

ORIGINAL ARTICLE

Single-Dose Azithromycin for the Treatment of Cholera in Adults

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ABSTRACT

BACKGROUND

Single-dose azithromycin is effective in the treatment of severe cholera in children, but its effectiveness in adults has not been evaluated.

METHODS

We conducted a double-blind, randomized trial comparing the equivalence of azithromycin and ciprofloxacin (each given in a single 1-g dose of two 500-mg tablets) among 195 men with severe cholera caused by *Vibrio cholerae* O1 or O139. Patients were hospitalized for five days. A stool culture was performed daily. Primary outcome measures were clinical success (the cessation of watery stools within 48 hours after drug administration) and bacteriologic success (the inability to isolate *V. cholerae* after 48 hours).

RESULTS

Therapy was clinically successful in 71 of 97 patients receiving azithromycin (73 percent) and in 26 of 98 patients receiving ciprofloxacin (27 percent) ($P < 0.001$) and bacteriologically successful in 76 of 97 patients receiving azithromycin (78 percent) and in 10 of 98 patients receiving ciprofloxacin (10 percent) ($P < 0.001$). Patients who were treated with azithromycin had a shorter duration of diarrhea than did patients treated with ciprofloxacin (median, 30 vs. 78 hours); a lower frequency of vomiting (43 percent vs. 67 percent); fewer stools (median, 36 vs. 52); and a lower stool volume (median, 114 vs. 322 ml per kilogram of body weight). The median minimal inhibitory concentration of ciprofloxacin for the 177 isolates of *V. cholerae* O1 was 0.25 μg per milliliter, which was 11 to 83 times as high as that in previous studies at this site.

CONCLUSIONS

Single-dose azithromycin was effective in the treatment of severe cholera in adults. The lack of efficacy of ciprofloxacin may result from its diminished activity against *V. cholerae* O1 strains currently circulating in Bangladesh. (ClinicalTrials.gov number, NCT00229944.)

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CHOLERA CAUSED BY *VIBRIO CHOLERAE* O1 or O139 is an important cause of severe dehydrating diarrhea in Asia and Africa.¹ Antibiotic therapy is a useful adjunct to fluid replacement in the treatment of cholera by substantially reducing the duration and volume of diarrhea and thereby lessening fluid requirements and shortening the duration of hospitalization.² These benefits are especially important in resource-constrained settings in which intravenous fluids, skilled care, and hospital beds may be in short supply, especially during cholera epidemics.

The choice of antimicrobial drug for the treatment of cholera is guided by the patterns of resistance of the infecting organism. The development of resistance in *V. cholerae* O1 and O139 has diminished the use of a number of drugs that have historically been used in the treatment of cholera.^{3,4} Tetracycline and its derivatives have been the mainstay of cholera therapy for 40 years² and are effective when used in a single dose.⁵⁻⁷ There are situations, however, such as cholera infections in children or pregnant women, in which the use of the tetracycline class of drugs is relatively contraindicated because of the risk of toxicity. Resistance to tetracycline and its derivatives has also been reported.^{8,9}

Erythromycin has often been used as an alternative to tetracycline for the treatment of cholera.¹⁰ Unlike the tetracyclines, erythromycin has not been shown to be effective in a single dose, and currently recommended courses of treatment require 12 doses over a period of three days.¹⁰ As compared with erythromycin, azithromycin, a macrolide antibiotic derived from erythromycin, has better in vitro activity against *V. cholerae*,¹¹ has a longer half-life,¹² and has less gastrointestinal toxicity.¹³ It has also been shown to be effective when used in a single dose for the treatment of cholera in children.¹¹ In this study, we evaluated the equivalence in adults of single-dose azithromycin and single-dose ciprofloxacin, a regimen that we have previously demonstrated to be effective in the treatment of severe cholera in adults.¹⁴

METHODS

STUDY PATIENTS AND PROTOCOL

Patients were enrolled at the Dhaka Diarrhoea Treatment Centre of the ICDDR, B—Centre for Health and Population Research in Bangladesh

between December 11, 2002, and May 2, 2004. Eligible patients were men between the ages of 18 and 60 years who had had watery diarrhea for no more than 24 hours, severe dehydration (according to World Health Organization criteria¹⁰), a high purging rate (stool volume, ≥ 20 ml per kilogram of body weight during a four-hour observation period after initial rehydration), and *V. cholerae* O1 or O139 isolated from a culture of stool or a rectal-swab sample. Patients were excluded from the study if they had a concomitant illness or had received an antimicrobial agent effective in the treatment of cholera. Women were excluded from the study because of difficulty in separating urine from stool and because social norms make it difficult for them to stay away from their homes.

Consecutive patients meeting initial eligibility requirements who presented for care at the Dhaka Diarrhoea Treatment Centre from 6 a.m. to 6 p.m. daily were identified. Such patients were rehydrated during a period of two to four hours and screened for *V. cholerae* O1 or O139 infection with the use of dark-field microscopy of a stool specimen. Patients with a presumptive diagnosis of cholera who had a volume of diarrhea of at least 20 ml per kilogram during the next four hours were eligible for participation in the study.

Eligible patients who provided written informed consent to participate in the study were randomly assigned, in a double-blind fashion, to receive orally either two 500-mg tablets of azithromycin and a placebo formulation of ciprofloxacin or two 500-mg tablets of ciprofloxacin and a placebo formulation of azithromycin. (Pfizer provided the azithromycin and azithromycin placebo tablets, and Square Pharmaceuticals provided the ciprofloxacin and ciprofloxacin placebo tablets but had no other role in study design, data accrual or interpretation, or the writing or approval of the manuscript.) Patients were admitted to the study ward of the treatment center for five days. (Study days were enumerated from the time of the administration of the first dose of study drug.) Every six hours, vital signs, the presence of watery stool (defined as stool that could be poured), and fluid balance (volume of stool, urine, vomitus, and oral and intravenous fluid intake) were assessed. Each day after admission, interval histories were obtained and physical examinations were performed. Hydration was maintained with a rice-based oral rehydration prepa-

ration, and intravenous fluids were administered only if the oral intake of fluid was insufficient to maintain hydration. Patients were asked to return for a follow-up visit 7 to 10 days after discharge to assess clinical and bacteriologic status.

A stool specimen for the isolation of *V. cholerae* O1 or O139, salmonella, shigella and *Campylobacter jejuni* was obtained before administration of the study drug, on study day 3, and at the follow-up visit. A rectal-swab sample for isolation of *V. cholerae* O1 or O139 was obtained before drug administration, daily while patients were in the treatment center, and at the follow-up visit if a stool sample could not be obtained. Microscopical examination of stool for semiquantitative measurement of leukocytes and erythrocytes and for detection of enteric parasitic infection was performed before the initiation of the study drugs. A blood sample was obtained after rehydration but before the study drug was administered for a complete blood count and a determination of serum electrolyte and creatinine levels. *V. cholerae* isolates were tested for susceptibility to azithromycin and ciprofloxacin by both the disk-diffusion test and the E test (AB Biodisk). Susceptibility to tetracycline, trimethoprim-sulfamethoxazole, chloramphenicol, erythromycin, and furazolidone was done with the disk-diffusion method only. The study protocol was approved by the ethics review committee of the ICDDR, B—Centre for Health and Population Research and the institutional review board of the New England Medical Center, where Dr. Bennish was affiliated at the time of the study.

STUDY OUTCOMES

The primary study outcomes were the clinical success of therapy (defined as the cessation of watery stools within 48 hours after the administration of the study drug) and bacteriologic success of therapy (defined as the inability to isolate *V. cholerae* O1 or O139 from stool or rectal-swab samples within 48 hours after the administration of the study drug). Secondary outcome measures were the rate of clinical or bacteriologic relapse (defined, respectively, as the reappearance of watery stool or the isolation of *V. cholerae* from the stool at any time during the hospital stay after being absent for 24 hours), the duration of diarrhea (defined as the time to the end of the last 6-hour period in which there was watery stool), the total volume of watery stool, the frequency and volume of vomitus, the duration of excretion

of *V. cholerae*, and the volume of oral and intravenous fluids that was administered. All secondary outcome measures were determined from the time of administration of antimicrobial therapy.

STATISTICAL ANALYSIS

Sample size was calculated for an equivalence study. A regimen of 1 g of oral ciprofloxacin had a rate of clinical success of 94 percent and a rate of bacteriologic success of 95 percent in a previous study.¹⁴ With a type I error of 5 percent and a type II error of 20 percent, 91 patients were required in each treatment group to show that the 95 percent confidence interval for the difference in the rates of clinical and bacteriologic success between the treatment groups did not exceed 10 percent.¹⁵

The binomial method was used to calculate differences in medians between study groups and the confidence intervals for those differences; Newcombe's method was used to determine confidence intervals for differences in proportions.¹⁶ We constructed a Kaplan–Meier survival curve to show differences in the duration of diarrhea and of excretion of *V. cholerae* between the treatment groups and tested the significance of the differences in duration with the use of the log-rank test. All tests of significance were two-tailed. To determine factors that were independently associated with the clinical success or failure of therapy, we performed a backward, stepwise, multiple logistic-regression analysis, including variables in the initial model that could be associated biologically with the failure of therapy and that occurred in at least 10 percent of patients.

The analysis of the primary outcomes was conducted on an intention-to-treat basis, with all patients eligible for study who were assigned to treatment included in the analysis. Treatment was considered to have failed clinically and bacteriologically in patients in whom the primary end points could not be assessed because the patients did not complete the study. Analyses of secondary outcomes were conducted only among patients who completed the study.

RESULTS

ENROLLMENT AND CHARACTERISTICS OF PATIENTS

A total of 198 of the 325 patients who were screened met the eligibility criteria and consented to take

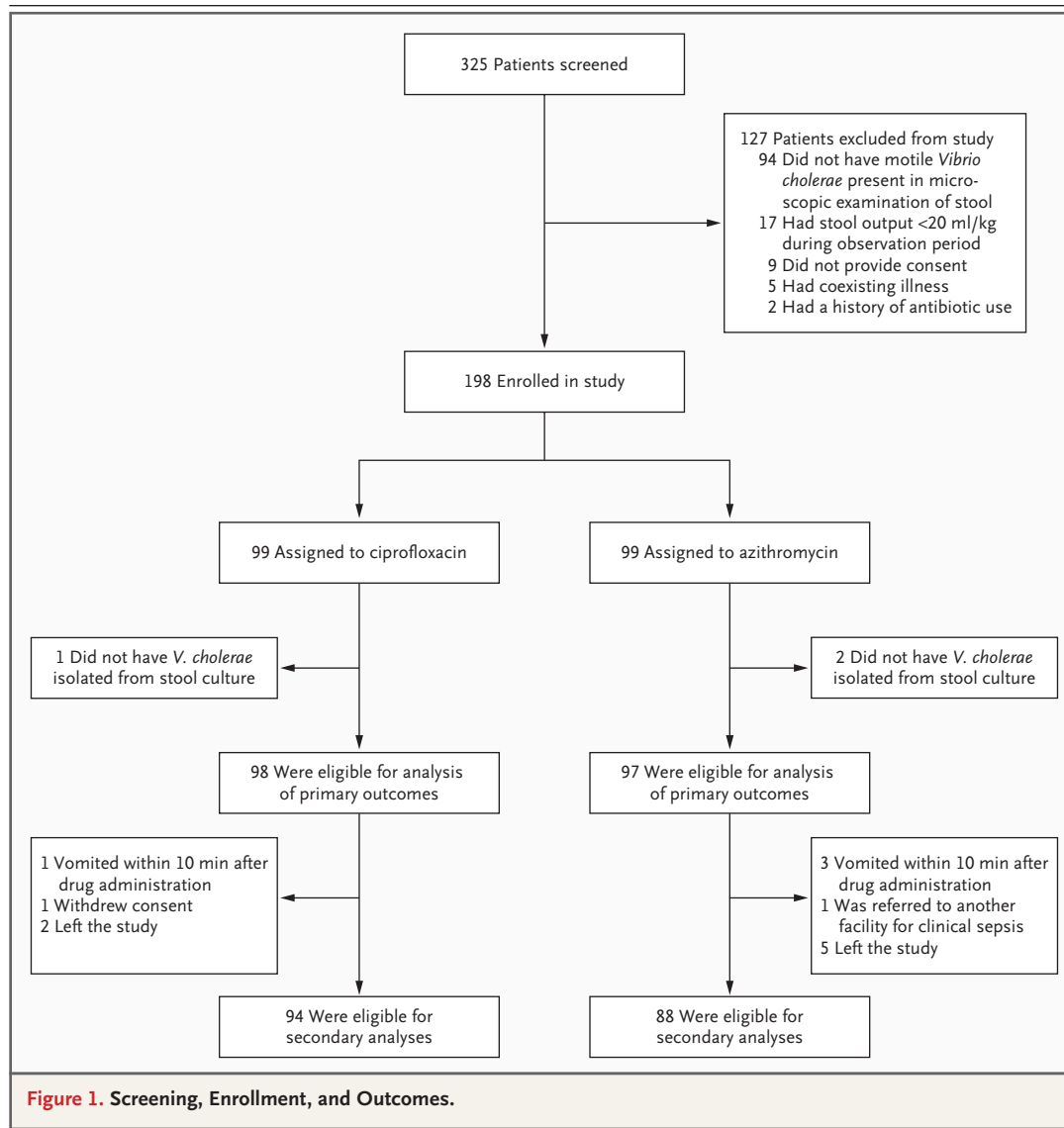
part in the trial, with 99 patients being assigned to each of the treatment groups (Fig. 1). One patient in the ciprofloxacin group and two in the azithromycin group did not have *V. cholerae* O1 or O139 isolates and were excluded from the analysis. Four patients in the ciprofloxacin group and nine in the azithromycin group did not complete the study, and treatment in these patients was considered to have failed (Fig. 1).

The two treatment groups had small but significant differences in a number of pretreatment characteristics, including the duration of illness before coming to the treatment center and the volume of diarrhea during the observation period (Table 1). The proportions of patients with *V. chol-*

erae O1 isolates were similar in the two groups. All isolates were El Tor biotype. Shigella was isolated from the stool culture of seven patients in the ciprofloxacin group and two in the azithromycin group; no other pathogenic enteric coinfections were identified.

PRIMARY OUTCOMES

Azithromycin was clinically successful in 71 of 97 patients (73 percent), and ciprofloxacin was clinically successful in 26 of 98 patients (27 percent) (absolute difference, 47 percent; 95 percent confidence interval, 33 to 58 percent; $P < 0.001$) (Table 2). Bacteriologic success was achieved in 76 patients treated with azithromycin (78 percent)



Characteristic	Azithromycin (N=97)	Ciprofloxacin (N=98)	Difference (95% CI)†	P Value
Age — yr				
Median	25	25	1 (0 to 3)	0.12
Interquartile range	20 to 30	20 to 30		
Duration of diarrhea after the onset of illness before admission — hr				
Median	10	7	1.7 (0.7 to 3.0)	0.01
Interquartile range	7 to 13	5 to 11		
No. of stools after the onset of illness before admission				
Median	12	10	2 (0 to 4)	0.03
Interquartile range	10 to 20	6 to 18		
No. of vomiting episodes after the onset of illness before admission				
Median	4	5	0 (0 to 0)	0.51
Interquartile range	3 to 8	3 to 10		
Weight				
On arrival — kg				
Median	46	44	2 (0 to 3)	0.02
Interquartile range	42 to 51	41 to 48		
After initial hydration — kg				
Median	50	47	2 (0 to 3)	0.02
Interquartile range	46 to 55	45 to 52		
Change in weight — %				
Median	9	9	0 (-1 to 0)	0.23
Interquartile range	8 to 10	8 to 10		
Packed-cell volume — %				
Mean	41±5	41±6	0 (-1 to 2)	0.58
Serum creatinine level — μmol/liter				
Mean	139±37	143±37	-4 (-14 to 7)	0.50
4-Hr observation period after rehydration				
No. of stools				
Median	8	7	1 (-1 to 2)	0.23
Interquartile range	4 to 13	4 to 11		
No. of vomiting episodes				
Median	0	0	0	0.73
Interquartile range	0 to 1	0 to 2		

and in only 10 patients treated with ciprofloxacin (10 percent) (absolute difference, 68 percent; 95 percent confidence interval, 56 to 77 percent; $P<0.001$) (Table 2).

In a per-protocol analysis of patients who completed the study, therapy was clinically success-

ful in 71 of 88 patients receiving azithromycin (81 percent) and in 26 of 94 patients receiving ciprofloxacin (28 percent) (absolute difference, 53 percent; 95 percent confidence interval, 39 to 64 percent) and bacteriologically successful in 76 patients (86 percent) and 10 patients (11 percent),

Table 1. (Continued.)

Characteristic	Azithromycin (N=97)	Ciprofloxacin (N=98)	Difference (95% CI) [†]	P Value
Fluid balance — ml/kg/hr				
Stool				
Median	9.4	11.7	-1.7 (-3.1 to -0.5)	0.004
Interquartile range	5.9 to 13.2	7.6 to 15.5		
Vomitus				
Median	0	0	0 (0 to 0)	0.49
Interquartile range	0 to 2.7	0 to 4.3		
Intravenous fluids				
Median	0	0	0 (0 to 0)	0.04
Interquartile range	0 to 0	0 to 1.1		
Oral rehydration solution				
Median	8.4	8.7	0.1 (-0.9 to 1.1)	0.88
Interquartile range	6.6 to 12.0	6.2 to 11.7		
<i>Vibrio cholerae</i> serogroup isolated — no. (%)				
O1	89 (92)	91 (93)	-1 (-7 to 9) [‡]	0.98
O139	8 (8)	7 (7)	1 (-7 to 9) [‡]	0.98
Other stool pathogen — no. (%) [§]	2 (2)	7 (7)	5 (-1 to 12) [‡]	0.10
Microscopical analysis of stool				
No. of leukocytes/high-powered field [¶]				
Median	1 to 10	1 to 10	NA	0.19
Interquartile range	0 to 1–10	0 to 1–10		
No. of erythrocytes/high-powered field [¶]				
Median	0	0	NA	0.49
Interquartile range	0 to 1–10	0 to 1–10		
Vegetative <i>Giardia lamblia</i> — no. (%)	6 (6)	4 (4)	2 (-5 to 9) [‡]	0.54

* Plus-minus values are means \pm SD. To convert the values for creatinine to milligrams per deciliter, divide by 88.4.

NA denotes not applicable.

[†] Differences between medians in the two groups were estimated by calculating the median of all possible differences between patients in the two groups, rather than the arithmetic difference in the population median. CI denotes confidence interval.

[‡] The difference between the groups is a proportion.

[§] The nine other pathogens identified were all shigella species.

[¶] The numbers of leukocytes and erythrocytes in stool were assigned to one of five semiquantitative categories: 0, 1 to 10, 11 to 20, 21 to 50, and more than 50 per high-powered field. Differences between groups were tested with the chi-square test.

respectively (absolute difference, 75 percent; 95 percent confidence interval, 64 to 83 percent).

and oral fluids and excreted *V. cholerae* for a shorter period (Table 2 and Fig. 2).

SECONDARY OUTCOMES

Patients who were treated with azithromycin had a significantly shorter duration of diarrhea, fewer stools, a lower volume of stool, and a lower frequency of vomiting than did patients who received ciprofloxacin. They also required less intravenous

FOLLOW-UP

Of the patients who completed the study, 67 of the 88 who received azithromycin (76 percent) and 69 of 94 who received ciprofloxacin (73 percent) returned for a follow-up visit. No patient reported having diarrhea after discharge from the treatment

Outcome	Azithromycin (N=97)	Ciprofloxacin (N=98)	Difference (95% CI)*	P Value
Primary outcome†				
Clinical success — no. (%)	71 (73)	26 (27)	47 (33 to 58)‡	<0.001
Bacteriologic success — no. (%)	76 (78)	10 (10)	68 (56 to 77)‡	<0.001
Secondary outcomes§				
Duration of diarrhea — hr				
Median	30	78	42	<0.001
Interquartile range	24 to 42	47 to 96	30 to 48	
No. of stools				
Median	36	52	16	<0.001
Interquartile range	25 to 54	33 to 91	7 to 25	
Vomiting — no. (%)	38 (43)	63 (67)	24 (9 to 37)‡	0.002
No. of vomiting episodes per patient				
Median	0	4	2	<0.001
Interquartile range	0 to 2	0 to 12	0 to 5	
Intravenous fluid — no. (%)	19 (22)	49 (52)	30 (17 to 43)‡	<0.001
Fluid balance — ml/kg of body weight¶				
Watery stool				
Median	114	322	164	<0.001
Interquartile range	77 to 202	148 to 501	101 to 233	
Vomitus				
Median	0	28	17	<0.001
Interquartile range	0 to 15	0 to 74	4 to 31	

center, and none had a stool or rectal-swab sample that yielded *V. cholerae* O1 or O139 on culture.

ADVERSE EVENTS

Three patients in the ciprofloxacin group and one in the azithromycin group reported having abdominal pain. There were no serious adverse events attributable to either drug during the hospital stay or at follow-up.

ANTIMICROBIAL SUSCEPTIBILITY

All 168 isolates of *V. cholerae* O1 obtained from patients in the study were susceptible to tetracycline, doxycycline, erythromycin, azithromycin, and ciprofloxacin and were resistant to furazolidone and trimethoprim-sulfamethoxazole when tested by the disk-diffusion method. The 14 isolates of *V. cholerae* O139 were susceptible to all seven drugs. All *V. cholerae* O1 and O139 isolates

were susceptible to azithromycin and ciprofloxacin when tested by the E test with the use of standard threshold levels for susceptibility.^{17,18} However, median minimal inhibitory concentrations (MICs) of ciprofloxacin for *V. cholerae* O1 isolates were 11 times as high as those for *V. cholerae* O139 isolates (0.250 μg per milliliter vs. 0.0230 μg per milliliter), with a difference of 0.227 (95 percent confidence interval, 0.174 to 0.234; $P=0.001$) and 11 to 83 times as high as those for *V. cholerae* O1 isolates in previous studies of single-dose ciprofloxacin therapy for cholera.^{14,19}

OUTCOMES OF THERAPY

Therapy failed in 98 of the 195 patients in the study (50 percent). Factors predictive of treatment failure were the receipt of ciprofloxacin as treatment, the number of stools before admission, and stool volume during the observation period (Table 3).

Table 2. (Continued.)

Outcome	Azithromycin (N=97)	Ciprofloxacin (N=98)	Difference (95% CI)*	P Value
Urine				
Median	449	333	100	<0.001
Interquartile range	323 to 584	250 to 458	46 to 151	
Intravenous fluids				
Median	0	292	189	<0.001
Interquartile range	0 to 181	0 to 1003	0 to 360	
Oral-rehydration solution				
Median	802	1369	432	<0.001
Interquartile range	612 to 1081	761 to 1883	243 to 631	
Weight at discharge — kg§				
Median	49.6	47.0	2.8	0.001
Interquartile range	46.7 to 54.2	43.7 to 50.5	1.3 to 4.4	
Change in weight from start of drug administration to discharge — kg§				
Median	0.08	-0.36	0.61	0.008
Interquartile range	-0.94 to 1.4	-1.2 to 0.23	0.14 to 1.06	
Clinical relapse — no. (%)	2 (2)	3 (3)	-1 (-7 to 5)‡	1.00
Bacteriologic relapse — no. (%)	3 (3)	9 (10)	-6 (-14 to 1)‡	0.17

* Differences between medians in the two groups are estimated by calculating the median of all possible differences between patients in the two groups, rather than the arithmetic difference in the population median. CI denotes confidence interval.

† For the intention-to-treat analysis, therapy was assumed to have failed both clinically and bacteriologically for nine patients in the azithromycin group and four patients in the ciprofloxacin group who did not complete the study.

‡ The difference between the groups is a proportion.

§ Results are for 88 patients in the azithromycin group and 94 patients in the ciprofloxacin group who completed the study.

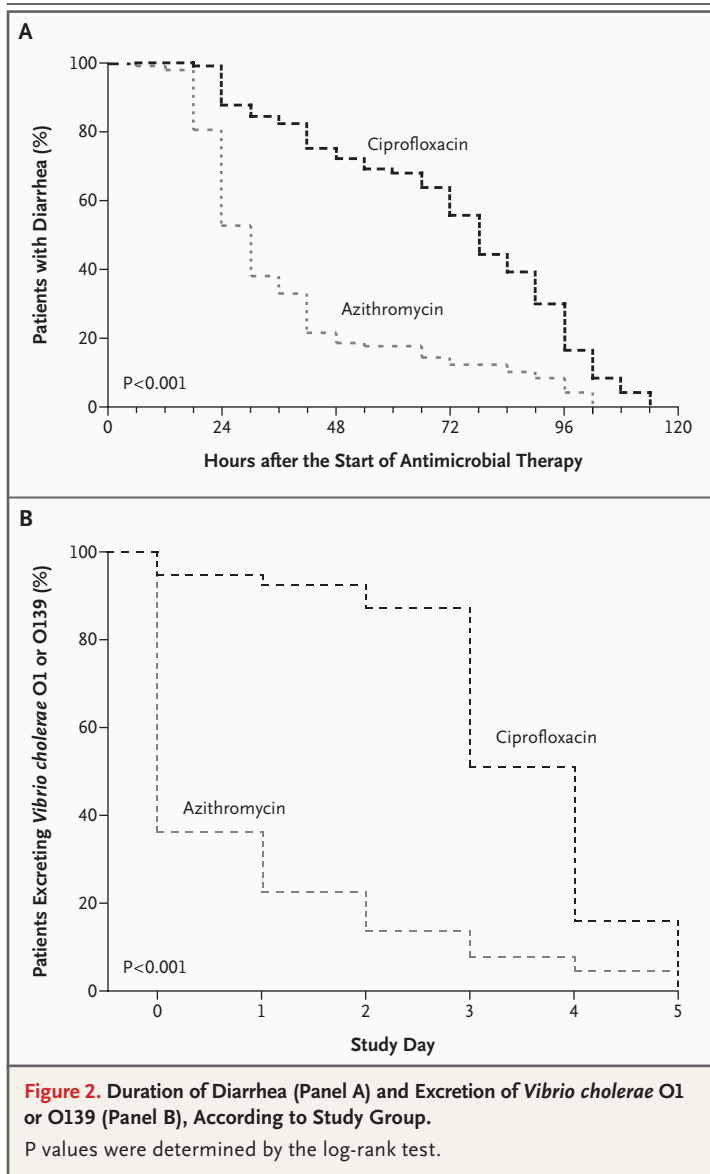
¶ Results are based on discharge weight.

DISCUSSION

Our study has three important findings: a single dose of azithromycin is effective in the treatment of cholera; a single dose of ciprofloxacin is clinically and bacteriologically ineffective in the treatment of cholera caused by strains of *V. cholerae* O1 that have diminished in vitro susceptibility to ciprofloxacin, such as those found in patients in this study; and the current thresholds of antimicrobial susceptibility to ciprofloxacin may be inappropriate for *V. cholerae* O1. In this study, the duration of watery diarrhea with azithromycin (median, 30 hours; mean, 39 hours) was similar to that previously reported for a single 300-mg dose of doxycycline (median, 32 hours),⁵ a single 1-g dose (mean, 35 hours) or 2-g dose of tetracycline (mean, 43 hours),⁶ and a single 1-g dose of ciprofloxacin in the treatment of fully susceptible

strains of *V. cholerae* O1 or O139 (median, 30 hours; mean, 31 hours),¹⁴ and it was shorter than that for a single 400-mg dose of furazolidone (mean, 74 hours).²⁰ The frequency and volume of stool, the need for intravenous fluids, the frequency and volume of vomiting, and bacteriologic success rates also compared favorably with those of other single-dose treatment regimens.^{5-7,14,20}

In contrast, despite previous reports^{14,19} of the efficacy of ciprofloxacin for the treatment of cholera, measures of clinical outcome in this study of the 87 patients with *V. cholerae* O1 infection treated with ciprofloxacin were similar to those of patients with cholera in previous studies who received placebo or no antimicrobial treatment.^{6,20} The most likely reason for the lack of efficacy of ciprofloxacin was the diminished susceptibility of *V. cholerae* O1 isolates. The median MIC of *V. cholerae* isolates in this study was 83 times as great



as that for *V. cholerae* O1 isolates in a 1996 study of single-dose ciprofloxacin among 66 adults (which showed a 94 percent rate of clinical success and a 95 percent rate of bacteriologic success¹⁴), 11 times as great as that recently reported in a study of single-dose ciprofloxacin therapy for *V. cholerae* O1 infection among 78 children (which showed a 60 percent rate of clinical success and a 42 percent rate of bacteriologic success¹⁹); and 11 times as great as that for *V. cholerae* O139 isolates in this study (which showed a 100 percent rate of clinical success and a 57 percent rate of bacteriologic success). This fail-

ure of therapy occurred despite the ability of ciprofloxacin to achieve concentrations in stool that are considerably higher than the MIC of the *V. cholerae* O1 isolates in this study¹⁴ — a finding that emphasizes the limitations in our understanding of the pharmacodynamics of antimicrobial therapy.²¹

All *V. cholerae* O1 isolates in this study were susceptible to ciprofloxacin according to the MIC, as determined by the E test (with susceptibility defined as a MIC $\leq 1 \mu\text{g}$ per milliliter) or the disk-diffusion method (zone of inhibition, ≥ 21 mm).²² In our study, the lack of clinical response of infections caused by *V. cholerae* O1 with diminished susceptibility is similar to the findings of studies of salmonella with diminished susceptibility to the fluoroquinolones²³ and, to a lesser degree, of *Neisseria gonorrhoeae*.²⁴ The changing susceptibility of *N. gonorrhoeae* resulted in a decision by the Centers for Disease Control and Prevention to adopt new dilution breakpoints for the interpretation of resistance of *N. gonorrhoeae* to the fluoroquinolones.²⁴

Our study had a number of limitations, including the fact that the trial was conducted only among men; however, there is no reason to think that women would have had a different response. There were differences between the two treatment groups on admission and during the observation period. It is unlikely, however, that these differences accounted for the very large differences in outcome between the two groups. In a multiple logistic-regression analysis, the drug treatment that patients received was the most important predictor of clinical outcome.

What are the practical implications of this study? First, single-dose azithromycin has now been established as an effective drug for the treatment of cholera caused by susceptible strains of *V. cholerae* in both adults and children. Inexpensive generic formulations of the drug are now available in many countries. (The cost of 1 g of azithromycin in Bangladesh is 95 cents, similar to the 90-cent cost of 12 250-mg doses of erythromycin.) Unfortunately, since azithromycin has been used for this indication, strains of *V. cholerae* O1 that are resistant to both erythromycin and azithromycin have been identified.²⁵

Second, for the clinician treating patients with cholera or for sentinel surveillance programs, a determination of whether ciprofloxacin will be

Table 3. Multivariate Logistic-Regression Analysis of Variables Predicting Clinical Failure of Therapy among 195 Patients with Cholera Treated with Azithromycin or Ciprofloxacin.*

Variable	Odds Ratio (95% CI)	P Value
Ciprofloxacin treatment (vs. azithromycin)	10.2 (4.8–21.5)	<0.001
No. of stools before admission†	1.1 (1.0–1.1)	0.02
Stool volume during 4-hr observation period‡	1.1 (1.1–1.2)	0.002

* Variables that were considered in the model were treatment received, the duration of illness before admission, the number of stools after the onset of illness and before admission, the weight on arrival, the change in weight between arrival and full hydration, the serum creatinine level, and the volume and numbers of stool during the observation period. CI denotes confidence interval.

† For each additional stool before admission, the risk of clinical failure increased by an odds ratio of 1.1.

‡ For each additional milliliter of stool per kilogram of body weight per hour, the risk of clinical failure increased by 1.1.

effective for the treatment of cholera will be problematic without adequate support from a microbiologic laboratory. In most areas where cholera is endemic or epidemic, if susceptibility testing is done at all, the simpler disk-diffusion method

is likely to be used.²⁶ On the basis of currently defined thresholds for resistance, the use of the disk-diffusion method will not identify strains of *V. cholerae* with diminished susceptibility that may be clinically resistant to single-dose, and possibly multiple-dose, ciprofloxacin therapy.

Third, this study emphasizes the critical problem posed by increasing antimicrobial resistance. Since *V. cholerae* O1, in Bangladesh and elsewhere, has developed substantial antimicrobial resistance to trimethoprim-sulfamethoxazole, furazolidone, and tetracycline, and resistance is emerging to ciprofloxacin and azithromycin, options for effective antimicrobial treatment are meager. There is a great need for the development of new, affordable, effective antimicrobial compounds.²⁷

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Dr. Bennish reports having spoken at a conference sponsored by Pfizer in January 2005, with the speaker's fee donated to charity. No other potential conflict of interest relevant to this article was reported.

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