Traveler's Diarrhea : A clinical review

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Abstract: IMPORTANCE: Acute diarrhea is the most common illness that affects travelers to low-income regions of the world. Although improved hygiene has reduced the risk of traveler's diarrhea in many destinations, the risk remains high in others. OBJECTIVE: To review the current state of knowledge on the etiology, risk factors, prevention, and management of traveler's diarrhea. EVIDENCE REVIEW: A search of the PubMed, Google Scholar, and Cochrane Library databases for the period 2012-April 2014 was performed for articles on traveler's diarrhea. The database search yielded 2976 articles, of which 37 were included in this review. These were added to 85 articles previously identified by the authors. FINDINGS: Improved hygiene has reduced the risk of traveler's diarrhea from 20% or more (for a 2-week stay) to between 8% and 20% in some parts of the world. Acquiring traveler's diarrhea causes 12% to 46% of travelers to change their travel plans. Returning travelers seeking medical care have a diagnosis of gastrointestinal disturbance in approximately one-third of all cases. Postinfectious irritable bowel syndrome may occur in 3% to 17% of patients who have had traveler's diarrhea. Prevention of traveler's diarrhea by dietary avoidance measures is often not successful. Chemoprophylaxis should be restricted to travelers who are at risk of severe complications of diarrhea. Ciprofloxacin is the standard treatment in self-therapy of traveler's diarrhea except when patients are in South or Southeast Asia, where azithromycin is preferred. CONCLUSIONS AND RELEVANCE: Diarrhea remains a common problem for international travelers. Persons intending to travel to at-risk countries should be counseled regarding prevention measures and may be given a travel pack that includes medications for self-treatment should they become ill.

DOI: https://doi.org/10.1001/jama.2014.17006

Review

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A Clinical Review

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CONCLUSIONS AND RELEVANCE Diarrhea remains a common problem for international travelers. Persons intending to travel to at-risk countries should be counseled regarding prevention measures and may be given a travel pack that includes medications for self-treatment should they become ill.

JAMA. 2015;313(1):71-80. doi:10.1001/jama.2014.17006

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Section Editor: Mary McGrae McDermott, MD, Senior Editor.

Despite the description of the syndrome of traveler's diarrhea more than 50 years ago by B. H. Kean,[1] the discovery of enterotoxigenic *Escherichia coli* (ETEC) as a key etiology a decade later,[2] and effective treatment soon thereafter,[3] the incidence of traveler's diarrhea during a 2-week trip remains 10% to 40%, depending on destination and traveler characteristics. In addition, the GeoSentinel database, a global network of clinics sharing data about travel-related morbidity, documented that acute and chronic diarrhea accounted for 335 of every 1000 medical visits by returned travelers.[4] Reduction in the incidence of traveler's diarrhea is more closely related to the level of sanitation at the destination rather than specific interventions implemented by the traveler.[5] Therefore, travelers need to be prepared to manage illness that may occur during their trips overseas.

Methods

We searched the PubMed, Google Scholar, and Cochrane Library databases for publications on the incidence, etiology, and management of traveler's diarrhea and the risks of developing it. The search was limited to 2012 to April 2014 to update previous searches conducted by the authors.[6-9] Search terms included were *travel*, *diarrhea*, *returned travelers*, *irritable bowel*, *etiology*, *treatment*, *prevention*, and *prophylaxis*. Articles were reviewed for the quality of evidence and whether they brought new information to the understanding of traveler's diarrhea. Citations in these articles were similarly reviewed. The current review is based on the authors' libraries used in prior reviews and updated by the literature search. Studies were included if published in English,

German, French, or Spanish. The online database search yielded 2976 articles, of which 37 were included in this article and added to the 85 articles existing in the authors' database.

Results

Epidemiology of Traveler's Diarrhea

Traveler's diarrhea is usually viewed from the perspective of individuals originating in high-income countries and traveling to lower- and middle-income countries. The disease is present if travelers develop at their destination 3 or more unformed stools per 24 hours plus at least 1 additional symptom, such as abdominal cramps, tenesmus, nausea, vomiting, fever, or fecal urgency.[9] A window of the first 2 weeks is usually used to define the incidence rate, as the incidence of developing traveler's diarrhea changes with time. For example, in a Kenyan study, the incidence of diarrhea decreased from 36.7% in the first week to 9.9% in the second week and to 3.3% in the third week of stay.[10] Risk of developing traveler's diarrhea is considered high when the disease's incidence is 20% or higher during the initial 2 weeks. Intermediate risk is defined as an incidence rate between 8% and 20% and low risk less than 8% (**Figure**).

ETEC *enterotoxigenic* Escherichia coli

IBS *irritable bowel syndrome*

PI-IBS *postinfectious irritable bowel syndrome*

STEC *Shiga toxin–producing* Escherichia coli

A retrospective observational study from the GeoSentinel network showed reported rates of gastrointestinal infection in Western and Northern Europe to be inversely related to the income level of the country visited.[15] The incidence of traveler's diarrhea has decreased in countries with increasing economies and in some previously high-risk destinations with improved tourism infrastructure. Overall, the incidence of traveler's diarrhea is declining, with current rates ranging from 10% to 40%[16] compared with 65% 2 decades ago.[17] Two Dutch studies documented an incidence rate (or incidence density) of 0.58 to 4.89 cases of traveler's diarrhea per 100 travel days depending on the destination.[18,19] South Asia and West/Central Africa remain the destinations with the highest risk of traveler's diarrhea. Decreasing rates have occurred in South America and East and Southeast Asia.[20] In North Africa, estimated risks for traveler's diarrhea range from intermediate[16] to high.[11,12,19,21]

Risk Groups

Environmental Factors

The risk of traveler's diarrhea (**Table 1**) depends not only on the destination and duration of exposure but also on the travel style, particularly the available budget, that often determines where a traveler purchases meals. Backpackers often favor street vendors, which are known to have a high risk of contaminated food.[13] However, the perceived quality of a hotel does not ensure protection from acquiring foodborne illness. Studies of some 5-star hotels found high traveler's diarrhea incidence rates, particularly following social events that serve buffet-style food exposed to warm environmental conditions.[14,32,33] Two decades ago, the incidence rates of traveler's diarrhea in 8 Jamaican hotels visited by at least 1000 clients for 1 week varied between 14% and 30% and were related to the hygienic conditions in the kitchen.[34] However, because of application of a hazard analysis critical control point strategy (a systematic approach to prevent hazards to food safety during production processes) in tourist hotels and restaurants, diarrhea has been reduced by 72%.[34]

Beach vacations are associated with slightly lower rates of traveler's diarrhea relative to travel for the purpose of visiting friends and relatives, multistop adventure tours, and "all-inclusive" hotel arrangements.[17,35]

Travelers on cruise-based package holidays have a lower incidence of stomach upset compared with those on land-based holidays.[36] But cruise ship passengers and staff are at risk of large outbreaks of norovirus that are difficult to contain once they have begun.[37] Decontamination of an entire ship after outbreaks is difficult because of the large physical space that needs to be decontaminated, the low inoculum of virus necessary to cause illness, and its relative resistance to cleaning. Outbreaks of ETEC have also been seen in cruise ships when water is bunkered in foreign ports. Although these outbreaks garner a great deal of attention, the overall incidence of diarrheal episodes on cruise ships is declining.[36]

Seasonal variations exist for the risk of traveler's diarrhea, with lower rates occurring in winter[17]; in Mexico, traveler's diarrhea risk increases with warmer temperatures and greater rainfall.[38] Exposure to recreational waters has been associated with acquisition of several infections, including gastrointestinal tract infections, irrespective of preventive water treatment measures.[39,40] However, most studies of this relationship involved local swimmers, not travelers.

Host Factors

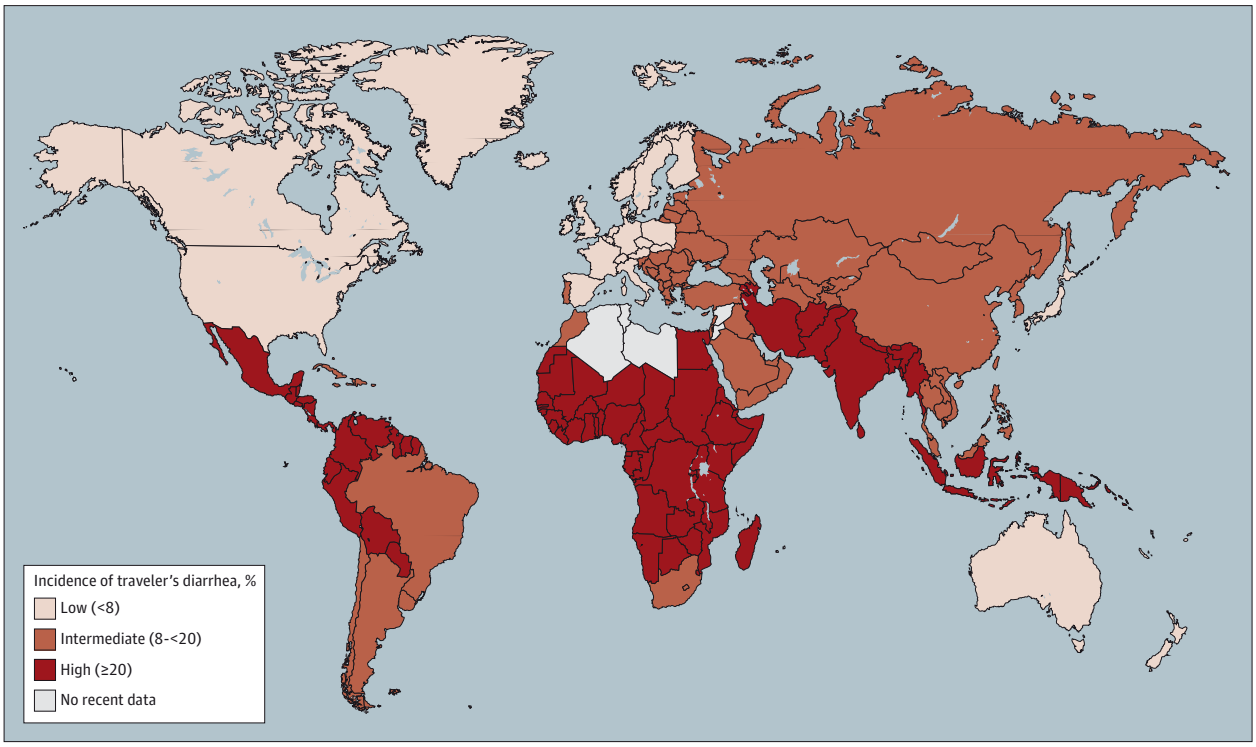
Younger travelers tend to have a greater risk of acquiring traveler's diarrhea, with infants and toddlers often having more severe disease and a greater propensity to require hospitalization.[17,41-44] Apart from being more adventurous,[14] younger travelers may also eat more food, resulting in the ingestion of a larger inoculum of pathogens.[16] Numerous studies have shown that there is an equal incidence of traveler's diarrhea between men and women[16,17,44]; however, women are more likely to seek medical care once they have traveler's diarrhea (odds ratio, 1.13; 95% CI, 1.09-1.38).[45] Several genetic factors are associated with increased risk of traveler's diarrhea (Table 1). Any association of the use of proton pump inhibitors and diarrhea comes from nontraveler studies.[23,46] Residence in areas with high incidence of traveler's diarrhea and exposure to ETEC can result in partial immunity. There is no difference in the incidence or duration of traveler's diarrhea in travelers taking immunosuppressive agents; however, patients with inflammatory bowel disease have a higher incidence of traveler's diarrhea and longer duration of diarrhea and abdominal pain relative to controls.[47]

Clinical Manifestations and Course of Traveler's Diarrhea

The syndrome of traveler's diarrhea has been described above.[9] When pathogens invade the intestinal mucosa, resulting in systemic disease with gross blood mixed with stools and/or fever, traveler's diarrhea has evolved into dysentery.

The average duration of untreated traveler's diarrhea is 4 to 5 days. Passage of more than 10 unformed stools per 24 hours is reported in only 3% of cases.[19] Between 12% and 46% of patients with traveler's diarrhea have short-term disability; higher rates occur in

Figure. Incidence Rates of Traveler's Diarrhea in the Initial 2 Weeks of Stay in Various Regions of the World Among Visitors Residing in Industrialized Countries, 1996-2008



Adapted from Greenwood et al,[15] Pitzurra et al,[16] Belderok et al,[18] Soonawala et al,[19] and Mues et al.[21]

destinations with high incidence rates. On average, the mean duration of incapacitation is usually less than 1 day.[17,19,44,48]

Long-term complications of traveler's diarrhea can occur: postinfectious irritable bowel syndrome (PI-IBS) after traveler's diarrhea may occur in 3% to 17% of patients.[49-51] Irritable bowel syndrome can occur in travelers who did not experience traveler's diarrhea.[52,53] Chronic gastrointestinal symptoms other than IBS (eg, persistent or chronic diarrhea) can also be seen at a higher rate.[54] In Houston, 8% of patients with idiopathic IBS and 16% of those with PI-IBS had a history of international travel within 6 months before they developed chronic gastrointestinal disease.[55] Several factors have been associated with development of PI-IBS, including severity of traveler's diarrhea, the number of episodes, pretravel diarrhea, pretravel adverse life events, and infection with heat-labile toxin–producing ETEC.[51,53,54] Development of PI-IBS emphasizes the need to better characterize the incidence of and risk factors for the syndrome and determine if prophylactic or treatment measures will decrease the incidence of PI-IBS.

Reactive arthritis, often associated with HLA-B27, and Guillain-Barré syndrome have been associated with traveler's diarrhea[52]; a cluster of 26 cases of Guillain-Barré syndrome occurred in residents and travelers on the Yuma County, Arizona, and Sonora, Mexico, border that was linked to *Campylobacter jejuni* infection.[56]

Etiology/Microbiology

Traveler's diarrhea is caused by ingestion of fecally contaminated food and beverages. When complete microbiology assessment is performed, pathogens can be identified in 50% to 94% of patients with traveler's diarrhea.[8,57-59] As with all infectious diseases, recovery of a pathogen from a nonsterile area of the body may not have etiological significance. However, in the absence of further research (eg, determining immune response to the pathogen), it is reasonable to assume a recovered pathogen is etiologically important.

Most cases of traveler's diarrhea are caused by bacterial enteropathogens,[59-61] whereas bacterial pathogens cause less than 15% of endemic diarrhea cases in adults living in their home country. The most important causes of traveler's diarrhea occurring in developing regions, in decreasing order, are ETEC (heat-labile and heat-stable toxin producing), enteroaggregative *E coli*, diffusely adherent *E coli*, noroviruses, rotavirus, *Salmonella* species, *Campylobacter jejuni*, *Shigella* species, *Aeromonas* species, *Plesiomonas shigelloides*, enterotoxigenic *Bacteroides fragilis*, and *Vibrio* species; the parasites *Giardia duodenalis*, *Cryptosporidium* species, *Entamoeba histolytica*, and *Microsporidium* species show regional importance (**Table 2**). There is an emerging role for *Arcobacter* species,[57,65,66] and infection with more than 1 pathogen is common.[57,62,67] Although Shiga toxin–producing *E coli* (STEC) is uncommon in travelers, the large outbreak of sprout-associated STEC infection (*E coli* O104:H4) that occurred in Germany and France in 2011 is a reminder that this pathogen can be travel associated.[68] Surveillance of enteric infections in the United States has documented travel as a risk factor for STEC.[69,70]

The global distribution of pathogens causing traveler's diarrhea is listed in Table 2. ETEC is the most common pathogen for many

Table 1. Factors Associated With Increased Risk of Acquiring Traveler's Diarrhea

Factors	Mechanism	Predictable Pathogens
Adventure travel, visiting friends and relatives	Varying exposure to contaminated food and beverages	All that cause traveler's diarrhea[22]
Age	Unknown; possibly more pathogens ingested (crawling infants, larger appetite in adolescents)	All that cause traveler's diarrhea[22]
Lack of caution in beverage and food selection	Varying exposure to contaminated food and beverages	All that cause traveler's diarrhea[22]
Use of proton pump inhibitor therapy	Altered killing of enteric pathogens from gastric hydrochloric acid	All bacterial, some parasitic (studies only in nontravelers)[23]
Certain genetic factors (mostly polymorphism associations)	Interleukin 8 AA: high producers leading to greater intestinal inflammation	SNP increases frequency of enteroaggregative *Escherichia coli*, *Clostridium difficile*[24,25]
	Lactoferrin: high producers leading to greater intestinal inflammation	SNP increases frequency of all that cause traveler's diarrhea and traveler's diarrhea with intestinal inflammation[26]
	High producers of interleukin 10 are more susceptible to TD, which may reflect immunomodulatory effects of heat-labile toxin of enterotoxigenic *E coli* stimulating increases in interleukin 10	SNP increases frequency of enterotoxigenic *E coli* traveler's diarrhea[27]
	Osteoprotegerin: immunoregulatory member of tumor necrosis factor receptor superfamily that may function as an anti-inflammatory modulator that increases susceptibility to traveler's diarrhea	Especially inflammatory forms of all that cause traveler's diarrhea[28]
	CD14: receptor for bacterial lipopolysaccharide binding associated with the innate immune response to enteric infection and inflammation; different SNPs may increase susceptibility to traveler's diarrhea; others may lead to protection	SNPs leading to high production are associated with traveler's diarrhea[29]
	Type O blood may influence enteric infection through uncertain mechanisms	Cholera and severe cholera caused by *Vibrio cholerae* O1[30]
	Not possessing the nonsense mutation in *FUT2* gene that provides resistance to infection related to virus attachment and internalization	Noroviruses[31]

Abbreviation: SNP, single-nucleotide polymorphism.

Table 2. Estimated Regional Differences in the Etiology of Traveler's Diarrhea[a]

	Reported Pathogens, %			
Organism	Latin America and Caribbean	Africa	South Asia	Southeast Asia
Enterotoxigenic *Escherichia coli*	≥35	25-35	15-25	5-15
Enteroaggregative *E coli*	25-35	<5	15-25	No data
Campylobacter	<5	<5	15-25	25-35
Salmonella	<5	5-15	<5	5-15
Shigella	5-15	5-15	5-15	<5
Norovirus	15-25	15-25	5-15	<5
Rotavirus	15-25	5-15	5-15	<5
Giardia	<5	<5	5-15	5-15

[a] Compilation of data from several studies conducted in 2002-2011.[8,60-64] Studies do not uniformly report on all pathogens; no pathogen is identified in up to 50% of cases.

areas of the world, although it is less common in traveler's diarrhea arising from Southeast Asia, including Thailand, where *Campylobacter* and *Aeromonas* more commonly occur.[71] Polymerase chain reaction methods are being developed to determine etiology of diarrhea and may identify a broad array of pathogens in a single multiplex assay, as well as increase the sensitivity for detection of ETEC,[72,73] although there may be false-positive results if there is transient colonization by an agent not causing the diarrhea. Diarrhea cases without definable etiology are probably due to bacterial pathogens such as undetected ETEC and other diarrhea-producing *E coli*, viruses, and parasites.[74] That bacterial pathogens cause diarrhea in these cases is suggested by the effectiveness of antibiotics in shortening the duration of illness.[75] ETEC can also be identified in many initially pathogen-negative cases if more colonies of *E coli* are tested than the conventional practice of investigating ETEC status for only 5 *E coli* colonies.[58]

Parasites often cause prolonged diarrhea, as do the invasive bacterial pathogens *Shigella*, *Salmonella*, and *Campylobacter*.[63,76]

Prevention of Traveler's Diarrhea

Dietary Precautions

The advice to avoid potentially contaminated food and beverages by following the rule "boil it, cook it, peel it, or forget it" makes biological sense but often does not reduce the likelihood of getting traveler's diarrhea.[5] Most studies on this prevention strategy have been retrospective and subject to recall bias. A prospective cohort study

Table 3. Chemoprophylaxis and Chemotherapy for Traveler's Diarrhea in Adults[a]

Pharmacologic Agent	Recommended Dosage	Effectiveness and Adverse Events
Chemoprophylaxis of traveler's diarrhea for trips ≤14 d		
Bismuth subsalicylate[82]	2 tablets chewed well 4 times daily	Only moderately effective Turns stool and tongue black from harmless hydrogen sulfide May cause tinnitus from systemic salicylate levels
Ciprofloxacin[83]	500 mg once or twice daily	Many fluoroquinolones are effective against most bacterial enteropathogens other than *Campylobacter jejuni* Adverse effects can include Achilles tendon damage or *Clostridium difficile* infection
Rifaximin[84]	200 mg once or twice daily with meals	Only moderately effective; uncertain if prevents invasive forms of traveler's diarrhea like *Campylobacter* or *Salmonella* Considered safe as it is not absorbed
Chemotherapy for traveler's diarrhea[b]		
Bismuth subsalicylate[85]	525 mg (1 oz liquid or 2 tablets) chewed well 4 times daily	Moderately effective in improving diarrhea symptoms Turns stool and tongue black from harmless hydrogen sulfide May cause tinnitus from systemic salicylate levels
Loperamide[86]	4 mg initially, then 2 mg after each unformed stool, not to exceed 8 mg/d	Most rapid relief of diarrhea, particularly when combined with an antibiotic Should not take as single medication with fever or dysentery; take lowest effective dose to prevent post-traveler's diarrhea constipation
Ciprofloxacin[87]	500 mg or 750 mg once daily for 1-3 d	Many fluoroquinolones are effective against most bacterial enteropathogens other than *C jejuni* *C difficile* infection has been rarely described Often first choice for use except in South and Southeast Asia
Rifaximin[59]	200 mg 3 times daily for 3 d	Ineffective against mucosally invasive pathogens (*Shigella*, *Salmonella*, *Campylobacter*) Considered safe as it is not absorbed
Azithromycin[71]	500 mg daily for 3 d or 1000 mg in single dose	Effective against invasive and noninvasive pathogens, but nausea is a frequent adverse event First choice for use in South and Southeast Asia

[a] All evidence presented has a strength of evidence of A (good scientific evidence; benefits substantially outweigh potential risks) and a quality of evidence of I (≥1 properly controlled randomized clinical trial performed).[88]

[b] All patients should receive fluids and electrolytes (soup, crackers, bananas, etc) to treat and prevent dehydration.

suggested that the risk of traveler's diarrhea increased with the number of dietary mistakes, but the response rate for the survey was only 31%, resulting in uncertainty about this conclusion.[77]

That caution in food and beverage selection does not always correlate with decreased traveler's diarrhea risk likely reflects sanitation practices at eating establishments that may not be apparent to the customer. Enteropathogens are killed at 100°C and most food items served piping hot at 60°C are safe.[78] However, foods are often not brought to an adequate temperature to kill pathogens. Foods may have been left at a warm ambient temperature in a setting where there are neither screens at the windows to prevent the entry of flies nor sinks for employees to wash their hands after a visit to the toilet.[5] In some Mexican restaurants, both sauces and vegetables have been contaminated by pathogens.[79] In Bangkok tourist restaurants, enteric pathogens were detected in cooked and raw food.[80] Organisms in contaminated ice will survive concentrations of alcohol found in drinks mixed with hard alcohol.[81]

Only a minority of travelers strictly adhere to all restrictive recommendations; despite advice, many will select salads from buffets or accept ice cubes in their drinks.[14,17] Although it is appropriate to warn travelers to exhibit caution in food selection,[9] it is unrealistic to rely entirely on a risk avoidance strategy.[7] One of the many purposes of travel is to sample different foods in their cultural context. Risk avoidance may help reduce the risk of serious infections, such as acquisition of intestinal helminths.

Preventive Medication

Several antibiotic and nonantibiotic agents have been evaluated for prevention of traveler's diarrhea (**Table 3**).

Although the use of synbiotics, prebiotics, and probiotics to minimize the risk of development of traveler's diarrhea is appealing because of their safety, the data supporting their use are not consistently strong and they are not recommended for this purpose.[7,89,90]

Bismuth subsalicylate provides modest protection against traveler's diarrhea. It is mostly marketed in North America and reduces the traveler's diarrhea rate by 65% when given 4 times daily while traveling.[7,91] Bismuth subsalicylate adverse effects include turning the tongue and stools black. Because it contains salicylate, it should be avoided in patients taking anticoagulants or long-term salicylate therapy. Toxicity is rare, but poorly soluble bismuth compounds can result in encephalopathy when used for a long term or by patients with AIDS.[92]

Rifaximin is a poorly absorbed, gut-selective antibiotic. In a meta-analysis of 4 trials, rifaximin significantly reduced the incidence of noninvasive traveler's diarrhea.[84,93] A more recent trial confirmed a moderate beneficial effect of this agent; compared with placebo, rifaximin had 48% effectiveness in travelers to South and Southeast Asia.[94] Since diarrheal pathogens were not identified in this study,[94] it remains unclear if rifaximin protects against invasive forms of traveler's diarrhea,[95] although the drug did prevent experimental shigellosis in a small study in volunteers challenged with

Shigella.[95,96] Rifaximin is approved in more than 30 countries, including, for example, the United States, Canada, Australia, and some European countries, for treatment of traveler's diarrhea caused by noninvasive enteric pathogens or specifically *E coli* infections.

Systemic antibiotics taken prophylactically can reduce the incidence of traveler's diarrhea by more than 90%.[97,98] Because of resistance to other antibiotics, fluoroquinolones typically are most often considered. However, antibiotic chemoprophylaxis is controversial. Concerns exist about adverse events and development of resistance by both extraintestinal and intestinal bacteria. In general, antibiotic chemoprophylaxis is recommended only for a few travelers and, when used, given for not more than 2 to 3 weeks.[7,99] Antibiotic prophylaxis may be appropriate for high-risk travelers who are prone to complications from diarrhea. Such persons include those who must avoid dehydration (eg, with history of stroke or transient ischemic attacks, insulin-dependent diabetes mellitus, or chronic renal failure), those prone to complex diarrheal episodes (eg, with inflammatory bowel disease and AIDS), and those with ileostomies or colostomies. Prophylaxis can also be considered for travelers on short trips who have important duties precluding time off for an illness.[97]

No vaccine offers satisfactory protection against traveler's diarrhea. Typhoid vaccines are moderately effective against enteric fever caused by *Salmonella enterica* serotype Typhi, although this disease may not be associated with diarrhea.[100,101] The only commercially available cholera vaccine (not licensed in the United States) offers limited cross-protection against heat-labile toxin–producing ETEC. However, the estimated efficacy against traveler's diarrhea from all causes is low and it is predicted to protect 7% or less of travelers.[102,103] Oral cholera vaccine for prevention of cholera can be considered for travelers who will be in areas of poor sanitation in cholera-endemic regions or where there is a current cholera outbreak.

Treatment of Traveler's Diarrhea

Management of an episode of traveler's diarrhea follows standard guidance (Table 3): avoid dehydration; mitigate the symptoms of diarrhea, abdominal cramps, and nausea; and prevent any interruption to travel plans.[104] Information about the typical symptoms of traveler's diarrhea should be provided to travelers; they should be instructed about maintaining proper hydration and how to manage an episode of diarrhea. Infants, toddlers, elderly persons, and those with chronic medical conditions can use oral rehydration solutions to prevent or reverse dehydration. These are commercially available in packets and can be made up with bottled water by a traveler who becomes ill. Healthy older children and adults can usually maintain hydration with tea with some sugar, soups, and a gradual increase in diet to regular foods.[105]

There is strong evidence for the efficacy of self-treatment of traveler's diarrhea.[6] When symptoms are mild (1-3 loose stools per 24 hours with or without mild enteric symptoms and activities not affected), treatment is usually effective with a nonantibiotic agent such as bismuth subsalicylate or the antimotility agent loperamide. A decision to start therapy with the first signs of illness relates to the initial intensity of diarrhea, the severity of coexistent signs or symptoms, and whether relief of symptoms is necessary in view of travel plans. Loperamide can promptly decrease the number of loose stools when the traveler cannot accommodate frequent bowel movements; bismuth subsalicylate effectively controls nausea but takes longer to reduce diarrhea than loperamide.[86] Loperamide should not be given to children younger than 2 years, and it should not be used as a single medication without antibiotics in patients with traveler's diarrhea who have a temperature greater than 38.5°C or when bloody stools are passed. For severe nausea and vomiting, ondansetron, a serotonin antagonist, has proven effective in children,[106] and the antihistamine promethazine can be used orally or in suppository form for adolescents and adults. Ondansetron and promethazine may be offered to long-term travelers or to those with little access to medical care overseas. Domperidone is often recommended for travel kits among Europeans and is frequently used by patients with nausea in destination countries. Although probiotics may be helpful in treating acute childhood diarrhea,[107,108] their role in treating traveler's diarrhea has not been established.[109]

Antibiotics shorten the overall duration of moderate to severe traveler's diarrhea to about a day and a half.[110] The choice of the agent depends on the geographic location of the traveler. For most destinations, a fluoroquinolone (ciprofloxacin or levofloxacin) is the drug of choice.[62,111] However, where *Campylobacter* species are a common etiology, such as in South and Southeast Asia, azithromycin is a better choice, as most *Campylobacter* species are resistant to fluoroquinolones.[62,71,112] It is important to assess *Campylobacter* sensitivity to macrolides to ensure continued susceptibility.[113] For all antibiotics, single-dose therapy or treatment for up to 3 days is usually sufficient to cure illness (Table 3). Although azithromycin is tolerated well by most persons and can be used during pregnancy and in children, it is associated with brief-duration nausea, particularly in the 1-g dose used for adults. It should be used cautiously in travelers with cardiovascular disease because of a rare risk of sudden cardiovascular death.[114]

Rifaximin is noninferior to ciprofloxacin when noninvasive enteric bacteria are treated, but it should not be used when there are signs of invasive illness accompanied by fever and when *Shigella*, *Campylobacter*, or invasive *Salmonella* are suspected.[59] *Campylobacter* species are routinely resistant to rifaximin.[115] Another nonabsorbable antibiotic, rifamycin SV, formulated with enteric coating for delivery in the distal small bowel and colon, has been well tolerated and effective at shortening the duration of traveler's diarrhea; this agent is not yet marketed anywhere.[116,117]

A combination of loperamide and an antibiotic can be taken when prompt reversal of symptoms is necessary.[118] In a meta-analysis of loperamide with one of several different antibiotics, the time to normalization of bowel habits was a median of 17 hours with a range of 2 to 23 hours.[118]

Antiparasitic agents are usually not included in travel kits.[6] They might be considered for long-term travelers in remote locations.

Evaluation of Patients With Traveler's Diarrhea on Returning Home

Uncomplicated Diarrhea

Most patients returning home with diarrhea spontaneously improve and do not seek or need medical attention. Antibacterial therapy is indicated without stool workup in many returned travelers who are ill enough to seek medical attention on return, as bacterial agents are the most common etiologies in this group.[8] Traveler's diarrhea in adults without fever or dysentery can be treated

with rifaximin, 200 mg 3 times daily for 3 days[119]; ciprofloxacin, 750 mg once daily for 1 to 3 days[87]; or azithromycin, 500 mg once daily for 3 days or 1000 mg in a single dose[71] (Table 3).[120]

Traveler's Diarrhea Complicated by Fever or Passage of Bloody Stools

Indications for laboratory evaluation of ill returned travelers are temperature exceeding 101.3°F, dysentery, cholera-like diarrhea with any degree of dehydration, or persistent (≥14 days) diarrhea. Fever may be caused by infection with *Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*, or noroviruses. When travelers have diarrhea and fever or bloody stools, a stool culture should be performed.[112,121] When systemic toxicity and fever are present, bacteremic salmonellosis including typhoid fever should be considered; blood cultures and stool cultures should be obtained. With dehydrating watery diarrhea, *Vibrio cholerae* O1 and the invasive bacterial pathogens should be suspected and stool culture performed after asking the laboratory to look for conventional pathogens and *V cholerae*. *Clostridium difficile*–associated diarrhea should be considered in patients who self-medicated with fluoroquinolones for traveler's diarrhea and present with persistent diarrhea.[122] STEC-associated enteric disease should also be considered.

Traveler's Diarrhea Complicated by Persistent or Refractory Diarrhea

Persistent diarrhea is present when diarrhea lasts for longer than 14 days; it occurs in approximately 2% of traveler's diarrhea cases. Refractory diarrhea is diagnosed when traveler's diarrhea fails to respond to antimicrobial therapy or recurs after an apparent clinical response. When this occurs, antibiotic-resistant bacteria[62] and protozoan parasites, usually *Giardia* or *Cryptosporidium*,[63,76,121] should be suspected. A stool sample should be collected and processed for *Salmonella*, *Shigella*, and *Campylobacter*.[76] Protozoal pathogens should be evaluated by microscopy or enzyme immunoassay.[60] Screening of asymptomatic returned travelers for intestinal parasites has a low yield unless they are at risk of schistosomiasis following freshwater exposure in Africa.[123] Treatment of patients with persistent diarrhea depends on identification of the enteric pathogen responsible for illness and, in the case of bacterial diarrhea, antimicrobial susceptibility testing. Occasionally, more comprehensive gastroenterological assessment may be indicated to exclude colonic cancer or inflammatory bowel disease.

Conclusions

Although much has been learned about the etiologies, prevention, and management of traveler's diarrhea over the last 50 years, several questions remain unanswered. Investigations should continue for the 10% to 40% of persons who do not have currently identified etiologies for their traveler's diarrhea; this should yield new etiologies or new mechanisms for currently identified pathogens. The contributions of host experience with intestinal organisms as well as the role of genetic polymorphisms may help increase understanding of susceptibility to illness and provide opportunities for disease prevention. The long-term sequelae of traveler's diarrhea, particularly PI-IBS, should be better defined and correlated with host genetics, pathogen, or severity of illness. The role of the gut microbiome in pathogenesis and therapy of traveler's diarrhea needs study. Because many agents contribute to traveler's diarrhea, it may not be realistic to consider a traveler's diarrhea vaccine; however, efforts at vaccine development, particularly for ETEC, should also yield benefits for those most affected by diarrhea, namely, children in low-income settings.[124] As pathogen susceptibility changes over time, monitoring of the success of antimicrobial interventions for treatment of traveler's diarrhea must be continued.

ARTICLE INFORMATION

Author Contributions: Dr Hill had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: Steffen, Hill.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Administrative, technical, or material support: Hill, DuPont.
Study supervision: Steffen, DuPont.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Steffen reports receipt of consulting fees/honoraria and support for travel from Dr Falk Pharmaceuticals and payment for lectures/speakers bureaus and support for travel from various vaccine producers unrelated to traveler's diarrhea. Dr DuPont reports consultancy for Salix Pharmaceuticals and Cubist and payment for lectures/speakers bureaus from Merck, Cubist, and Salix Pharmaceuticals (paid to him) as well as consultancy for Merck and GlaxoSmithKline and grants from Satarus, Sanofi Pasteur, GlaxoSmithKline, and Viropharma (paid to his institution).

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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