

Update on Travelers' Diarrhea: Practical Strategies for Prevention and Treatment



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Travelers' diarrhea can be caused by a variety of enteric pathogens, including bacteria, viruses, and parasites. The most common causative agent is *Escherichia coli*, which is usually transmitted by fecally contaminated food and water. Occurrence varies by region but is higher in developing countries. Commonsense preventive measures regarding hygiene and the source of food and drink are effective but difficult for most travelers to strictly follow. While travelers' diarrhea is self-limiting, treatment with an antimotility drug like loperamide is effective in reducing the symptoms and duration of illness. Combination therapy with an antimicrobial drug should be considered in more severe invasive or prolonged diarrhea, or for patients at high risk of complications, such as the elderly, diabetics, cirrhotics, and immunocompromised patients. Self-treatment is a safe and effective approach in most cases. Travelers should be advised before departure about dietary precautions and means of self-treatment.

INTRODUCTION

In an age of increasing globalization and ease of travel, physicians can expect to encounter growing numbers of patients who have contracted travelers'

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diarrhea (TD) and others who seek medical advice and prophylactic treatment before setting out. With proper education about prudent dietary and hygiene practices, patients can reduce their risk of contracting TD. In addition, with appropriate instructions, patients can safely and effectively reduce the symptoms and duration of the diarrhea without physician intervention.

TD is by definition self-limited and poses a risk to certain vulnerable populations such as infants, the elderly, and those who are immunosuppressed. Symp-

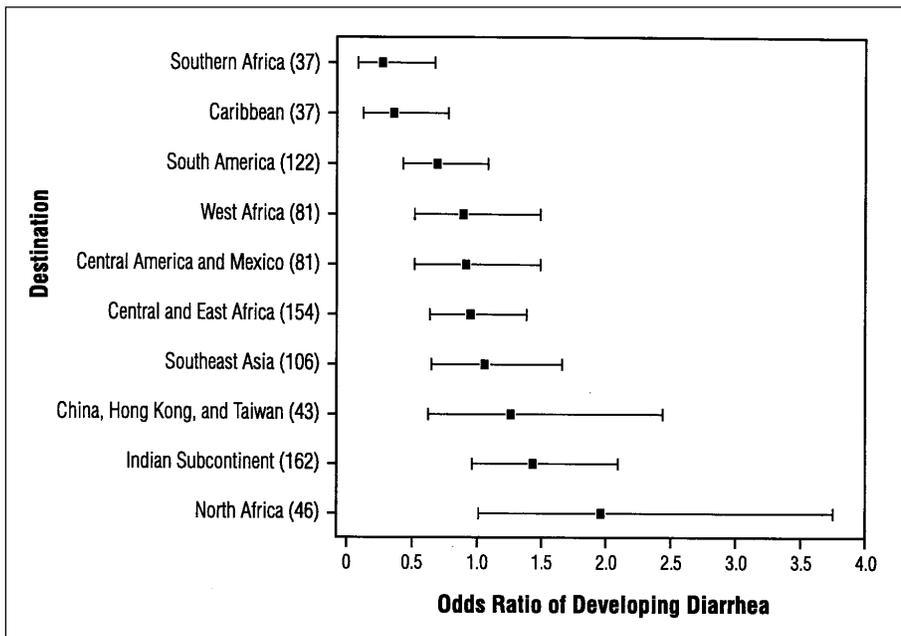


Figure 1. Odds ratio of developing diarrhea by destination using a logistic regression analysis. The number in parentheses after each region represents the number who traveled to the area. Bars indicate 95% confidence intervals. * $P < 0.03$. Reprinted with permission from Hill DR. *J Travel Med*, 2000;7:261.

omatic treatment is justified by the inconvenience and cost of travel days lost due to the illness. Early treatment with antimotility agents, such as loperamide for mild diarrhea, provides relief of symptoms with few side effects. Antimicrobial agents are not recommended for the prevention of TD.

EPIDEMIOLOGY

Each year an estimated 50 million people travel from industrialized to developing countries (1). It is estimated that more than 7 million cases of TD occur each year (2). The risk of contracting TD varies with the geographic location of travel. Regions associated with high risk are the developing countries of Latin America, Africa, the Middle East, and Asia. Intermediate-risk regions include Southern Europe and a few Caribbean islands. Low-risk regions include Canada, Northern Europe, Australia, New Zealand, the United States, and a number of Caribbean islands (3,4). The likelihood of developing diarrhea according to destination is presented in Figure 1.

The rate of attack is estimated to be between 20% to 50% among travelers to high-risk regions (3,4). Among a cohort of 784 Americans traveling to developing countries, 46% experienced diarrhea and 34% met a strict definition for TD defined as >3 unformed stools/d with or without cramping, fever, vomiting, or gross blood, or <3 stools/d plus one or more symptoms (5). While the attack rates are approximately equal in men and women, there is a greater incidence of TD in younger adults (4).

Definition and Symptoms

TD is defined as a twofold or greater increase in the frequency of unformed bowel movements (4). Commonly associated symptoms include nausea, bloating, urgency, abdominal cramps, fever, and malaise. While bloody stools, vomiting, or high fever occur in a minority of TD cases (4), these symptoms may indicate the presence of more serious disease.

Disease Course

The onset of TD usually occurs within 2 to 3 days of travel, and more than 90% of cases occur within the first 2 weeks of stay in a developing country (1,6). TD typically results in 4 to 5 loose or watery stools per day, for a median duration of 3 to 4 days. However, 10% of cases persist beyond 1 week, approximately 2% last longer than 1 month, and less than 1% last beyond 3 months (3).

While TD is rarely life-threatening (3), it is important to differentiate it from other, potentially more serious, diseases. An important element in the differential diagnosis of TD is the presence or absence of fever. Food poisoning due to *Staphylococcus aureus*, *Clostridium perfringens*, and *Bacillus cereus* and hem-

orrhagic colitis due to *Escherichia coli* 0157:H7 do not usually produce fever. Patients with acute diarrhea due to *Salmonella*, *Shigella*, and *Campylobacter* invariably have fever (7). Blood or mucus in the stool suggests a complication or infection with an enteroinvasive organism that may require specific treatment (3,8).

It is possible to culture a stool sample to identify the pathogen. However, the utility of stool culture is considered questionable because symptoms from TD usually stop before results are available (9); however, when there is presence of blood in stools, a stool culture should be obtained (8).

CAUSES OF TRAVELERS' DIARRHEA

Most cases of TD are caused by infection and can be acquired from fecally contaminated food and/or water (3,4), and from contact with the contaminated hands of

an infected person (4). Bacterial pathogens are the main cause of TD, in particular, enterotoxigenic *E coli*, which is found up to 50% of the time when bacteria are isolated from patients with TD (Table 1) (1,4). The relative virulence of these pathogens can vary: *Shigella* can cause illness with as few as 10 organisms whereas *Salmonella* requires large numbers of bacteria (100,000) to cause illness (1,10).

Viral pathogens such as rotavirus and norovirus (ie, Norwalk-like viruses) play an unclear role in TD because they are often isolated from the feces of asymptomatic travelers (4). Noroviruses, however, have been implicated as the cause of TD on cruise ships (11). Parasitic pathogens may have a role in some cases of TD. However, few studies of TD have included examination for parasites (4).

Certain populations are at increased risk for TD, for example, patients with atrophic gastritis, those taking a long-term course of acid suppressants or proton-pump inhibitors (12), and those who are elderly or immunosuppressed (13). TD also may exacerbate pre-existing inflammatory bowel disease, such as ulcerative colitis or Crohn's disease (1).

PREVENTION MEASURES

Food and Beverage Preparation

There are steps travelers can take to prevent TD. Exercising care in food and beverage preparation is paramount (Table 1) (1). The saying, "boil it, cook it, peel it, or forget it" is catchy but achieving behavior modification can be a problem (6). Risk level varies with eating place: it is lowest in private homes, higher in restaurants, and highest in food purchased from street vendors (3).

TD risk also varies according to food type. There is high risk in eating raw vegetables, meat, seafood, and dairy products, and travelers should avoid unpeeled fruits and vegetables, salads, and dairy products (4). There also is high risk in drinking unpasteurized milk, untreated tap water, and ice made from untreated tap water. Water can be made safe to drink if it is boiled for 5 minutes or treated chemically, particularly with iodine products (1,4,6).

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Table 1
Causes of Travelers' Diarrhea

| Cause | Percent Isolation |
|--------------------------------|-------------------|
| Bacteria | 50–75 |
| <i>Escherichia coli</i> | 5–70 |
| Enterotoxigenic | 5–70 |
| Enteroadhesive | ? |
| Enteroinvasive | ? |
| Enterohemorrhagic | ? |
| <i>Campylobacter</i> spp | 0–30 |
| <i>Salmonella</i> spp | 0–15 |
| <i>Shigella</i> | 0–15 |
| <i>Aeromonas</i> | 0–10 |
| <i>Plesiomonas</i> | 0–5 |
| Other | 0–5 |
| Protozoa | 0–5 |
| <i>Giardia lamblia</i> | 0–5 |
| <i>Entamoeba histolytica</i> | 0–5 |
| <i>Cryptosporidium</i> spp | ? |
| <i>Cyclospora cayetanensis</i> | ? |
| Viruses | 0–20 |
| Rotavirus | 0–20 |
| Enteroviruses | ? |
| No pathogen isolated | 10–40 |

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CHEMOPROPHYLAXIS

The prophylactic use of non-antimicrobial medications is not recommended. Prophylactic use of difenoxin, the active metabolite of diphenoxylate, may actually increase the incidence of TD, in addition to producing undesirable side effects (3). Bismuth subsalicylate may prevent TD, but benefit is achieved when it is given four times a day with meals, a schedule that is often impractical. Absorption of salicylate may cause tinnitus and raises concern about interactions with aspirin (1,6).

The role of antimicrobial agents in the prevention of TD is controversial. The risks of adverse events and developing antimicrobial resistance are reasons for not recommending antimicrobial prophylaxis. However, under certain circumstances, such as a military mission, short-term diplomatic mission, or vital business trip, the use of antibiotics as a preventive strategy might be reasonable (8,14).

Immunization

Development and evaluation of vaccines against enterotoxigenic *E coli* and *Shigella* are under way, but they are not yet available for routine use (6). Preliminary results suggest that such vaccines are immunogenic in volunteers and populations at risk of infection. However, the duration of any conferred immunity or whether vaccines will actually reduce attack rates of infection remains to be seen (15-18).

TREATMENT MEASURES

The general approach to treatment of TD is to ascertain the frequency of stools and the patient's level of distress, and then prescribe loperamide, bismuth preparations, and/or antimicrobials as warranted (19). A decision flowchart is provided in Figure 2.

Returning travelers who present with acute diarrhea will most likely experience a short, self-limiting

Table 2
Dietary Advice for Avoiding Travelers' Diarrhea

| | <i>Safe</i> | <i>Probably Safe</i> | <i>Unsafe</i> |
|-------------------|---|--|---|
| Food | Piping hot Peeled fruit Processed/packaged Cooked vegetables | Dry Jelly/syrup Washed vegetables | Cold salads Uncooked, cold sauces Hamburgers Unpeeled fruit Some cold desserts Fresh soft cheese Raspberries/strawberries |
| Beverages | Carbonated Boiled water Iodized water Irradiated milk | Fresh citrus juices Packaged, machine-made ice Bottled water | Tap water Uncarbonated, bottled fruit juices Chipped ice |
| Dietary practices | Considering heat of food | Eating in recommended restaurants Using alcohol judiciously | Patronizing street vendors Eating buffet food at room temperature Using alcohol excessively |

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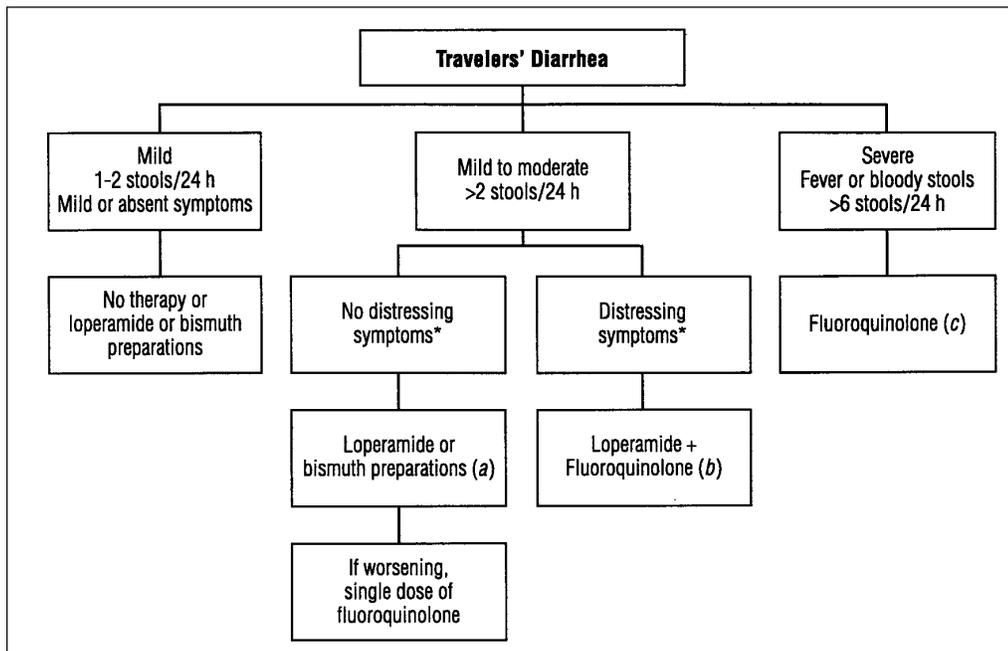


Figure 2. General approach to therapy for Travelers' diarrhea (a, travelers on critical trips might consider earlier addition of a single dose of a fluoroquinolone; b, reassess symptoms after 24 hours and discontinue use of antimicrobials if diarrhea has stopped; c, avoid intentional use of antimotility agents, unless a critical trip or activity is planned, and administer a fluoroquinolone for 1 to 3 days). *Distressing symptoms include severe abdominal cramps and pain as well as systemic toxicity. Reprinted with permission from Adachi JA, et al. *Clin Infect Dis*, 2000;31:1081.

illness. If the diarrhea persists more than 14 days, evaluation should include stool analysis for parasites and culture for specific enteric pathogens (8).

Nonspecific Agents

Among the nonspecific agents available for the treatment of TD, the "adsorbents" such as kaolin, pectin, and activated charcoal may give stools more consistency; however, they do not reduce abdominal cramps, frequency of stools, or duration of symptoms (1,3,20). Attapulgit is silicate clay that appears to provide some subjective benefits in TD (21). It is well-tolerated and safe to use in pregnancy (1). Zaldaride maleate, a drug currently being researched, acts as an antisecretory agent by inhibiting calmodulin (8).

Antimotility Agents

The antimotility agents diphenoxylate and loperamide both provide prompt but temporary symptomatic relief

of acute diarrhea. A summary of five major studies with observation periods ranging from 24 to 72 hours concludes that loperamide is superior to diphenoxylate and bismuth subsalicylate on measures of stool consistency, frequency, and timing (22).

Diphenoxylate with atropine requires a prescription and is in general less effective than loperamide for acute diarrhea (20). It can be associated with anticholinergic side effects. Since it has a Category C pregnancy warning, diphenoxylate with atropine should be avoided during pregnancy. It is not appropriate for young children.

Another disadvantage of this drug is the concern for its potential for abuse.

Loperamide has antimotility and antisecretory properties and is the antimotility drug of choice in patients 6 years of age for the control of symptoms associated with mild to moderate TD (1). It is rapidly absorbed and provides faster and more effective relief than bismuth subsalicylate, which takes nearly 4 hours to begin exerting its effect (1,6,23). Loperamide has a Category B pregnancy warning so it is safe for use in pregnant women, if necessary (20). It is a peripherally acting opioid devoid of abuse potential because it does not cross the blood-brain barrier and undergoes extensive hepatic extraction and fecal excretion (20).

Loperamide should not be used if patients develop a high fever or if their stool is black/bloody. If symptoms worsen or if patients do not experience clinical improvement within 48 hours, loperamide should be discontinued and they should be advised to consult

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Table 3
Formula for the WHO-Recommended Rehydration Solution

1 liter drinking water
1 level teaspoon (5 mL) salt
8 level teaspoons sugar

Mix sugar and salt into drinking water. Molasses may be substituted for sugar. Do not use too much salt, because this can be harmful; the solution should be no saltier than tears.

World Health Organization Dehydration Treatment Plans. Available at http://rehydrate.org/dehydration/treatment_plans.htm. Accessed December 16, 2002.

their physician. Theoretically, antimotility agents may prolong the course of disease caused by invasive enteropathogens. Loperamide, however, given in conjunction with an antimicrobial, has not been shown to prolong or worsen diarrheal illness (1,20). In fact, the benefit of the combination of antibiotic and loperamide has been studied. In one study, more than half of the subjects passed no further unformed stools once combination therapy commenced (24). However, in cases of bloody diarrhea or proven infection with Shiga toxin-producing *E coli*, antimotility agents should be avoided (9).

Antimicrobial Treatment

Antimicrobial agents effective against enteropathogens have been shown to be effective in earlier relief of symptoms of TD (19). A typical 3- to 5-day illness can be shortened to 1 to 1.5 days (3). Based on controlled clinical studies and improved knowledge of epidemiology and resistance patterns, the duration of antimicrobial therapy has been reduced from as many as 10 days in earlier studies to a single dose (19).

Trimethoprim-sulfamethoxazole (TMP-SMZ) was formerly the treatment of choice. However, use of TMP-SMZ has been limited due to increasing pathogen resistance worldwide (19).

Fluoroquinolones now are the antimicrobials of choice in empiric therapy for moderate to severe TD in adults (19). Empiric treatment with a quinolone can be considered for patients who are at high risk of complications, such as the elderly, diabetics, cirrhotics, and immunosuppressed patients (25). Rifaximin is a safe and effective alternative to ciprofloxacin currently being studied for the treatment of diarrhea (26). Azithromycin also is being studied to evaluate its role in the treatment of TD (26).

The impact of antibiotic therapy is modest in some patients and must be weighed against the progressive increase in resistance among enteric pathogens (25). Furthermore, there is a strong association between antibiotic treatment and the development of hemolytic-uremic syndrome in children (and possibly adults) with entero-hemorrhagic *E coli* infections. Therefore, the risk of administering antibiotics to patients who might be infected with pathogens for which antibiotics are contraindicated (ie, entero-hemorrhagic *E coli*) may exceed the potential benefit (27).

Probiotics

There have been few studies examining the potential benefit of probiotics (live microbial supplements containing bacterial strains and yeasts) in the treatment or prevention of TD. Several studies have suggested that probiotics (eg, *Lactobacillus* spp and *Saccharomyces* spp) may reduce the duration and severity of acute diarrhea in children (28,29). Some studies have reported that *Lactobacillus GG* is effective in the prevention of TD (30), however the effects appear to be inconsistent and may depend on geographic area or population studied (31,32). Specific agents with proven safety and efficacy need to be evaluated in well-controlled, double blind studies before formal recommendations can be made.

DIETARY RESTRICTIONS

Solid Food

There has been controversy about fasting and resumption of solid food. Fasting is logical if diarrhea is asso-

ciated with nausea and vomiting. Unlike adults, children may recover sooner by early resumption of feeding and solid food intake (20). The BRAT diet is commonly used in children who have begun eating solid food (33). BRAT is an acronym for bananas, rice (or other starchy food), applesauce, and toast.

Another benefit of early resumption of solid food is that solutes from food may be as effective as solutes from oral rehydration solutions in promoting net fluid absorption.(20)

Oral Fluids

Severe dehydration is not a risk for most healthy adults with TD (4). Consequently, fluid and electrolyte replacement is not a high priority for most adults with TD, especially if treated with loperamide (19). Oral rehydration therapy in addition to loperamide offers no benefit over loperamide alone (34). Should it become a treatment issue for a specific patient, oral rehydration solutions (glucose/electrolyte mixtures such as the World Health Organization (WHO) formula) are highly effective. They are the treatment of choice for infants and young children, the frail, and the very elderly. A formula for home preparation of an oral drink to prevent dehydration or to replace fluids in a patient with mild dehydration has been developed by WHO (Table 3) (35).

While they are effective at preventing dehydration, oral rehydration solutions do not reduce the duration of diarrhea or the number of stools. They provide no additional benefit to adults who can maintain sufficient fluid intake (20).

In uncomplicated cases, it is possible to maintain electrolyte balance with fruit juice, caffeine-free soft drinks, and salted crackers. Milk and other dairy products should be acutely avoided as they can aggravate diarrhea (4).

ADVICE TO TRAVELERS

It is worth reminding travelers before their journey that transient changes in stool consistency or frequency can be caused by changes in diet, stress, menstruation, or excessive alcohol consumption (19). However, persistent symptoms can usually be managed with self-therapy.

Approach to Self-Medication

Self-therapy for TD is a valid approach (19), and algorithms exist for self-medication (1). In particular, self-medication is safe and effective for those in previously good health, over the age of 12, and who have no high fever, blood in the stools, or obvious dehydration (20).

Empiric treatment with a combination of antimicrobial agents and loperamide can reduce symptoms, disease duration, inconvenience, and loss of planned activities (2). Self-treatment of TD was 83% effective among a cohort of American travelers (5). Loperamide is the drug of choice; other antidiarrheal agents are not recommended because of uncertain efficacy, delay in onset of action, or potential side effects (20). It has been recommended that travelers to developing countries carry loperamide to use for self-treatment if they develop diarrhea (1). An antibiotic (preferably a fluoroquinolone) may also be considered for travelers to self-administer in the event of severe diarrhea with systemic symptoms.

Impact on quality of life is more than sufficient justification for alleviation of symptoms (20). In a cost-benefit analysis, the biggest cost factor in TD is the cost of incapacitation due to illness (36).

CONCLUSION

While TD is a self-limiting illness, it afflicts many travelers—especially those going to developing countries—and it exacts a significant cost in terms of inconvenience and missed opportunities. Travelers should be advised to use commonsense preventive measures regarding food and drink. Abundant evidence shows that the symptoms associated with and duration of mild or moderate TD can be safely reduced by treatment with loperamide alone. Intentional use of loperamide or other antimotility agents should be avoided in more severe cases of TD (ie, patient has a fever, or stool is bloody or black). In cases where TD symptoms are more severe, antimicrobial agents are indicated. Their use, however, remains controversial, because of the tendency for bacteria to become resistant to these medications if used excessively. ■

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