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Travel Medicine (O Vielemeyer, Section Editor)

Acute Traveler's Diarrhea: Initial Treatment

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Opinion statement

Diarrhea is the most common health issue affecting travelers to destinations across the world. This paper reviews the options for initial treatment of acute traveler's diarrhea (TD). Its prevention, including but not limited to vaccines and safe travel and eating habits, is an important consideration but is beyond the scope of this paper. Treatment of TD has three arms: volume repletion, antibiotics, and antimotility/antisecretory agents. Patients should be advised to continue a diet that they can tolerate and maintain adequate fluid intake. In most cases, neither oral rehydration therapy nor dietary restrictions are likely to provide significant benefit. As yet, there is no evidence to support probiotic use for treatment of this type of diarrhea. Given that bacteria are the most frequent cause of TD, adult patients with moderate to severe disease should be treated empirically with a short course of antibiotics. In many instances, these will be prescribed pre-travel with instructions for proper usage when typical symptoms occur while abroad. However, such travelers should be advised to see a physician or seek emergency treatment if symptoms are severe or persist beyond 3 days. Antibiotic selection must take into account the epidemiology of resistant enteric pathogens. Fluoroquinolones are usually effective, although resistance of *Campylobacter* to this class of drugs in South and Southeast Asia warrants azithromycin as first-line empiric therapy in travelers to those regions. One day of therapy is often sufficient but can be extended to 3 days. Rifaximin is an alternative in non-invasive disease only. The antimotility agent loperamide is safe and effective and should be considered as adjunctive therapy in most cases of TD and can similarly be prescribed pre-travel. In non-pregnant adults, bismuth subsalicylate can also provide some symptomatic relief. Where available, racecadotril may be a safe alternative in both adults and children, although never specifically studied in TD. In cases of severe symptoms, or those lasting longer than 3 days, the patient should be evaluated for non-bacterial

etiologies as well as possible *Clostridium difficile* infection. Certain travelers are more vulnerable to severe complications related to TD. Children, particularly infants, may need more aggressive fluid resuscitation with oral rehydration therapy. Several of the antidiarrheal agents must be avoided. Elderly patients and those with impaired cardiovascular reserve or immune-deficient states are more prone to complications as well. Treatment recommendations also differ for pregnant women. We generally advise adult non-pregnant travelers to follow smart eating and drinking practices and to bring a supply of bismuth subsalicylate and loperamide. We also prescribe an empiric antibiotic course (ciprofloxacin or azithromycin for up to 3 days) that is to be used for moderate to severe cases of TD.

Introduction

Acute diarrheal illness remains a frequent problem for travelers. The Centers for Disease Control and Prevention (CDC) GeoSentinel Surveillance System found that, at 22 %, acute diarrhea was the most common of the diagnostic groupings among confirmed or probable travel-related diagnoses [1]. TD is defined by the CDC as the passage of ≥3 unformed stools per day with at least one associated enteric symptom, such as abdominal pain or cramps, in a traveler after destination arrival [2]. In general, and in this review, this definition applies to people travelling from developed countries to underdeveloped countries, and thus, the following may not apply to indigenous populations.

When identified, the main causes of traveler's diarrhea are bacteria, principally *Escherichia coli*, *Campylobacter*, *Shigella*, *Salmonella*, *Plesiomonas*, *Aeromonas*, and *Vibrio* spp. Overall, enterotoxigenic *E. coli* is most frequently isolated, though significant geographic variations exist—for example, *Campylobacter* is the most frequently isolated pathogen in Southeast Asia. Viruses such as norovirus and rotavirus as well as helminthes and protozoa such as *Entamoeba histolytica*, *Giardia*, and *Cryptosporidium* can also lead to TD. Even when diagnostic tests are performed, in a large percentage of cases, no known pathogen can be identified [3, 4]. Interestingly, at least a proportion of these cases still respond to antibacterial therapy, indicating that other bacteria not routinely recovered are implicated [5]. The epidemiology continues to evolve; for example, *Arcobacter* and enterotoxigenic *Bacteroides fragilis* have recently been associated with diarrhea, including TD [6, 7•, 8]. In the future, use of non-culture-based methods to identify pathogens—including multiplex PCR techniques and mass spectrometry-based identification methods—may help recognize additional pathogens that cause TD.

Since food and water are the main routes of transmission for pathogens causing TD, the adage has long been to "boil it, cook it, peel it, or forget it," as well as to avoid tap water. Interestingly, however, many studies have failed to find a consistent correlation between food selection and prevention of diarrhea [9]. Theories for why this occurs include poor restaurant food handling, improper sanitation, and tap water purification; the difficulty in making consistently safe food choices; and possibly the ubiquitous nature of enteric pathogens making avoidance nearly impossible. However, attempts should be made to reduce the risk by practicing common sense dietary and water precautions, and travelers should be counseled appropriately. Other preventative methods, including the role of vaccines against *Salmonella typhi* and hepatitis A, of prophylactic antibiotics and probiotics and of prophylactic bismuth, have been studied and are continuing to be researched. However, they are beyond the scope of this review, which focuses on the initial treatment that should be employed once symptoms occur.

Initial treatment overview

- The three mainstays of TD treatment in returning travelers from developed countries are volume repletion, antibiotics (mostly

empiric), and symptomatic relief with antimotility/antisecretory medications.

- The main goal of pharmacologic treatment is to shorten severity and duration of symptoms. While there is also discussion about the effect of initial treatment on long-term non-infectious sequelae of TD, no conclusive data exists for this to date.
- As most cases are self-limited, in afebrile patients with mild disease it is reasonable to attempt loperamide and volume repletion with the addition of antibiotics only if symptoms persist or progress.
- Travelers can be prescribed an antibiotic to bring to high-risk areas (most of Asia, the Middle East, Africa, Mexico, and Central and South America) to self-treat when they meet the definition of traveler's diarrhea: ≥3 unformed stools per day with at least one associated enteric symptom. It is unknown whether treatment for milder cases or before at least three unformed stools have been passed is beneficial. In our practice, we do not recommend use of empiric antibiotics for mild cases of TD.
- Given the self-limited and mild nature of TD in the large majority of cases, the potential side effects of antibiotics, and the possibility of generating resistant bacteria, some authors question the practice of routine prescribing of antibiotics [10•, 11].
- There is no evidence that antibiotic therapy as currently recommended prevents post-diarrheal complications such as irritable bowel syndrome, transient lactase deficiency, or sprue, but further study is required regarding the utility of early treatment (i.e., starting antibiotics with the first unformed stool).
- Much of the data in this field comes from outpatient management of TD; thus, those requiring inpatient hospitalization for diarrhea acquired while travelling may be a different population with different epidemiology. Therefore, they may require different antimicrobial therapy and may need more aggressive hydration, and the role for and potential hazards of antimotility/antisecretory agents may require more careful consideration.
- Some concerns remain regarding the use of antimicrobials in cases of shiga-like toxin-producing *E. coli* (STEC) and whether they precipitate or exacerbate a feared complication of this enteric infection called hemolytic uremic syndrome (HUS). Overall, in the population of travelers to developing countries, STEC as a cause of TD has remained rare, and there have been no documented cases of HUS in returning travelers that had been given empiric antibiotics [12, 13]. Indeed, from 2004 to 2009, only 6.6 % of all cases of STEC in the Foodborne Disease Active Surveillance Network (FoodNet) of the CDC (www.cdc.gov/foodnet/) were travel-associated, with the number dropping to 2.7 % when only considering STEC O157; there were only 257 cases of STEC in the USA, accounting for 3.1 % of all travel-associated cases of diarrhea, over 5 years [14]. It should be noted that non-STEC *E. coli* infections, as well as other causes of traveler's diarrhea,

were not included in these numbers, likely making STEC an even smaller contributor to TD overall.

- Subacute and chronic diarrhea after travel.
  - In a small percentage of travelers, diarrhea extends beyond 7 days. Non-bacterial pathogens including protozoa should be considered.
  - When empiric antibiotics are given for TD, theoretically *Clostridium difficile* infection can ensue. Such cases, while reported, remain rare [15].
  - A great review of chronic diarrhea, especially as it pertains to non-infectious causes, following travel can be found elsewhere—see "Chronic diarrhea in travelers"[16] and "Post-infectious sequelae of travelers' diarrhea" [17].

Diet and lifestyle

Patients can eat any diet as tolerated without restriction. Volume repletion remains an important primary intervention, although the vast majority of cases of TD are mild enough that specific use of oral rehydration therapy is unnecessary in adults. Probiotics have not been shown to be helpful for the treatment of TD.

- **Diet restriction**. Restriction of some foods could theoretically produce benefits in acute gastroenteritis—for example, if fatty acids were malabsorbed or complex carbohydrates left undigested, this could exacerbate diarrhea. One study of 105 US college students travelling to Mexico who were receiving antibiotics for diarrhea found no symptom benefit to dietary restriction. Those in the restricted group removed consumption of dairy, fatty foods, spicy foods, and complex carbohydrates [18]. Although a larger study would be necessary to define any benefit to significant dietary modifications, maintaining and advancing diet as tolerated is likely sufficient in the majority of cases.
- **Oral rehydration therapy**. In healthy adults with mild symptoms, addition of oral rehydration therapy (ORT) is unlikely to provide discernable clinical benefit as compared to ad libitum fluid intake. In the only study of this population, students given loperamide with or without ORT showed almost no difference in any symptoms or stool quality [19, 20]. Although TD rarely causes excessive dehydration, those with moderate dehydration, infants, and the elderly may benefit from specific use of ORT. The treatment can be lifesaving in cases of cholera, and thus, travelers going to areas with known outbreaks should have ready access.
- **Probiotics**. One recent meta-analysis of 74 studies of probiotics in eight different gastrointestinal diseases found no significant effect of probiotics on treatment of TD, but this remains a controversial topic that continues to be studied [21]. Interestingly, in non-travelling children with acute gastroenteritis, several studies have shown a benefit for *Saccharomyces boulardii* or *Lactobacillus rhamnosus* strain GG [22, 23]. However, at this time, it cannot be recommended for the treatment of TD.

Of note, there may be some limited evidence of a preventative effect of the same probiotics, but further study is required [23, 24, 25•, 26].

Pharmacologic treatment

Antimicrobial treatments

First-line therapy is a fluoroquinolone, unless travelling to South or Southeast Asia, where a single dose of azithromycin is preferable. Rifaximin, since it is not absorbed, should only be considered for non-invasive disease. Treatment considerations for children and pregnant women are detailed in a separate section below.

- **Fluoroquinolones** are DNA gyrase inhibitors with excellent oral bioavailability. Since clinical trials in the late 1980s demonstrated efficacy in reducing symptom duration as compared to placebo, they have become the first-line agent in TD for most regions of the world [27–29]. In the 1990s, single-dose therapy was shown to be effective in many instances, and combination with loperamide was found to control symptoms more quickly than the antibiotic alone [28, 30•]. For those cases that do not respond to single-dose therapy, the course can be extended to 3 days. Resistance is emerging, especially in South and Southeast Asia, but in susceptible TD, no other antibiotic class has been found to be clearly superior. Ciprofloxacin achieves high gastrointestinal drug concentrations, but no specific fluoroquinolone has been clinically tested against the others in class for specific efficacy in TD. Some consider all fluoroquinolines equivalent for this particular indication [28]. Of note, ulifloxacin, the active component of prulifloxacin, was found to have a similar spectrum to ciprofloxacin but was 2–4-fold more potent in in vitro testing against gastroenteritis-causing pathogens [31]. Prulifloxacin is available in Japan and several European countries but not in the USA.

  Overall, the fluoroquinolones are well tolerated. Common side effects as a class include nausea, diarrhea, headache, and dizziness. Musculoskeletal complaints, including arthropathies, tendinitis, and tendon rupture, occur more frequently than with other antibiotics. Concomitant steroid use appears to enhance the risk of tendinitis. Although the more serious adverse events, such as tendon rupture, are rare and mostly associated with longer treatment courses, the medication should be discontinued with the first sign of tendon pain. This drug class may not be the best choice if the primary purpose of travel is physical activity, such as running, climbing, or hiking. QTc prolongation is also noted to occur and must be considered. In this regard, ciprofloxacin seems the safest choice as compared to levofloxacin or moxifloxacin. Finally, disorders of glucose homeostasis, including both hyperglycemia and hypoglycemia, have also been known to occur, but rarely [32]. It is currently available at an average wholesale price (AWP) of about $9.80 per dose of ciprofloxacin, making it one of the most affordable of antibiotic options for TD [33].

- **Azithromycin** belongs to the class of macrolides and is generally a safe alternative to fluoroquinolones. It should be the first-line antibiotic in travelers to South and Southeast Asia due to significant resistance to fluoroquinolones among *Campylobacter* isolates [34••]. When a single oral dose of azithromycin was compared in a double-blind, randomized clinical trial to levofloxacin in travelers to Mexico, there were no significant differences in time to last unformed stool, treatment failures, or adverse events [35]. In Thailand, where *Campylobacter* resistance is a concern, a single 1-g dose of azithromycin led to significantly higher cure rates (96 %) compared to 3 days of 500 mg azithromycin (85 %) or 3 days of levofloxacin (71 %) [34••]. Equivalency in using combination therapy with loperamide compared to levofloxacin with loperamide was noted in US military families deployed to Turkey [36]. Although generally well tolerated, both latter studies found an increase in mild nausea after the 1-g azithromycin dose was administered [34••, 36]. In terms of serious adverse events, azithromycin is associated with QTc prolongation and a perhaps slight increase in cardiac risk comparable to that of levofloxacin [37]. These events are rare and may be limited to at-risk groups, such as those with QTc prolongation or severe cardiac risk factors.

  It should be noted that some strains of *Arcobacter* and *Campylobacter* resistant to azithromycin have been identified in Thailand [6]. Furthermore, in Nepal, overall resistance among various recovered enteropathogens was similar between azithromycin and the fluoroquinolones, with 80 % of the pathogens sensitive to either antibiotic [38]. Overall, these findings suggest that in travelers to South and Southeast Asia, azithromycin should remain first line, with a fluoroquinolone remaining a reasonable option for treatment failures.

  As of this writing, the AWP per 1000 mg of azithromycin is about $31.10, which in most cases would be the entire treatment course [33].
- **Rifaximin** is a well-tolerated, water-insoluble derivative of rifamycin that inhibits RNA synthesis and has little impact on intestinal flora by culture colony counts [39, 40]. It is minimally absorbed, even in patients with colonic inflammation, as tested with volunteers with shigellosis [41]. When compared to placebo in adult travelers to Kenya, Mexico, and Guatemala, it shortened the duration of diarrhea by ~28 h [42]. A study comparing rifaximin to ciprofloxacin in travelers to Mexico and Jamaica found no difference in duration of illness or clinical improvement in the first 24 h [43•]. As with the other antibiotics, combination therapy with loperamide provides a more rapid symptomatic relief as compared to either agent alone [44]. For non-invasive infections, it is a safe and effective empiric alternative to fluoroquinolones and should be combined with loperamide. Of note, the studies were generally performed with a 3-day course of rifaximin, and this duration is recommended, as opposed to the 1-day options for the fluoroquinolones and azithromycin.

  In a subset of patients with invasive pathogens, rifaximin is clinically comparable to placebo and less effective than ciprofloxacin [45]. It

should be avoided in patients with known invasive pathogens or with signs and symptoms of infection with invasive organisms (hematochezia, fever).

Given the recommendation for a 3-day course, and the AWP per 200-mg pill at $17.64, a course of rifaximin is currently more expensive than ciprofloxacin or azithromycin [33].

- Due to widespread resistance among enteric pathogens including *E. coli*, Salmonella, and Shigella, empiric treatment with trimethoprim-sulfamethoxazole is no longer recommended [46].

Non-antimicrobial agents

Antimotility and antisecretory agents remain the mainstay of treatment in almost all cases of TD and should be used without antibiotics in mild cases. For more severe cases in adults, loperamide in combination with the appropriate antibiotic is safe to use and improves symptoms most quickly. In those with invasive disease and bloody diarrhea, further study is required regarding its safety and efficacy. For other populations, including pregnancy and pediatrics, please see the corresponding section.

- **Bismuth subsalicylate (BSS)**, marketed in the USA as Pepto-Bismol, has been used since the 1900s for the treatment of diarrhea [47]. Although the mechanism of action is not completely elucidated, the salicylate component may be antisecretory, and the bismuth molecule may play more of a role in diarrhea prevention [25•].

  Older studies indicate that BSS is significantly better than placebo in reducing the number of stools [48]. In children, studies of BSS in developing countries have found modest benefits for acute gastroenteritis, but concerns have been raised regarding the unevaluated potential for Reye syndrome and bismuth-associated encephalopathy [47, 49, 50]. Furthermore, the frequent dosing and the side effects of black discoloration of the tongue and stools should be noted and may make loperamide preferable.

  This drug is not readily available in Europe, Australia, and New Zealand but is available over-the-counter in the USA for a cost of $10–15 for a 2-week course [51]. It should not be used in children or during pregnancy.

  Also of note, the cations in the vehicle of liquid Pepto-Bismol can interfere with doxycycline absorption, a drug used for malaria prophylaxis [26].

- **Loperamide**, marketed as Imodium, slows intestinal motility by activating μ-opioid receptors and likely also inhibits intestinal secretion [52, 53]. Several studies and a meta-analysis have shown that in non-invasive traveler's diarrhea, the combination of loperamide and an appropriate antibiotic reduces stool frequency and shortens duration of diarrhea as compared to antibiotics alone [44, 52–54, 55••]. While data regarding its utility in high-volume diarrhea and invasive disease are generally lacking, it does not appear harmful in these situations. For example, in a 1993 study of 88 patients with dysentery, only 21 of whom had *Shigella* or enteroinvasive *E. coli*, and received loperamide

noted no prolonged duration of fever or extended excretion of pathogens [56]. However, as many studies exclude patients with invasive disease and dysentery, the risk and benefits of loperamide in this population have yet to be fully defined, and some avoid its use in patients with high fever and bloody diarrhea [24, 55••]. Loperamide is inexpensive and available over the counter [33].

- **Zaldaride maleate** is a calmodulin antagonist that has antisecretory properties without decreasing gastrointestinal transit time. It has been compared to loperamide alone and placebo for TD and was found to be effective but slower acting than loperamide, possibly due to loading dose effect. Adverse events were similar in all groups [57]. Its safety and efficacy in children and during pregnancy remain unknown. It has not yet been marketed [26].
- **Crofelemer** is a plant derivative that inhibits two distinct chloride channels and has been investigated for secretory diarrheas [58]. In a 2002 phase 2 study of 184 travelers to Jamaica, Mexico, and US border areas, the drug reduced duration of diarrhea by 8 h as compared to placebo [59]. Minimally absorbed and well tolerated, it has since become FDA approved for symptomatic relief in HIV-infected patients with non-infectious diarrhea [60]. Crofelemer's specific utility in TD remains to be further defined, and although trials have not demonstrated serious adverse drug events, it has not been evaluated in children and pregnant women.
- **Racecadotril** is an enkephalinase inhibitor that prevents breakdown of natural enkephalins and thus produces antisecretory activity without affecting intestinal transit time [61, 62]. Although never specifically tested in a population of travelers, it has been shown in single-blinded, multi-center studies to be comparable to loperamide in clinical efficacy for acute diarrhea [61–64]. Some of these studies have included children and the elderly. However, it was not different from placebo when tested specifically in patients with cholera [65]. Adverse reactions are generally mild to moderate, but hypersensitivity has been reported [61, 66]. Constipation is overall reported less with this drug than with loperamide [61, 63, 64]. It is not approved for use in the USA, but, where available, may be a safe alternative that might reduce the μ-opioid side effects of loperamide.
- Diphenoxylate hydrochloride, marketed with atropine as Lomotil, is not usually recommended for TD because of the possibility of central nervous system depression from the diphenoxylate and other events from the atropine component; these adverse events may be especially prominent in the elderly or if children gain access to the medication [13, 25•].
- Adsorbing agents, such as kaolin, pectin, activated charcoal, and activated attapulgite, theoretically work by adsorbing toxins and bacterial by-products while coating the inflamed mucosa. Older studies did not show any reduction in stool frequency and fluid loss, although the stools may be cosmetically more formed in

appearance [67]. Animal models have demonstrated that kaolin-pectin mixtures promote large potassium and sodium losses and kaolin OTC formulations have been reported to cause hypokalemia [67, 68]. It should be noted that the product Kaopectate originally contained kaolin and pectin; in the USA, it now primarily contains BSS but may have other active ingredients in other regions [25•]. Given the lack of demonstrable efficacy and potential for side effects, these agents are not recommended.

Considerations for specific populations, including pediatrics

Immunocompromised patients, including those with HIV, have some unique considerations. Recommendations also differ for pregnant women and in the pediatric population.

- **Immunocompromised host**. In patients with immunocompromised states, drug interactions should carefully be checked prior to prescription of antibiotics and antimotility agents. If rifaximin is prescribed, some authors have recommended having azithromycin or a fluoroquinolone for breakthrough in this population [69]. The duration of the trip and degree of immune suppression may also shift the risk/benefit for prophylactic measures, including prophylactic antibiotics, and this should be considered and discussed pre-travel.
- **HIV**. Traveler's diarrhea may be more severe or become chronic in patients with HIV, especially when the CD4 count is low. Initial treatment recommendations, however, remain the same. Azithromycin has little interaction with antiretrovirals. Fluoroquinolones, outside of decreasing didanosine levels, have no clinically significant interactions with antiretroviral therapy (ART). Potential interactions with rifaximin are less well studied, but the interaction would have to occur prior to ART absorption. Loperamide can be used safely in this population [70, 71].
- **Pregnancy**. Due to concerns regarding cartilage damage, ciprofloxacin and the other fluoroquinolones are category C in pregnancy. Azithromycin is category B; recent studies have not shown any consistent associations between macrolide exposure and birth defects, including in a retrospective case-control study published in 2014 with 4132 infants with congenital heart disease and 735 infants with pyloric stenosis [72, 73]. This is in line with other recent studies, although its safety is not definitively assured given the power and retrospective nature of these studies [74]. However, macrolides are often used during pregnancy and, given its overall safety profile, should be first line for antibiotic choice for TD during pregnancy. Although the exposure to the fetus for non-absorbed rifaximin is expected to be low, no studies have examined any human teratogenicity. Loperamide is category B and safe for use in pregnancy. In

contrast, BSS is listed as category D and should therefore not be taken during pregnancy [73].

- **Pediatrics**. Data remains limited, but the etiologic agents causing diarrhea in this population are likely similar to those of adults [12]. Treatment, however, differs in noteworthy ways.
  - **Diet and ORT**. Children, especially those younger than 2 years old, are more likely to have significant volume depletion, and thus, the threshold for starting ORT is low—some advocate for starting ORT when symptoms develop in this age group [73, 75]. If ORT is used, commercially available products are recommended to reduce the risk of errors in preparation, which can be harmful [75, 76]. Other common beverages should be avoided, including juices, sports drinks, and soft drinks because many of these drinks have a high osmolality and few electrolytes [76]. If currently breastfeeding, this should be continued throughout the duration of the illness [75, 76]. There is no indication for the outdated practice of "bowel rest" or a bananas, rice, applesauce, and toast (BRAT) diet, and children should return to foods as tolerated after a 3–4-h period of rehydration [12, 76]. There is also no specific evidence to support switching to lactose-free formula or diet, unless there is a notable increase in diarrhea with a milk-based diet [76].
  - **Antibiotics**. Azithromycin has emerged as treatment of choice in the pediatric population given its efficacy, safety, and tolerability [12, 73, 75, 77]. The fluoroquinolones are not FDA approved for this indication for the pediatric population, although it has gained limited approval for children with resistant urinary tract infections and inhalational anthrax. It has also been widely used in pediatric patients with cystic fibrosis; in this group, musculoskeletal complaints do seem to occur but appear overall rare [12]. Data is lacking regarding its safety in the pediatric population with a short course of 1–3 days, as would be used for TD. Thus, the risk/benefit should be considered on an individual level—if treatment with azithromycin is intolerable or fails, a short course of off-label ciprofloxacin may be considered if antibiotics are indicated by symptoms and clinical course. Rifaximin is approved for use in non-invasive types of TD for those aged 12 and older [75]. Overall safety data is lacking for younger children, but a small study of children 3–5 for tropical enteropathy and small studies of children over the age of 8 with inflammatory bowel disease found no serious adverse events [78, 79].

    Nalidixic acid, a liquid, non-fluorinated quinolone, has been used in children with TD but has largely been replaced

by the newer quinolones. Furizolidone is another liquid antimicrobial used in children with TD but is mainly used for cholera or giardiasis. Both require administration four times per day [12, 75].

- **Antimotility/antisecretory agents**. As noted earlier, this group of medications should be utilized with care, if used at all, in the pediatric population. The American Academy of Pediatrics does not endorse the use of antimotility agents in this age group [12, 76].
- **BSS** has been studied in non-travelling children with diarrhea in endemic countries, including a 1993 randomized, placebo-controlled trial of 275 Peruvian male infants and boys that found a significant difference in duration of symptoms, total stool output, and duration of hospitalization [47, 50]. No significant adverse events were noted, and serum bismuth levels remained low [50]. However, it should be noted that the difference was seen after 72 h, in a patient population requiring admission and who were not travelers; thus, the disease and the host may be significantly different to the point that any benefit for the majority of children with TD may be lost. Concerns over bismuth encephalopathy and potential for Reye's syndrome remain as well, although the studies would suggest that the risk is low for short treatment courses [47, 50, 75].
- **Loperamide** has been associated in children with serious adverse events in case reports, such as ileus and lethargy. A 2007 systematic review and meta-analysis found eight instances of serious adverse events including ileus, lethargy, and death among 927 children who received loperamide for acute diarrhea. All children with serious adverse events were younger than 3 years of age. The paper concluded that it was a likely useful adjunct in those children with mild symptoms and minimal dehydration older than 3 but should be avoided in those younger than 3 years, have moderate to severe dehydration, or other complications [80••].
- **Racecadotril**, as above, has been studied in pediatrics but not the population of travelling children. Trials, primarily in hospitalized children with acute gastroenteritis, noted decreases in stool output and duration of illness compared to placebo [62, 81, 82]. Few adverse effects have been noted. In guidelines from the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Paediatric Infectious Diseases, racecadotril is noted as "may be considered in the management of AGE" with the caveat that "well-designed prospective studies" in the outpatient setting should be performed [83].

Compliance with Ethics Guidelines

Conflict of Interest
Kohta Saito has no potential conflicts of interest relevant to this article.
Ole Vielemeyer has no potential conflicts of interest relevant to this article.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest have been highlighted as:
- • Of importance
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