

Therapy for and Prevention of Traveler's Diarrhea

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Acute diarrhea associated with international travel is commonly caused by enterotoxigenic *Escherichia coli*, enteroaggregative *E. coli*, or noroviruses. Early studies to define these enteropathogens took place at the University of Maryland during the Theodore E. Woodward years. Although a reduction in the rate of diarrhea may be possible through avoidance of foods and beverages likely to be contaminated, a more effective preventive strategy is to administer nonabsorbed (<0.4%) rifaximin each day during trips to areas where the risk of traveler's diarrhea is high (i.e., high-risk areas). For the self-treatment of diarrhea that occurs during travel, all persons planning trips to high-risk areas should take with them medication with expected activity against the prevalent bacterial enteropathogens: rifaximin (for the treatment of common afebrile, nondysenteric diarrhea), a fluoroquinolone, or azithromycin. Further study is needed to determine whether it is possible to avoid important morbidity associated with diarrhea and the development of postinfectious irritable bowel syndrome with chemoprophylaxis and/or early effective treatment.

The most common illness among persons moving from industrialized regions to developing countries is traveler's diarrhea. Chemoprophylaxis and immunoprophylaxis may reduce the risk of traveler's diarrhea, whereas empirical antibacterial therapy is effective in shortening illness.

The present article discusses the early historical contributions of B. H. Kean to the topic and then moves to the University of Maryland, Baltimore, where early studies of the etiology of the illness were performed. Finally, the focus of the review is the studies conducted by my group at the University of Texas–Houston. The present review of chemoprophylaxis and treatment of traveler's diarrhea is divided into 5 sections: (1) early history, (2) studies at the University of Maryland that were important in identifying the etiologic agents of traveler's diarrhea, (3) development of a model of traveler's diarrhea among US students in Mexico by the University of Texas–Houston, (4) chemoprophylaxis and chemotherapy trials, and (5) future studies.

EARLY HISTORY

In the 1950s and 1960s, B. H. Kean and colleagues studied US travelers and students in Mexico and demonstrated that antibacterial drugs were effective in preventing traveler's diarrhea [1–3]. This was the first evidence that bacterial agents were responsible for the illness. In 1957, a surprising 35% of surveyed travelers leaving Mexico City for their homes in the United States had taken antibacterial drugs during their time in Mexico to prevent illness [4].

UNIVERSITY OF MARYLAND STUDIES IMPORTANT IN IDENTIFYING ETIOLOGIC AGENTS

After completing internal medicine training at the University of Minnesota, Minneapolis, I joined the Epidemic Intelligence Service of the US Centers for Disease Control and Prevention and was assigned to the University of Maryland, which provided me with the opportunity to work with 2 inspirational leaders, Dr. Theodore E. Woodward and his Infectious Diseases Section chief, Dr. Richard B. Hornick (figure 1). After graduation from Emory Medical School in Atlanta, Georgia, I was interested in a career in cardiology. Once I reached the University of Maryland and the Centers for Disease Control and Prevention, and after I fell

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Figure 1. The architects of the University of Maryland Division of Infectious Diseases in the 1960s and 1970s were Theodore E. Woodward and Richard B. Hornick. *Left to right*, Richard B. Hornick, H.L.D., Jonas A. Shulman, and Theodore E. Woodward, in Baltimore, Maryland, in May 1977.

under the considerable influence of Dr. Woodward and Dr. Hornick, I was committed to the fields of enteric infectious diseases and epidemiology. The focus of the studies performed at the University of Maryland was evaluation of the etiology, pathogenesis, immunology, and chemoprophylaxis of acute infectious diarrhea, working with volunteers from the Maryland House of Correction in nearby Jessup, Maryland.

Escherichia coli isolates recovered from US troops in Vietnam and from other subjects with acute diarrhea were evaluated in animal models and adult volunteers and were found to either produce cholera-like enterotoxin(s) associated with the production of acute watery diarrhea or show *Shigella*-like penetration of the gut mucosa leading to febrile and dysenteric diarrhea [5]. The study helped to define enterotoxigenic *E. coli* and enteroinvasive *E. coli* as causative agents in diarrhea.

During the same time, University of Maryland faculty worked with colleagues from the National Institutes of Health to establish the human infectivity of bacteria-free stool filtrates recovered during an outbreak of gastroenteritis at an elementary school in Norwalk, Ohio, in 1968. The biological properties of the viral pathogen, later called “Norwalk virus,” were characterized [6].

In more recent years, Dr. James P. Nataro from the University

of Maryland demonstrated aggregative attachment of diarrhea-producing strains of *E. coli* to tissue culture cells [7–9]. These so-called enteroaggregative *E. coli* strains were found by our group of investigators to be important causes of traveler’s diarrhea in diverse world regions.

DEVELOPMENT OF A US STUDENT MODEL OF TRAVELER’S DIARRHEA IN MEXICO BY THE UNIVERSITY OF TEXAS–HOUSTON

In 1973, after moving to the newly created University of Texas–Houston Medical School, I developed a center for the study of enteric diseases. Laboratory methods for the identification of important pathogens were established, and, following the lead of Kean 2 decades earlier, populations of US students traveling to Mexico for short-term study opportunities were identified. Students from the United States for whom high rates of diarrhea were demonstrated after their arrival in Mexico developed immunity after a short time in the country [10]. In our student population, we found that enterotoxigenic *E. coli* and enteroaggregative *E. coli* were principal causes of illness [11–13]. It was with the US student model that many studies of

the therapy for and chemoprophylaxis of traveler's diarrhea were performed.

CHEMOPROPHYLAXIS AND CHEMOTHERAPY TRIALS

With knowledge of the causes of traveler's diarrhea and of the sources of enteric infection in international travelers, pharmacologic approaches to the prevention of and therapy for the disease were developed. Because bacterial enteropathogens were the most important causes of disease, antibacterial drugs were most frequently used for chemoprophylaxis and chemotherapy.

Prevention of Traveler's Diarrhea

Prevention of traveler's diarrhea in persons traveling to high-risk areas is an important objective, considering the temporary disability produced. Although unproven, it is theoretically possible to reduce the occurrence of diarrhea by paying careful attention to the foods and beverages consumed. The most successful approach to disease prevention has been chemoprophylaxis (table 1).

Antibacterial drugs in chemoprophylaxis. After the early studies by Kean and colleagues cited above, a rebirth of the use of antimicrobial chemoprophylaxis occurred when Drs. Brad and David Sack organized studies involving US Peace Corps volunteers who received doxycycline on a daily basis to successfully prevent diarrhea during relocation to Kenya [14]. The drug was found to be less effective in preventing diarrhea when it was evaluated in areas where antibacterial-resistant strains of diarrheogenic *E. coli* were present.

Ciprofloxacin [15] and norfloxacin [16] were evaluated for the prevention of traveler's diarrhea and were found to provide a protection rate of ~80%, which is comparable to that noted for licensed bacterial vaccines used in travel medicine. The fluoroquinolones are highly absorbed and produce adverse effects in a subset of subjects, including irritability and insomnia, gastrointestinal symptoms, skin rash, joint symptoms in chil-

dren, and, rarely, Achilles tendon rupture. Because of the importance of this class of drugs in the treatment of respiratory tract and urinary tract infections, for persons taking antimicrobial chemoprophylaxis, there is concern about the stimulation of antibacterial resistance among endogenous bacteria destined for extraintestinal infections. These arguments led a Consensus Development Conference hosted at the US National Institutes of Health in 1985 to recommend against the use of absorbed antibacterial drugs in the prevention of traveler's diarrhea [17].

Our group had earlier demonstrated that the poorly absorbed antibacterial bicozamycin [18] reduced the occurrence of diarrhea when used as a chemoprophylactic agent in travelers. The drug was not further developed for use in humans. The nonabsorbed (<0.4%) rifamycin derivative rifaximin, which had been used for more than a decade in Europe for bacterial diarrhea, was later considered for use in the prevention of traveler's diarrhea. With rifaximin, there was less concern about the development of resistance and adverse effects than would be the case with absorbed drugs. In the summer of 2003, a multidose trial was performed among US students traveling to Mexico [19]. The subjects were randomized to receive one, two, or three 200-mg tablets or a placebo 3 times daily for 14 days in a double-blind study. When diarrheal illness (defined as ≥ 3 unformed stools in 24 h plus a symptom of enteric infection, such as cramps or pain) occurred in the treated subjects, they were considered to have drug treatment failure and were removed from the study. The 3 doses of rifaximin were equally effective in preventing illness, with protection rates of 72% and 77% noted for diarrheal illness and diarrhea requiring treatment, respectively, in subjects presenting to the clinic and requiring antibiotic treatment. The drug also prevented milder forms of diarrhea and moderate to severe intestinal symptoms. Rifaximin produced only minimal changes in fecal flora during the 2 weeks that it was administered.

A second study evaluating a single 600-mg dose of rifaximin

Table 1. Chemoprophylaxis for the prevention of traveler's diarrhea.

Chemoprophylactic drug	Dose and duration	Protection rate ^a and comments
BSS	Two 263-mg tablets with meals and at bedtime	65%; will cause darkening of tongues and stools and, on occasion, mild tinnitus
LGG or SB	LGG, 2×10^9 bacteria/day; SB, 250–1000 mg/day	47% for LGG; available probiotics provide low protection rates and are safe in immunocompetent persons
Ciprofloxacin	500 mg once daily	80%; adverse effects and encouragement of resistance remain concerns
Norfloxacin	400 mg once daily	80%; adverse effects and encouragement of resistance remain concerns
Rifaximin	200 mg twice daily or 600 mg once daily	72%–77%; safe and the best option for chemoprophylaxis

NOTE. BSS, bismuth subsalicylate; LGG, *Lactobacillus* GG; SB, *Saccharomyces boulardii*.

^a [Diarrhea rates in the placebo group–diarrhea rates in the active drug group]/diarrhea rates in the placebo group.

versus placebo was repeated during the summer of 2005 in Mexico and was found to produce similar levels of protection [20]. In the 2 previously conducted studies, compliance rates were well over 90%, as determined by pill counts and diaries. A third study examining the value of rifaximin for chemoprophylaxis is currently being undertaken in Thailand; Swiss travelers are enrolled in this study in Zurich, Switzerland, by Dr. Robert Steffen, and, then, while the travelers are vacationing in Phuket, Thailand, they are monitored by Dr. Steffen and H.L.D. for the occurrence of diarrhea.

Bismuth subsalicylate (BSS) as chemoprophylaxis. BSS as chemoprophylaxis was evaluated when the drug and the intestinal bismuth reaction products were found to have antimicrobial effects. When BSS was taken in a dose of 2 oz given 4 times a day with meals and at bedtime (total daily BSS dose, 4.2 g), a protection rate of 62% was seen. When two 263-mg tablets were given at mealtime and bedtime (total daily dose, 2.1 g), a protection rate of 65% was seen [21]. The subjects commonly experienced black tongue and stools as a result of harmless bismuth sulfide. A small percentage of subjects experienced mild tinnitus during treatment.

Probiotics in chemoprophylaxis. Living microbial cultures have been used in attempts to populate the gut and produce protective interference against ingested enteropathogens. The 2 leading candidate probiotics in travel medicine are *Lactobacillus* GG and *Saccharomyces boulardii*. Although safe for use in immunocompetent subjects, the probiotic preparations have provided minimal protection against the development of traveler's diarrhea [22–24].

Principles of Therapy for Traveler's Diarrhea

In 1974, the US Food and Drug Administration announced to the pharmaceutical industry that nonprescription over-the-counter antidiarrheal compounds would need to be evaluated for efficacy, whereas the only previous requirement was that the medications be safe [25]. Over the next decade, researchers in the center for the study of enteric infectious diseases at the University of Texas–Houston conducted a series of studies examining the various symptomatic antidiarrheal compounds in our US student population in Mexico. A partial summary of the results is provided here.

The clays. Kaolin, pectin, and hydrated magnesium aluminum silicate (attapulgite) were found to cause only minimal improvement in stool formation without producing other useful effects. Commercial use of these compounds in the United States has been largely abandoned, on the basis of their lack of efficacy. The popular antidiarrheal drug Kaopectate (Pfizer), formerly a combination of kaolin and pectin, is currently reformulated as BSS in the United States.

The antisecretory agents. Although the bismuth molecule appears to be the active part of the preparation when used for the prevention of enteric infection, the active moiety of BSS for antidiarrheal effects is believed to be associated with antisecretory salicylate. A number of novel antisecretory agents are being evaluated for use as therapy for acute diarrhea. They include SP-303 (now known as “crofelemer”; Napo Pharmaceuticals) [26], which blocks gut chloride channels and leads to decreased fluid loss; racecadotril [27], an enkephalinase inhibitor that inhibits degradation of endogenous opiates; and

Table 2. Empirical treatment of traveler's diarrhea.

Chemotherapeutic drug	Dose and duration	Comments
BSS	Two 263-mg tablets or a 2-oz liquid preparation given every 30 min for 8 doses for a maximum of 2 days	Moderately effective, leading to a 40% reduction in the number of stools passed without treatment
Crofelemer ^a	10 mg 4 times daily for 2 days	Moderately effective, leading to a 40% reduction in the number of stools passed without treatment
Loperamide	4 mg (in 2 capsules) initially followed by 2 mg after each unformed stool but not to exceed 8 mg/day	Reduces the number of unformed stools passed each day by 60%, compared with no treatment
Fluoroquinolones	750 mg of Cpx as a single dose, 500 mg of Cpx twice daily, or 500 mg of Lvx once daily for 1–3 days	Cures diarrhea 24 h after treatment initiation; treatment failures occur with diarrhea due to resistant <i>Campylobacter</i> species
Rifaximin	200 mg 3 times daily for 3 days	Cures diarrhea 24 h after treatment initiation; not effective in the treatment of febrile dysenteric diarrhea due to mucosally invasive bacterial diarrhea
Azithromycin	1000 mg once or 500 mg once daily for 1–3 days	Cures diarrhea 24 h after treatment initiation

NOTE. BSS, bismuth salicylate; Cpx, ciprofloxacin; Lvx, levofloxacin.

^a Manufactured by Napo Pharmaceuticals. Previously known as SP-303.

zaldaride [28], a calmodulin inhibitor leading to the alteration of intracellular calcium and transport processes. The antisecretory drugs are modestly effective in reducing acute diarrhea, leading to an ~40% reduction in the number of stools produced, compared with no treatment or placebo. Studies of the various antisecretory compounds have provided information to suggest that transmucosal movement of fluid and electrolytes is commonly seen in patients with acute diarrhea and that the secretory alterations in acute diarrhea may be modulated by a variety of pathways.

The antimotility drugs. Diphenoxylate hydrochloride with atropine (Lomotil; Pfizer) was the first readily available antimotility drug. This compound is not recommended, because atropine confers objectionable adverse effects without antidiarrheal effects, and because diphenoxylate hydrochloride is associated with central opiate depression, which is potentially important in children taking an overdose of their parents' medication. Loperamide offers the most impressive antidiarrheal effects, reducing the number of diarrheal stools passed by 60%. The mechanism of this class of drugs is enhancement of fluid and salt absorption resulting from the slowed movement of the luminal column [29]. Although it is considered to be an antimotility drug, loperamide also has mild antisecretory properties that are exerted through calmodulin inhibition.

Antibacterial Therapy

Soon after bacterial enteropathogens were identified as important causes of traveler's diarrhea, antibacterial drugs were used in therapy. The first 2 drugs used for the empirical treatment of traveler's diarrhea were trimethoprim-sulfamethoxazole [30] and nonabsorbed bicozamycin [31]. Both drugs shortened the duration of cases of diarrheal illness for which bacterial pathogens were definable but etiology was not established. In the past 20 years, resistance to trimethoprim-sulfamethoxazole has occurred among enteric bacterial pathogens, leading to the search for newer drugs [32].

More recent studies have taken place involving fluoroquinolones [33–37], rifaximin [38], and azithromycin [39] (table 2). These agents, if active in vitro, shorten the duration of diarrhea by ~48 h. Ciprofloxacin-resistant *Campylobacter* strains have emerged as a problem in Asia and develop in all regions of the world, including the United States. These strains may be inhibited by newer fluoroquinolones [40] that have not yet been evaluated in the treatment of bacterial diarrhea. Although many cases of traveler's diarrhea will respond to single-dose treatment with a fluoroquinolone or azithromycin, travelers should be provided, before travel, with sufficient medication for 3 days of treatment, because a proportion of cases will not respond to single-dose treatment.

Rifaximin is an ideal antibacterial drug for the empirical treatment of afebrile, nondysenteric traveler's diarrhea. It is not

effective for the invasive form of diarrhea associated with fever and passage of bloody stools, which is noted in <5% of cases of traveler's diarrhea in the Americas and Africa and which, in Asia, is noted at approximately twice that frequency. The best drug for the treatment of febrile dysenteric traveler's diarrhea may be azithromycin [41], which is active against *Shigella* species [42], ciprofloxacin-susceptible and ciprofloxacin-resistant *Campylobacter* strains [43], and diarrheogenic *E. coli* [32].

In studies performed in Mexico and involving travelers from the United States, loperamide provided added clinical benefit when combined with antibacterial treatment [44]. More recently, studies have used ofloxacin [33] or rifaximin [45]. The antimotility drug provided rapid control of diarrhea, whereas the antibacterial drug led to an illness cure that was not seen when loperamide was given alone. Less impressive additive effects were noted in studies of combination treatment performed in Egypt or Thailand among US troops with diarrhea [46, 47]. Table 3 presents the additive effects noted when curative antibacterial therapy was combined with rapidly active symptomatic therapy with loperamide.

FUTURE STUDIES

Chemoprophylaxis with rifaximin is likely to become a more important approach to the prevention of diarrhea- and post-diarrhea-associated complications, including irritable bowel syndrome, which occurs only in persons who experience diarrhea. It is not certain whether rifaximin will prevent the invasive forms of traveler's diarrhea. Preventing diarrhea due to invasive bacterial enteropathogens by the use of a nonabsorbed drug should be far easier than treating an extensive intramucosal infection. Rifaximin is active against *Shigella* strains, whereas its activity against prevalent *Campylobacter* strains is less impressive. In studies performed by Taylor et al. [49], rifaximin was 100% effective in preventing experimental shigellosis and *Shigella*-induced dysentery in volunteers fed a virulent strain of *Shigella flexneri* 2a. We are performing a study of rifaximin prophylaxis in Swiss travelers to Thailand, where ciprofloxacin-resistant *Campylobacter* strains are known to be important in the examination of the value of the drug against other forms of invasive diarrhea.

Table 3. Combination treatment for traveler's diarrhea: curative antibacterial therapy plus rapidly active symptomatic therapy with loperamide.

Antibacterial drug	Additive effects noted	Study location [reference]
Ofloxacin	Important	Mexico [34]
Ciprofloxacin	Minimal	Egypt [47]
Ciprofloxacin	Minimal	Thailand [46]
Azithromycin	Important	Mexico [48]
Rifaximin	Important	Mexico [45]

The optimal dose of rifaximin and the length of time that the drug can be administered as a diarrhea preventive during travel need to be established. A dose of 200 mg (1 tablet) given twice daily with the major daily meals may be the proper dose for prophylaxis [19]. We are evaluating the use of 600 mg of rifaximin once daily for prophylaxis, in studies currently under way in Thailand. The objective of our current study is to determine whether the single larger dose given daily will effectively prevent enteric infection and diarrhea due to invasive bacterial enteropathogens. One of the concerns about recommending rifaximin broadly for travelers is the development of antibacterial resistance. Our 2 studies conducted to date have shown that resistance in gut flora has not occurred with rifaximin use. Also, with the drug's very low absorption rate (<0.4%), it is unlikely to produce resistance among extraintestinal bacteria, a potential problem of absorbed drugs.

It is my current recommendation that rifaximin be used daily for trips of up to 3 weeks' duration. Recommendations for longer durations of use should await future study. The cost of rifaximin is \$3.50 to \$4.00 per 200-mg tablet. When 2 tablets are given daily, the cost of chemoprophylaxis is approximately \$8.00/day, or \$112 for a 2-week stay. Although a formal cost-effectiveness analysis has not been performed, many persons would find this cost acceptable if illness were prevented. Obviously, a cost-benefit advantage to taking the drug would become more obvious if chemoprophylaxis were shown in a future study to prevent longer-term sequelae.

The type of travelers for whom rifaximin prophylaxis should be recommended remains controversial. It is reasonable to offer to all future travelers to high-risk areas a prescription for daily rifaximin for the prevention of diarrhea and, possibly, postdiarrhea complications. It could be helpful to develop a list of travelers who might receive the most benefit from chemoprophylaxis, to help guide recommendations. One well-thought-out approach is to recommend rifaximin prophylaxis for persons who follow tight schedules (e.g., politicians, musicians, athletes, and lecturers); those who have previously experienced the illness, which indicates the possibility of increased susceptibility; and those future travelers who request prophylaxis [50]. A fourth group to add to the published recommendations could be immunocompromised persons and infirm individuals, which could include patients with chronic illness, including AIDS, cancer, insulin-dependent diabetes, and heart failure [51].

Persons taking rifaximin on a daily basis while traveling should also take along medication for use as rescue medication for the treatment of rare illness that is not prevented. The ideal drug for this purpose is probably azithromycin, which is active against the majority of bacterial enteropathogens, as was described above [41].

Although combination treatment with loperamide and antibacterial drugs appears to be the most effective strategy for

the management of traveler's diarrhea in many travelers, newer antisecretory agents should also be evaluated in combination with antibacterial drugs. It may be that one of the newer antisecretory drugs will provide early effective relief of acute diarrhea without producing the postdiarrhea constipation occasionally seen with loperamide.

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