Antibiotic Therapy for Acute Watery Diarrhea and Dysentery

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ABSTRACT Diarrheal disease affects a large proportion of military personnel deployed to developing countries, resulting in decreased job performance and operational readiness. Travelers' diarrhea is self-limiting and generally resolves within 5 days; however, antibiotic treatment significantly reduces symptom severity and duration of illness. Presently, azithromycin is the preferred first-line antibiotic for the treatment of acute watery diarrhea (single dose 500 mg), as well as for febrile diarrhea and dysentery (single dose 1,000 mg). Levofloxacin and ciprofloxacin are also options for acute watery diarrhea (single dose 500 mg and 750 mg, respectively) and febrile diarrhea/dysentery in areas with high rates of *Shigella* (500 mg once for 3 days [once daily with levofloxacin and twice daily with ciprofloxacin]), but are becoming less effective because of increasing fluoroquinolone resistance, particularly among *Campylobacter* spp. Another alternate for acute watery diarrhea is rifaximin (200 mg 3 times per day for 3 days); however, it should not be used with invasive illness. Use of loperamide in combination with antibiotic treatment is also beneficial as it has been shown to further reduce gastrointestinal symptoms and duration of illness. Because of regional differences in the predominance of pathogens and resistance levels, choice of antibiotic should take travel destination into consideration.

INTRODUCTION

Travelers visiting less developed nations are commonly affected by episodes of acute watery diarrhea or travelers' diarrhea (TD), which is characterized per study definitions by having at least three unformed stools within 24 hours frequently associated with other clinical symptoms, including vomiting, abdominal pain or cramping, and nausea.[1,2] In general, TD is an acute syndrome commonly self-resolving within 3 to 5 days. Nonetheless, in a small number of cases, approximately 3% of patients may develop persistent TD with symptoms lasting for at least 2 weeks, whereas up to 20% are bedbound for 1 to 2 days and 40% experience decreased ability to complete planned activities during the 1 to 2 days of peak illness.[1–3] A more severe form of TD is dysentery, which is characterized by bloody diarrhea often accompanied by fever.[1,2] Bacterial enteropathogens, including diarrheagenic *Escherichia coli* (predominantly enterotoxigenic *E. coli* [ETEC] and enteroaggregative *E. coli*), *Campylobacter* spp., *Shigella* spp., and nontyphoidal *Salmonella* spp., are the predominant etiologic agents associated with TD.[2] Although the circumstances of travel are different, deployed military personnel are also at risk for developing TD and/or dysentery.[4–10]

Even with mild symptoms, diarrheal disease among deployed military personnel may impact operational readiness. In particular, job performance declines as the affected soldier misses patrols or other duties as a result of dehydration requiring intravenous fluids, having fecal incontinence, confined to bed, and/or hospitalization. Assessment of military personnel serving in support of operations in Iraq and Afghanistan found that 45% of individuals with diarrhea reported decreased job performance over a median of 3 days.[8] Another survey of deployed military personnel found that 24%, 28%, and 32% had at least one diarrheal episode while serving in Kuwait, Iraq, and Afghanistan, respectively, with a mean duration of 2.7 days of illness. Among the personnel with diarrheal symptoms, 14% in Kuwait reported a decrease in job performance, whereas it was 21% for both Iraq and Afghanistan (median of 2 days with impacted job performance).[11]

Empiric antibiotic therapy has been proven to be effective at managing the clinical symptoms and reducing the duration of diarrheal illness to approximately 1.5 days.[5,12,13] In a Cochrane meta-analysis of six randomized, double-blind, placebo-controlled trials several years ago, the efficacy of antibiotic treatment with TD was assessed. Antibiotics examined in the trials included trimethoprim/sulfamethoxazole, bicozamycin, norfloxacin, ciprofloxacin, and fleroxacin. The findings indicated a significantly greater number of patients with clinical cure (i.e., resolution of diarrheal illness and associated symptoms) at 72 hours in the antibiotics group compared to placebo (overall odds ratio: 5.9; 95% confidence interval: 4.1–8.6). In addition, the time to last unformed stool (TLUS) ranged from 25 to 39 hours with antibiotic use, whereas it was 54 to 64 hours with the placebo.[12]

Over the past two decades, recommendations related to antibiotic regimens have changed. Initially, treatment for TD involved a 3- to 5-day course of antibiotics[2,13,14]; however,

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findings from multiple randomized control trials supported the shift to single-dose regimens in recent guidelines.[15,16] Single-dose regimens were found to be as or more effective than a 3-day regimen in many trials.[10,17,18] The use of a single dose has a higher likelihood of compliance compared to multiple doses more than 3 to 5 days.

Antimotility agents (e.g., loperamide) are frequently used in combination with antibiotic therapy. Used on its own, loperamide provides symptomatic relief over placebo, but does not result in clinical cure.[2,19–21] A separate meta-analysis of seven randomized, double-blind, placebo-controlled trials and two randomized, evaluator-blind clinical trials assessed the benefit of using loperamide in combination with antibiotic therapy (Fig. 1). The studies involved different antibiotic regimens, including trimethoprim/sulfamethoxazole, ciprofloxacin, ofloxacin, rifaximin, and azithromycin. When the 24-hour clinical cure rates were evaluated, use of combination therapy (antibiotics plus loperamide) showed a benefit compared to use of antibiotic alone (overall odds ratio: 2.6; 95% confidence interval: 1.8–3.6).[21]

When deployed personnel experience diarrheal symptoms, the main objective is to effectively treat the illness to allow the individual to expedite their return to full duty status. Because of geographic differences in the distribution of pathogens, the choice of antibiotic is often dependent on the destination.[2,22] Furthermore, increased levels of resistance have reduced the effectiveness of previously preferred first-line antibiotics. Trimethoprim/sulfamethoxazole is one example of an antibiotic that is no longer commonly prescribed as a result of the increased resistance of ETEC and *Salmonella* spp., as well as inactivity against *Campylobacter jejuni*.[2] Antibiotic agents currently being prescribed are azithromycin, ciprofloxacin, levofloxacin, and rifaximin (Table I). The following sections summarize information related to antibiotic management of TD with a focus on efficacy, safety, and adjunct loperamide therapy of these agents.

AZITHROMYCIN

Efficacy

Azithromycin is an azalide antibiotic in the macrolide family (includes erythromycin) with activity against common enteropathogens.[23] Oral administration of azithromycin (500 mg dose) results in 37% bioavailability with a peak serum concentration of 0.4 mg/L. High intracellular levels of azithromycin are also found in the tissues 12 to 24 hours after oral dosing (mean >2 mg/L), which may persist for days (half-life of 2.3 days in prostate and 3.2 days in tonsillar tissue).[24]

Because of the increasing resistance of enteropathogens to first-line antibiotics (e.g., fluoroquinolones and trimethoprim/sulfamethoxazole), azithromycin has become a preferred choice for the treatment of TD, particularly in regions of the world where prevalent *Campylobacter* spp. are largely resistant to fluoroquinolones, such as Southeast Asia.[10,17] In a randomized, double-blind trial in Mexico, patients received a single dose of either azithromycin (1,000 mg) or levofloxacin (500 mg). Rate of treatment failure (9.5% versus 7.5%) and median TLUS (22.3 versus 21.5 hours) was not significantly different between the azithromycin and levofloxacin groups,

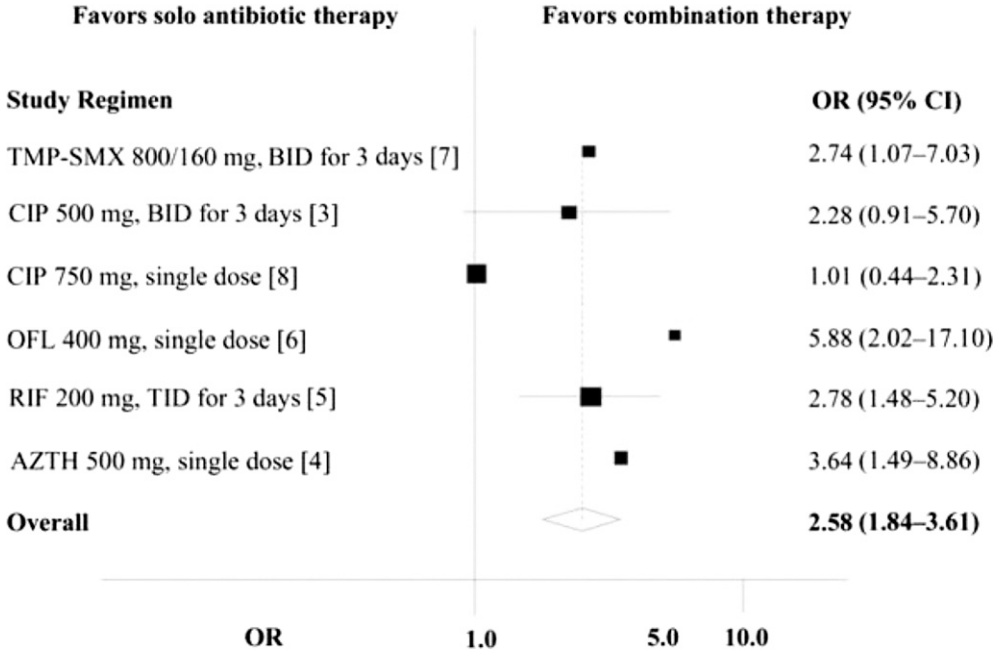

FIGURE 1. Forest plot of odds ratios for clinical cure at 24 hours comparing treatment with antibiotics alone to combination of antibiotics with loperamide. A pooled summary estimate is also included. This figure has been reprinted from Riddle et al[21] by permission of Oxford University Press.

TABLE I. Empiric Antibiotic Therapy for Acute Watery Diarrhea

Antibiotic	Dosage (Adult)	Indication	Notes
Azithromycin[a]	500 mg (single dose)	Preferred agent in all regions of the world;	Antibiotic susceptibility across broad geographic range supports empiric use (particularly important in Southeast Asia with high rates of *Campylobacter* spp.)
	(1,000 mg [single dose] or 500 mg [once daily for 3 days] for febrile diarrhea or dysentery)	To be used when invasive pathogens (e.g., *C. jejuni*) are suspected as etiologic agent	
Fluoroquinolones[a]			
Levofloxacin	500 mg (single dose) (500 mg [once a day for up to 3 days] for febrile diarrhea or dysentery)	Re-evaluate 12–24 hours after single dose; continue for up to 3 days if diarrhea not resolved	In cases of febrile diarrhea/dysentery in regions with high rates of *Shigella*, Levofloxacin may be used; becoming less effective worldwide because of increasing antimicrobial resistance
Ciprofloxacin	750 mg (single dose); 500 mg twice a day (up to 3 days)		
Rifaximin	200 mg 3 times a day (3 days)	Effective when noninvasive *E. coli* is etiologic agent; Should only be used with acute watery diarrhea	Inactive against invasive causes of diarrhea

[a]Single-dose use is an off-label indication on the basis of several randomized clinical trials and published practice guidance.[15,16]

respectively. It was noted that a significantly lower proportion of subjects in the azithromycin group had a TLUS of zero hours compared to those in the levofloxacin group (8% versus 21%, respectively; $p = 0.01$), indicating that the levofloxacin patients had a more rapid clinical response. Overall, it was concluded that a single oral dose of azithromycin was as effective as that of levofloxacin for the treatment of TD.[17]

The effectiveness of azithromycin regimens (single dose of 1,000 mg or 500 mg/day for 3 days) with levofloxacin (500 mg/day for 3 days) was also assessed in a randomized, double-blind trial involving military personnel with TD in Thailand, with the outcome being clinical cure at 72 hours. *Campylobacter* spp. were the predominant etiologic agent (recovered from 64% of subjects, of which 95% was *C. jejuni*) followed by nontyphoidal *Salmonella* spp. (17%). The median TLUS was 35 and 45 hours for the single-dose and 3-day azithromycin regimens, respectively, compared to 50 hours with levofloxacin (significantly different compared to single-dose azithromycin; $p = 0.03$). The single dose of azithromycin resulted in the highest 72-hour cure rate (96%) followed by 85% with the 3-day regimen and 71% with levofloxacin ($p = 0.001$). Furthermore, the microbiological cure rates of *Campylobacter* spp. infections was 96% and 100% for the azithromycin single-dose and 3-day regimen, respectively, compared to only 21% with levofloxacin ($p = 0.001$). There was no significant difference in TLUS between the antibiotic regimen groups with non-*Campylobacter* spp. infections. These data indicate the effectiveness of azithromycin in treating TD in regions with increasing fluoroquinolone resistance.[10] Prior studies have reported similar effectiveness of azithromycin at decreasing the duration of diarrhea when compared to ciprofloxacin.[25,26]

Safety

Mild and self-limiting adverse events have been reported by patients prescribed azithromycin; however, they are not significantly different from adverse events reported with levofloxacin. The majority of complaints involve gastrointestinal symptoms (e.g., mild abdominal pain, fecal urgency, nausea, vomiting, constipation, and flatulence). Fatigue, insomnia, heartburn, chills, body ache, and headaches have also been reported and one subject had a transient skin rash along with anxiety.[17] Nausea within 30 minutes of dosing has been reported among a higher proportion of patients taking a single dose of 1,000 mg (with/without loperamide) compared to those prescribed levofloxacin.[10,27] A recent analysis also found an increased risk of ventricular arrhythmia (odds ratio: 4.32; 95% confidence interval: 2.95–6.33) and cardiovascular death (odds ratio: 2.62; 95% confidence interval: 1.69–4.06) associated with azithromycin use.[28] Further research is needed to determine whether the risk is directly related to azithromycin usage or the result of interactions with other medications and/or the comorbid illness.

Adjunct Therapy

As use of loperamide has been observed to reduce clinical symptoms associated with TD, a randomized, double-blind trial among travelers in Mexico with TD examined whether the combination of loperamide with azithromycin therapy provided an added benefit. Patients received a single dose of azithromycin alone (500 or 1,000 mg) or in combination with loperamide (azithromycin: 500 mg; loperamide: 4 mg initially with 2 mg after each unformed stool; not exceeding 16 mg/day for 2 days). The average duration of diarrhea was significantly shorter in the azithromycin/loperamide combination group compared to both doses of azithromycin alone (11 versus 34 hours; $p = 0.0002$). Within 24 hours of treatment, there were also significantly fewer loose unformed stools passed in the azithromycin/loperamide group (1.2 versus 3.4; $p < 0.0001$). Furthermore, the proportion of subjects with treatment failure was significantly lower in

the azithromycin/loperamide group (4%) compared to both doses of azithromycin alone (20%–21%; $p = 0.01$).[29]

Another randomized, double-blind trial among military personnel with TD in Turkey was conducted to assess if the combination of loperamide with azithromycin therapy was as effective as the use of loperamide with levofloxacin. Patients received a single dose of either azithromycin (1,000 mg) or levofloxacin (500 mg) with loperamide (4 mg initially with 2 mg after each unformed stool; not exceeding 16 mg/day). A higher proportion of subjects reported nausea within 30 minutes of dosing in the azithromycin group compared to levofloxacin (8% versus 1%; $p = 0.004$). There was no significant difference regarding median TLUS (13 and 3 hours) and proportion of patients with clinical cure at 24 hours (33% and 39%) between the azithromycin and the levofloxacin groups, indicating that azithromycin with loperamide was as effective as the combination of loperamide with levofloxacin.[27]

Summary

Azithromycin is well tolerated and has been shown to be effective using a single dose at reducing the duration of TD to less than 1 day for the majority of patients. It is also significantly more effective against *Campylobacter* spp. infections than levofloxacin, so it should be considered the preferred agent in regions where there is high fluoroquinolone resistance, which has been increasing worldwide. In addition, there is a benefit to use of adjunct therapy with loperamide as it does significantly further reduce both symptoms and duration of diarrheal illness.

FLUOROQUINOLONES

Efficacy

Ciprofloxacin

Ciprofloxacin is a fluoroquinolone antibiotic with a wide spectrum of antimicrobial activity and low cross resistance to nonquinolone antibiotic classes. Oral administration of ciprofloxacin results in rapid absorption through the gastrointestinal tract with approximately 70% to 80% bioavailability (~19% excreted in feces). A short half-life (3.5–5 hours) also allows for multiple doses per day.[30]

Multiple studies have demonstrated the ability of ciprofloxacin to significantly reduce the time from diarrheal disease onset to clinical cure. In a randomized, blinded control study, patients with gastroenteritis received 500 mg ciprofloxacin or a placebo twice a day for 5 days. *Campylobacter jejuni* (predating emergence of fluoroquinolone resistance) and *Salmonella enteritidis* were the predominant etiologic agents. The duration of clinical illness was significantly shorter in the ciprofloxacin group compared to the placebo group (2.2 versus 4.6 days; $p < 0.0001$) with 4% and 21% treatment failure ($p < 0.001$), respectively.[31] In another randomized trial, British marines stationed in Belize who developed TD were given a single 500 mg dose of ciprofloxacin or a placebo. The mean TLUS was significantly reduced in the ciprofloxacin group (25 versus 54 hours in placebo; $p < 0.001$) with a mean 5.3 unformed stools compared to 11.7 in the placebo group ($p < 0.0001$).[18] Finally, TD patients in Mexico, Guatemala, India, and Peru were randomized in parallel-group, double-blind study and received ciprofloxacin (500 mg twice per day and one placebo), rifaximin (200 mg 3 times per day), or a placebo for 3 days. The median TLUS for ciprofloxacin was significantly reduced compared to the placebo (29 versus 66 hours; $p = 0.0003$). Ciprofloxacin also had a significantly lower proportion of treatment failure versus placebo (7% versus 27%; $p < 0.05$).[32]

Levofloxacin

Levofloxacin is another fluoroquinolone antibiotic with a similar spectrum of activity to ciprofloxacin. Oral administration of 500 to 1,000 mg levofloxacin results in approximately 99% absolute bioavailability with high concentrations remaining in the tissues. The mean half-life of levofloxacin is approximately 6 to 9 hours, allowing for a single dose per day.[33]

As with ciprofloxacin, levofloxacin is also frequently prescribed for the treatment of TD because of ability to reduce the time to clinical cure as well as being well tolerated by patients.[13] A single dose of levofloxacin is frequently effective; however, a 3-day regimen may be required with some etiologic agents (e.g., *Campylobacter* spp.) or suspicion of invasive disease.[2] In a randomized, double-blind trial in Mexico (see Azithromycin Efficacy section), patients received a single dose of either levofloxacin (500 mg) or azithromycin (1,000 mg). Patients in the levofloxacin group had a median TLUS of 21.5 hours and 21% of patients had rapid resolution of symptoms (i.e., zero loose unformed stools after treatment). Except for having a more rapid clinical response ($p = 0.01$), there was no significant difference between the results with the levofloxacin and azithromycin groups.[17]

Military personnel stationed in Thailand with TD were also included in a randomized, double-blind trial comparing levofloxacin (500 mg for 3 days) to two different regimens of azithromycin (1,000 mg single dose or 500 mg for 3 days) (see Azithromycin Efficacy section). The significantly decreased rate of clinical and microbiological cure in the levofloxacin group, particularly when *Campylobacter* spp. was the etiologic agent (only 21% achieved microbiological cure), demonstrates the decreasing effectiveness of levofloxacin against *Campylobacter* spp. infections.[10]

Safety

Approximately 5% of patients prescribed fluoroquinolones have reported mild and self-limiting adverse events, frequently involving gastrointestinal symptoms, such as nausea, vomiting, diarrhea, flatulence, and constipation.[34] Other less common complaints include central nervous effects (e.g.,

headache and dizziness), fever, rash, vaginitis, tenesmus, fatigue, insomnia, heartburn, chills, body ache, rash, and phototoxicity.[17,30,32,33,35–37] In 2008, the U.S. Food and Drug Administration released a warning regarding the increased risk of tendinopathy (i.e., tendinitis and ruptured tendon) in patients receiving fluoroquinolones.[38] The risk was highest in patients over 60 years of age, transplant recipients, and individuals on steroid therapy. A recent analysis also found an increased risk of ventricular arrhythmia or cardiovascular death (odds ratio: 1.62; 95% confidence interval: 1.20–2.17) associated with levofloxacin use[28]; however, it is unknown whether the risk is directly linked to the antibiotic or the result of drug interactions or comorbid illness. Furthermore, use of fluoroquinolones has been shown to negatively impact the microbiome[39] and pose a significant risk for *Clostridium difficile*–associated diarrhea,[40] as well as community-associated infections or colonization with extended-spectrum β-lactamase-producing bacteria.[41–43]

Adjunct Therapy

The benefit of adding loperamide to a fluoroquinolone treatment regimen has been examined in a number of studies. In a randomized, double-blind trial, dysentery patients in Thailand were given ciprofloxacin (500 mg twice daily for 3 days). Half of the patients received loperamide (4 mg initially followed by 2 mg after each unformed stool; not exceeding 16 mg/day), whereas the other half were given a placebo. Patients in the ciprofloxacin/loperamide combination group had a significantly reduced duration of diarrheal illness compared to ciprofloxacin alone (19 versus 42 hours; $p = 0.028$). In addition, a significantly lower median number of total unformed stools was reported in the ciprofloxacin/loperamide group (2.0 versus 6.5; $p = 0.016$).[44] Use of loperamide was also examined in a randomized, double-blind trial involving military personnel with TD in Egypt. All patients received 500 mg ciprofloxacin twice daily for 3 days with approximately half receiving loperamide (4 mg initially followed by 2 mg after each unformed stool; not exceeding 16 mg/day) and the other half a placebo. Clinical cure within 24 hours was reported for 84% of the patients in the ciprofloxacin/loperamide group compared to 67% in the ciprofloxacin alone group ($p = 0.08$). No significant reduction was reported for the mean number of unformed stools between the groups. Although not statistically significant, 78% of patients with ETEC identified as the etiologic agent showed improvement within 24 hours in the ciprofloxacin/loperamide group compared to 69% with ciprofloxacin alone.[45]

In a randomized, double-blind trial among military personnel with TD in Turkey, patients received a single dose of either levofloxacin (500 mg) or azithromycin (1,000 mg) along with loperamide (4 mg initially with 2 mg after each unformed stool; not exceeding 16 mg/day) (see Azithromycin Adjunct Therapy section). Use of levofloxacin with loperamide resulted in a median TLUS of 3 hours with 39% of patients achieving clinical cure within 24 hours. In addition, the proportion of patients with nausea and vomiting before treatment (61% and 25%, respectively) decreased during the 3-day observation period after treatment was initiated (54% and 15%).[27] Although patients did not receive levofloxacin without loperamide in the trial, a prior study reported a median TLUS of 21.5 hours with levofloxacin use,[17] indicating the addition of loperamide was beneficial.

Summary

Fluoroquinolones are generally well tolerated among the majority of patients with comparable efficacies between ciprofloxacin and levofloxacin. Mild and self-limiting adverse effects (e.g., nausea and vomiting) occur in approximately 5% of patients. Serious adverse effects, such as tendinopathy and *C. difficile*–associated diarrhea, are also associated with fluoroquinolone use, but are less frequent. Furthermore, increasing fluoroquinolone resistance worldwide has reduced the effectiveness of this antibiotic.[10,46–48] In particular, *Campylobacter* spp. have become increasingly resistant over the last two decades (most well documented in Southeast Asia), so fluoroquinolones are not recommended for use in regions where *Campylobacter* is common. When fluoroquinolones are prescribed, loperamide should also be considered because of its added benefit of further reducing symptoms and duration of illness.

RIFAXIMIN

Efficacy

Rifaximin is a rifamycin-based antibiotic with broad-spectrum activity against aerobic and anaerobic bacteria. Oral administration of rifaximin results in poor absorption (<0.4% bioavailability) with ~97% being excreted unchanged in the feces.[49,50] Although rifaximin has been shown to be effective against many enteropathogens, it is largely inactive against invasive pathogens, including *Campylobacter* spp.[50,51]

In a randomized, parallel-group, double-blind, multicenter study in Guatemala, Mexico, and Kenya, patients with TD received one of two rifaximin regimens for 3 days (200 and 400 mg 3 times daily) or a placebo. The predominant etiologic agent identified was ETEC. Median TLUS was significantly decreased in both the rifaximin groups (33 hours for both) compared to the placebo group (60 hours; $p = 0.0001$). When locations were compared, Kenya had the longest TLUS (30 and 43 hours for low- and high-dose rifaximin groups, respectively; 74 hours for placebo) and Guatemala had the shortest (23 and 29 hours for rifaximin groups, respectively; 49 hours for placebo). A significantly higher rate of clinical cure at 120 hours was reported in the rifaximin groups (79% and 81%, respectively, versus 61%; $p = 0.001$). In addition, treatment failure occurred in 16% to 17% of the rifaximin groups, respectively, compared to 35% in the placebo group ($p = 0.001$).[52]

The effectiveness of rifaximin has also been compared with other antibiotics. In a randomized, parallel-group, double-blind study in Mexico, Guatemala, India, and Peru, TD patients received rifaximin (200 mg 3 times per day), ciprofloxacin (500 mg twice per day and one placebo), or a placebo for 3 days. The median TLUS for rifaximin was significantly reduced compared to the placebo (32 versus 66 hours; $p = 0.001$). In addition, among patients with non-invasive *E. coli*, the median TLUS was 24 hours compared to 38 hours in the placebo group ($p = 0.045$). When the rifaximin and ciprofloxacin groups were compared, there was no significant difference related to median TLUS (32 versus 29 hours; $p = 0.35$). Nonetheless, ciprofloxacin had a significantly lower proportion of treatment failure than rifaximin (7% versus 15%; $p = 0.05$). When patients with invasive pathogens (i.e., *Shigella*, *C. jejuni*, and *Salmonella*) were assessed, the median TLUS could not be calculated for the rifaximin group because over half of the patients did not achieve clinical wellness within 24 hours (i.e., lack of watery stools and no more than two soft tools without other clinical symptoms except for mild flatulence in 24-hour period). When patients from the Goa site were excluded (>50% lost to follow-up), there was no statistically significant difference in TLUS between the rifaximin and placebo groups among patients with invasive pathogens (44 versus 48 hours; $p = 0.5$). Furthermore, the proportion of clinical wellness among patients with invasive pathogens was 68% in the rifaximin group compared to 56% and 86% in the placebo and ciprofloxacin groups, respectively.[32]

In another randomized, double-blind, clinical study, patients with TD in Mexico and Jamaica received either rifaximin (400 mg twice per day) or ciprofloxacin (500 mg twice per day) for 3 days. There was no significant difference in median TLUS (26 versus 25 hours) or treatment failure (10% versus 6%) between the rifaximin and ciprofloxacin groups.[36] Similar findings were reported in a randomized, double-blind study in Korea with no significant differences in rifaximin and ciprofloxacin group median TLUS (34 and 35 hours) and treatment failure rates (9% and 12%).[53]

Safety

Patients prescribed rifaximin have reported adverse events such as nausea, excess flatulence, abdominal pain or cramps, fecal urgency, vomiting, headache, constipation, and fatigue at rates similar to placebo recipients,[32,36,52,53] indicating that oral rifaximin is safe for use in treating TD. Although diarrheagenic *E. coli* minimum inhibitory concentrations for rifaximin have shown mild increases among patients with persistent infections, there has been no impact on clinical treatment efficacy.[32,54]

Adjunct Therapy

The use of loperamide in combination with rifaximin was examined in a randomized, double-blinded study. Patients received rifaximin alone (200 mg 3 times per day for 3 days), loperamide alone (4 mg initially with 2 mg after each unformed stool; not exceeding 8 mg/day), or rifaximin with loperamide (same dosing as when given alone). Median TLUS was significantly decreased in the rifaximin alone and combination groups (median 33 and 27 hours, respectively) compared to the loperamide-alone group (69 hours; $p = 0.0019$). Although the proportion of clinical cure within 120 hours (longer period than typically assessed) was similar between the patients who received rifaximin alone and in combination with loperamide (77% and 75%, respectively), the mean number of total unformed stools during the study was significantly lower in the rifaximin/loperamide combination group (3.99 versus 6.23; $p = 0.004$).[55]

Summary

Rifaximin is a safe, well-tolerated, nonabsorbable antibiotic effective against diarrheagenic *E. coli*. Because of its reduced efficacy in treating TD caused by invasive pathogens, such as *Campylobacter*, *Salmonella*, and *Shigella* spp., caution should be applied in regions where these etiologies are common. Importantly, rifaximin is specifically not recommended for use in patients with invasive illness, which includes diarrhea with fever or dysentery.[32] Data indicate that there is an added benefit to use of loperamide with rifaximin therapy.

DISCUSSION

The development of TD among deployed military personnel impacts both the individual and the operational readiness as job performance declines with the onset of diarrheal symptoms. The morbidity is also further intensified in hot environments, such as Iraq where the daytime temperatures are approximately 100°F. In particular, a soldier may lose 2 L of sweat per hour with exercise[56] and this increased loss of fluid and/or electrolytes may lead to earlier clinical symptoms associated with dehydration during an episode of TD.

Early antibiotic treatment is recommended to reduce the duration of diarrheal illness and mitigate the impact on job performance. Nevertheless, deployed military personnel experiencing TD symptoms do not always seek immediate medical treatment. Instead, personnel may wait days and only request medical attention if symptoms persist or worsen.[5] Standardized guidance recommending medical treatment for personnel experiencing watery diarrhea or bloody stools at the first onset of symptoms is needed.

Although further data are needed, there is also the potential that the use of early antibiotic therapy may help prevent long-term complications, resulting from postinfectious sequelae. One such sequela is irritable bowel syndrome (IBS), which is characterized by relapsing gastrointestinal symptoms. In an analysis of military personnel, the occurrence of IBS was associated with antecedent infectious gastroenteritis (odds ratio: 2.05; 95% confidence interval: 1.53–2.75).[57] Another cohort study found 3% of travelers developed postinfectious

IBS 6 months after their travel with risk factors, including pretravel diarrhea (odds ratio: 2.5; 95% confidence interval: 1.2–5.2) and TD (odds ratio: 3.6; 95% confidence interval: 1.7–7.5).[58] *Campylobacter* spp. infections have also been associated with the development of Guillain–Barré syndrome.[59,60] In particular, *C. jejuni* infections have been significantly associated with a Guillain–Barré syndrome outbreak in Mexico (odds ratio: 8.1; 95% confidence interval: 1.5 to infinity).[61] Furthermore, rheumatoid disorders (e.g., reactive arthritis) have been observed to develop following episodes of diarrheal disease (odds ratio: 2.7; 95% confidence interval: 1.1–6.5).[62]

The choice of antibiotic depends on the predominant etiologic agents in the travel destination, as well as regional antimicrobial resistance rates.[22] It is important to remember that antibiotics are ineffective when the cause of TD is viral (i.e., norovirus, rotavirus, or astrovirus) or protozoan (e.g., *Giardia* spp.).[1] Moreover, the preference of the traveler may impact the choice of antibiotic. Specifically, travelers may prefer not to use an antibiotic if they had adverse effects with it during a prior course of treatment. The cost of antibiotics (per civilian pharmacy estimates) is another factor. Ciprofloxacin is the least expensive at approximately $19, followed by azithromycin that averages approximately $25 to $47. Presently, rifaximin is the most expensive at approximately $160 for a 3-day regimen.[63]

Another factor to consider is that use of empiric antibiotics to treat self-limiting illnesses may result in increased antimicrobial resistance, emphasizing the importance of limiting use to moderate-to-severe illness. Antibiotics that were previously effective at treating TD (e.g., trimethoprim/sulfamethoxazole) are no longer active against enteropathogens. Presently, the preferred first-line antibiotic is azithromycin with fluoroquinolones (i.e., ciprofloxacin and levofloxacin) as alternative first-line agents (Table I). In cases with noninvasive diarrheagenic *E. coli*, rifaximin is also an option. Single-dose regimens of these azithromycin and fluoroquinolones are highly effective, particularly when use with adjunct therapy, and are recommended in recently published guidance.[15,16]

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