MAJOR ARTICLE

Traveler's Diarrhea in Thailand: Randomized, Double-Blind Trial Comparing Single-Dose and 3-Day Azithromycin-Based Regimens with a 3-Day Levofloxacin Regimen

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(See the editorial commentary by DuPont on pages 347–9)

Background. Traveler's diarrhea in Thailand is frequently caused by *Campylobacter jejuni*. Rates of fluoroquinolone (FQ) resistance in *Campylobacter* organisms have exceeded 85% in recent years, and reduced fluoroquinolone efficacy has been observed.

Methods. Azithromycin regimens were evaluated in a randomized, double-blind trial of azithromycin, given as a single 1-g dose or a 3-day regimen (500 mg daily), versus a 3-day regimen of levofloxacin (500 mg daily) in military field clinics in Thailand. Outcomes included clinical end points (time to the last unformed stool [TLUS] and cure rates) and microbiological end points (pathogen eradication).

Results. A total of 156 patients with acute diarrhea were enrolled in the trial. *Campylobacter* organisms predominated (in 64% of patients), with levofloxacin resistance noted in 50% of *Campylobacter* organisms and with no azithromycin resistance noted. The cure rate at 72 h after treatment initiation was highest (96%) with single-dose azithromycin, compared with the cure rates of 85% noted with 3-day azithromycin and 71% noted with levofloxacin ($P = .002$). Single-dose azithromycin was also associated with the shortest median TLUS (35 h; $P = .03$, by log-rank test). Levofloxacin's efficacy was inferior to azithromycin's efficacy, except in patients with no pathogen identified during the first 24 h of treatment or in patients with levofloxacin-susceptible *Campylobacter* isolates, in whom it appeared to be equal to azithromycin. The rate of microbiological eradication was significantly better with azithromycin-based regimens (96%–100%), compared with levofloxacin (38%) ($P = .001$); however, this finding was poorly correlated with clinical outcome. A higher rate of posttreatment nausea in the 30 min after receipt of the first dose (14% vs. <6%; $P = .06$) was observed as a mild, self-limited complaint associated with single-dose azithromycin.

Conclusions. Single-dose azithromycin is recommended for empirical therapy of traveler's diarrhea acquired in Thailand and is a reasonable first-line option for empirical management in general.

In Thailand, surveys conducted among deployed US military personnel have shown that *Campylobacter jejuni* and *Campylobacter coli* account for 20%–60% of cases of diarrhea [1–3]. In recent years, fluoroquinolone (FQ) resistance has been noted in >85% of *Campylobacter* isolates from Thailand [4]. Increasing FQ resistance led US Department of Defense researchers to investigate azithromycin as an alternative therapy for

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traveler's diarrhea in Thailand in 1993 [2]. The efficacy of azithromycin, 500 mg daily, was comparable to that of ciprofloxacin, 500 mg daily, administered in a 3-day regimen. Limited statistical power prevented detection of differences in effects. There were only 2 clinical failures, both of which occurred in patients with *Campylobacter*-associated diarrhea treated with ciprofloxacin ($n = 37$). Improved eradication of *Campylobacter* organisms by use of azithromycin therapy did not translate into clinical differences. A reduced duration of illness was noted in association with the use of ciprofloxacin in as many as 40% of cases of non–*Campylobacter*-associated diarrhea, and this finding led experts to cautiously recommend continued first-line therapy with FQs at that time [5].

The rate of FQ resistance among *Campylobacter* organisms in the previous trial was ~65%. This rate increased to ⩾80% by 1998, with observational data suggesting decreasing effectiveness of FQs [3]. The objective of the present study was to compare a 3-day FQ regimen with 2 azithromycin-based regimens (a 3-day multidose regimen and a single-dose regimen).

PATIENTS AND METHODS

Participants and subject eligibility. The trial was conducted during May 2000 in Nakhon Sri Thammarat. Thailand, and during May 2001 in Phitsanulok, Thailand. US military personnel who presented with acute diarrhea at a field clinic were enrolled in the trial after they provided written informed consent. Diarrhea was defined as the occurrence of either ⩾3 loose stools or ⩾2 loose stools with ⩾1 associated complaint (e.g., abdominal cramps, nausea, vomiting, or fever) during a 24-h period. Additional inclusion criteria included symptoms with a duration of ⩽96 h and ambulatory management. Exclusion criteria included pregnancy, an allergy to macrolides or FQs, and receipt of antibiotics (excluding malaria prophylaxis) in the 72 h before enrollment. The use of antidiarrheal medications (e.g., loperamide) after enrollment was not allowed.

Dose selection, treatment assignment, randomization, and blinding procedures. The rationale for use of the 1000-mg single dose of azithromycin was the efficacy noted when a total of 1.5 g was administered over 3 days [2], as well as more recent experience demonstrating the efficacy of a single 1000-mg dose in the treatment of *Shigella* dysentery [6]. Adverse gastrointestinal effects associated with the use of azithromycin administered in single doses of >1 g, particularly for patients who had diarrheal illness with frequent nausea and vomiting at baseline, were also a consideration. The Clinical Research Division of Pfizer Pharmaceuticals supplied the study medications—azithromycin (500 mg daily for 3 days or a single 1000-mg dose) and levofloxacin (500 mg daily for 3 days)—and identical-appearing placebos at no cost. Medicines were dispensed in a 3-day package, with a separate bottle provided for each treatment day. The Pfizer pharmacy supplied computer-generated random-number codes with a block size of 6, which were sequentially assigned at presentation. The blinding procedure was maintained during the laboratory and analysis phases of the trial.

Clinical monitoring. A standardized medical evaluation was used with rehydration therapy, as necessary. The first antibiotic dose was administered under direct observation, with volunteers observed for 30 min. A diary card was provided to record the number of loose stools (per 6-h period), symptoms, functional ability, and medication compliance. Clinical follow-up at 24 h and 72 h monitored for outcomes and drug toxicity. A stool specimen was collected at 5–7 days after treatment initiation, to evaluate pathogen eradication.

Stool microbiological analysis. Primary stool microbiological analysis was undertaken at a field laboratory, as described elsewhere [3]. *Campylobacter* species were isolated using a membrane filter method on nonselective blood agar [7]. Isolates were transported to the Armed Forces Research Institute of Medical Sciences in Bangkok, Thailand, for species identification performed as described elsewhere [8, 9]. Stool specimens were examined for the presence of rotavirus and calicivirus antigens by use of a commercially available ELISA (Rotazyme; Abbott Laboratories) and a noncommercial antigen-capture *Calicivirus* ELISA [10].

Campylobacter antibiotic susceptibility testing was performed using the E test strip methods (AB Biodisk) for azithromycin, levofloxacin, and ciprofloxacin [11], with incubation conducted at 37°C in microaerobic conditions. Established interpretative criteria for Enterobacteriaceae were used [12]. Resistance criteria for *Campylobacter* species, according to the drug received, were as follows: for ciprofloxacin, an MIC ⩾4 μg/mL; for levofloxacin, an MIC ⩾8 μg/mL; and for azithromycin, an MIC ⩾8 μg/mL [13]. The upper limit of the FQ MIC was 64 μg/mL (this value was coded for calculation purposes). Antibiotic susceptibility testing of non-*Campylobacter* isolates was performed using the disk diffusion method [4].

Outcome measures. The primary outcomes were abatement of diarrhea and the duration of illness. Clinical cure was defined as resolution of diarrhea and associated symptoms within 72 h. The time to the last unformed stool (TLUS) was defined as the time to the last loose/liquid stool occurring in a 24-h period and meeting the definition of diarrhea. A microbiological cure was defined as eradication of isolates 48–72 h (inclusive period, days 5–9) after the last treatment day. Isolate eradication was evaluated for an association with clinical outcomes.

Statistical analysis. The outcome used to estimate study size (60 participants per group) was the clinical cure rate determined using a 20% effect size (80% power), given previously observed FQ cure rates of 75% at 72 h (D.R.T., unpublished data). Lower rates of diarrhea in year 2 led to lower-than-

expected enrollment. Intention-to-treat analysis is presented with the subject outcome coded as treatment failure if follow-up is lacking. The majority of the results presented are based on data for evaluable subjects. An evaluable subject was defined as a patient completing a regimen and 72 h of follow-up or a patient requiring treatment modification because of illness progression during the monitoring period.

Characteristics at baseline and summary findings were compared using analysis of variance, Kruskal-Wallis tests, and χ^2 tests, as appropriate [14]. Confidence intervals were generated using a normal approximation to the binomial distribution. Differences in recovery times were evaluated using Kaplan-Meier analyses, log-rank tests, and generalized Wilcoxon tests [14]. All tests were 2-tailed, and $P < .05$ was considered to be statistically significant. Data were entered into EpiInfo software, version 6.04 (Centers for Disease Control and Prevention). Statistical analyses were performed using SPSS software for Windows, version 10.1 (SPSS).

Study approval. This study was approved by the ethics review committees of the Naval Medical Research Center (protocol #31528), the Walter Reed Army Institute of Research (protocol #792), and Uniformed Services University of the Health Sciences (protocol G187MT), in compliance with all federal regulations governing the protection of human subjects.

RESULTS

Patient enrollment and characteristics. A total of 156 (70%) of 222 military personnel met the criteria for entry into the trial (63% of patients were enrolled in 2000). The median patient age was 26 years; the participants were predominantly male (89%) and of junior enlisted rank (71%). Previous travel in Thailand was reported by 27% of patients. A previous episode of traveler's diarrhea was relatively uncommon (16% of patients). Malaria prophylaxis was used for 87% of patients overall, with doxycycline used for 97% of these patients and mefloquine used for the remainder. There were no differences in these characteristics between groups. Observed differences between groups included a slightly higher percentage of women among recipients of single-dose azithromycin (19% vs. 4%–9%), as well as a history of less frequent traveler's diarrhea (6% vs. 22%–26%) and travel to Thailand (17% vs. 31%–33%) among levofloxacin recipients. Table 1 shows group comparisons of clinical manifestations.

A total of 8 volunteers were disenrolled from the trial for the following reasons: treatment modification ($n = 4$), being lost to follow-up ($n = 3$), and noncompliance ($n = 1$). Treatment modification occurred as a result of persistent diarrhea without improvement in 1 patient (at day 3) and progression to dysenteric illness in 2 patients (at days 3 and 6). The other patient who had treatment modification sought care for worsening symptoms on the night after enrollment and was prescribed azithromycin by a nonstudy provider. The decision to provide azithromycin to these 3 patients was based on preliminary culture results (patients were *Campylobacter* positive) and the known high rates of FQ resistance. These 3 patients were later confirmed to have received levofloxacin and were infected with levofloxacin-resistant *C. jejuni*. All 4 patients experienced symptom resolution within 3 days and were censored for time-to-event analyses. Patients that met the criteria for clinical failure were most commonly provided symptomatic support (79%) and were monitored until symptom resolution.

Distribution of enteric pathogens. An enteric pathogen, typically bacterial, was identified in 81% of patients, with multiple isolates identified in 18% (table 2). *Campylobacter* species was the most commonly isolated pathogen (recovered from 64% of patients; *C. jejuni* was isolated from 95% of these patients, and *C. coli* was isolated from the remainder of the patients), followed by nontyphoidal *Salmonella* species (recovered from 17% of patients). According to the E test, no *Campylobacter* species demonstrated azithromycin resistance (MIC_{50}, 0.047 μg/mL; MIC_{90}, 0.094 μg/mL), whereas 50% of isolates were levofloxacin resistant (MIC_{50}, 6.0 μg/mL; MIC_{90} >64.0 μg/mL) and 93% were ciprofloxacin resistant (MIC_{50}, 16.0 μg/mL; MIC_{90}, >64.0 μg/mL). The rates of antibiotic resistance among non-*Campylobacter* bacterial isolates were as follows: for *Escherichia coli* ($n = 18$), the rate of levofloxacin resistance was 3.8% and that of azithromycin resistance was 5.6%; for *Salmonella* organisms ($n = 28$), there was no levofloxacin resistance, but the rate of azithromycin resistance was 14%; and for *Plesiomonas* species ($n = 11$), there was no levofloxacin resistance or azithromycin resistance.

Clinical outcomes. Clinical resolution was uncommon by 24 h, irrespective of the regimen followed, with levofloxacin associated with the highest cure rate (25%), primarily among patients with no pathogen identified (table 3). Azithromycin regimens had significantly improved cure rates, compared with levofloxacin regimens, as early as 48 h after treatment initiation (53%–65% vs. 38%; $P = .02$) and, also, at 72 h (85%–96% vs. 71%; $P = .001$). Intent-to-treat analysis demonstrates similar clinical cure outcomes. The 72-h cure rate for single-dose azithromycin was 94%, compared with 80% for a 3-day regimen of azithromycin and 70% for levofloxacin ($P = .006$). A direct comparison of azithromycin-based regimens, by use of intent-to-treat analysis, demonstrated the superior cure rate of the 1-g single-dose regimen ($P = .04$). A trend toward improved cure in evaluable patients was observed for the single-dose azithromycin group, compared with group following the 3-day regimen ($P = .09$). No notable differences were noted for other measures of clinical outcome, including the mean number of loose stools, the median time to the last loose stool or first formed stool, and the duration of non–diarrhea-associated symptoms.

Table 1. Clinical manifestations, laboratory findings, and management at presentation, by treatment group.

Variable	Azithromycin		3-Day levofloxacin regimen (n = 53)
	Single-dose regimen (n = 52)	3-Day regimen (n = 51)	
Clinical manifestation			
Duration of illness before treatment, mean days ± SD	1.6 ± 0.8	1.7 ± 1.0	1.6 ± 0.8
Diarrhea frequency 24 h before treatment, mean no. of stools ± SD	7.5 ± 6.4	6.7 ± 4.9	7.1 ± 4.3
Subjective fever	28 (54)	24 (47)	26 (49)
Documented fever[a]	16 (31)	8 (16)	9 (17)
Abdominal cramps	47 (90)	45 (88)	47 (89)
Gross blood in stools	8 (16)	6 (12)	8 (15)
Nausea	36 (69)	27 (53)	36 (68)
Vomiting	15 (29)	7 (14)	10 (19)
Myalgia	27 (52)	22 (43)	20 (38)
Arthralgia	10 (19)	7 (14)	8 (15)
Headache	29 (56)	28 (55)	29 (55)
Orthostatic hypotension	13 (26)	15 (30)	14 (26)
Laboratory finding			
Hemoccult positive[a]	17 (33)	20 (40)	21 (41)
Fecal leukocytes present[c]	17 (39)	22 (48)	15 (31)
Fecal lactoferrin positive[d]	42 (81)	38 (78)	42 (81)
Patient assessment and management			
Activity limitation			
None	14 (27)	12 (25)	15 (28)
Reduced	26 (51)	27 (55)	27 (51)
Unable	11 (22)	10 (20)	11 (21)
Received nonantibiotic therapy before enrollment			
Loperamide	8 (15)	5 (10)	7 (13)
Bismuth subsalicylate	1 (1.9)	2 (3.9)	4 (7.5)
Received intravenous fluids	11 (21)	8 (16)	9 (17)
Initial disposition			
Return to duty	35 (67)	40 (78)	42 (79)
Sick in quarters	17 (33)	11 (22)	11 (21)

NOTE. Data are no. (%) of patients, unless otherwise indicated. No statistically significant differences were noted between treatment groups. Microscopic examination of fresh stool specimens was used to evaluate for stool parasites.

[a] Temperature, ≥37.8°C (≥100.0°F).

[b] Occult blood testing was performed using Hemoccult (Beckman Coulter).

[c] Fecal leukocytes were semiquantitatively determined using methylene blue–stained fecal smear specimens.

[d] Fecal lactoferrin was detected according the instructions of the manufacturer of Leuko-Test (TechLab).

TLUS indicated prolongation of illness in the levofloxacin group (figure 1) (P = .03, by log-rank test). The mean TLUS was 39 h (95% CI, 31–47 h) for patients receiving single-dose azithromycin, compared with 43 h (95% CI, 34–51 h) for those receiving the 3-day azithromycin regimen and 56 h (95% CI, 42–71 h) for those receiving levofloxacin. Figure 2 stratifies TLUS by isolation of *Campylobacter* species, demonstrating no differences among patients with non-*Campylobacter* diarrhea by treatment received. A prominent difference was observed in *Campylobacter*-associated diarrhea between patients receiving levofloxacin with levofloxacin-resistant isolates, compared with other patients (the mean TLUS was 41 h for patients receiving single-dose azithromycin, 41.2 h for patients with levofloxacin-susceptible pathogens, 47 h for patients receiving the 3-day azithromycin regimen, and 76.4 h for patients with levofloxacin-resistant pathogens).

Two patients in the group receiving the 3-day azithromycin regimen experienced relapse of illness. One patient had initial

Table 2. Distribution of enteric pathogens at presentation, by treatment group.

Stool microbiological finding	Azithromycin group		3-Day levofloxacin regimen (n = 53)
	Single-dose regimen (n = 52)	3-Day regimen (n = 51)	
Pathogen(s) identified			
Any	42 (81)	42 (82)	39 (75)
None	10 (19)	9 (18)	13 (25)
Multiple	12 (23)	7 (14)	9 (17)
Selected pathogen isolation			
Campylobacter species	37 (71)	30 (59)	32 (62)
Nontyphoidal *Salmonella* species	11 (21)	8 (16)	7 (14)
Enterotoxigenic *Escherichia coli*	1 (2.0)	2 (4.0)	2 (3.8)
Enteropathogenic *E. coli*	3 (5.9)	4 (8.0)	6 (12)
Plesiomonas shigelloides	3 (5.8)	5 (9.8)	3 (5.8)
Rotavirus	2 (4.3)	2 (4.4)	1 (2.0)
Norwalk virus	2 (4.5)	1 (2.2)	1 (2.0)

NOTE. *Shigella* species, enterohemorrhagic *E. coli*, enteroinvasive *E. coli*, and parasitic etiologies not identified. The enteropathogenic *Escherichia coli* (EPEC) designation was based on *eae*$^+$ probe results (all EPEC adherence factor and Shiga-like toxin probe results were negative, resulting in classification of these organisms as atypical EPEC, although no O serogrouping was done to verify serotype) [15]. The most common copathogens noted among *Campylobacter*-associated cases of diarrhea, identified in 22 (22%) of 99 isolates, included *Salmonella* species (n = 12), *Plesiomonas* species (n = 7), *eae*$^+$ *E. coli* (n = 6) and rotavirus (n = 4). No statistically significant differences were noted between treatment groups. Stool culture was not performed before treatment for 1 patient in the levofloxacin group.

cure at 54 h, followed by a 48-h symptom-free period and then by a 24-h episode in which 7 loose stools were noted without associated complaints. The second subject had initial cure at 72 h, followed by a 72-h symptom-free period and then by a 24-h episode in which 2–3 loose stools, mild nausea, and vomiting were noted. Neither subject required additional treatment. Follow-up microbiological analysis of stool specimens detected no pathogens. Both patients had pretreatment *C. jejuni* isolates, with eradication occurring by day 3 of treatment.

Microbiological outcome. Microbiological cure rates were much higher for azithromycin-based regimens, primarily as a result of *Campylobacter*-associated diarrhea (table 3). An eradication rate of ~100% was observed with azithromycin, compared with the 21% rate noted for levofloxacin ($P < .001$). Of patients receiving levofloxacin who had *Campylobacter*-susceptible strains before treatment (n = 8), 63% had in vivo resistance develop, with a posttreatment MIC >32 μg/mL; however, in vivo resistance was not associated with therapeutic failure or relapse. A single patient who had azithromycin-susceptible (MIC, 0.064 μg/mL) *C. coli* (Lior 55) treated with the 1-g dose had a Lior nontypeable, highly resistant (MIC, >256 μg/mL) isolate recovered on days 3 and 7. The patient reported a last diarrheal stool at 71 h after treatment without experiencing relapse. One patient in the group receiving the 3-day azithromycin regimen also had a highly susceptible (MIC, 0.064 μg/mL) *C. jejuni* (Lior 36) isolate before treatment, with recovery of a Lior nontypeable highly resistant (MIC, >256 μg/mL) isolate occurring on day 3 of treatment. This subject had resolution of diarrhea 4.5 h after receipt of the first dose and did not attend a follow-up visit for posttreatment stool culture.

Eradication of the pretreatment isolate did not correlate with clinical cure at the 72-h end point. In the azithromycin treatment groups, 6 patients experienced clinical failures at 72 h, and all had microbiological cure. In the levofloxacin treatment group, 7 clinical failures occurred, with only 2 patients (29%) having a microbiological cure. A similar rate of microbiological cure was observed in the 14 levofloxacin-treated patients who met the clinical cure outcome (36%). Overall, microbiological cure was observed in 84% and 62% of patients with or without clinical cure, respectively.

Adverse events. Surveillance demonstrated no severe side effects. Single-dose azithromycin was associated with an increased rate of mild to moderate nausea not associated with vomiting and lasting ~1 day (table 4). The complaint was uncommon, with 14% of patients reporting nausea 30 min after receipt of the first dose and with 1 episode associated with vomiting (without pill contents), and with 17% of patients reporting nausea as a new symptom occurring over the next 3 days. Self-limited vaginal pruritus not requiring medication was reported in 2 patients receiving levofloxacin. Transient rash that

was most consistent with heat rash was observed in 1 patient in each of the azithromycin treatment groups. Headache was reported in 22%–35% of patients, and transient dizziness was reported in 8%–12% of patients, without group differences.

DISCUSSION

Azithromycin was definitively demonstrated to be the preferred antibiotic for empirical treatment of traveler's diarrhea in Thailand. An equivalent time to recovery for patients infected with susceptible *Campylobacter* strains was observed for levofloxacin and azithromycin. Levofloxacin resistance measured in vitro was shown to correlate with a significantly prolonged time to recovery. The single 1-g dose had superior efficacy. Azithromycin has favorable pharmacokinetics for single-dose treatment of bacterial diarrhea, with an 11–14-h half-life, 46% of active drug passed in the feces, and high levels in the gut lumen (>200 μg/mL) [16, 17]. A single lower dose would be desirable, given dose-related nausea and vomiting. Rates of new-onset nausea (8%–17%) higher than those reported in association with nongastrointestinal infections (<1%–3%) are likely caused by exacerbating effects of the primary illness [18]. Given the superior efficacy, improved compliance, and ease of dosing, the mild transient side effects would seem to be outweighed toward selection of the single-dose regimen.

A single 1-g dose of azithromycin was efficacious in travelers to Mexico [19]. Among azithromycin recipients, 52% of patients had enterotoxigenic *E. coli* (ETEC) recovered, 5% had *Shigella* strains recovered, and no patients had *Campylobacter* strains recovered; in addition, azithromycin recipients also had a TLUS <24 h and no increase in nausea/vomiting, 58% had microbiological eradication, and 9.5% experienced treatment failure. More rapid abatement of diarrhea, compared with that noted in our study, is consistent with therapeutic responses observed in trials conducted in regions where ETEC is the

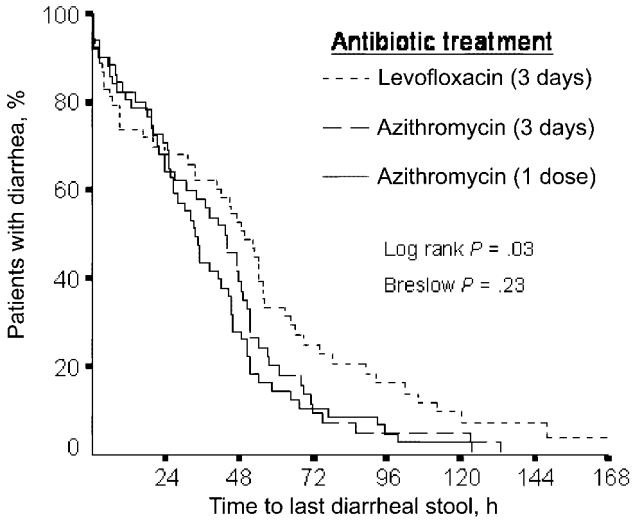

Figure 1. Time to cure (after receipt of the first antibiotic dose), by treatment group.

Table 3. Clinical and microbiological outcomes, by treatment group.

Outcome measure	Azithromycin		3-Day levofloxacin regimen (n = 53)
	Single-dose regimen (n = 52)	3-day regimen (n = 51)	
Clinical cure, % (95% CI)			
By 24 h	20 (9.8–33.1)	18 (8.6–31.4)	25 (13.8–38.3)
By 48 h	65 (50.1–77.6)	53 (38.3–67.5)	38 (25.3–53.0)[a]
By 72 h	96 (86.5–99.5)	85 (72.2–93.9)	70 (56.9–82.9)[b]
Time to event, median h (IQR)			
Last febrile episode	0.5 (0.5–12.0)	4.0 (0.5–12.0)	12.0 (0.5–24.0)
Last diarrheal stool	35 (19.5–52.5)	45 (19.7–54.6)	50 (8.8–69.1)
Loose stools, mean no. ± SD			
24 h before treatment	7.5 (6.4)	6.7 (4.9)	7.1 (4.3)
During treatment			
1st 24 h	4.5 (4.2)	3.2 (2.8)	3.7 (3.6)
2nd 24 h	2.7 (2.8)	2.4 (2.1)	4.0 (4.4)
3rd 24 h	1.1 (1.5)	1.6 (2.0)	2.3 (2.6)
4th 24 h	0.6 (1.2)	0.7 (1.8)	1.1 (2.0)
Microbiological cure, % (95% CI)			
Overall	96 (81.0–99.9)	100 (87.2–100)	38 (18.8–59.4)[b]
For *Campylobacter*-associated cases	96 (80.0–99.9)	100 (81.5–100)	21 (6.1–45.6)[b]

[a] P = .02.
[b] P = .001.

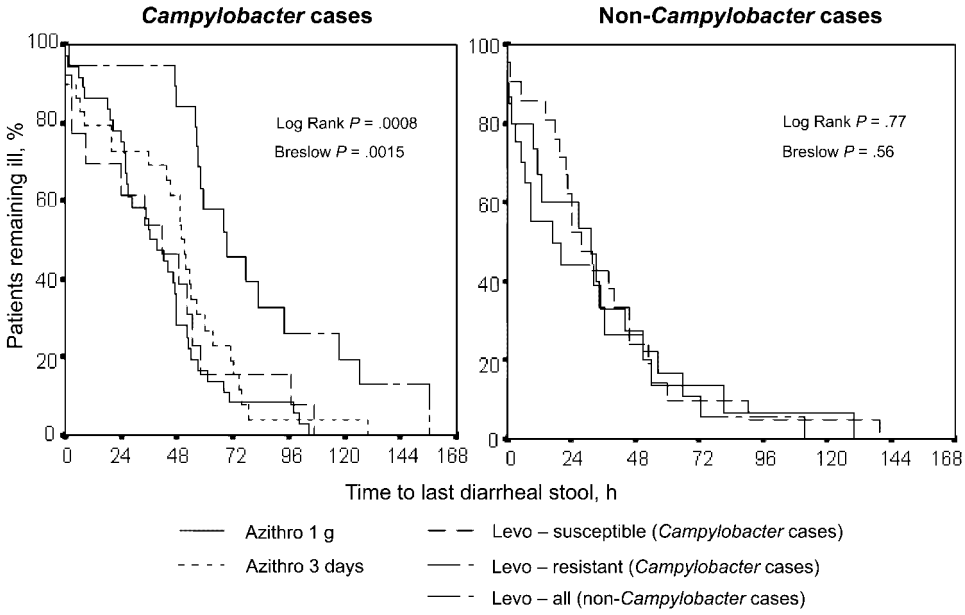

Figure 2. Time to cure (after receipt of the first antibiotic dose), by treatment group, as stratified by diagnosis of *Campylobacter* infection. Azithro, azithromycin; Levo, levofloxacin.

predominant pathogen, even without the use of antimotility agents [1, 2, 20, 21]. Lower 24-h cure rates (36%–38%) noted in an FQ-based trial in Thailand, where *Campylobacter*-associated diarrhea accounted for 41% of cases, are more comparable, although cure rates of >20% are still observed [1]. The current trial enrolled patients with a broader spectrum of illness, whereas the earlier study excluded patients with dysentery and fever (temperature, >38.3°C), likely accounting for the higher 24-h cure rates [1]. The rapid cures (those occurring in <24 h) noted in patients with "no pathogen isolated" who were receiving levofloxacin may represent unrecognized enteroaggregative *E. coli* or other pathogenic *E. coli* diarrhea [22].

Acquired in vivo ciprofloxacin resistance is well described in persons with *Campylobacter* infection [23]. Frequently, the acquired resistance occurs with the patient experiencing no adverse clinical effects, although it also occurs in the context of clinical relapse [1]. In some studies surveying for acquired resistance, such resistance has either not been observed [2, 24] or has occurred in as many as 6 of 9 patients [25]. Our study documented a 63% rate of acquired resistance without clinical relapse. The clinical relevance of the difference in rates of resistance between ciprofloxacin and levofloxacin among the *Campylobacter* isolates is unknown. Levofloxacin was reported to be 2-fold more potent than ciprofloxacin against *C. jejuni* in vitro [26]. MIC thresholds using clinical correlation for diarrheal illness remain to be defined [27].

The concurrent use of doxycycline for malaria prophylaxis in a majority of patients complicates the interpretation of results. Stratified analysis did not demonstrate a confounding effect. Doxycycline prophylaxis for traveler's diarrhea has been extensively studied in travel destinations or regions where ETEC is the predominant pathogen, with prophylactic efficacy ranging from 44% to 90% [28, 29]. Doxycycline had no effect on resistant ETEC or on rates of diarrhea or distribution of pathogens among deployed military personnel in Thailand [28–30]. *Campylobacter* isolates had high rates of tetracycline resistance (86%), as was also observed for *E. coli* isolates (83%) and *Salmonella* isolates (89%), compatible with selective pressure.

Campylobacter eradication secondary to azithromycin was near 100% as early as 3 days after treatment initiation, consistent with the reported time to clearance (mean, 1.1 days) of *C. jejuni* after erythromycin treatment [31]. Of concern, was the occurrence, although uncommon, of high-level azithromycin-resistant *Campylobacter* species in 2 azithromycin-treated patients. These patients possibly had coinfection with susceptible and resistant *Campylobacter* strains. Mixed infections with multiple *Campylobacter* species or strains have been reported at rates of 7.5% [32] and were observed in this study in pretreatment cultures (rate, 5.1%). Azithromycin is an antibiotic that is widely used, particularly for the treatment of acute respiratory infections. A concern regarding broadening azithromycin indications to include acute bacterial enteritis is the development of resistance, as has been observed with treatment with FQs. Macrolide resistance in *C. jejuni* has been relatively stable worldwide (rate of resistance, 0%–11% [with higher rates noted for *C. coli*]) [33]. Azithromycin resistance among *Campylobacter* strains has been observed in past surveys of military personnel (rate, 7%–15%) [34] and in Thai children

Table 4. Surveillance for posttreatment nausea and vomiting, by treatment group.

Surveillance period, symptom	Azithromycin group		3-Day levofloxacin regimen (n = 53)
	Single dose (n = 52)	3-Day regimen (n = 51)	
Immediately[a] after first dose			
Nausea	7 (14)[b]	3 (5.9)	1 (1.9)
Vomiting	1 (1.9)	0	0
During remainder of 3-day observation period			
Nausea			
Present before treatment	17 (35)	8 (16)	17 (32)
Limited to after treatment	8 (17)[c]	4 (8.2)	3 (5.7)
Vomiting			
Present before treatment	13 (26)	7 (14)	10 (19)
Limited to after treatment	4 (8.0)	1 (2.0)	2 (3.8)

NOTE. Data are no. (%) of patients.

[a] 30 min.

[b] $P = .06$.

[c] $P = .03$.

with diarrhea (rate, 6% [with dual resistance to ciprofloxacin]) [35]. The current report demonstrated no azithromycin resistance among *Campylobacter* strains.

A recent multisite survey of azithromycin susceptibility (predominantly among ETEC, enteroaggregative *E. coli,* and *Salmonella* and *Shigella* strains) demonstrated an MIC_{90} of 0.0625 μg/mL providing greater confidence for broader clinical use [36]. Nontyphoidal *Salmonella* isolates with reduced nalidixic acid and FQ susceptibility have been documented in travelers returning from Southeast Asia (most commonly, Thailand) [4, 37]. FQ-resistant *Salmonella* isolates were not observed in this trial, although ~4% of the *E. coli* isolates were levofloxacin resistant, with rates of azithromycin resistance of 6%–14% noted for non-*Campylobacter* bacterial pathogens. Also of concern are nalidixic acid resistance rates of 43%, 17%, and 18% in *Salmonella, E. coli,* and *Plesiomonas* isolates, respectively.

Alternative antibiotics for traveler's diarrhea continue to be needed, given progressive emergence of resistance. FQ-resistant travel-associated and domestic *Campylobacter*-associated diarrhea in industrialized countries have increasingly been reported and are not restricted to such countries as Thailand and Spain [38, 39]. An alternative agent is the nonabsorbable antibiotic rifaximin, which has documented efficacy equal to that of ciprofloxacin in regions where ETEC is predominant [40]. Rifaximin was ineffective in the treatment of *Campylobacter*-associated diarrhea, with a clinical cure rate of only 23.5% (as detailed in the package insert), making this a poor choice for an area such as Thailand.

Antibiotic therapy for acute diarrhea should be restricted to patients with moderate to severe illness, individuals at risk for poor clinical outcomes based on comorbid illnesses, or high-tempo settings with complicating issues, such as the risk of heat-associated illness (which frequently is the case in deployed military personnel). In addition, given current azithromycin use in children and during pregnancy, these data for acute bacterial enteritis can likely be extrapolated for clinical application where concerns exist for FQ use and alternative antibiotics are lacking. In conclusion, single-dose (1-g) azithromycin is recommended for empirical therapy of travelers' diarrhea acquired in Thailand and, on the basis of a synthesis of the clinical studies, is a reasonable first-line option for empirical management of traveler's diarrhea.

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