

**ST06 Advances and Challenges in Travelers' Diarrhea****ST06.1 Rifaximin Pharmacokinetics and Mechanisms of Action**

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Rifaximin is an oral antibiotic that acts by inhibiting the DNA-dependent RNA polymerase of the target microorganism, thus suppressing initiation of chain formation in RNA synthesis. Rifaximin is poorly absorbed from the gastrointestinal tract, with low peak plasma levels. It is almost completely excreted in the feces unchanged, and a small percentage is excreted unchanged in the urine. Because of its poor absorption (< 0.4%), rifaximin reaches high concentrations in the colon.<sup>1</sup>

Rifaximin's lack of effect on normal gut flora<sup>2</sup> suggests a novel mechanism of action. It may be that rifaximin alters the virulence of enteric bacterial pathogens without killing them, or it may offer an antimicrobial protective effect to the intestine. Rifaximin's pattern of water insolubility and bile solubility indicates that it might be more effective in the small bowel than in the colon. Rifaximin has broad-spectrum activity against both gram-positive and gram-negative aerobic and anaerobic bacteria.<sup>3</sup> In vitro, it has been shown to have a MIC<sub>50</sub> ranging between 12.5 and 128 µg/mL and a MIC<sub>90</sub> ranging from 25 to 256 µg/mL against bacterial isolates from patients with travelers' diarrhea. The antibacterial activity of rifaximin is apparently related to its high intestinal concentration (>8,000 µg/g) and inhibition of bacterial pathogen growth.<sup>1,3</sup>

Several clinical trials have shown rifaximin to be effective in shortening the duration of travelers' diarrhea and reducing the number of unformed stools passed. In these studies, rifaximin has demonstrated efficacy equivalent to that of absorbed antibiotics such as ciprofloxacin, although the drug is not as effective in eradicating the infecting organism.

Resistance to rifaximin has remained very low to date. As it is used more broadly, it will be important to monitor for the possible emergence of resistant bacterial strains. Several other potential uses for rifaximin are also under exploration. Currently, it is a safe and effective preventive and therapeutic agent for travelers' diarrhea.

**References**

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**ST06.2 Antimicrobial Treatment of Travelers' Diarrhea**

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The most common causes of travelers' diarrhea (TD) are enterotoxigenic and enteroaggregative *Escherichia coli*, which together cause more than 50% of cases. Thus, antibacterial therapy is the first-line empiric treatment for TD.<sup>1</sup> High levels of resistance to trimethoprim-sulfamethoxazole have reduced its value in treating TD. Fluoroquinolones are effective, although resistance to this class of drugs is also increasing. Azithromycin has the added advantage of being considered safe for children and pregnant women. Rifaximin, a poorly absorbed derivative of rifamycin, has a low potential for inducing resistance and has shown equivalent efficacy and safety to those of ciprofloxacin in TD.<sup>1,2</sup> In clinical trials with patients with pathogens unidentified prior to treatment, rifaximin shortened the duration of diarrhea versus placebo and led more rapidly to clinical wellness.<sup>3</sup>

Combination therapy with loperamide plus an antibacterial has been proven effective. A trial with travelers to Mexico showed that the duration of diarrhea was shorter and the number of unformed stools passed was lower with a combination of loperamide plus azithromycin than with azithromycin alone.<sup>4</sup> In another trial, rifaximin, both alone and in combination with loperamide, reduced the duration of TD significantly more (P=.0019) than did loperamide alone. The combination reduced the number of unformed stools passed more than either drug did alone.<sup>5</sup>

Travelers should be advised to self-treat diarrhea with rehydration and electrolyte replacement and avoid dairy products and caffeine. Prompt empiric therapy with loperamide plus an antibiotic such as a fluoroquinolone, azithromycin, or rifaximin effectively reduces the time to the last unformed stool. Only a minority of patients (10%-25%) have invasive symptoms; for them, a fluoroquinolone or azithromycin is the drug of choice. Patients should be prescribed these drugs to have available on their travels, and they must be instructed in detail about their use. Additionally, they should be advised not to purchase antibiotics while abroad.<sup>6</sup>

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**ST06.3 Persistent Complications of Travelers' Diarrhea**

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Although most cases of travelers' diarrhea (TD) are acute and self-limited, it has become apparent that in some individuals the illness may be complicated by persistent complications such as reactive arthritis, Guillain-Barre syndrome, or persistence of gastrointestinal symptoms.

Some studies show up to 10% of patients with TD developing chronic diarrhea, bloating, and abdominal discomfort. A diagnosis of postinfectious irritable bowel syndrome (PI-IBS) can be made for those who meet Rome III criteria following a bout of TD.

Enteropathogens such as enterotoxigenic and enteroaggregative *Escherichia coli*, *Campylobacter* spp, *Shigella* spp, and *Salmonella* spp may predispose patients to PI-IBS,<sup>1</sup> although PI-IBS occurs more frequently after infection with *Campylobacter* spp and *Shigella* spp. The duration of the initial infectious illness appears to be the strongest risk factor for the development of PI-IBS.<sup>2</sup> PI-IBS may persist for years after the initial TD episode.<sup>2</sup>

Epidemiological and experimental evidence suggests that prophylaxis, early treatment, or self-treatment of TD may be the best preventative measure against PI-IBS.

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**ST06.4 Chemoprophylaxis in Travelers' Diarrhea**

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The 4 types of prevention against travelers' diarrhea (TD) are avoidance, nonpharmacologic therapy, antibiotic prophylaxis, and immunization. Appropriate food hygiene is the logical solution, but this is not always feasible and travelers may not always observe these cautions. Chemoprophylaxis with antibacterial drugs was seen initially as highly effective. The increase in antibiotic resistance and difficulty identifying appropriate candidates led to a consensus that this practice was not advisable. Recently, newer agents have been identified, including over-the-counter bismuth subsalicylate, probiotics, and antibiotics. Among the latter are neomycin, whose use is discouraged because of adverse effects; sulfonamides, trimethoprim-sulfamethoxazole, and fluoroquinolones, to which resistance is increasing; and rifaximin, a poorly absorbed agent with few systemic side effects and little risk of encouraging resistance. Three vaccines are also showing promise against enterotoxigenic *Escherichia coli*.<sup>1</sup>

One argument against chemoprophylaxis is that for some populations, eg, military personnel and refugees, the impracticality and costs of daily therapy are prohibitive. Workers such as embassy personnel who relocate because of their jobs likely have access to medical care at their destinations. As the risks of long-term prophylaxis are unknown, a more practical approach for these groups would be to educate them to prevent TD and either obtain medical treatment or self-treat, as both have proven highly successful. People who travel frequently for business are likely to be easily educated to avoid risks, and both they and vacationers may be sufficiently affluent to afford self-treatment.<sup>2</sup>

With these concepts in mind, a more recent consensus was reached suggesting that chemoprophylaxis of TD should be reserved for patients with underlying conditions that make them more susceptible, those for whom TD might be more dangerous than it is for the general population, and people such as diplomats who might not be able to refuse certain foods for fear of offending their hosts.<sup>3</sup> The concept of offering chemoprophylaxis to most short-term travelers at high risk of acquiring TD remains highly controversial, but the recent availability of a safe and efficacious agent such as rifaximin has prompted renewed discussion.

**References**

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