New Developments in Traveler's Diarrhea

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Abstract: Traveler's diarrhea (TD) is a crucial area for research, as it affects millions of tourists each year and creates a large economic burden. More than 60% of TD cases are caused by a variety of bacterial enteropathogens: diarrhea-producing *Escherichia coli*, *Shigella*, *Campylobacter, Salmonella*, *Aeromonas*, *Plesiomonas*, and noncholera Vibrios. Noroviruses are also an important cause of morbidity among travelers. Recent studies have identified host genetic risk factors associated with susceptibility to pathogen-specific TD. Prevention strategies should be emphasized, as all individuals with TD experience approximately 24 hours of disability and 5–10% experience chronic functional bowel disease. Poorly absorbed rifaximin provides protection for trips lasting 2 weeks or less. TD vaccines are also currently in development. All individuals planning trips to developing regions should be armed with 1 of the 3 agents that have shown efficacy for self-treatment of TD: ciprofloxacin (or levofloxacin), rifaximin, or azithromycin, depending upon the location of the trip. Although global epidemiologic changes in etiologic agents as well as antibiotic resistance patterns have been better understood recently, changes should be expected during the next decade due to new prevention and treatment approaches.

Keywords
Traveler's diarrhea, enterotoxigenic *Escherichia coli*, rifaximin, azithromycin, irritable bowel syndrome

More than 100 million individuals travel from industrialized countries to developing regions of the tropical or semitropical world each year, placing themselves at risk for developing diarrhea. So-called "traveler's diarrhea" (TD) is characterized by 3 factors: susceptibility to enteric infectious agents, residence in an industrialized country, and travel to a region of the tropical or semitropical world with lower levels of hygiene. Recent research has helped to define TD, identify new causes, show the incidence of important complications, and provide recommendations for prevention and therapy. In this paper, we will focus on recent developments in TD.

Importance of Traveler's Diarrhea

By far, the most common medical illness seen in international travelers is diarrhea. TD occurs in 15–50% of individuals traveling to high-risk regions of tropical or semitropical areas of Latin America, the Caribbean (Haiti and the Dominican Republic), southern Asia, and Africa. Approximately 100 million individuals from developed countries travel each year to one of these high-risk regions, resulting in up to 40 million cases of TD each year.[1] The risk of acquiring TD in a region is influenced by a number of factors, including the level of food contamination, the season (ie, rainy seasons are associated with a higher risk than dry seasons for TD caused by most enteric bacterial pathogens, with the opposite true for viruses), the local weather conditions, and the type of travel (ie, camping and backpacking are associated with a higher risk of TD than business travel). It appears that the rate of TD in high-risk regions has not changed significantly in the past 50 years.

TD rates for travel to intermediate-risk regions, such as China, Russia, and some of the Caribbean islands, range from 8% to 15%. Individuals traveling from 1 low-risk area to another low-risk area have a low likelihood of developing TD (~4%) during their visit. The same rate is also seen in international travelers from high-risk regions who are visiting low-risk regions.

Table 1. Causative Agents in Traveler's Diarrhea

Etiologic agent	Estimated importance in Latin America (%)	Estimated importance in Africa (%)	Estimated importance in South Asia (Indian subcontinent; %)
ETEC	34	31	31
EAEC	24	2	16
Shigella	7	9	8
Salmonella	4	6	7
Campylobacter	3	5	8
Aeromonas	1	3	3
Plesiomonas	1	3	5
Noroviruses	17	13	Unknown
Protozoa*	3	3	9
No pathogen	49	45	39

EAEC=enteroaggregative *Escherichia coli*; ETEC=enterotoxigenic *E. coli.*

*Protozoa include *Giardia*, *Cryptosporidium*, *Cyclospora*, and *Entamoeba histolytica*.

Data obtained from Shah N, DuPont HL, Ramsey DJ.[6]

Etiology of Traveler's Diarrhea

Studies conducted in the 1950s and 1960s demonstrated the efficacy of antibiotics for preventing TD.[2] These studies provided the first evidence that bacterial pathogens were important causes of the disease. Table 1 lists important etiologic agents that cause TD, with their estimated importance according to host region. Table 2 lists laboratory methods for detecting pathogens that cause TD.

The principal causes of TD are diarrhea-producing *Escherichia coli*, *Shigella*, *Campylobacter, Salmonella*, *Aeromonas*, *Plesiomonas*, and noncholera Vibrios. Parasitic agents are uncommon causes of TD, but they should be suspected in subacute and chronic illness. Enterotoxigenic *E. coli* (ETEC) has been reported to be the most important pathogen responsible for TD since the 1970s.[3] ETEC produces plasmid-encoded secretory toxins, including cholera-like, heat-labile (LT) and small molecular weight, heat-stable toxins. The other *E. coli* strain that is important in TD is enteroaggregative *E. coli* (EAEC), which has an aggregative attachment pattern to HEp-2 cells as well as a number of definable virulence properties. Two other diarrheagenic *E. coli* strains that are implicated in less than 10% of TD cases are enteroinvasive *E. coli* (EIEC), which possesses *Shigella*-like virulence properties, and diffusely adherent *E. coli* (DAEC).[4,5] In approximately 40% of TD cases, an etiologic agent cannot be found, though using polymerase chain reaction (PCR) in stool may identify ETEC or DAEC as the pathogen responsible for some of these cases.[5] ETEC and EAEC cause approximately half of TD cases in Latin America, Africa, South Asia, and the Middle East.[6,7]

Invasive bacterial pathogens, such as *Campylobacter, Shigella,* and *Salmonella*, are relatively more important in South and Southeast Asia.[7-9] In Southeast Asia, *Campylobacter* rivals ETEC as the most important cause of illness.[10] Fluoroquinolone-resistant strains of *Campylobacter* outnumber susceptible strains in virtually all regions of the world.[11] In some areas, parasites can be implicated as important causative agents in TD.[10] According to limited studies, genotype I or II noroviruses are commonly found in travelers to Latin America and Africa and, less commonly, to Asia.[9] *Aeromonas* and *Plesiomonas* are seen in up to 10% of TD cases in all high-risk regions.[6] In one study, travelers to the Middle East were most commonly infected by ETEC and *Campylobacter*, with infecting strains showing resistance patterns similar to those in the Indian subcontinent.[7] The pattern of pathogen distribu-

Table 2. Detection Methods for Enteropathogens That Cause Traveler's Diarrhea

Enteropathogen	Laboratory detection methods
ETEC	Standard microbiology isolation of *Escherichia coli* followed by tests for LT and ST by PCR, DNA hybridization, or ELISA
EAEC	HEp-2 cell assay or PCR for definable EAEC virulence property (eg, *aggR*)
DAEC	HEp-2 cell assay or PCR for DAEC virulence factor
EIEC	Standard microbiology isolation of *E. coli* followed by PCR for *Shigella*-like invasion genes (*ipaH*, *invE*)
Shigella, *Salmonella*, *Aeromonas*, *Plesiomonas*	Standard microbiology isolation
ETBF	Anaerobic culture and testing for *Bacteroides fragilis* toxin gene by PCR in suspicious colonies
Campylobacter	Standard microbiology isolation
Noroviruses	Reverse transcriptase PCR
Giardia	Commercial EIA
Cryptosporidium	Commercial EIA
Cyclospora	Modified acid-fast stain (modified safranin technique and Kinyoun staining) and fluorescence microscopy
Microsporidium	Modified trichrome stains and fluorescence microscopy (Uvitex 2B, Calcofluor White M2R)
Blastocystis hominis	Stained smears or wet mounts (formol-ethyl acetate sedimentation concentration technique or trichrome stains)

DAEC=diffusely adherent *E. coli*; EAEC=enteroaggregative *E. coli*; EIA=enzyme immunoassay; EIEC=enteroinvasive *E. coli*; ELISA=enzyme linked immunoassay; ETBF=enterotoxigenic *B. fragilis*; ETEC=enterotoxigenic *E. coli*; LT=heat-labile toxin of ETEC; PCR=polymerase chain reaction; ST=heat-stable toxin of ETEC.

tion in TD cases among military populations appears to mirror the findings among nonmilitary populations in the same region.[12]

Although not part of normal human gut flora, strains of *Arcobacter*, including the normally nonpathogenic species *A. cryaerophilus* and the diarrheagenic *A. butzleri*, appear to cause TD.[13] A recent study found that *A. butzleri* caused 8% of TD cases in Mexico, Guatemala, and India.[14] *Arcobacter* is undoubtedly underestimated as an etiologic agent of TD. *Arcobacter* has been identified in food at tourist restaurants in Thailand, suggesting a foodborne pathway of transmission. Most *Arcobacter* strains isolated in Thailand have been resistant to azithromycin and susceptible to ciprofloxacin, which complicates therapeutic recommendations for travel to Asia.[15]

Enterotoxigenic *Bacteroides fragilis* (ETBF) has recently been identified as a cause of diarrhea associated with colonic inflammation that is accompanied by watery diarrhea and fecal inflammatory products such as interleukin (IL)-8, tumor necrosis factors, and lactoferrin.[14,16,17] In one study, ETBF was identified via PCR in the stool of 13% of patients with TD traveling to India and in 4% of TD cases occurring in Guatemala.[14]

Noroviruses appear to be the third most important cause of TD, behind ETEC and EAEC.[18] This pathogen has been reported to be a cause of TD throughout the world. Although noroviruses may be the only pathogen isolated from stools of travelers with diarrhea, co-infection with other bacterial pathogens, most importantly ETEC, is seen in up to 39% of cases.[9,19] Travel conditions can affect the incidence of norovirus gastroenteritis. One study that examined returning international travelers from Europe found norovirus gastroenteritis to be particularly important in those who were backpacking or on adventure trips.[20] Increasing the time spent at the destination was found to influence the incidence of norovirus gastroenteritis, with the illness often developing during the last days of the trip.[20,21] Norovirus has been called the cruise ship virus because of its importance as a cause of gastroenteritis in that setting; it has been associated with approximately 80% of diarrhea and vomiting outbreaks on cruise ships.[22] The second most important cause of cruise ship outbreaks is ETEC, which is brought onboard when ships dock in foreign ports. Norovirus transmission also occurs during long flights, most often due to restroom visits of ill individuals. Transmission is facilitated by the low dose required to produce norovirus infection. Short flights are associated with a lower frequency of norovirus transmission.[23,24]

Microsporidiosis has been diagnosed in a small number of travelers to tropical regions with persistent diarrhea. Even after treatment and resolution of diarrhea, *Microsporidia* may be found in stool.[25] *Microsporidia* infection can be diagnosed by examining diarrheal stools via light microscopy or more sensitive tests, such as PCR.[26]

Diarrhea due to *Cyclospora cayetanensis* in international travelers has been shown to follow consumption of fruits and vegetables that cannot be peeled, salads, or contaminated water.[27,28] This parasite should be suspected in travelers presenting with persistent diarrhea that is

occasionally associated with heartburn and fever.[29,30] *Cyclospora* diarrhea in immune-suppressed patients is characteristically chronic and associated with weight loss.

Although rarely reported as an etiologic agent of TD, *Blastocystis hominis* has been identified as a source of waterborne diarrhea outbreaks and may be associated with TD.[31,32]

Host Risk Factors and the Influence of Host Genetics

Table 3 summarizes host risk factors associated with an increased rate of TD. The hygiene levels of the countries of origin and destination are fundamental to TD. The traveler's age is also a factor; toddlers who place objects in their mouths show a high attack rate, as do adolescents, who often have large appetites. Food is the main source of enteric pathogens during international travel. Exercising care in what is eaten may protect individuals against TD, although there is minimal evidence that individuals can exercise the dietary precautions needed to lower rates of TD attack.[33,34] The type of travel is also important to the development of TD. Individuals who remain close to locals, engage in low-budget travel, or backpack will have a higher risk of TD compared to older travelers and individuals on an organized tour or business trip.[35]

Some host risk factors cannot be changed by behavior. Genetic risk factors help to explain why 1 family member may become ill while another does not, despite the same environmental risks. Along with colleagues, we have shown that a number of single nucleotide polymorphisms (SNPs) have been associated with an increased risk of TD or diarrhea due to a specific TD pathogen.[36-39] Genetic polymorphisms in histo-blood group antigens, such as ABO type, secretor status, and Lewis antigen presence, are associated with higher susceptibility to infection by norovirus strains.[40-43] The presence of certain host SNPs in inflammation marker genes has been associated with a higher susceptibility to TD, including IL-8 (a precursor of polymorphonuclear leukocytes), IL-10 (an anti-inflammatory cytokine), lactoferrin (a neutrophil granule component), and osteoprotegerin (a member of the tumor necrosis factor receptor superfamily).[36-39] Other TD risk factors are listed in Table 3.

Complications

The definition of classic TD is passage of at least 3 unformed stools per day plus 1 or more signs or symptoms of an enteric infection, such as nausea, vomiting, fever, abdominal pain, cramps, fecal urgency, dysentery, or tenesmus. All individuals with this illness will show a degree of disability. Some patients develop chronic complications from TD.

Table 3. Risk Factors for Acquiring Traveler's Diarrhea (TD) During Visits to High-Risk Regions of the Tropical or Semitropical World

• Travel from an industrialized country to a developing tropical or semitropical region
• Being a toddler or adolescent
• No previous travel to a developing region (as opposed to an individual who makes frequent trips to high-risk regions)
• Lack of dietary discretion (ie, failure to exercise care in eating and drinking choices)
• Contraction of TD on a previous trip (suggesting increased susceptibility)
• Genetic risk factors for TD
• Daily use of a proton pump inhibitor
• Low-budget or adventure travel
• Living among the inhabitants of a high-risk region (eg, a Peace Corp volunteer or missionary)

Early Complications

Although TD is a nonfatal illness, it causes serious morbidity and can ruin a trip for an affected individual. On average, individuals with TD will experience a 24-hour period of total disability.[44] Many patients will seek medical attention during their trip or once they return home.

Chronic Complications

Upon returning to their country of origin, patients with TD may continue to complain of an array of persistent or intermittent gastrointestinal symptoms, including diarrhea, constipation, abdominal pain or discomfort, or bloating.[45] Between 5% and 10% of travelers with TD will later fulfill the Rome II criteria for irritable bowel syndrome (IBS).[46,47] When IBS begins after a discrete bout of diarrhea or gastroenteritis, it is referred to as postinfectious (PI)-IBS. PI-IBS characteristically follows a bacterial infection in the gut of a genetically susceptible individual that may lead to chronic intestinal inflammation, gut motility changes with small-bowel bacterial overgrowth, and alterations of gut permeability.[48] The risk of developing PI-IBS is 5 times higher in returning travelers who had TD than travelers who did not develop diarrhea during their trip.[47] Long-term effects of PI-IBS have been evaluated in multiple studies, with more than half of the cases persisting for over 5 years.[49,50] Independent risk factors for chronic PI-IBS include female gender, younger age, prior anxiety or depression, fever or weight loss during acute enteric illness, and infection by toxi-

genic *Campylobacter.*[51,52] In a US clinic for patients with IBS, approximately 10% had traveled internationally 6 months prior to their IBS onset, suggesting a possible link between TD and development of PI-IBS.[53]

Current Recommendations for Therapy

All individuals traveling to a high-risk area are encouraged to bring an antibiotic for self-treatment of TD. To date, 3 antibiotics have been found to be effective for shortening the duration of TD. Geography (and, thus, the likely pathogens in the region) and clinical illness influence which drug is recommended. In order of evaluation and development, these drugs include fluoroquinolone (ciprofloxacin or levofloxacin), rifaximin (Xifaxan, Salix), and azithromycin. Rifaximin is as effective as the other drugs for uncomplicated watery diarrhea, which is seen in 95% of diarrhea cases when TD is acquired during travel to Latin America or Africa and 90% of cases acquired during travel to South Asia (the Indian subcontinent). Because rifaximin is unabsorbed, it has fewer systemic side effects and is associated with fewer concerns regarding the development of resistance by extraintestinal flora. Because invasive bacterial enteropathogens are the most likely causes of TD during travel to South Asia, some travel medicine experts recommend that travelers to this part of the world be preferentially given azithromycin for self-treatment of TD. Fluoroquinolones are more effective than rifaximin for treatment of inflammatory diarrhea caused by *Shigella* strains. Neither fluoroquinolones nor rifaximin are likely to be effective for treatment of *Campylobacter* diarrhea due to the expected antimicrobial resistance patterns. Treatment with antibiotics is recommended in all cases of TD with moderate-to-severe abdominal pain, cramps, or diarrhea, particularly if there is any fever or dysentery.

It is unclear when a traveler should administer antibiotic treatment after the onset of symptoms. Most TD studies have initiated treatment after passage of the third unformed stool and the presence of an enteric symptom (following the classic definition of TD) to be certain that an enteric infection has been established. After beginning antibiotic treatment, TD lasts approximately 24 hours, compared to 50–70 hours for placebo-treated TD.[54,55] There may be advantages to starting an antibiotic with the passage of the first unformed stool rather than waiting until full-blown illness has been established. Waiting for the development of classic TD to initiate treatment does not prevent PI-IBS.

Figure 1 outlines recommended treatment strategies based upon clinical symptoms and severity of TD. Loperamide can also be used with any of the 3 antibiotics.[56-58] In addition, antibiotic resistance patterns should be watched closely to determine current usage of these drugs. We are already beginning to see development of ciprofloxacin resistance among pathogens that are common in Latin America and Asia (unpublished data).

Prevention

Because of the frequency of developing TD when traveling to high-risk areas and the strong association between TD and postdiarrheal functional bowel disease, a higher priority is being given to the prevention of TD. The 3 methods for decreasing the risk of TD are diet and beverage restrictions (which has already been discussed), chemoprophylaxis via antidiarrheal and antibacterial drugs, and immunoprophylaxis via vaccines. The latter 2 methods are discussed below.

Chemoprophylaxis

Kean was the first to show that antibiotics prevented a large proportion of TD.[2] In the 1970s and 1980s, doxycycline and fluoroquinolones were successfully used to prevent TD.[59,60] In 1985 at a Consensus Development Conference at the National Institutes of Health, experts in travel medicine voted to discourage the use of absorbable antimicrobial agents for TD prophylaxis because of concerns regarding side effects and development of resistance among extraintestinal bacteria, limiting the value of these agents in later management of systemic infectious diseases.[61] These concerns for systemic antibiotics were not seen with poorly absorbed rifaximin. Two published studies demonstrated the effectiveness of rifaximin for preventing TD among young adults from the United States who were traveling to Mexico.[62,63] Rifaximin provided a protection rate of 58–77% against TD, effectively preventing those percentages of diarrhea cases that would have occurred without medication. The use of rifaximin for 1 or 2 weeks for prevention of TD had minimal effects on colonic flora.[62]

Other pharmacologic agents have been used to prevent TD. Bismuth subsalicylate (BSS) administered in full doses 4 times per day has been shown to provide a protection rate of 65% against TD.[64,65] The bismuth moiety of BSS provides antimicrobial effects.[66] The high blood level of salicylate associated with BSS prophylaxis causes tinnitus in some patients. Probiotics (*Lactobacillus* GG and *Saccharomyces boulardii)* have been used for TD chemoprophylaxis, with somewhat lower protection rates.[67-69]

An evidence-based review of the use of chemoprophylactic agents for prevention of TD has recently been published.[70]

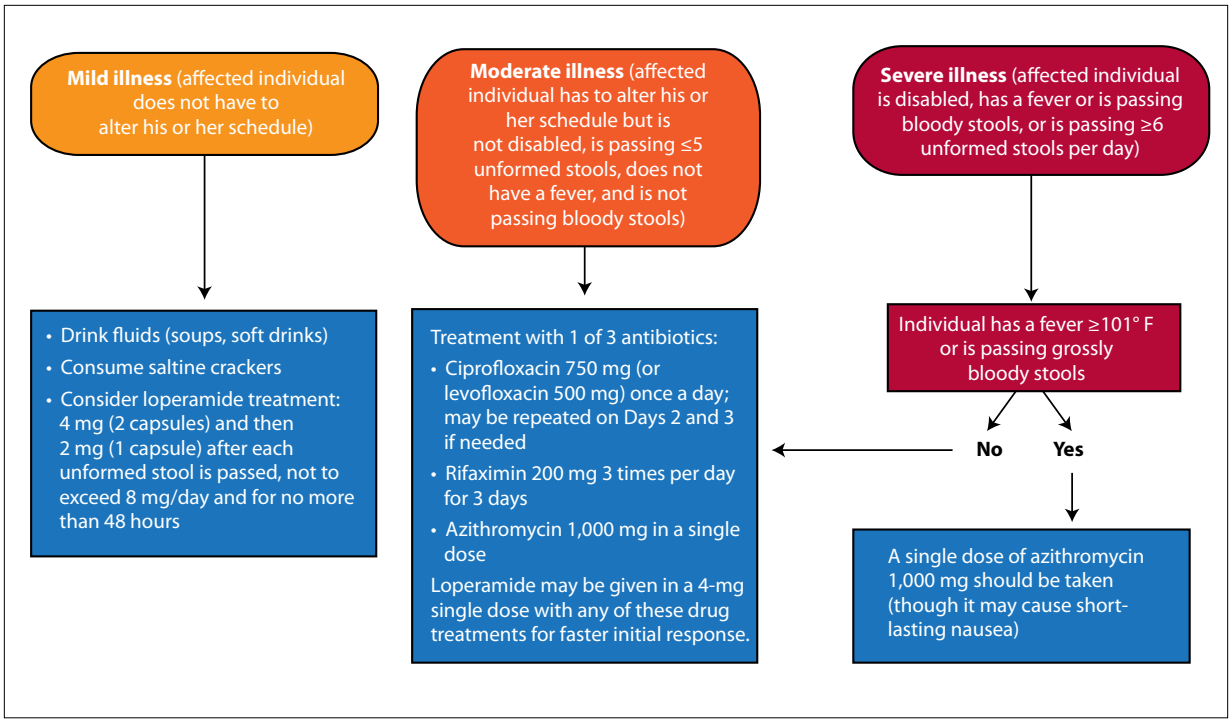

Figure 1. Treatment algorithm for the management of traveler's diarrhea based upon clinical expression of the disease.

Immunoprophylaxis

It has been known for more than 60 years that individuals who move from low-risk areas to high-risk areas experience a high rate of diarrhea, though this rate significantly decreases as they remain in the area, suggesting the occurrence of natural immunization against prevalent pathogens.[71] In addition, individuals from one developing area who visit another high-risk area show reduced rates of diarrhea, suggesting that agents found in one area of low hygiene are present in a similar region and that the induced immunity is widespread in these areas.[72] This finding of natural immunity with exposure to local microbes has driven development of vaccines for the prevention of TD. The discovery that ETEC strains are the most common causes of TD and that ETEC infection occurs only in newly arrived travelers has led to the development of anti-ETEC vaccines.[73]

One advancement in chemoprophylaxis was made by showing that the binding (B) subunit of *V. cholerae* was antigenetically and biochemically similar to the LT of ETEC. When cholera toxin B (CTB) was given orally as a vaccine in an endemic area field trial, it provided short-term protection against ETEC diarrhea.[74] A recombinant CTB vaccine given orally has been successfully used against ETEC diarrhea in Finnish tourists traveling to Morocco.[75] This preparation is commercially available in Europe and Canada.

The most exciting recent development in ETEC vaccines is the LT skin patch application of ETEC. Abrasion of the stratum corneum followed by application of the patch plus LT has been shown to produce a brisk serum antitoxin antibody response.[76] Administered to volunteers in a challenge study, the LT patch prevented severe cases of ETEC diarrhea.[77] In a phase II trial, the LT patch provided greater-than-70% protection against moderate and severe TD in a field study conducted in Mexico and Guatemala.[78] This vaccine is currently being evaluated in a phase III study of immunized subjects from Europe traveling to Mexico and Guatemala.

An oral attenuated ETEC vaccine strain is in development and has been shown to be immunogenic.[79] Cost-benefit analysis supports the use of vaccination against TD caused by ETEC in leisure and business travelers to high-risk areas[80]; however, more research is needed in TD vaccines to establish their value in disease prevention.

Summary

TD continues to be a worldwide disease that affects millions of tourists. Constant developments in prevention and discovery of new pathogens responsible for TD continually change our understanding of the disease. Antibacterial agents are remarkably effective for TD therapy, though abdominal symptoms persist for long periods of

time in certain patients, leading to chronic functional bowel disease and PI-IBS. A better understanding of the pathophysiology of the events leading to disease chronicity is needed. The best therapeutic agents should be selected according to the travel destination and developing illness. Pathogen- and geographic-based approaches to TD treatment should be encouraged. Fluoroquinolones and nonabsorbable rifaximin are the drugs of choice for travelers to high-risk areas in which *E. coli* is the predominant etiologic agent (Latin America, the Caribbean [Haiti and the Dominican Republic], and Africa), leaving azithromycin for travelers to South and Southeast Asia as well as patients with febrile dysenteric illnesses acquired in any region. A greater emphasis on TD prevention via drugs or vaccines is needed due to the importance of post-TD functional bowel disease. Close epidemiologic surveillance will also be needed, as changes are expected during the next decade due to the emergence of resistance and use of TD vaccines.

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