

## AN OBSERVATIONAL CLINIC-BASED STUDY OF DIARRHEAL ILLNESS IN DEPLOYED UNITED STATES MILITARY PERSONNEL IN THAILAND: PRESENTATION AND OUTCOME OF *CAMPYLOBACTER* INFECTION

J. W. SANDERS, D. W. ISENBARGER, S. E. WALZ, L. W. PANG, D. A. SCOTT, C. TAMMINGA, B. A. OYOFO,  
W. C. HEWITSON, J. L. SANCHEZ, C. PITARANGSI, P. ECHEVERRIA, AND D. R. TRIBBLE

National Naval Medical Center, Bethesda, Maryland; Armed Forces Research Institute of the Medical Sciences, Bangkok, Thailand;  
Naval Medical Research Center, Silver Spring, Maryland 20910-7500; Portsmouth Naval Medical Center, Portsmouth, Virginia  
23708-2197; Naval Medical Research Unit No. 2, Jakarta, Indonesia; U.S. Army Medical Department (AMEDD) Center and School,  
Fort Sam Houston, Texas; Naval Medical Research Center-Detachment Unit 3800, Lima, Peru

**Abstract.** *Campylobacter* is a leading cause of traveler's diarrhea in Thailand. Since resistance to quinolones is high among *Campylobacter* isolates, empiric therapy with quinolones for traveler's diarrhea may be ineffective in this region. We conducted an observational study among 169 U.S. military personnel with acute diarrhea and compared their microbiologic findings to those of 77 asymptomatic personnel deployed to Thailand in May 1998. Of 146 pathogenic bacterial isolates, the most common were nontyphoidal *Salmonella* ( $n = 31$ ), enterotoxigenic *Escherichia coli* ( $n = 24$ ), and *C. jejuni/coli* ( $n = 23$ ). *Campylobacter* was strongly associated with disease (odds ratio = 5.9; 95% confidence interval = 1.3–37.3), with a more severe clinical presentation, and with a reduced functional ability at presentation ( $P = 0.02$ ). In vitro resistance to ciprofloxacin was observed in 96% of the *Campylobacter* isolates. Sub-optimal treatment response to ciprofloxacin was observed in 17% of the cases of *Campylobacter* infection versus 6% due to other causes. These results highlight the importance of *Campylobacter* as a cause of severe traveler's diarrhea in Thailand and illustrates the ongoing problem with antibiotic-resistant strains and associated treatment problems.

### INTRODUCTION

Acute infectious diarrhea is a common illness of travelers to developing countries and is a significant problem for deployed military troops. Enterotoxigenic *Escherichia coli* (ETEC) is the most common cause of traveler's diarrhea worldwide, but *Campylobacter* species have emerged as the most common cause in travelers to Thailand, accounting for up to 52% of isolates in some series.<sup>1,2</sup>

Traveler's diarrhea typically presents in the first week of travel with symptoms of mild to moderate diarrhea frequently associated with abdominal pain, nausea, and malaise. It is difficult to distinguish infecting organisms based on their clinical presentation, but it has been reported that infections with *Campylobacter* species may be more severe than infections with other causes of traveler's diarrhea.<sup>3</sup> Furthermore, while the fluorinated quinolones remain highly effective in the treatment of traveler's diarrhea due to most causes, reports of increasing resistance to the quinolones among *Campylobacter* species have raised questions about the continued efficacy of the quinolones in this setting.<sup>4</sup>

To better clarify questions concerning the etiologies, clinical presentation, and treatment of traveler's diarrhea in Southeast Asia, especially that caused by *Campylobacter* species, we performed an observational and clinical follow-up study of U.S. military personnel deployed to Thailand who developed acute diarrhea.

### MATERIALS AND METHODS

**Study protocol.** U.S. military personnel deployed to Thailand from April through June 1998 who presented to a field medical unit with acute diarrhea or an undifferentiated febrile illness were enrolled in a cross-sectional observational study. Diarrhea was defined as three or more loose stools in a 24-hour period or two or more loose stools in a 24-hour period with one or more associated gastrointestinal complaints,

such as abdominal cramps, nausea, or vomiting. A fever was defined as a temperature of 38°C (100.4°F) or higher. Patients were evaluated by clinicians using a standardized questionnaire and medical examination forms. Patients were then asked to provide a stool specimen, and the clinicians prescribed a course of therapy based on their evaluation. There was no dictated course of therapy, but most patients were treated with either ciprofloxacin (500 mg orally twice a day for three days) or azithromycin (500 mg orally once a day for three days), with or without loperamide (a 2-mg capsule after each loose stool, maximum of 16 mg per day).

Patients were provided a diary card to record the number of loose stools for each six-hour period; the presence of abdominal cramps, nausea, vomiting, fever, or bloody stools in each 24-hour period; and an assessment of their daily functional ability. Daily functional ability referred to a patient's ability to work or recreate and was divided into three categories: normal ability, decreased ability, and unable. The patients were asked to return with their card in 72 hours for re-evaluation. Clinical cure was defined as resolution of their diarrhea within 72 hours of initiating therapy. Relapse was defined as resolution of diarrhea for at least 24 hours followed by a recurrence of symptoms. If patients were still having diarrhea at 72 hours, treatment was modified at the discretion of the clinician with follow-up in three days.

To obtain a comparison population to be able to assess the significance of microbiologic findings, personnel who reported to the medical units for complaints other than diarrhea or fevers were asked to provide a stool sample for microbiologic examination. Exclusion criteria included diarrhea, fevers, or use of antimicrobials other than malaria prophylaxis in the prior week. No attempt was made to match these personnel to cases.

Participation in the study was completely voluntary and informed consent was obtained from all subjects. The study was approved by the Institutional Review Board of the Naval Medical Research Center.

**Laboratory studies.** Stool specimens were cultured on-site in Kanchanaburi and Utapao, Thailand. Isolate identification and antibiotic susceptibility testing was done at the Armed Forces Research Institute of the Medical Sciences in Bangkok. Primary plating included MacConkey, Hektoen Enteric, thiosulfate-citrate bile salts-sucrose, and *Brucella* with 5% sheep blood (BA) agars for overnight incubation. *Campylobacter* was isolated using a membrane filter method on non-selective BA agar before and after enrichment.<sup>5</sup> Selenite F broth, alkaline peptone water, and Doyle's Media were used as enrichment media. Following overnight incubation, specimens were subcultured and refrigerated at 4°C until transport to Bangkok.

Enteric pathogens were identified using standard morphologic and biochemical criteria as previously described.<sup>6,7,8</sup> Five lactose-fermenting and five non-lactose-fermenting *E. coli* colonies per specimen were tested using DNA probes for detection of ETEC toxins, enteroinvasive *E. coli*, enterohemorrhagic *E. coli*, locally adherent enteropathogenic *E. coli*, and attaching and effacing *E. coli* (*eaec*+ *E. coli*).<sup>9,10</sup>

Stool specimens were examined for the presence of rotavirus by a commercially available enzyme-linked immunosorbent assay (Rotazyme; Abbott Laboratories, North Chicago, IL). A reverse transcription-polymerase chain reaction assay was performed as previously described to detect the presence of Norwalk virus.<sup>11,12</sup>

**Statistical analysis.** Statistical analyses were performed using Epi-Info, version 6 (Centers for Disease Control and Prevention, Atlanta, GA). Differences in clinical findings at presentation and illness outcome between *Campylobacter*-associated cases and cases without isolation of *Campylobacter* species were evaluated by the chi-square test. Associations of specific pathogen isolation and diarrheal illness were evaluated using odds ratios with 95% confidence intervals. All tests were two-tailed, and *P* values < 0.05 were considered statistically significant.

## RESULTS

Of the approximately 5,000 U.S. military troops deployed, 169 presented to one of the clinics and met the case definition for acute diarrhea acquired in Thailand. Two of the 169 patients actually initially presented with an undifferentiated febrile illness, but subsequently developed diarrhea. Most (92%) of the patients were male and their average age was 28.4 years. Fifteen percent of the patients had experienced an illness in Thailand prior to this episode of diarrhea, but only 4.2% had received antimicrobials (excluding malaria prophylaxis) in the two weeks prior to presentation with diarrhea. Thirty-one percent of the patients were taking doxycycline for malaria prophylaxis. One hundred forty-three (85%) of the symptomatic patients submitted stool specimens. Potential pathogens were recovered from 83% of these specimens (126 bacterial isolates and 7 viral isolates). Seventy-seven asymptomatic patients also submitted stool specimens, and potential pathogens were isolated in 22% (19 bacterial isolates and 2 viral isolates) (Table 1). No pathogen was isolated from 29 (17%) of the cases and from 60 (78%) of the asymptomatic personnel. Common isolates in cases versus asymptomatic personnel included non-typhoidal *Salmonella*, *n* = 31 (18.3%) versus 9 (11.7%); *eaec*+ *E. coli*, *n* = 28 (16.6%)

TABLE 1

Bacterial isolates (%) from patients with diarrhea and asymptomatic personnel on deployment to Thailand in 1998

Isolate	Cases (n = 169)	Asymptomatic (n = 77)	Odds ratio (95% CI)*
<i>Campylobacter (jejuni/coli)</i>	13.6	2.6	5.91 (1.3–37.3)
<i>Salmonella</i> , Non-typhoidal	18.3	11.7	1.70 (0.7–4.1)
<i>Shigella</i>	0.6	0	
ETEC	14.2	2.6	6.21 (1.4–39.1)
VNAG	1.8	1.3	1.37 (0.1–34)
VPARA	3.6	0	
<i>Plesiomonas</i>	5.3	0	
EIEC	0.6	0	
<i>eaec</i> +EC	16.6	6.5	2.86 (0.99–8.8)
Rotavirus	4.1	2.6	1.62 (0.3–11.6)
Norwalk virus	0	0	0
No pathogen isolated	17	78	0.06 (0.03–0.12)

\* CI = confidence interval; ETEC = enterotoxigenic *Escherichia coli*; VNAG = non O:1 *Vibrio cholerae*; VPARA = *Vibrio parahemolyticus*; EIEC = enteroinvasive *E. coli*; *eaec*+EC = attaching and effacing *E. coli*.

versus 5 (6.5%); ETEC, *n* = 24 (14.2%) versus 2 (2.6%); and *C. jejuni/coli*, *n* = 23 (13.6%) versus 2 (2.6%). Rotavirus was detected in seven (4.1%) case specimens versus two (2.6%) asymptomatic specimens, but Norwalk virus was not detected. Multiple isolates were recorded from the stools of 27 patients with diarrhea (16%) and one patient without diarrhea (1.3%) (*P* < 0.001). Twenty-two cases and one control sample had two organisms, four cases had three organisms, and one case had four organisms. *Salmonella* was the organism most frequently found in polymicrobial infections, occurring in 18 diarrhea specimens and one asymptomatic specimen. Other isolates included ETEC (*n* = 10), *Campylobacter* (*n* = 8), and Rotavirus (*n* = 6). The most common combinations were *Salmonella* and *eaec*+ *E. coli* (five cases and one asymptomatic patient) and *Salmonella* and *Campylobacter* (four cases).

Diarrheal symptoms had typically been present for one day prior to visiting the clinic. They lasted approximately 1.5 days (median = 39 hours), with an average of eight loose stools during the illness. Common associated symptoms included abdominal cramps (72%), fever (26%), nausea (51%), vomiting (19%), headaches (43%), myalgias (25%), arthralgias (18%), and gross blood in stools (6%) (Table 2). After excluding cases with multiple isolates, no significant differences

TABLE 2

Frequency (%) of presenting symptoms among patients with diarrhea, Cobra Gold, 1998

Symptom	% (95% confidence interval)	Days prior to presentation mean (range)
Diarrhea*	98.8† (95.8–99.9)	1.9 (1–10)
Fever	26 (19.6–33.3)	1.5 (1–7)
Blood in Stool	5.9 (2.9–10.6)	1.1 (1–2)
Nausea	50.9 (43.1–58.7)	1.6 (1–10)
Vomiting‡	18.9 (13.3–25.7)	1.2 (1–3)
Cramps	72.2 (64.8–78.8)	1.7 (1–9)
Headache	43.2 (35.6–51.0)	1.6 (1–10)
Myalgias	24.8 (18.5–32.1)	1.6 (1–3)
Joint pains	17.8 (12.3–24.4)	1.6 (1–7)

\* Stools in last 24 hours: 6 (1–30)[the patient with only one stool in last 24 hours reported 4 stools in 36 hours and went on to meet clinical definition after treatment]; stools since start of symptoms: 10.7 (2–70).

† 167 patients presented with diarrhea; 2 patients developed diarrhea after initial presentation.

‡ Episodes of vomiting: 4.6 (1–20).

were observed in the frequency of cramping, nausea, or vomiting based on bacterial isolate. However, *Campylobacter*-induced disease was more severe than that caused by the other pathogens, with a significantly increased median total number of stools (20 versus 8), median duration of symptoms (78 hours versus 39 hours), and rates of fever (65% versus 22%), myalgias (53% versus 20%), arthralgias (47% versus 11%), and fecal leukocytes (41% versus 15%) (Table 3). Patients with *Campylobacter*-associated disease were also more likely to report a decreased ability or inability to perform their duties at time of presentation than patients with non-*Campylobacter*-associated disease (94% versus 58%). Other than more frequent complaints of nausea with *eae*<sup>+</sup> *E. coli*, no differences in presentation were apparent among the other three most common bacterial isolates, each of which was associated with fewer systemic symptoms and a better functional status than infection with *Campylobacter* (Table 4).

Antimicrobial therapy was initiated in 133 (78.7%) of the patients with ciprofloxacin prescribed for 96.2% of the cases. Eighty-two percent of the patients treated with antimicrobials and 75% of those patients not treated with antimicrobials had resolution of symptoms within 72 hours. Overall, cure (full recovery by 72 hours) was observed in 136 (80%) of the patients. A sub-optimal response to therapy, either failure or relapse, occurred in 15 patients (9%), and 18 (11%) of the patients were lost to follow-up. Of the 15 patients with sub-optimal outcome, initial therapy included loperamide alone (n = 2), ciprofloxacin alone (n = 2), ciprofloxacin plus

TABLE 3

Clinical presentation and response to treatment in *Campylobacter*-induced diarrhea versus non-*Campylobacter*-induced diarrhea (excluding mixed infections)

Findings at presentation	Percent affected (95% confidence interval)	
	<i>Campylobacter</i> -induced (n = 17)	Non- <i>Campylobacter</i> -induced (n = 123)
Fever*	65 (38.3–85.8)	22 (15.0–30.3)
Abdominal cramps	88 (63.6–98.5)	73 (64.4–80.8)
Nausea	53 (27.8–77.0)	52 (42.8–61.1)
Vomiting	18 (3.8–43.4)	21 (14.3–29.4)
Headache	65 (38.3–85.8)	39 (30.4–48.2)
Myalgias*	53 (27.8–77.0)	20 (13.6–28.5)
Arthralgias*	47 (23.0–72.2)	11 (6.4–18.4)
Blood in Stools	12 (1.5–36.4)	6 (2.3–11.4)
Fecal Leukocytes	41 (18.4–67.1)	15 (8.9–22.1)
Initial functional assessment <sup>1</sup>		
Normal	6 (0.2–28.7)	42 (33.4–51.5)
Decreased	47 (23.0–72.2)	32 (23.6–40.7)
Not able	47 (23.0–72.2)	27 (19.2–35.6)
Persistent decrease in functional assessment <sup>2</sup>		
24 hours*	94 (71.3–99.9)	65 (55.9–73.4)
48 hours	41 (18.4–67.1)	25 (17.8–33.8)
72 hours	24 (6.8–49.9)	8 (4.0–14.4)
96 hours	13 (1.5–36.4)	5.1 (1.8–10.3)
Therapy		
Antimicrobial treatment	82 (56.6–96.2)	85 (77.9–91.1)
Ciprofloxacin	76 (50.1–93.2)	83 (75.1–89.1)
Azithromycin	6 (0.2–28.7)	1.6 (0.2–5.8)
IV volume repletion	12 (1.5–36.4)	15 (8.9–22.1)
Response to therapy		
Sub-optimal response*	25 (6.8–49.9)	9 (4.6–15.4)
Median duration of symptoms*	78 hours	39 hours
Median number of stools*	20 (5–72)	8 (2–79)

\* P &lt; 0.05.

IV = intravenous

TABLE 4

Clinical presentation and response to therapy (%) of other common bacterial isolates (excluding mixed infections)\*

	ETEC (n = 13)	<i>Salmonella</i> (n = 14)	<i>eae</i> <sup>+</sup> <i>E. coli</i> (n = 16)
Symptoms at presentation			
Fever	7.7 (0.2–36.0)	36 (12.8–64.9)	25 (7.3–52.4)
Abdominal cramps	92 (64.0–99.8)	86 (57.2–98.2)	75 (47.6–92.7)
Nausea	31 (9.1–61.4)	29 (8.4–58.1)	69 (41.3–89.0)
Vomiting	7.7 (0.2–36.0)	7.1 (0.2–33.9)	6.3 (0.2–30.2)
Headache	31 (9.1–61.4)	43 (17.7–71.1)	38 (15.2–64.6)
Myalgia	15 (1.9–45.5)	29 (8.4–58.1)	19 (4.1–45.7)
Arthralgia	7.7 (0.2–36.0)	14 (1.8–42.8)	19 (4.1–45.7)
Blood in stool	0	0	6.3 (0.2–30.2)
Fecal leukocytes	0	14 (1.8–42.8)	25 (7.3–52.4)
Initial functional assessment			
Normal	31 (9.1–61.4)	43 (17.7–71.1)	44 (19.8–70.1)
Decreased	39 (13.9–68.4)	29 (8.4–58.1)	25 (7.3–52.4)
Unable	23 (5.0–53.8)	29 (8.4–58.1)	31 (11.0–58.7)
Response to therapy			
Sub-optimal	9 (0.2–36.0)	7 (0.2–33.9)	6 (0.2–30.2)

\* ETEC = enterotoxigenic *Escherichia coli*. Values in parentheses are 95% confidence intervals.

loperamide (n = 7), and no treatment (n = 4). After 72 hours, two of the patients not initially given antimicrobials were given ciprofloxacin. One of the two had resolution of his symptoms within 24 hours and the other was lost to follow-up. Two patients were given azithromycin after 72 hours of using only loperamide, and both had resolution of their symptoms within 24 hours. Ten patients with sub-optimal response at 72 hours were given azithromycin instead of ciprofloxacin. Eight of these patients had resolution of their symptoms within the subsequent 72 hours, but two were lost to follow-up.

Loperamide was prescribed in 105 (62%) of the patients. There was no difference in overall outcomes based on whether patients received loperamide (92% cure in both groups), and there was no difference in loperamide use between *Campylobacter* and non-*Campylobacter* cases (57% versus 70%).

Antimicrobials were prescribed for 82% of the *Campylobacter* cases and 85% of the non-*Campylobacter* cases, with ciprofloxacin being used in 76% and 83% respectively. *In vitro* resistance to ciprofloxacin was observed in 24 (96%) of 25 of the *Campylobacter* isolates and in none of the non-*Campylobacter* isolates. Among the resistant isolates, mean inhibitory concentrations (MICs) ranged from 4 to 64 µg/ml, but there was no correlation between therapeutic response and the MIC. Azithromycin was used initially in four (3%) cases, including one case in which no organism was isolated, and as the second agent after a poor response to the first agent in 12 (7.1%) of the cases. There were no isolates found to be resistant to azithromycin.

## DISCUSSION

As previously observed,<sup>1,2,13,14</sup> enteropathogenic *Campylobacter* species are among the most common causes of travelers' diarrhea in U.S. military troops deployed to Thailand. *Campylobacter* was the fourth most common pathogen isolated from the patients presenting with diarrhea, but along with ETEC, was the most likely to be associated with disease

(Table 1). Most of the personnel reported buying food from local vendors, either on base or while on liberty. Almost one-third of our patients were taking doxycycline for malaria prophylaxis, but this has not been shown to either increase or decrease the incidence of diarrhea in this region.<sup>15</sup>

Most attempts to correlate clinical presentation with microbiologic etiology have been unsuccessful, but several researchers have suggested that infection with *Campylobacter* may be more severe than with other common causes of travelers' diarrhea.<sup>3</sup> Watson and others studied 351 patients with infectious diarrhea, 21% of whom were infected with *Campylobacter*, and found that young patients with abdominal cramps and vomiting were more likely to have campylobacteriosis.<sup>16</sup> Svanteson and others studied 731 patients with infectious diarrhea and 240 controls to determine the etiology and clinical presentation of infectious diarrhea in adults in Sweden. *Campylobacter* was the most frequently isolated pathogen, occurring in 18% of the patients surveyed. They found an association with intense diarrhea, which they defined as > 10 stools per day, and fever with *Campylobacter* infection when compared with other common pathogens.<sup>14</sup> Mattila evaluated 126 Finnish tourists who developed diarrhea after visiting Morocco, 12 of whom were identified as being infected with *Campylobacter*. *Campylobacter* caused the most severe disease in this study characterized by increased abdominal pain, nausea, vomiting, and fever.<sup>3</sup> Our findings support these earlier observations of more severe disease due to *Campylobacter* than with other pathogens (although *Shigella* was uncommon in these studies). The median number of stools was more than twice that caused by other pathogens and the median duration of symptoms lasted twice as long. *Campylobacter*-induced illness was associated with more systemic inflammatory symptoms reflected by the significantly increased incidence of fevers, myalgias, and arthralgias. More importantly, *Campylobacter* appeared to have a greater impact on our patients' functional status with 94% of patients infected with *Campylobacter* reporting a decreased ability or incapacitation in performing their jobs or recreational activities versus only 58% decrease in functional capacity of patients with diarrhea due to other causes ( $P = 0.02$ ) (Table 3).

Resistance to quinolone antibiotics has been a growing problem in Southeast Asia and Europe and has recently been reported in the United States.<sup>4,18,19</sup> *Campylobacter* isolates from military troops deployed to Thailand in 1987 and 1990 were all susceptible to quinolones.<sup>4,20</sup> A subsequent survey in 1993 found 40% quinolone resistance, which increased to 50% in 1994 and to 84% in 1995.<sup>1,2,4</sup> Despite the rapidly developing resistance, quinolones have remained the treatment of choice for traveler's diarrhea in Southeast Asia, and it is not clear that there is a better alternative. A randomized, controlled trial in 1993 compared azithromycin (500 mg a day) and ciprofloxacin and found equal efficacy in treating *Campylobacter*-induced diarrhea. However, ciprofloxacin was used at a dose of 500 mg a day rather than at the usual dose of 500 mg twice a day. Patients with non-*Campylobacter* etiologies still recovered more quickly if treated with ciprofloxacin.<sup>1</sup> Furthermore, 7–15% of the *Campylobacter* isolates from 1994 and 1995 were resistant to azithromycin, raising concerns that it may not continue to be effective.<sup>2,4</sup>

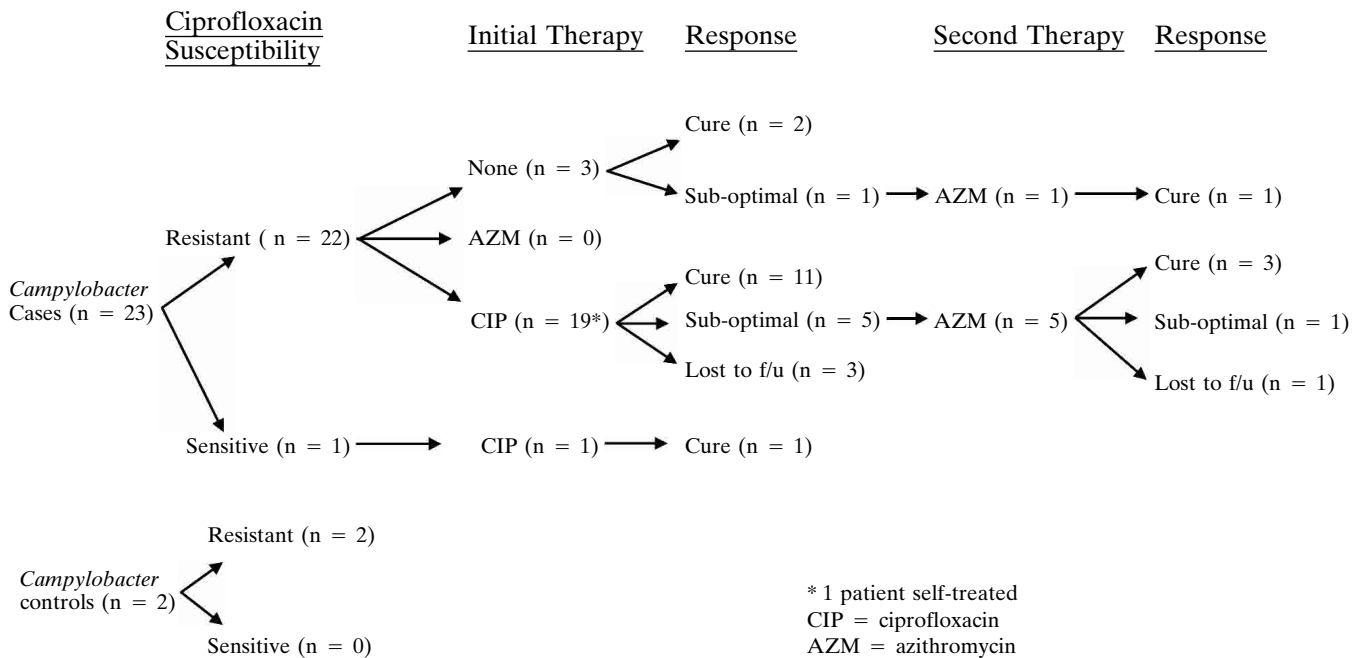
Our study demonstrates the sustained high rates of qui-

nonolone resistance among *Campylobacter* isolates from Thailand. Twenty-four (96%) of the 25 *Campylobacter* isolates were found to have *in vitro* resistance to ciprofloxacin, but none of the other non-*Campylobacter* isolates were resistant to ciprofloxacin. No *Campylobacter* isolates were resistant to azithromycin. Of the 23 *Campylobacter* cases, 22 isolates showed *in vitro* resistance to ciprofloxacin. The patient with the sensitive isolate was treated with ciprofloxacin and was cured. Of the 22 patients with a resistant isolate, 19 were treated with ciprofloxacin, and 11 (58%) achieved a cure, 5 (26%) were not cured at 72 hours, and 3 (16%) were lost to follow-up. Two of the three patients not receiving antibiotic therapy had resolution of their symptoms. All six patients with persistent symptoms at 72 hours had their medication changed to azithromycin. Four of the six patients resolved within the following 72 hours, but one remained symptomatic, and one was lost to follow-up (Figure 1).

The observational nature of the study and the limited number of patients with *Campylobacter* infection restrict the ability to assess efficacy of ciprofloxacin therapy. However, in the 1993 study in which 50% of *Campylobacter* isolates were ciprofloxacin resistant,<sup>1</sup> 91% of *Campylobacter*-induced diarrhea had resolved by 72 hours compared with 60% in our study. The difference may be due to study design and follow-up variation. However, if the three ciprofloxacin-treated patients lost to follow-up were assumed to be cures, then maximal cure rate would still be only 75%.

Despite the predilection for increasing disease severity in cases of *Campylobacter* infection, there was no uniform presentation or response to therapy. For example, two patients presented initially with fevers, headaches, and myalgias without gastrointestinal complaints. Stool specimens collected at presentation were of firm consistency, but grew *Campylobacter* on culture. They went on to develop frequent, loose stools at one and three days, respectively, and cultures performed at that time also grew *Campylobacter*. Both patients had symptom resolution within 48 hours of receiving ciprofloxacin despite resistant isolates. In contrast, eight patients presented with watery diarrhea and cramps without systemic symptoms. Three of these patients, including one with 40 loose stools in two days, achieved cure after receiving ciprofloxacin despite *in vitro* resistance. One had resolution of symptoms without treatment, two were lost to follow-up, and two had initial improvement with ciprofloxacin, but were still having diarrhea at 72 hours. The medication of these last two patients was changed to azithromycin and resulted in a resolution of the symptoms. The other 12 patients presented with diarrhea and systemic symptoms including fever, nausea, headaches, myalgias, and arthralgias. One was lost to follow-up after receiving ciprofloxacin. Eight were cured with ciprofloxacin, including one with a sensitive isolate. Three of the patients continued to have symptoms when taking ciprofloxacin and their medication was changed to azithromycin. Two of the patients were cured with azithromycin, and the other was lost to follow-up.

In summary, we continued to document the growing trend of quinolone resistance among *Campylobacter* isolates in Southeast Asia, with 96% of our isolates being ciprofloxacin resistant. We did not have enough cases to make a definitive statement about the efficacy of ciprofloxacin for *Campylobacter*-induced travelers' diarrhea, but we did see a lower rate of cure by 72 hours in patients receiving ciprofloxacin com-

FIGURE 1. Treatment and response of *Campylobacter* isolates.

pared with earlier reports. Furthermore, while earlier studies had shown that azithromycin resistance might also become a problem, we did not find any *Campylobacter* isolates resistant to azithromycin, and azithromycin appeared to be an effective alternative treatment for infection with *Campylobacter*. This may be especially important since *Campylobacter* appears to present with more severe symptoms than other pathogens. Early recognition of distinguishing clinical features may provide physicians the opportunity to tailor therapy. Further studies, including a well-designed, randomized treatment trial, are needed to clarify the presentation of *Campylobacter* compared with other pathogens and to determine the efficacy of current therapies.

Authors' addresses: J. W. Sanders, National Naval Medical Center, Bethesda, MD 20889. D. W. Isenbarger, L. W. Pang, C. Pitarangsi, and P. Echeverria, Armed Forces Research Institute of the Medical Sciences, Bangkok, Thailand. S. E. Walz, D. A. Scott, and D. R. Tribble, Naval Medical Research Center, Silver Spring, MD. C. Tamminga, Portsmouth Naval Medical Center, Portsmouth, VA. B. A. Oyoyo, Naval Medical Research Unit No. 2, Jakarta, Indonesia. W. C. Hewitson, AMEDD Center and School, Fort Sam Houston, TX 78234. J. L. Sanchez, Naval Medical Research Center-Detachment, Unit 3800, APO AA 34031-3800 Lima, Peru.

## REFERENCES

- Kuschner RA, Trofa AF, Thomas RJ, Hoge CW, Pitarangsi C, Amato S, Olafson RP, Echeverria P, Sadoff JC, Taylor DN, 1995. Use of azithromycin for the treatment of *Campylobacter* enteritis in travelers to Thailand, an area where ciprofloxacin resistance is prevalent. *Clin Infect Dis* 21: 536-541.
- Murphy GS, Jr., Echeverria P, Jackson LR, Arness MK, LeBron C, Pitarangsi C, 1996. Ciprofloxacin- and azithromycin-resistant *Campylobacter* causing traveler's diarrhea in U.S. troops deployed to Thailand in 1994. *Clin Infect Dis* 22: 868-869.
- Mattila L, 1994. Clinical features and duration of traveler's diarrhea in relation to its etiology. *Clin Infect Dis* 19: 728-734.
- Hoge CW, Gambel JM, Srijan A, Pitarangsi C, Echeverria P, 1998. Trends in antibiotic resistance among diarrheal pathogens isolated in Thailand over 15 years. *Clin Infect Dis* 26: 341-345.
- Steele TW, McDermott SN, 1984. The use of membrane filters applied directly to the surface of agar plates for the isolation of *Campylobacter jejuni* from feces. *Pathology* 16: 263-265.
- Echeverria P, Taylor DN, Leksomboon U, Bhaibulaya M, Blacklow NR, Tamura K, Ssakazaki R, 1989. Case-control study of endemic diarrheal disease in Thai children [published erratum appears in *J Infect Dis* 1989 Jul;160(1):182]. *J Infect Dis* 159: 543-548.
- Echeverria P, Sethabutr O, Pitarangsi C, 1991. Microbiology and diagnosis of infections with Shigella and enteroinvasive Escherichia coli. *Rev Infect Dis* 13 Suppl 4: S220-S225.
- Echeverria P, Hoge CW, Bodhidatta L, Tungtaem C, Herrmann J, Imlarp S, Tamura K, 1994. Etiology of diarrhea in a rural community in western Thailand: importance of enteric viruses and enterovirulent Escherichia coli. *J Infect Dis* 169: 916-919.
- Echeverria P, Seriwatana J, Sethabutr O, Chatkaeomorakot A, 1990. *Detection of Escherichia coli Using Nucleotide Probes*. San Diego: Academic Press.
- Jerse AE, Martin WC, Galen JE, Kaper JB, 1990. Oligonucleotide probe for detection of the enteropathogenic Escherichia coli (EPEC) adherence factor of localized adherent EPEC. *J Clin Microbiol* 28: 2842-2844.
- Ando T, Monroe SS, Gentsch JR, Jin Q, Lewis DC, Glass RI, 1995. Detection and differentiation of antigenically distinct small round-structured viruses (Norwalk-like viruses) by reverse transcription-PCR and southern hybridization. *J Clin Microbiol* 33: 64-71.
- Oyoyo BA, Soderquist R, Lesmana M, Subekti D, Tjaniadi P, Fryauff DJ, Corwin AL, Richie E, Lebron C, 1999. Norwalk-like virus and bacterial pathogens associated with cases of gastroenteritis on board a US Navy ship. *Am J Trop Med Hyg* 61: 904-908.

13. Taylor DN, Pitarangsi C, Echeverria P, Diniega BM, 1988. *Campylobacter* enteritis during doxycycline prophylaxis for malaria in Thailand [letter]. *Lancet* 2: 578-579.
14. Echeverria P, Jackson LR, Hoge CW, Arness MK, Dunnivant GR, Larsen RR, 1993. Diarrhea in U.S. troops deployed to Thailand. *J Clin Microbiol* 31: 3351-3352.
15. Arthur JD, Echeverria P, Shanks GD, Karwacki J, Bodhidatta L, Brown JE, 1990. A comparative study of gastrointestinal infections in United States soldiers receiving doxycycline or mefloquine for malaria prophylaxis. *Am J Trop Med Hyg* 43: 608-613.
16. Watson B, Ellis M, Mandal B, Dunbar E, Whale K, Brennan J, 1986. A comparison of the clinico-pathological features with stool pathogens in patients hospitalised with the symptom of diarrhoea. *Scand J Infect Dis* 18: 553-559.
17. Svanteson B, Thoren A, Castor B, Barkenius G, Bergdahl U, Tufvesson B, Hansson HB, Mollby R, Juhlin I, 1988. Acute diarrhoea in adults: aetiology, clinical appearance and therapeutic aspects. *Scand J Infect Dis* 20: 303-314.
18. Rautelin H, Renkonen OV, Kosunen TU, 1991. Emergence of fluoroquinolone resistance in *Campylobacter jejuni* and *Campylobacter coli* in subjects from Finland. *Antimicrob Agents Chemother* 35: 2065-2069.
19. Smith KE, Besser JM, Hedberg CW, Leano FT, Bender JB, Wicklund JH, Johnson BP, Moore KA, Osterholm MT, 1999. Quinolone-resistant *Campylobacter jejuni* infections in Minnesota, 1992-1998. Investigation Team [see comments]. *N Engl J Med* 340: 1525-1532.
20. Petruccioli BP, Murphy GS, Sanchez JL, Walz S, DeFraitres R, Gelnett J, Haberberger RL, Echeverria P, Taylor DN, 1992. Treatment of traveler's diarrhea with ciprofloxacin and loperamide. *J Infect Dis* 165: 557-560.