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Disease Due to Enterotoxigenic *Escherichia coli* in Bangladeshi Adults: Clinical Aspects and a Controlled Trial of Tetracycline

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The clinical characteristics of disease due to enterotoxigenic *Escherichia coli* (ETEC) were determined in 88 adult males admitted to a hospital in Dacca, Bangladesh, with moderate to severe dehydration. Persons infected with ETEC strains producing both heat-labile toxin (LT) and heat-stable (ST) toxin had more dehydration and acidosis, longer duration of illness, and greater stool volume than persons infected with strains producing only ST. Tetracycline therapy, evaluated in 63 cases, resulted in slightly earlier termination of illness in the patients with LT-ST strains but had no effect on illness in the patients with ST strains. In both groups of patients tetracycline shortened the duration of excretion of organisms. Because of its limited effectiveness and the generally excellent response of ETEC diarrhea to rehydration therapy alone, tetracycline is not warranted for use in treatment of ETEC diarrhea in adults in this population.

A number of studies have demonstrated the importance of enterotoxigenic *Escherichia coli* (ETEC) as a cause of dehydrating diarrhea worldwide. In Bangladesh these organisms are responsible for many cases of acute dehydrating watery diarrhea [1–3], accounting for ~25% of diarrhea cases seen at one rural treatment center [4]. Because ETEC diarrhea can be clinically indistinguishable from cholera, a disease in which it is known that tetracycline reduces stool volume and shortens duration of diarrhea [5], it has been common practice to treat these cases on clinical grounds with an antibiotic such as tetracycline. However, there has been no evidence of the benefit of this therapy, and one study of the efficacy of oral tetracycline in the treatment of hypotensive patients with nonvibrio, cholera-like disease in Calcutta suggested that the antibiotic did not have significant effect on its clinical course [6].

In this study we attempted to define in hospitalized patients the detailed clinical features of ETEC disease and the effect of tetracycline on its clinical course.

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Materials and Methods

Clinical procedures and specimen collection. Admission procedures. We studied 176 adult males presenting to the Cholera Research Laboratory Hospital in Dacca, Bangladesh (now the International Centre for Diarrhoeal Diseases Research, Bangladesh), from October to December 1976 with a history of acute watery diarrhea and who appeared to have lost ≥5% of body weight. In all patients the admission stools were negative for *Vibrio cholerae* by dark-field microscopy. On admission, the patients were weighed, a history was taken, and a physical examination was performed. A liquid stool specimen was then obtained by rectal catheter for microbiologic studies (see below) and determination of stool electrolytes (Na^+, K^+, HCO_3^-, Cl^-) and osmolarity, and a venous blood sample was drawn for measurement of serum electrolytes (Na^+, K^+, HCO_3^-, Cl^-) and specific gravity and for acute serology. Within 2 hr of admission the estimated fluid deficit was replaced with iv fluid (composition in meq/liter:

Na^+, 134; K^+, 13; Cl^-, 86; HCO_3^-, 48). Four hours after admission a blood sample was obtained from the finger tip for measurement of plasma-specific gravity (to ensure that the total admission fluid deficit had been replaced) and a complete blood count.

Administration of tetracycline. On admission all patients wre randomly given tetracycline or placebo therapy in a double-blind manner. Capsules of 500 mg were given to patients weighing ≥30 kg, and capsules of 250 mg, to those weighing <30 kg. This dosage was chosen on the basis of previous studies [6]. Capsules were given beginning 2 hr after admission and then every 6 hr for 72 hr.

Follow-up observations. All stool losses after admission were replaced only with iv fluid, and fluid replacement and stool volume were recorded every 2 hr. Patients were not discharged until diarrhea had ceased for at least 24 hr. All patients were weighed before discharge.

Follow-up stool cultures were obtained by rectal swabs every 24 hr for four days, and when possible on days 7 and 14 after admission. Convalescent-phase sera were obtained from 102 patients on day 14 after admission.

Microbiologic studies. Admission stool specimens. All admission stools were promptly plated on salmonella-shigella, taurocholate-tellurite-gelatin, thiosulfate-citrate-bile salts-sucrose, and MacConkey's agar plates and examined for salmonellae, shigellae, and vibrios as previously described [7]. Stools from the first 100 patients were also streaked onto a salmonella-shigella and a MacConkey's agar plate immediately and again two weeks after enrichment in phosphate-buffered saline (pH 7.4) at 4 C and examined for yersinia-like organisms.

Up to 10 lactose-positive colonies with morphology typical of *E. coli*, a pool containing the first five colonies, and a pool of all of the selected colonies (usually 10) were picked from the MacConkey's agar plates, stored on nutrient agar slants for less than one month at room temperature (about 24 C), and examined in the Cholera Research Laboratory for production of heat-labile toxin (LT) by the Chinese hamster ovary cell assay and for production of heat-stable toxin (ST) by the infant mouse assay as previously described [7]. The first enterotoxigenic and the first nonenterotoxigenic organisms isolated from each patient were confirmed as *E. coli* [8] and serotyped at the World Health Organization Collaborating Centre in Copenhagen, Denmark, as previously described [9]. Antibiotic sensitivity testing was also performed by the method of Bauer et al. [10] on these isolates. Antibiotics tested included triple sulfa (sulfadiazine, sulfamethazine, and sulfamerazine), tetracycline, streptomycin, chloramphenicol, ampicillin, kanamycin, gentamicin, naladixic acid, trimethoprim-sulfamethoxazole, and cephalothin.

Five of the lactose-positive colonies isolated from 100 patients and all lactose-negative colonies isolated from any patient that were not identified as *Salmonella*, *Shigella*, or *Vibrio* were tested for invasiveness by the Sereny test [11].

From each patient a stool aliquot was frozen at −20 C and transported in dry ice to the National Institutes of Health (Bethesda, Md.), where it was examined for the presence of rotavirus antigen by enzyme-linked immunosorbent assay [12, 13].

Follow-up stool cultures. Follow-up stool cultures were plated promptly on MacConkey's agar plates; 10 individual colonies and five and 10 pools were selected as described for the admission specimens [7]. Colonies and pools isolated from patients who had ETEC in their admission stools were tested at Baltimore City Hospitals (Baltimore, Md.) for LT production by the adrenal cell assay [7] (if the *E. coli* isolated from their admission stool produced only LT or both LT and ST) or for ST production by the infant mouse assay [7] (if the *E. coli* isolated from their admission stool produced only ST).

Serologic studies. Paired sera were assayed for antibodies to LT by the adrenal cell assay [14], and for antibody to rotavirus by CF [15] and enzyme-linked immunosorbent [16] assays.

Results

Laboratory findings. A potential pathogen was isolated or detected in stools from 147 (86%) of the 176 patients (table 1); 23 patients (13%) had mixed infections. ETEC were isolated from 109 patients (62%); 69 (65%) of these were infected with strains producing LT and ST, 34 (31%) with strains producing only ST, and six (6%) with strains producing only LT. Results of toxin-testing have been reported previously [7]. Twenty-three (61%) of 38 patients with LT-ST-producing strains and three of four patients with LT-produc-

Table 1. Organisms found in stools of 176 adult patients with acute dehydrating diarrhea.

Organism	No. of isolations (%)	No. of cases in which indicated organism was only pathogen isolated (%)
Enterotoxigenic *Escherichia coli*	109 (62)	95 (54)
*Shigella**	16 (9)	4 (2)
Vibrio cholerae	14 (8)	12 (7)
Noncholera vibrios	14 (8)	5 (3)
Rotavirus	9 (5)†	1 (1)
Vibrio parahaemolyticus	6 (3)	6 (3)
Invasive *E. coli*	1 (1)	1 (1)
Salmonella group C	1 (1)	1 (1)

* Includes 11 patients with *Shigella flexneri*, three with *Shigella boydii*, and two with *Shigella sonnei*.

† Includes nine persons with serologic evidence of rotaviral infection, eight of whom had rotavirus detected in their stool.

ing strains had a fourfold or greater rise in titer of antibody to LT; none of 22 patients with ST-producing strains and only one of 38 patients with a non-cholera vibrio, *Shigella*, rotavirus, or no pathogen identified in their stool had a rise in titer of antibody to LT.

Eleven (16%) of the 69 LT-ST-producing strains of *E. coli* were resistant to one or more antibiotics, in comparison to 11 (32%) of 34 ST-producing strains of *E. coli* ($P = 0.06$, χ^2 analysis), and 28 (37%) of 76 nonenterotoxigenic strains of *E. coli* ($P < 0.01$, χ^2 analysis). Eleven (50%) of the 22 LT-ST- and ST-producing antibiotic-resistant strains had resistance only to triple sulfa and streptomycin. Significantly more LT-ST-producing strains of *E. coli* (96%) were sensitive to tetracycline than were ST-producing strains (80%) ($P < 0.05$, χ^2 analysis) or nonenterotoxigenic strains (67%) ($P < 0.001$, χ^2 analysis). Five of seven strains of ST-producing *E. coli* resistant to tetracycline were resistant only to that antibiotic.

E. coli. Eighty-eight of the 109 ETEC patients had only ETEC isolated from their stool and reported not taking tetracycline before admission. These patients included 55 with LT-ST-producing, 30 with ST-producing, and three with LT-producing strains.

Clinical and laboratory features at admission. Almost all of these *E. coli* patients had vomiting before admission; on the average it began 4.9 hr

Table 2. Clinical features on admission of 88 adult males infected with enterotoxigenic *Escherichia coli*.

	Symptoms				Signs				
								Clinical severity of dehydration‖	
Toxins of infecting strain of *E. coli**	Vomiting†	Interval from diarrhea onset to vomiting onset (hr)‡	Muscle cramps†	Abdominal pain†	Temperature (>100 F axillary)†	Duration of fever (hr)§	Systolic blood pressure (mm Hg)§	Moderate	Moderate-severe	Severe
LT-ST	53 (96)	4.8 ± 0.8	37 (67)	25 (46)	9 (16)	5.7 ± 1.3	78 ± 5	15#	26	14
ST	28 (94)	5.1 ± 1.2	20 (66)	18 (60)	8 (27)	8.2 ± 2.0	84 ± 7	16#	13	1
All	84 (96)	4.9 ± 0.7	58 (66)	45 (51)	17 (19)	6.9 ± 1.2	80 ± 4	31	42	15

* These patients had only enterotoxigenic *E. coli* isolated from stool samples taken at admission, and they had not taken tetracycline before admission. Fifty-five patients were infected with strains producing both heat-labile toxin (LT) and heat-stable toxin (ST); 30 patients were infected with strains producing only ST; three were infected with strains producing only LT.

† No. of patients (%) with clinical feature.

‡ Mean ± 1 SEM.

§ Mean ± SE.

‖ Moderate = signs of 5%–7.5% loss of body weight; moderate-severe = 7.5%–10% loss of body weight; severe = signs of loss of >10% of body weight.

Difference was significantly different ($P < 0.02$, $\chi^2 = 9.1$).

Table 3. Laboratory features on admission of 88 adult males infected with enterotoxigenic *Escherichia coli*.

Measurement	Laboratory findings (mean ± SE) in patients with strains producing		
	LT-ST	ST	All toxins
Serum			
Na^+ (meq/liter)	133 ± 0.4	135 ± 0.6	134 ± 0.4
K^+ (meq/liter)	4.8 ± 0.1	4.7 ± 0.1	4.8 ± 0.1
Cl^- (meq/liter)	102 ± 0.7	102 ± 0.6	102 ± 0.5
HCO_3 (meq/liter)	16 ± 0.5†	18 ± 0.5†	16.9 ± 0.4
Specific gravity	1.0341 ± 0.0004‡	1.0322 ± 0.0004‡	1.0334 ± 0.0003
Hematocrit (%)*	37.9 ± 0.7	38.3 ± 0.9	38.1 ± 0.5
White blood cells (cells/mm³)	15,067 ± 733	15,168 ± 1,548	15,121 ± 705
Stool			
Na^+ (meq/liter)	108 ± 4	108 ± 6	110 ± 3
K^+ (meq/liter)	27 ± 2	24 ± 3	26 ± 2
Cl^- (meg/liter)	78 ± 3	72 ± 4	76 ± 3
HCO_3 (meq/liter)	45 ± 4	37 ± 2	40 ± 2
Osmolarity (osmoles/liter)	306 ± 3	327 ± 14	312 ± 4

NOTE. These patients had only enterotoxigenic *E. coli* isolated from stool samples taken at admission, and they had not taken tetracycline before admission. The 55 LT-ST patients were infected with strains of *E. coli* producing both heat-labile (LT) and heat-stable (ST) toxins; 30 patients were infected with strains producing only ST, and three were infected with strains producing only LT. Data on stools were taken from 50 LT-ST patients, 23 ST patients, and three LT patients.

* Values were measured 4 hr after admission.

† $P < 0.01$, *t*-test.

‡ $P < 0.01$, *t*-test.

after onset of diarrhea (table 2). Two-thirds of the patients had muscle cramps, 51% had abdominal pain, and 19% had an axillary temperature of ≥100 F. Only two patients had a temperature of >101 F. Evidence of severe dehydration was present in 17% of the patients.

Serum electrolyte values at admission were indicative of isotonic dehydration and acidosis (table 3). The mean specific gravity of serum was 1.0334, and the mean serum bicarbonate value was 16.9 meq/liter. The mean hematocrit value measured 4 hr after admission was 38.1%, and the mean total white blood cell count was 15,121 cells/mm³; 32 patients (36%) had >20% band neutrophils. Stool electrolyte values demonstrated high losses of sodium and bicarbonate ions.

The clinical and laboratory features of the patients with LT-ST- and ST-producing strains were similar at admission; however, the patients with LT-ST-producing strains had a significantly greater degree of dehydration (table 2) and a significantly higher mean specific gravity of serum and lower serum bicarbonate value than the patients with ST-producing strains (table 3).

Clinical course. Table 4 presents data comparing the clinical course of illness in 31 of the patients with LT-ST-producing strains and 16 of the patients with ST-producing strains who received placebo (no tetracycline) therapy. Although the duration of diarrhea before hospital admission was the same in both groups, the total duration of diarrhea in the patients with LT-ST-producing strains (32.5 hr) was significantly greater than that in those with ST-producing strains (22.5 hr). Pa-

Table 4. Comparison of disease due to *Escherichia coli* producing both heat-labile (LT) and heat-stable (ST) toxins and disease due to *E. coli* producing only ST, in patients treated with placebo.

Factor	Mean values (± SE)		
	LT-ST (n = 31)	ST (n = 16)	P value
Weight loss (%)*	7.5 ± 0.5	6.3 ± 0.8	0.4†
Duration of diarrhea (hr)			
Before admission	11.8 ± 1.0	11.7 ± 1.5	
Total	32.5 ± 3.3	22.5 ± 2.3	<0.05‡
Total stool volume (ml/kg)	35 ± 9	11 ± 4	0.03†
Total iv fluid replacement volume (ml/kg)	111 ± 10	81 ± 6	<0.05‡
Duration of excretion of enterotoxigenic *E. coli* in stool (days)	2.4 ± 0.2	2.1 ± 0.4	

* Calculated in all tables as ([discharge weight − admission weight]/discharge weight).

† By Mann Whitney U test.

‡ By *t*-test.

tients with LT-ST-producing strains also purged a significantly greater volume of stool than those with ST-producing strains (35 ml/kg vs. 11 ml/kg) and required significantly more iv fluid (111 ml/kg vs. 81 ml/kg). The duration of excretion of ETEC in stool was 2.4 days for patients with LT-ST-producing strains and 2.1 days for those with ST-producing strains.

Effect of tetracycline. The effect of tetracycline on the clinical course of illness was determined in 45 of the patients with LT-ST-producing strains (25 treated with placebo; 20 treated with tetracycline) and 18 of the ST patients (10 treated with placebo; eight treated with tetracycline) who had tetracycline-sensitive ETEC strains and who purged stool for at least 4 hr after admission. In assessing the effect of tetracycline on duration of excretion of ETEC, patients who did not purge were also included.

Patients with LT-ST-producing strains. On admission the clinical and laboratory features of the tetracycline- and placebo-treated cases were similar (table 5). There were no significant differences observed in the duration of diarrhea, stool volume, or iv fluid requirement between the groups. To assess further the effect of tetracycline on duration of diarrhea, a graphic comparison was made of the duration of diarrhea after hospitalization in the placebo- and tetracycline-treated groups (figure 1). Eight (32%) of 25 cases in the placebo-treated group and one (5%) of 20 cases in the tetracycline-treated group had illness for >28 hr ($P = 0.025$, Fisher's exact test).

There was a highly significant difference in the mean duration of excretion of ETEC in the two groups—2.2 days in the placebo-treated group and 0.6 days in the tetracycline-treated group. This effect was apparent after only one day of therapy (table 6). At 24 hr after admission 25 of 29 placebo-treated patients were still culture-positive, as compared with nine of 22 treated with tetracycline. This difference became more significant over the next 72 hr. One patient in each group was positive in the day 7 or 14 follow-up culture.

Thirteen (72%) of 18 placebo-treated patients and six (50%) of 12 tetracycline-treated patients had a fourfold or greater rise in titer of antibody to LT; the difference was not significant. Similarly, the mean acute- and convalescent-phase titers (units/ml) in the placebo-treated (acute-phase,

Table 5. Effect of tetracycline on disease due to enterotoxigenic *Escherichia coli* producing heat-labile and heat-stable toxins, in patients infected with tetracycline-sensitive strains who purged stool for at least 4 hr after hospital admission.

Factor	Placebo-treated patients (n = 25)	Tetracycline-treated patients (n = 20)
Age (years)	34 ± 4	31 ± 4
Discharge weight (kg)	41.9 ± 2.0	39.5 ± 2.3
Systolic blood pressure at admission (mm Hg)	72 ± 8	88 ± 6
Weight loss (%)	7.6 ± 0.6	6.7 ± 0.5
Clinical severity of dehydration (no. of patients)*		
Moderate	6	5
Moderate-severe	11	11
Severe	8	4
Serum specific gravity at admission	1.0347 ± 0.0347	1.0337 ± 0.0007
Serum HCO_3^- (meq/liter) at admission	16.1 ± 0.7	16.4 ± 0.7
Duration of diarrhea (hr)		
Before admission	11.8 ± 1.2	11.6 ± 1.1
In hospital	25.0 ± 2.9	18.8 ± 2.1
Stool volume (ml/kg)	43 ± 10	28 ± 6
Volume of iv replacement (ml/kg)	120 ± 11	106 ± 9
Duration of excretion of enterotoxigenic *E. coli* in stool (days)	2.3 ± 0.3†	0.7 ± 0.3†

NOTE. All values are mean ± SE except for clinical severity.
* See table 2 for definitions.
† $P < 0.001$, t-test.

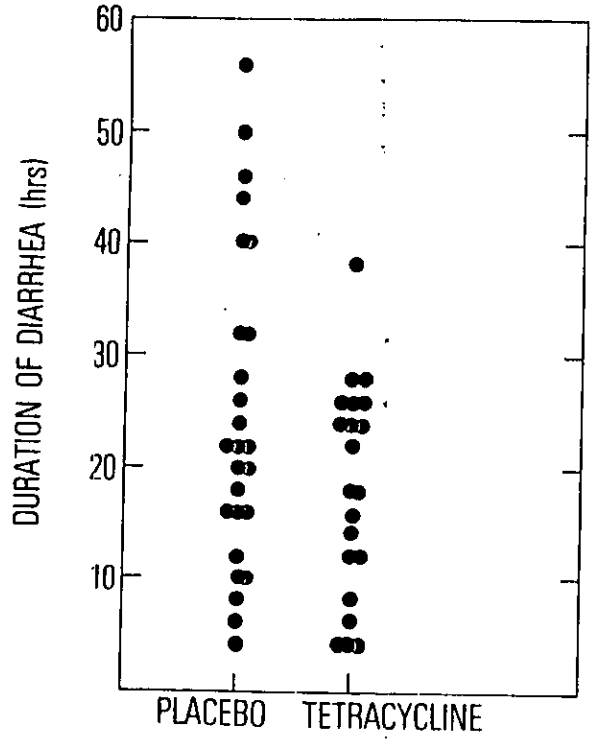

Figure 1. Duration of diarrhea after admission in patients infected with strains of *Escherichia coli* producing both heat-stable and heat-labile toxins, according to therapeutic group. Each dot represents one patient. The difference between the groups is statistically significant ($P = 0.025$).

3.0; convalescent-phase, 21.2) and tetracycline-treated (acute-phase, 6.1; convalescent-phase, 16.4) groups were not significantly different.

Patients with ST-producing strains. Although the number of patients with ST-producing strains was small, the placebo- and tetracycline-treated groups were well matched except for age (table 7). Tetracycline had no effect on duration of diarrhea, stool volume, or iv fluid requirement. However, tetracycline did significantly shorten the duration of bacterial excretion from 1.8 days in the placebo-treated group to 0.4 days in the tetracycline-treated group. As was the case in LT-ST disease, this effect was statistically significant within 24 hr after admission (table 6). Twelve of 14 placebo-treated patients were positive for ST-producing organisms at 24 hr, as compared with four of 10 tetracycline-treated patients. By 72 hr only placebo-treated patients were still culture-positive. No patients were culture-positive on days 7 or 14.

Discussion

This study has confirmed the results of earlier studies done at the Cholera Research Laboratory [1–3] (two of them conducted during the same time of year [1, 2]), which demonstrated that ETEC is a common cause of acute, severe cholera-like diarrhea. As demonstrated by our extensive microbiologic studies, ETEC disease presented in a manner clinically indistinguishable from diarrhea associated with isolation of other enteric pathogens including *V. cholerae*, shigellae, and rotavirus. That ETEC was usually responsible for disease in the patients from which it was isolated was suggested by three findings. (*1*) ETEC was the only pathogen isolated in 95 (87%) of 109 ETEC-infected patients. (*2*) In ETEC-infected patients clinical improvement correlated with disap-

Table 6. Duration of excretion of enterotoxigenic *Escherichia coli* (ETEC) in stools of patients infected with strains producing both heat-labile (LT) and heat-stable (ST) toxins or strains producing only ST who were treated with tetracycline or placebo.

Time after admission	No. of patients with LT-ST-producing strains excreting ETEC			No. of patients with ST-producing strains excreting ETEC		
	Placebo ($n = 29$)	Tetracycline ($n = 22$)	*P* value*	Placebo ($n = 14$)	Tetracycline ($n = 10$)	*P* value*
24 hr	25	9	< 0.01	12	4	<0.05
48 hr	21	3	<0.001	8	1	<0.05
72 hr	16	1	<0.001	6	0	<0.05
96 hr	5	0	. . .	2	0	. . .
7 days†	1 (24)	0 (14)	. . .	0 (12)	0 (9)	. . .
14 days†	0 (17)	1 (11)	. . .	0 (11)	0 (7)	. . .

* By *t*-test.

† Number in parentheses is number cultured.

Table 7. Effect of tetracycline on disease due to enterotoxigenic *Escherichia coli* producing heat-stable toxins, in patients infected with tetracycline-sensitive strains who purged stool for at least 4 hr after hospital admission.

Factor	Placebo-treated patients (n = 10)	Tetracycline-treated patients (n = 8)
Age (years)	25 ± 3*	40 ± 5*
Discharge weight (kg)	41.0 ± 2.3	43.3 ± 2.7
Systolic blood pressure at admission (mmHg)	88 ± 10	90 ± 13
Weight loss (%)	4.2 ± 0.9	3.9 ± 1.0
Clinical severity (no. of patients)†		
Moderate	8	4
Moderate-severe	1	4
Severe	1	0
Plasma specific gravity at admission	1.0326 ± 0.0009	1.0315 ± 0.0009
Serum HCO_3^- (meq/liter) at admission	18.3 ± 0.9	19.2 ± 0.9
Duration of diarrhea (hr)		
Before admission	10.5 ± 1.5	8.0 ± 1.2
In hospital	17.2 ± 2.0	15.5 ± 2.9
Stool volume (ml/kg)	17 ± 5	24 ± 5
Volume of iv replacement (ml/kg)	85 ± 10	86 ± 7
Duration of excretion of enterotoxigenic *E. coli* in stool (days)	1.8 ± 0.4‡	0.4 ± 0.3‡

NOTE. All values are mean ± SE except for clinical severity.
* P = 0.03, Mann Whitney U test.
† See table 2 for definitions.
‡ P = 0.01, Mann Whitney U test.

pearance of the organism from the stool. (*3*) A rise in antitoxin titer to LT was demonstrable in 61% of patients with LT-ST-producing strains and three of four patients with LT-producing strains, but in only one of 38 patients in whom ETEC was not isolated. Similar frequencies of antitoxin titer rises to LT were reported in a study of ETEC cases in Calcutta [17] but have not been found in travelers to areas where cholera is not endemic [18, 19]. Although there are no similar detailed descriptions of ETEC disease, previous reports from this hospital [20] and Calcutta [21] had described a noncholera illness with many clinical features of the ETEC disease described here, and it is likely that many of the cases described in these earlier studies were caused by ETEC.

During the period of the study, more than 95% of the adult patients with ETEC seen at our hospital were infected with LT-ST- or ST-producing strains. This predominance of LT-ST- and ST-producing strains was in contrast to findings from other geographic areas [18, 22], where LT-producing strains have been more frequently reported. The reasons for this apparent difference in distribution of enterotoxin types was not entirely clear, although the more frequent isolation of LT-producing strains in persons with milder diarrhea visiting a rural treatment facility in Bangladesh [4] suggested that LT-producing strains may produce a milder illness in this population than LT-ST- or ST-producing strains.

We observed that the patients with LT-ST- and ST-producing strains presented with a similar clinical picture and laboratory findings, including values for serum electrolytes indicative of isotonic dehydration. Vomiting was almost universal, and its pathophysiology warrants further study. The values of stool electrolytes and osmolarity were consistent with the known pathophysiology in diarrhea caused by LT and ST, which, like cholera, is secretory in nature [23, 24]. Although the stool electrolyte values of the patients with LT-ST- and ST-producing strains were similar to those seen in severe cholera [25], including the continued loss of bicarbonate ion in the presence of acidosis, the mean losses of sodium ion in stool were lower, a finding consistent with the somewhat lower purging rates in these severe ETEC cases as compared with severe cholera cases [26].

Although they had similar clinical presentation,

we found that the patients with LT-ST-producing strains had more dehydration and acidosis on admission and longer duration of diarrhea, greater stool volume, and greater iv fluid requirement during hospitalization as compared with the patients with ST-producing strains. These clinical observations were consistent with experimental data from rabbit ileal loop studies, which have demonstrated that LT has a longer duration of action than ST [27]; it is tempting to speculate that these differences in presentation and clinical course may be due to the additive effect of the LT. Further clinical studies of cases of ETEC in adults and children are needed to confirm these observations and test this hypothesis, and these should include study of adult patients with LT-producing strains.

Although a large number of patients were not included in the controlled trial of tetracycline, our data indicated that tetracycline therapy may have resulted in slightly earlier termination of diarrhea in LT-ST disease and had no effect on ST disease. These observations were consistent with the earlier evaluation of tetracycline in treatment of noncholera diarrhea in Calcutta [6]. Although these findings are in apparent contrast to the high efficacy of tetracycline in treatment of severe cholera, the efficacy of tetracycline in cholera is not detected until the second day of therapy [5], the time at which diarrhea had terminated in most of our placebo-treated patients. Tetracycline did not decrease the antitoxin response to LT after infection, a result similar to its lack of effect on the antitoxin response after cholera infection [28].

In both the patients with LT-ST- and ST-producing strains, tetracycline treatment resulted in a shorter duration of excretion of organisms, which could be detected within 24 hr of therapy. By seven and 14 days after presentation to the hospital, organisms were rarely isolated in either the treatment or placebo groups. We suspect that tetracycline eradicated the organisms from the small intestine, although we cannot exclude the possibility that in a few patients it only suppressed their growth, as we did not obtain stool cultures in the period from 24 to 96 hr after therapy was stopped.

Our finding that ST-producing strains had more frequent antibiotic resistance than LT-ST-producing strains, including resistance to tetracycline, suggests that plasmids coding for tetracycline resistance may be more readily acquired by ST-producing strains than LT-ST-producing strains; this difference may be related to the larger size of the plasmids from the LT-ST-producing strains [29]. Despite the general sensitivity of our ETEC strains to tetracycline (in contrast to strains from the Far East [30]), we do not feel that the benefit derived from use of tetracycline in treatment of ETEC disease justifies its administration, at least to adults in our population. This conclusion is particularly true because patients with ETEC and other acute watery diarrheas can be readily treated with oral rehydration therapy [31]. In addition, treatment of hospital patients would have little, if any, impact on public health; a subsequent community-based study in Bangladesh has shown that only 3% of patients with ETEC infections come to the hospital (R. Black, personal communication). Unfortunately, there are no means clinically to differentiate cases of *E. coli* diarrhea from cases of cholera, so that during the cholera season tetracycline, which is being administered to patients with severe cholera, will also be given to patients with ETEC.

The fact that tetracycline diminished the duration of excretion of organisms in the patients with LT-ST- and ST-producing strains and may have minimally shortened LT-ST disease does suggest that antibiotic therapy might be considerably more effective and advantageous in treatment of travelers from industrialized countries with ETEC disease, which is generally longer in duration [18, 32, 33]. This possibility is also suggested by the documented effect of doxycycline prophylaxis in prevention of ETEC diarrhea in travelers [32, 33] and is an important area for further study.

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