia coli*, enterotoxigenic *E coli*, and enteroaggregative *E coli* explain approximately half of the TD cases. Viral agents, particularly noroviruses, cause 5%–15% of the illness. Protozoal parasites explain a small percent of TD. Parasites are important causes of TD among travelers to Russia and in those visiting any region of the developing world who develop persistent diarrhea.

Figure 1 outlines the important clinical presentations of TD. Approximately 85% of cases of TD consist of passage of increased numbers of stools of decreased form when compared with normal (watery diarrhea). Approximately 10% of subjects with TD experience gastroenteritis with vomiting as the primary feature of the disease. Febrile dysentery is seen in 3%–5% of TD cases that develop in Latin America and Africa and in 5%–10% among people who acquire their illness in south Asia. The invasive bacterial enteropathogens, *Shigella*, *Campylobacter*, and *Salmonella* cause most of the dysenteric illness. Rarely (<1%) *Entamoeba histolytica* (amoebiasis) may be seen as a cause of dysentery in travelers. Persistent diarrhea (illness lasting \geq 14 days) occurs in 3%–5% of travelers. With persistent diarrhea, the parasitic pathogens *Giardia*, *Cryptosporidium*, *Cyclospora*, and *Entamoeba* should be sought. Post infectious irritable bowel syn-

drome (PI-IBS) has been well documented to occur following bacterial diarrhea including TD. PI-IBS causing chronic abdominal discomfort, bloating, and change in stool form, has been shown to last for more than 5 years in a majority of affected persons. Rarely TD may unmask inflammatory bowel or celiac disease.

The most important pathophysiologic mechanism of acute travelers' diarrhea is secretion where salt and water move across the small bowel and colonic mucosa and are lost in the gut lumen. Newer antisecretory drugs are being developed for the therapy of acute diarrhea recognizing the importance of intestinal secretion in the disease.

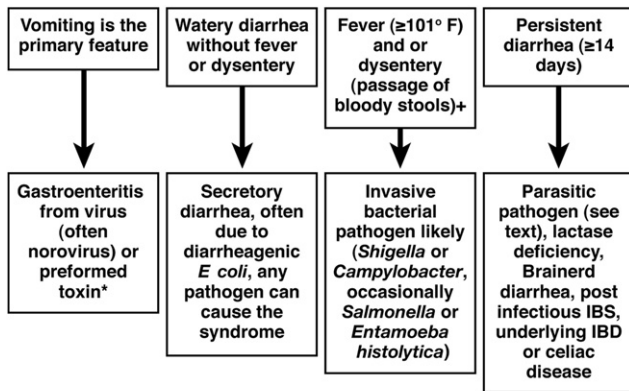
Management Strategies and Supporting Evidence

There are two means of TD prevention to consider. The first is exercising care with what is eaten and drunk and the second is employing chemoprophylaxis during visits to high risk regions (see Figure 2). Both will be considered here.

Prevention of TD by Care in Food and Beverage Selection

The evidence implicating food as the source of most cases of TD is strong. Bacterial pathogens can survive in or on food if not heated to 60° C before consumption. Bacteria need moisture for growth and will regularly be found in moist foods maintained at room temperature. The outer cover of unwashed fruits and vegetables often is contaminated by bacterial enteropathogens. The high sugar content of syrups, jellies, jams, and honey inhibit the growth of bacteria. Bottled beverages, with an intact seal upon opening the top and especially carbonated beverages are considered safe even for persons with immune

Abbreviations used in this paper: BSS, bismuth subsalicylate; IBS, irritable bowel syndrome; ISTM, International Society of Travel Medicine; PI-IBS, post infectious irritable bowel syndrome; TD, travelers' diarrhea.



Diarrheagenic *E coli* = enterotoxigenic *E coli* (ETEC), enteroaggregative *E coli* (EAEC) or diffusely adherent *E coli* (DAEC); IBS = irritable bowel syndrome; IBD = inflammatory bowel disease

*Toxin from *Staphylococcus aureus* or *Bacillus cereus*

+ Rarely Shiga toxin producing *E coli* can produce bloody diarrhea, usually without fever

Figure 1. Clinical presentation and pathophysiologic alterations in enteric infection among travelers from industrialized countries to developing regions. IBD, inflammatory bowel disease.

deficiency. In **Figure 2** the usually safe foods and beverages are briefly listed to help the cautious traveler concentrate on the items likely to be safe during high risk travel.

Prevention of TD by Employing Chemoprophylaxis

It has been known since the 1950s that antibacterial drugs taken daily prevent an important measure of the enteric illness seen in international travelers to high risk regions. This observation represents the first evidence that bacterial pathogens were responsible for most of the illness. While the fluoroquinolones are known to prevent the disease and azithromycin is likely to be effective there are 2 concerns related to recommending absorbed drugs as prophylactic agents. First, widespread use may encourage the development of antibiotic resistance to these important drugs among the extraintestinal bacterial flora, limiting their effectiveness in treating systemic infection. Secondly, their absorption may lead to potentially serious systemic side effects. Rifaximin, a poorly absorbed antibacterial drug, meets the ideal properties for chemoprophylaxis, with its low frequency of side effects and reduced concern about development of antibiotic resistance outside the gut. Although a single daily dose of rifaximin is effective in preventing TD, the recommended dose is one 200 mg tablet twice a day with major meals while in areas of high risk. Two doses are recommended for enhanced protection and to assure that at least 1 daily dose is taken by the poorly compliant traveler. In placebo-controlled, randomized trials, rifaximin prevented more than 60%–70% of TD cases that would have occurred without drug use. The causes of TD cases during chemoprophylaxis are largely unstudied although viruses and protozoa are likely. There are no known side effects of daily rifaximin use.

Bismuth subsalicylate (BSS) is an alternative agent for chemoprophylaxis in the prevention of TD. BSS may be as effective (65% protection rate) but it is a less convenient approach. The BSS dose for adults is 2 tablets with meals and at bedtime or 8

tablets a day (2.1 grams/d of BSS). BSS use is associated with blackening of tongues and stools and mild tinnitus.

Treatment of TD

There are 3 usually effective curative antibacterial drugs for TD therapy, given here in order of their development. Ciprofloxacin treats most of the non-*Campylobacter* causes of TD and is given in a dose of 750 mg once a day for 1–3 days. Ciprofloxacin may be less expensive than the other options due to its generic status, but the price may not be much lower in many pharmacies. Rifaximin is effective in most cases of TD when not caused by invasive bacterial enteropathogens. Rifaximin is given in a dose of 200 mg 3 times a day for 3 days. Azithromycin is effective for most pathogens and is the drug of choice for febrile dysenteric TD, given to adults in a dose of 1000 mg in a single dose. Children with moderate to severe TD can be treated with azithromycin, 10 mg/kg/d given in 1 daily dose for 3 days (maximum daily dose 500–1000 mg).

Loperamide may be given with 1 of the antimicrobial agents for optimal response. Loperamide provides rapid improvement in diarrhea while the antibacterial drug provides curative effects. When loperamide is employed as a single drug for adults, it is given in a dose of 4 mg initially followed by 2 mg after each unformed stool is passed, not to exceed 8 mg in a day for no more than 2 days. Post-diarrhea constipation is a common complaint in travelers with diarrhea treated with loperamide. It is suggested that if loperamide is added to antibacterial therapy for TD in adults that only the loading dose be given (4 mg) without further doses to prevent postdiarrhea constipation. Diphenoxylate hydrochloride with atropine (Lomotil) is likely to be as effective as loperamide, although it has some drawbacks including side effects from the atropine and more important central opiate effects, than would be seen by ingestion of loperamide, should a child inadvertently consume his or her parent's medication. **Figure 3** outlines recommended treatment

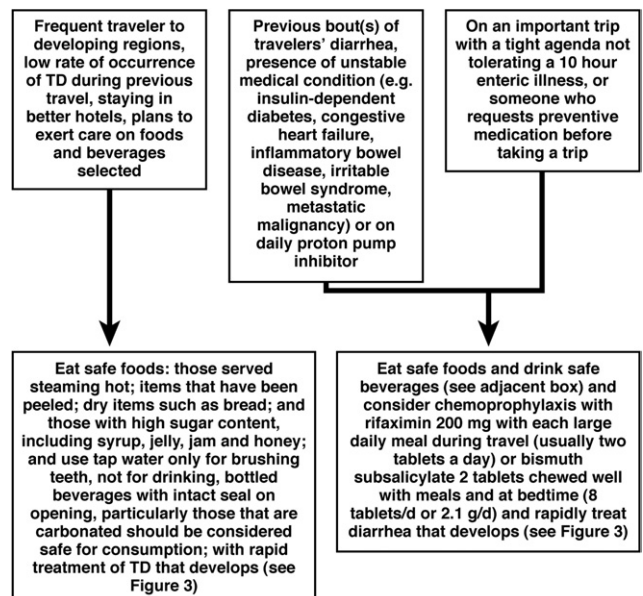


Figure 2. Prevention of TD among persons traveling to developing regions from industrialized countries.

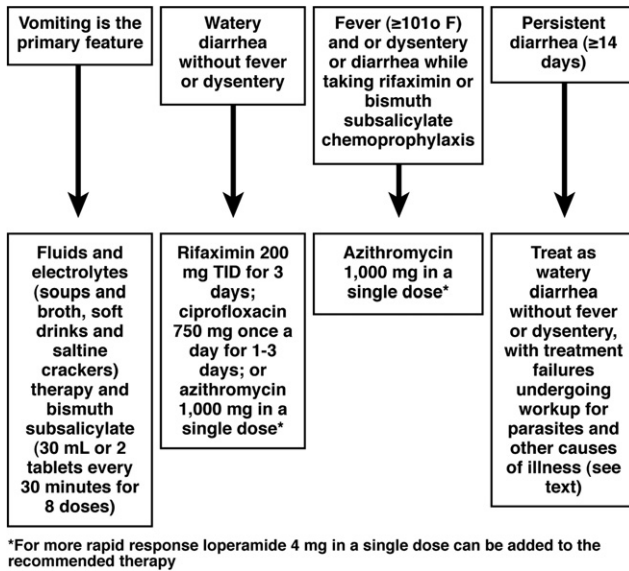


Figure 3. Empiric treatment of traveler's diarrhea based on clinical presentation. TID, three times a day.

approaches for patients with TD based on clinical features and travel destinations.

Evidence Supporting Management Strategy

The International Society of Travel Medicine (ISTM) employed a multicountry expert review of the existing evidence for the principles of therapy and prevention of travelers' diarrhea, published in the *Journal of Travel Medicine* (see suggested reading). These publications include the references providing the scientific evidence of the recommendations made in the 2 ISTM publications and made here.

Areas of Uncertainty

There remain 3 pressing issues with regard to TD treatment and prevention that need further study. The first area of uncertainty in TD prevention, do careful food and beverage precautions lead to reduced rate of enteric disease among international travelers? There is only 1 prospective study of the protective effect of dietary restrictions in the prevention of TD which shows a relationship of number of dietary indiscretions and TD rate. Other retrospective studies suggest it is hard to reduce rates of TD by being careful what is consumed or drunk. The second critical travel medicine question, does chemoprophylaxis prevent posttreatment complications including IBS? The available studies suggest that posttravel IBS occurs most commonly in those who have developed TD, suggesting that symptomatic disease is 1 of the important risk factors for development of chronic gastrointestinal symptomatology. If true, diarrhea prevention would reduce the occurrence of posttravel IBS. The third question needing answers relates to the drug selection for self-treatment of travelers' diarrhea. Ideally, travelers would take 2 drugs with them on trips to developing regions: (1) rifaximin to be employed in the empiric therapy of the commonly occurring acute watery diarrhea without fever or

dysentery, based on expected efficacy of the drug and safety profile and, (2) azithromycin for the low frequency of occurrence of febrile dysenteric illness. If travelers are reluctant to purchase and transport 2 drugs, any 1 of the 3 recommended drugs above is reasonable considering the self-limiting nature of untreated TD.

Published Guidelines

The Infectious Diseases Society of America developed guidelines that also identified the fluoroquinolones, rifaximin, and azithromycin as the key drugs for self treatment of TD. The Infectious Diseases Society of America publication indicated that the fluoroquinolones were the recommended class of drugs to use when chemoprophylaxis is employed for the prevention of TD. The ISTM review of the available scientific evidence did not consider the fluoroquinolones as the optimal drug for disease prevention. In their report, the ISTM indicated that rifaximin was the safest available drug with reduced concern about the development of systemic antibacterial resistance compared with fluoroquinolones and azithromycin due to its low level of absorption.

Recommendations

The patient earlier presented is likely to be suffering from PI-IBS. She experienced dysenteric illness and failed to respond to ciprofloxacin therapy, both suggesting she suffered from a *Campylobacter* infection, known to be important in TD acquired in southern Asia. *Campylobacter* appears to be particularly important to the development of PI-IBS. For patients with bloody diarrhea acquired during travel, azithromycin is the preferred treatment. Given the predictable importance of TD in persons from industrialized regions during trips to developing tropical and semitropical regions and the common occurrence of persistent symptoms after a bout of TD, a greater emphasis on prevention is currently being seen in travel medicine. All persons planning trips to developing tropical and semitropical regions should be armed pretravel with at least 1 of the effective antibiotics for self-treatment of TD. For returning travelers with diarrhea, empiric antibiotic treatment without workup for cause is recommended considering the lack of usefulness of a laboratory workup for the common causes of TD and the expected favorable clinical response to antibiotics. A laboratory and endoscopic evaluation is indicated for those with failure to respond to treatment, particularly when symptoms persist for more than 14–30 days.

Suggested Reading

1. DuPont HL, Jiang ZD, Okhuysen PC, et al. A randomized, double-blind, placebo-controlled trial of rifaximin to prevent travelers' diarrhea. *Ann Intern Med* 2005;142:805–812.
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 6. Shah N, DuPont HL, Ramsey DJ. Global etiology of travelers' diarrhea: systematic review from 1973 to the present. *Am J Trop Med Hyg* 2009;80:609–614.
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Conflicts of interest

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