

The role of rifaximin in the treatment and chemoprophylaxis of travelers' diarrhea

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Abstract: Travelers' diarrhea is a common illness among international travelers from developed to developing countries. Travelers' diarrhea is caused by ingestion of contaminated food and water. Bacteria are the primary cause of travelers' diarrhea. In most surveys, the most common diarrheal pathogen identified is enterotoxigenic *Escherichia coli*. There are several antimicrobial agents available for the treatment of travelers' diarrhea including rifaximin which is approved in the United States for the treatment of travelers' diarrhea due to noninvasive *E. coli* strains. In this review, we will review the most recent advances of rifaximin for the treatment and prevention of travelers' diarrhea, with regard to its pharmacokinetics, *in vitro* susceptibility profile, and efficacy and safety data from clinical trials.

Keywords: travelers' diarrhea, rifaximin, treatment, prevention

Introduction

Each year, approximately 50 million persons travel internationally from developed to developing countries. Although the rates of travelers' diarrhea vary according to the region of the world visited, on average, 40% of travelers will develop traveler's diarrhea.¹ Symptoms of clinical illness include passage of profuse and watery bowel movements, nausea, bloating, urgency, malaise, flatulence and abdominal cramping which typically occur within the first two weeks of travel. Travelers' diarrhea is acquired through the ingestion of contaminated food or water. Food items that contain moisture and remain at room temperatures for periods of time are of greatest concern.² The most common cause of food contamination are bacterial agents which are responsible for 80% of cases,³ and the remaining causes are parasites and viruses. Enterotoxigenic *Escherichia coli* (ETEC), enteroaggregative *E. coli* (EAEC), *Shigella* spp., *Salmonella* spp., *Campylobacter jejuni*, *Aeromonas* spp., *Plesiomonas* spp., and noncholerae *Vibrio* are the most commonly identified bacterial causes of travelers' diarrhea. There is a subset of travelers who develop diarrheal illness without identifiable causes but show improved clinical outcomes to antibacterial therapy suggesting that these cases may be due to bacterial agents yet to be characterized.⁴ While travelers' diarrhea is typically self-limited, illness may result in persistent diarrhea in at least 2% of cases, irritable bowel syndrome with post-infectious diarrhea in 4%–10% of travelers,⁵ and other chronic complications such as reactive arthritis with *Salmonella*, *Shigella*, and *Campylobacter*,⁶ and Guillain–Barre syndrome from *Campylobacter* infection.⁷ There are several antimicrobial agents available for the treatment of travelers' diarrhea. The treatment

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choice is dependent on the country visited by the traveler, the targeted coverage of diarrheagenic pathogens, the microbial resistance patterns associated with the geographical distribution, and the antimicrobial agent's safety profile including limited potential for drug interactions. Rifaximin is a poorly absorbed antibacterial agent with an excellent safety profile that is effective for travelers' diarrhea among travelers studied in different regions of the world. In this review, we will review the most recent advances of rifaximin with regard to its pharmacokinetics, *in vitro* susceptibility profile, and efficacy and safety data from clinical trials for treatment and chemoprophylaxis of travelers' diarrhea.

Rifaximin drug class and mechanism of action

Rifaximin is a rifamycin derivative with antimicrobial activity against a broad spectrum of microorganisms, including Gram-positive, Gram-negative, aerobic and anaerobic bacteria. The mechanism of its antimicrobial activity involves inhibition of bacterial RNA synthesis by binding to the beta-subunit of the bacterial DNA-dependent RNA polymerase.⁸

Rifaximin pharmacokinetics

One of the unique properties of rifaximin is its poor oral absorption in the human gastrointestinal tract, which augments its ability to inhibit replication of enteric pathogens with high fecal concentrations while limiting the amount of systemic absorption. Adults, with diarrheal illness, receiving rifaximin 800 mg per day for three days achieve fecal concentrations of rifaximin of approximately 8000 µg/g.⁹ Although systemic absorption of rifaximin is increased with food intake, less than 0.4% of the drug is absorbed from the gastrointestinal tract after oral administration. This low systemic absorption is reflected by the relatively low maximum drug concentration (C_{max} of 9.63 ng/mL) and area under the concentration time curve (AUC of 34.7 ng·h/mL) in the fed state. After oral administration of 400 mg of C¹⁴-rifaximin to healthy volunteers, 97% and 0.32% of rifaximin are recovered from the feces and the urine unchanged, respectively.^{8,10–12}

Drug interactions with rifaximin are relatively uncommon because of its poor oral absorption. Although *in vitro* studies have demonstrated that rifaximin is capable of inducing the cytochrome P450 3A4 (CYP3A4) isoenzyme, clinical drug–drug interaction studies using midazolam and an oral contraceptive containing ethinyl estradiol and norgestimate have not demonstrated such an interaction. Rifaximin does

not significantly affect drugs metabolized by the cytochrome P450 isoenzymes.^{13,14}

Since rifaximin is poorly absorbed, no dosage adjustments are necessary for hepatic dysfunction. Among patients with liver failure and hepatic encephalopathy who received rifaximin 800 mg three times daily for seven days, less than 0.1% of rifaximin was systemically absorbed.⁸

Rifaximin *in vitro* susceptibility

Rifaximin has broad coverage against the diarrheagenic pathogens associated with travelers' diarrhea. Our research group evaluated 284 isolates from diarrheal samples from travelers to India, Jamaica, Mexico, and Kenya.¹⁵ The minimum inhibitory concentration that inhibited 90% of microorganism growth (MIC_{90}) ranged from 4–64 µg/ml for enterotoxigenic (ETEC) and enteroaggregative *E. coli* (EAEC), *Salmonella*, *Shigella*, *Campylobacter*, *Plesiomonas*, and *Aeromonas* species. These susceptibility patterns have been validated by other studies.^{16,17} However, in an *in vitro* study of the activity of rifaximin against enteropathogens isolated as a cause of travelers' diarrhea among Spanish travelers to developing countries, the MIC_{90} of *C. jejuni* was 512 µg/ml.¹⁸

Although there is concern that resistance to rifaximin or cross resistance to rifampin may develop, the high fecal concentrations of the drug and limited systemic absorption are reasons to believe that the development of resistance and cross resistance is unlikely.

The frequency of development of ETEC and EAEC rifaximin-resistant mutants were 5.7×10^{-7} – 1.6×10^{-6} and 2.0×10^{-8} – 9.3×10^{-8} , respectively, by growth on plates containing serial dilutions of rifaximin above the bacterial MIC.¹⁹ In this *in vitro* study, 26 of 28 mutants exhibited MIC levels of 256 mg/L or higher without reversion towards the original MIC. Since rifaximin achieves fecal concentrations of approximately 8,000 µg/g,⁹ its effective concentration in the gastrointestinal tract is greater than 15–30-fold MIC_{90} for these bacterial pathogens and may explain why resistance among noninvasive strains of *E. coli* is uncommonly reported. In limited reported cases, resistance to rifaximin among *Bifidobacterium infantis* and *Clostridium difficile* has been associated with mutations in the *rpoB* gene, which encodes for the DNA-dependent RNA polymerase.^{20,21} However, it has not been shown whether these resistance mutations correlate with clinical failures. Rifaximin does not induce rifaximin or rifampin resistance in *Mycobacteria tuberculosis* strains isolated from humans²² or guinea pigs.²³

Despite the high fecal concentrations of rifaximin, the medication appears to have surprisingly little effect on the

intestinal microflora. After two weeks of rifaximin, there is approximately a 1 log reduction in coliforms per gram of stool.²⁴

Efficacy of rifaximin for the treatment of travelers' diarrhea

Rifaximin is approved in the United States and in some European countries for the treatment of patients with travelers' diarrhea caused by noninvasive strains of *E. coli* among patients aged ≥ 12 years.⁸

Several pivotal trials have demonstrated that rifaximin is more effective than placebo and as effective as conventional antibiotics for the treatment of travelers' diarrhea (Table 1). The predominant pathogens in these trials were *E. coli* strains, including enterotoxigenic (ETEC) and enteroaggregative (EAEC) *E. coli*. These clinical trials were well-designed, randomized, double-blind studies which evaluated the primary clinical endpoint as the time to last unformed stool (TLUS), defined as the time from the administration of the first dose to last unformed stool passed, after which clinical cure was declared.

Rifaximin was similar in efficacy to trimethoprim-sulfamethoxazole (TMP-SMX).²⁵ In a randomized, prospective, double-blind clinical trial including 72 US travelers to Mexico, no significant differences in the TLUS were observed in a clinical trial comparing five-day courses of rifaximin (200 mg, 400 mg, and 600 mg three times a day; [n = 55]) and TMP-SMX (160/800 mg two times a day; [n = 17]) among travelers to Mexico. There was a trend for shorter duration of diarrhea with the administration of rifaximin 200 mg three times a day. Although not statistically significant, clinical failure to respond to treatment occurred in six of 55 (11%) rifaximin-treated subjects versus five of 17 (29%) TMP-SMX-treated subjects.

Rifaximin is similar in efficacy to ciprofloxacin.²⁸ A randomized, double-blind clinical trial evaluated three days of either rifaximin 400 mg twice a day (n = 93) or ciprofloxacin 500 mg twice a day (n = 94) as treatment for travelers' diarrhea among travelers to Mexico or Jamaica. The principal pathogen identified in this study was enterotoxigenic *E. coli*, occurring in 39% of rifaximin-treated and 38% of ciprofloxacin-treated subjects who provided pretreatment stool samples. Invasive pathogens were uncommon. Rifaximin and ciprofloxacin were comparable in the median TLUS (25.7 hours vs 25.0 hours, respectively, $P = 0.47$) and comparable in the clinical cure rate (rifaximin 87% vs ciprofloxacin 88%, $P = 0.80$) and microbiological cure rate (rifaximin 74% vs ciprofloxacin 88%, $P = 0.22$).

Many experts consider ciprofloxacin as the standard of treatment for travelers' diarrhea. However, resistance to ciprofloxacin, the most commonly employed fluorquinolone for bacterial diarrhea is occurring among bacterial diarrheagenic pathogens especially among *Campylobacter* species in areas such as Thailand and other parts of Southern Asia.^{26,27}

A second randomized, double-blind clinical trial evaluated 399 travelers with travelers' diarrhea acquired in Mexico, Guatemala, or India.²⁹ Subjects received three days of either rifaximin 200 mg three times a day (n = 197), placebo (n = 101), or ciprofloxacin 500 mg two times a day (n = 101). The principal pathogens identified in this study were diarrheagenic *E. coli*, occurring in 37% of rifaximin-treated and 40% of ciprofloxacin-treated subjects. Invasive pathogens were uncommon. The median TLUS was shorter for the rifaximin group compared to the placebo group (32.0 hours vs 65.5 hours, $P = 0.001$) and was similar to the group receiving ciprofloxacin (28.8 hours, $P = 0.35$). A greater percentage of rifaximin patients experienced clinical cure (76.6%) compared to subjects receiving placebo (61.4%, $P = 0.004$) and was similar to the ciprofloxacin group (78.2%).

A third randomized, double-blind clinical trial evaluated 380 travelers with travelers' diarrhea acquired in Mexico, Guatemala, or Kenya.³⁰ Study participants were randomized to receive either three days of either rifaximin 200 mg three times a day (n = 125) or 400 mg three times a day (n = 126), or placebo (n = 129). The median TLUS was significantly shorter for both rifaximin groups compared to placebo (32.5 hours and 32.9 hours vs 60.0 hours, respectively, $P = 0.0001$). A greater proportion of patients who received rifaximin achieved clinical cure compared to the placebo group (79.2% and 81.0% vs 60.5%, $P = 0.001$).

Even when no enteric pathogen was detected in one third of patients with travelers' diarrhea, described as pathogen-negative travelers' diarrhea, in a subanalysis from two randomized, double-blind, placebo-controlled controlled trials, rifaximin was more effective than placebo for median TLUS (33 hours vs 68 hours, $P < 0.005$), mean number of unformed stools passed (6.5 vs 8.6, $P < 0.0001$), and clinical cure (77 vs 61%, $P = 0.01$).⁴ These findings suggest that pathogen-negative travelers' diarrhea cases may be due to undetected bacterial pathogens yet to be characterized by current diagnostic techniques.

Combining rifaximin with loperamide is a very effective combination for travelers' diarrhea.³¹ In a clinical trial, 310 adults with acute diarrhea were randomized to receive rifaximin 200 mg three times daily for three days (n = 102); loperamide 4 mg initially followed by 2 mg after each

unformed stool (n = 104); or a combination of both drugs using the same dosing regimen (n = 104). The primary end point was TLUS. Rifaximin and combination therapy significantly reduced the median time until passage of the last unformed stool (32.5 hours and 27.3 hours, respectively) compared to loperamide alone (69 hours; $P = 0.0019$). The mean number of unformed stools passed during illness was lower with combination therapy (3.9) compared with rifaximin (6.2; $P = 0.004$) or loperamide alone (6.7; $P = 0.002$).

Rifaximin use for invasive enteric pathogens

Rifaximin is not approved for the treatment of travelers' diarrhea associated with invasive enteric pathogens such as *Shigella* species, *Campylobacter jejuni*, and *Salmonella* species. In a clinical trial comparing the efficacy of rifaximin, to placebo and ciprofloxacin for travelers' diarrhea,²⁹ rifaximin was less effective than ciprofloxacin in shortening the duration of diarrheal illness and in resolving clinical illness for cases caused by invasive enteropathogens. The mean TLUS for three-day courses of rifaximin 200 mg three times a day, placebo, and ciprofloxacin 500 mg two times a day were 33.0 hours, 65.5 hours, and 28.8 hours, respectively. Median TLUS for invasive pathogens was 44 hours for rifaximin, 24 hours for ciprofloxacin, and 58 hours for placebo (rifaximin vs placebo; $P = 0.50$). Rifaximin was also evaluated among 13 patients orally challenged with *Shigella flexneri* who developed shigellosis.³² Eight of these thirteen patients required rescue treatment with ciprofloxacin after failing to respond to rifaximin. Rifaximin is solely an intraluminal agent and does not appear to be active against bacteria invading the gastrointestinal mucosal barrier. Therefore, rifaximin is not recommended for patients presenting with gastroenteritis complicated by fever or bloody diarrhea.

An option for travelers' diarrhea and bacterial dysentery due to *Campylobacter* species including ciprofloxacin-resistant strains is azithromycin. It has a long half-life and has excellent *in vitro* activity against common bacterial enteric pathogens and is effective in Southeast Asia (ie, Thailand and India) where fluoroquinolone-resistant *Campylobacter* species are prevalent.^{27,33} Azithromycin, in a single dose of 500 mg, has been found to be comparable to levofloxacin for the treatment of US travelers with acute diarrhea acquired in Mexico.³⁴ However, in this study *Campylobacter* species were uncommon.

Rifaximin as chemoprophylaxis for travelers' diarrhea

There is an ongoing debate regarding the use of antibacterial agents for chemoprophylaxis for travelers' diarrhea. In the

past, concerns regarding the promotion of antimicrobial resistance and exposure to potential adverse events for a self-limited disease such as travelers' diarrhea limited the support of antibiotics for the prevention of this illness.³⁵ Widespread administration of these drugs may select for resistance and limit the future usefulness of these drugs, especially fluoroquinolones, for the treatment of life-threatening bacterial infections.³⁶ However, with the increased recognition of persistent diarrhea and chronic conditions such as irritable bowel syndrome among patients after infectious diarrhea,³⁷ a renewed interest in chemoprophylaxis has arisen.

Rifaximin with its excellent safety profile, lack of drug interactions, and minimal effect on the intestinal microbiome appears to be an ideal prophylactic drug for travelers' diarrhea especially among travelers to high risk geographic areas especially for those who are on tight schedules, have become ill in past trips or have underlying comorbidities which may result in increased susceptibility. Rifaximin is currently being evaluated as a prophylactic antibiotic to prevent the acquisition of travelers' diarrhea.

A number of clinical trials have shown that rifaximin is effective as a prophylactic agent for the prevention of travelers' diarrhea.^{24,38,39} In a randomized, double-blind, placebo-controlled trial, 210 US travelers to Mexico were evaluated for prevention of travelers' diarrhea with rifaximin.²⁴ Subjects received either rifaximin 200 mg once daily (n = 50), rifaximin 200 mg twice daily (n = 52), rifaximin 200 mg three times daily (n = 54), or placebo (n = 54) for two weeks. In total, 15% of subjects receiving rifaximin developed travelers' diarrhea compared to 54% of subjects receiving placebo ($P = 0.0001$) with a protection rate against travelers' diarrhea of 72% for subjects receiving rifaximin ($P < 0.001$). All rifaximin doses were superior to placebo.

A second randomized, double-blind, placebo-controlled prophylaxis trial involving 210 travelers to Mexico compared a rifaximin 600 mg daily dose (n = 106) to matching placebo (n = 104) for 14 days. Persons receiving rifaximin prophylaxis were less likely to develop diarrhea compared to those receiving placebo (20% vs 48%, respectively, $P < 0.0001$) with a protection rate of 58% against travelers' diarrhea. Traveler's diarrhea-prevention studies among travelers to other geographic regions of the world, where the distribution of the enteric pathogens may differ, are necessary to determine whether rifaximin is an effective chemoprophylaxis outside Mexico. Additional rifaximin prevention trials are in progress or await publication, including a clinical trial evaluating Europeans in Thailand.³⁸

Table I Rifaximin clinical trials for the treatment and chemoprophylaxis of travelers' diarrhea

Study, reference	Study location	Study design	Number of subjects	Results
Treatment				
DuPont et al ⁴	Mexico	Randomized, prospective, double-blind	Rifaximin (200 mg, 400 mg, 600 mg three times a day [n = 55]) or TMP-SMX (160/800 mg two times a day [n = 17]) both for five days	Clinical failure: rifaximin 11% vs TMP-SMX 29%
DuPont et al ²⁸	Mexico, Jamaica	Randomized, prospective, double-blind	Rifaximin (400 mg twice a day; [n = 93]) or ciprofloxacin (500 mg two times a day; [n = 94]) both for three days	TLUS: rifaximin 25.7 h vs ciprofloxacin 25.0 h Clinical cure: rifaximin 87% vs ciprofloxacin 88%
Taylor et al ²⁹	Mexico, Guatemala, India	Randomized, prospective, double-blind	Rifaximin (200 mg three times a day; [n = 197]), placebo (n = 101) or ciprofloxacin (500 mg two times a day; [n = 101]) all for three days	TLUS: rifaximin 32.0 h vs placebo 65.5 h vs ciprofloxacin 28.8 h Clinical cure: rifaximin 76.6% vs placebo 61.4% vs ciprofloxacin 78.2%
Steffen et al ³⁰	Mexico, Guatemala, Kenya	Randomized, prospective, double-blind	Rifaximin (200 mg [n = 125], 400 mg three times a day [n = 126]) or placebo (n = 129) both for three days	TLUS: rifaximin 200 mg 32.5 h vs rifaximin 400 mg 32.9 h vs placebo 60.0 h Clinical cure: rifaximin 200 mg 79.2% vs rifaximin 400 mg 81.0% vs placebo 60.5%
DuPont et al ³¹	Mexico	Randomized, prospective, double-blind	Rifaximin 200 mg three times daily (n = 102) for three days, loperamide (n = 104) after each unformed stool, rifaximin plus loperamide (n = 104) for three days	TLUS: rifaximin plus loperamide 27.3 h vs rifaximin 32.5 h vs loperamide 69 h
Chemoprophylaxis				
DuPont ²⁴	Mexico	Randomized, prospective, double-blind	Rifaximin (200 mg once daily [n = 50], 200 mg twice daily [n = 52], 200 mg three times a day [n = 54]) or placebo (n = 54) both for 14 days	Developed diarrhea: rifaximin 15% vs placebo 54%
DuPont ³⁸	Mexico	Randomized, prospective, double-blind	Rifaximin (600 mg once daily [n = 106]) or placebo (n = 104) both for 14 days	Developed diarrhea: rifaximin 20% vs placebo 48%

Abbreviations: TMP-SMX, trimethoprim-sulfamethoxazole; TLUS, time to last unformed stool; h, hours.

Rifaximin may be effective in preventing travelers' diarrhea, even when invasive enteric pathogens are the causative agents. It is postulated that rifaximin may be active against invasive diarrheagenic pathogens in the gastrointestinal tract prior to mucosal penetration.³⁹ The effectiveness of rifaximin as a prophylactic agent against *Shigella flexneri* was evaluated in a randomized, double-blind, placebo-controlled trial in which 25 healthy adults were experimentally challenged with *S. flexneri*.⁴⁰ Subjects received either rifaximin 200 mg three times a day or placebo for three days prior to the *S. flexneri* challenge. None of the 15 rifaximin subjects developed diarrhea, while six of 10 placebo recipients developed shigellosis ($P = 0.001$). High MICs associated

with invasive enteric infections caused by *C. jejuni*, may limit the effectiveness of rifaximin in some regions of the world (ie, Thailand and India).¹⁸ More studies are needed to confirm whether rifaximin may serve as an appropriate prophylaxis against invasive diarrheagenic pathogens.

Off-label uses of rifaximin

Rifaximin has reported success for a variety other gastrointestinal disorders including irritable bowel syndrome,⁴¹⁻⁴³ portal systemic encephalopathy,^{44,45} small intestinal bowel overgrowth,^{46,47} antibiotic-associated diarrhea including *Clostridium difficile* infection,^{48,49} diverticulitis,^{50,51} inflammatory bowel disease,^{52,53} pouchitis,^{54,55} and prophylaxis for colonic surgery.^{56,57}

Rifaximin safety profile

The poor oral bioavailability of rifaximin contributes to its excellent safety profile and low incidence of adverse events. Over 1,000 subjects have enrolled in clinical trials evaluating rifaximin for travelers' diarrhea.^{24,25,20–30} In all of these studies, subjects receiving rifaximin reported similar or less adverse events compared to those receiving placebo or the active comparator (ciprofloxacin or TMP-SMX), respectively. Distinguishing true medication-related side effects from the underlying diarrheal illness can be challenging. In clinical trials, the most common adverse events associated with rifaximin are related to the gastrointestinal tract and include flatulence, abdominal pain, tenesmus, fecal urgency, and nausea.⁸ No serious adverse events or deaths were reported in clinical trials of rifaximin. Other studies of rifaximin for other gastrointestinal disorders confirm that rifaximin is a well-tolerated treatment.^{41,44,52}

Rifaximin is currently not approved for use in pregnant women or children aged less than 12 years. Although rifaximin, with its minimal systemic absorption, may be an ideal antidiarrheal agent for pregnant women and children, studies in these populations are lacking.⁸

Summary and recommendations

Travelers' diarrhea is a common illness among travelers from developed to developing countries. Illness develops after ingestion of contaminated food and water of which the majority are caused by bacterial pathogens such as enterotoxigenic *E. coli* (ETEC). The treatment of travelers' diarrhea is dependent on the country visited by the traveler, targeted coverage of diarrheagenic pathogens, the microbial resistance patterns associated with the geographical distribution, and the antimicrobial agent's safety and efficacy profile. There are many antibiotics that have been studied for the treatment of travelers' diarrhea including rifaximin which is indicated for the treatment of patients (aged ≥ 12 years) with travelers' diarrhea caused by noninvasive strains of *E. coli*. Rifaximin, a rifamycin derivative with activity against a broad spectrum of microorganisms, is a poorly absorbed oral agent. Since rifaximin is poorly absorbed, drug–drug interactions are uncommon and resistance and cross resistance with other rifamycins are uncommon. The recommended rifaximin dose is one 200 mg tablets taken three times a day for three days. Several clinical trials show rifaximin is more effective than placebo and as effective as TMP-SMX and ciprofloxacin using a primary endpoint of TLUS. Combination therapy with rifaximin and loperamide is

more effective and provides more rapid symptomatic resolution of diarrheal illness compared to rifaximin alone. Rifaximin is not approved for treatment of travelers' diarrhea complicated by fever or blood in the stool or diarrhea due to invasive enteric pathogens. Travelers who develop fever or blood in the stool or diarrhea especially in areas where fluoroquinolone resistant *Campylobacter* species are prevalent have two options for self-treatment of watery diarrhea: take rifaximin and have azithromycin reserved for the less common febrile dysentery or take azithromycin as the single drug. Although not currently indicated, clinical trials show that rifaximin is an effective chemoprophylactic agent for the prevention of travelers' diarrhea when compared to placebo. Rifaximin has an excellent safety profile because it is poorly absorbed from the gastrointestinal tract. Adverse events reported from clinical trials were similar or less than those from subjects receiving placebo or active comparator ciprofloxacin or TMP-SMX. The most common adverse events associated with rifaximin were related to gastrointestinal symptoms such as flatulence, abdominal pain, tenesmus, fecal urgency, and nausea that are difficult to distinguish from the underlying diarrheal illness. Rifaximin is an excellent choice for treatment of travelers' diarrhea due to its favorable pharmacokinetics, *in vitro* susceptibility profile, and efficacy and safety data from clinical trials. Although nondiscriminate chemoprophylaxis with antibacterial agents for travelers' diarrhea is controversial, we believe that chemoprophylaxis with rifaximin is useful especially among travelers to high risk geographic areas such as Mexico, particularly for those who are on tight schedules, have become ill in past trips or have underlying comorbidities which may result in increased susceptibility. For travelers who develop diarrhea despite prophylaxis with rifaximin, we recommend a single 1 g dose of azithromycin as empirical therapy especially when travel is to Southeast Asia where fluoroquinolone-resistant *Campylobacter* species are prevalent. Ongoing studies and continued analysis will clarify the role of rifaximin for chemoprophylaxis of travelers' diarrhea.

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