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Randomized Trial of High- and Low-Dose Ampicillin Therapy for Treatment of Severe Dysentery Due to *Shigella dysenteriae* Type 1

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To establish optimal therapy for severe dysentery due to *Shigella dysenteriae* type 1 and *Shigella flexneri*, we compared in a prospective randomized trial two oral ampicillin doses (50 and 150 mg/kg per day) in 57 children and 39 adults in Dacca, Bangladesh. Clinical failure did not occur in either group, indicating that conventional doses need not be increased even in severe disease. Among children 3 years of age or under, bacteriological relapses tended to be more frequent in the low-dose group and were not related to serum levels of ampicillin, nutritional status, or the severity of colitis on admission. Therefore, we recommend that younger children be treated with 100 mg/kg per day of oral ampicillin.

Bacillary dysentery due to *Shigella dysenteriae* type 1 recently occurred in epidemic proportions in Bangladesh (12) and Central America (9). Disease caused by this species is associated with a high mortality rate (2), often occurs as pseudomembraneous colitis, and can be complicated by an acute hemolytic-uremic syndrome (8, 11). The drug of choice for the treatment of shigellosis in Bangladesh is ampicillin as resistance is infrequent. Uncontrolled observations suggested that ampicillin doses in excess of 100 mg/kg per day may have been responsible for a more rapid clinical response and a lower complication rate in severe dysentery cases (Technical Committee Meeting, Cholera Research Laboratory, 1976).

There are no published controlled studies on the antibiotic treatment of severe shigellosis due to *S. dysenteriae* type 1. We designed a prospective randomized trial to compare the rate of recovery and complications between two doses of oral ampicillin (50 and 150 mg/kg per day) and to correlate serum ampicillin levels with clinical and bacteriological responses.

MATERIALS AND METHODS

A total of 122 patients, arriving at the Cholera Hospital acutely ill with blood, pus cells, and mucus in the stool were admitted to the study after signed consent. Reasons for exclusion were the inability to take oral medication, a history of ampicillin use during the current illness, or the presence of another infectious disease such as pneumonia. The etiology of clinical dysentery was established by stool and rectal swab cultures plated on MacConkey and *Shigella-Salmonella* agar. Fecal microscopy was performed to exclude hematophagous *Entamoeba histolytica* trophozoites.

A total of 11 patients with leukemoid reactions (leukocyte counts greater than 50,000/mm^3) were randomized as a separate group because of their increased risk of developing the hemolytic-uremic syndrome (8, 11), but only 4 were able to complete the study.

The severity of shigellosis was assessed on admission by a peripheral leukocyte count and proctoscopy. The appearance of the rectal mucosa was classified into the following five grades: I, edematous mucosa with visible folds and mucoid secretions; II, edematous mucosa with thin exudate and folds effaced; III, friable, ragged mucosa with abundant exudate; IV, island of thick, adherent exudate (pseudomembrane) overlying friable mucosa; and V, extensive pseudomembrane of necrotic mucosa overlying submucosa.

Recovery was assessed by axillary temperature taken every 4 h, the presence of visible blood in stools passed each 24 h, and stool cultures taken daily for the first 4 days and then on day 7. Patients were requested to return for a stool culture and proctoscopic exam between days 14 and 21.

At admission patients were randomly assigned to one of two treatment groups receiving 50 or 150 mg/kg per day in four divided doses orally for five complete 24-h periods. A total of 3 patients were subsequently found to have acute amebiasis, and 10 patients had no enteric pathogens isolated, thus leaving 96 patients who completed the study.

Serum levels of ampicillin were measured, in venous blood drawn 1 h (peak) and 5 h (valley) after the noon dose of day 3 of therapy, by the agar plate diffusion method with *Bacillus subtilis* ATCC 6633 as the assay organism (1). All infecting strains of shigellae isolated in study cases were susceptible to 10 μg of ampicillin per ml by the tube dilution assay in Mueller-Hinton broth.

RESULTS

The randomization of patients resulted in a similarity between high- and low-dose groups with respect to age, leukocyte count, and proc-

TABLE 1. *Results of ampicillin therapy for shigellosis in 57 children*

Ampicillin dose (mg/kg per day) against:	No. of children	Age (yr)[a]	Admission studies (leukocytes $\times 10^3$/mm^3)	Proctoscopy grade (I/II/III/IV/V)	Assessment of recovery (no. of days of blood in stool)	No. of days of diarrhea[b]	No. of cultures positive on day:			No. of deaths/ cases of hemolytic anemia
							3	7	14 to 21	
S. dysenteriae type 1										
150	19	5.3 ± 3.1	19.7 ± 6.7	1/10/5/2/0[c]	2.5 ± 2.0	5.0 ± 1.6	0/19	0/17	0/7	2/2
50	21	4.6 ± 2.9	22.1 ± 10.0	6/5/7/2/0[c]	2.2 ± 1.3	4.6 ± 1.7	0/21	0/21	2/10	0/0
S. flexneri										
150	10	3.2 ± 1.8	14.1 ± 6.4	6/4/0/0/0[d]	0.7 ± 0.9	3.3 ± 2.3	0/10	1/8	0/3	0/0
50	7	4.6 ± 1.6	15.6 ± 7.2	2/4/0/1/0[d]	0.7 ± 1.0	4.0 ± 2.0	0/7	1/7	1/3	0/0

[a] Mean ± standard deviation.
[b] Diarrhea is defined as four or more stools per day.
[c] One patient was not examined.
[d] *S. dysenteriae* caused more serious disease than *S. flexneri* by a comparison of mild proctitis (grades I and II) with severe proctitis (grades III and IV) ($P < 0.01$, chi-square test).

toscopy grade in both children (Table 1) and adults (Table 2). In children, *S. dysenteriae* type 1 (Shiga bacillus) produced a significantly higher mean admission peripheral leukocyte count than did *S. flexneri* ($20.9 \pm 8.6 \times 10^3$/mm^3 versus $14 \pm 7.3 \times 10^3$/mm^3; $P < 0.005$, Student's t test). In addition, colitis with heavy exudate, mucosal friability, or pseudomembrane (grade III or IV) was almost exclusively found in cases with *S. dysenteriae* type 1 on stool culture. In this series, excluding leukemoid cases, there were two deaths and two cases complicated by hemolytic anemia, all due to *S. dysenteriae* type 1 and all occurring in the high-dose group.

Seven children with leukemoid reactions (randomized separately) could not complete the study because of vomiting or other infections. Among the four who remained on oral ampicillin, two developed hemolysis, one from each dose group.

The rate of recovery, assessed by the persistence of visible blood in the stool and the duration of positive stool cultures, was not significantly different between the two ampicillin dose groups among nonleukemoid children (Table 1) and adults (Table 2). Clinical failure did not occur in either treatment group.

There was a trend toward a higher rate of bacteriological relapse in the low-dose group, but the difference was not significant as only small numbers of relapses occurred ($P = 0.15$, Fisher exact test) (Table 3). Bacteriological relapses were not associated with a recurrence of symptoms.

In children in the low-dose group, the three bacteriological relapses with serum ampicillin levels measured had levels comparable to those found among children without relapses (Table 3). Ampicillin levels in both treatment groups did not correlate with nutritional status as measured by weight in relation to height. In the 50-mg/kg-pediatric treatment group there was a correlation between ampicillin levels and age ($r = +0.29$; $P = 0.11$). In the 150-mg/kg-pediatric group no correlation was seen between ampicillin levels and age ($r = 0.004$).

DISCUSSION

Shigellosis in developing countries has a high morbidity and mortality due to malnutrition, coexisting infections, and other complications. In Bangladesh unique complications included the leukemoid reaction which was frequently followed by microangiopathic hemolytic anemia and renal insufficiency (hemolytic-uremic syndrome) (8, 11) due to *S. dysenteriae* type 1 and rarely to strains of *S. flexneri*.

We could not evaluate the effect of the oral ampicillin dosage on the development of the

TABLE 2. *Results of ampicillin therapy for shigellosis in 39 adults*

Ampicillin dose (mg/kg per day) against:	No. of adults	Age (yr)[a]	Admission studies (leukocytes $\times 10^3$/mm^3)	Proctoscopy grade (I/II/III/IV/V)	Assessment of recovery (no. of days of blood in stool)	No. of days of diarrhea[b]	No. of cultures positive on day:			No. of deaths
							3	7	14 to 21	
S. dysenteriae type 1										
150	15	24.9 ± 9.2	16.0 ± 11.7	7/5/3/0/0	1.5 ± 1.2	4.4 ± 1.7	0/15	0/13	0/9	0
50	14	23.9 ± 12.8	12.0 ± 4.3	6/5/1/0/0	1.4 ± 0.8	3.6 ± 1.9	1/14	1/13	0/5	0
S. flexneri										
150	4	29.3 ± 17.2	11.2 ± 8.0	3/1/0/0/0	1.5 ± 1.7	1.4 ± 0.8	0/4	0/4	0/3	0
50	6[c]	28.6 ± 10.8	13.0 ± 5.0	3/3/0/0/0	1.0 ± 0.0	1.0 ± 1.4	0/6	0/4	0/3	0

[a] Mean ± standard deviation.
[b] Diarrhea is defined as four or more stools per day.
[c] Includes one case caused by *S. dysenteriae* type 2 (Schmidt bacillus).

hemolytic-uremic syndrome in leukemoid children with shigellosis as only 4 of 11 children were able to complete the study. All children subsequently evaluated had leukocyte counts below 50,000/mm^3. In this study only children and adults with gross blood and mucus in their stool were studied, whereas most studies done in the United States included patients with milder disease (5, 6). No clinical failure occurred, and the recovery rate as measured by the disappearance of blood and bacteria from the stool was similar in both dose groups. The few complications in this study occurred only in the high-dose group, indicating that appropriate antibiotics, although crucial in treating acute shigellosis, will not prevent nonbacterial complications (hemolytic-uremic syndrome) once extensive colitis has developed.

Higher doses tended to be associated with a lower number of bacteriological relapses. Younger children appeared significantly more likely to have a bacteriological relapse than did older children. In a Texas study of children with shigellosis treated with the nonabsorbable antibiotic neomycin, data on ages and clinical failure rates indicated that whereas 8 of 10 children under the age of three were clinical failures, only 1 of 5 children over the age of three failed clinically ($P = 0.05$, Fisher exact test) (4).

Absorbable oral antibiotics shorten the clinical course of shigellosis due to susceptible strains (7). As oral ampicillin is absorbed erratically even in well-nourished children and particularly poorly in children under 2 years of age and below the third percentile for expected weight in relation to age (10), it was important to document whether failure or relapse was related to inadequate serum ampicillin levels. Children 3 years of age and under tended to have lower serum ampicillin levels than older children. This relationship was seen only in the group receiving the lower daily dose. As ampicillin levels of the four children who relapsed in the low dose groups were comparable to those of the entire group (Table 3), diminished ampicillin absorption cannot alone account for a bacteriological relapse, and other host factors associated with age are probably important. No relationship between nutritional status and either serum ampicillin levels or relapse was documented. We could not evaluate the increased ampicillin levels seen in better-nourished American children (10) (above the third percentile) as so few of our Bengali children (3 of 37 under 5 years of age) were able to meet this nutritional standard.

In summary, severe shigellosis, even when accompanied by malnutrition, can be treated in patients over the age of three with the customary dose (50 mg/kg per day) of ampicillin. In young

TABLE 3. *Relation of bacteriological relapses to age and ampicillin blood levels in children*

Ampicillin dose[a] (mg/kg)	Bacteriological outcome	No. of patients	Age (yr)		Mean ± SD[b] peak serum ampicillin level (μg/ml)
			≤3	>3	
37.5	Success	29	13	16	3.2 ± 1.8 (17)[c]
	Relapse	1	1	0	ND[d]
12.5	Success	28	10	18	1.3 ± 0.4 (18)
	Relapse	4[e]	4[f]	0	1.2 ± 0.2 (3)

[a] The doses of ampicillin given every 6 h were 37.5 and 12.5 mg/kg in the high- and low-dose groups, respectively.

[b] SD, Standard deviation.

[c] The high-dose group had a higher mean peak serum ampicillin level than the low-dose group ($P < 0.05$, Student's t test). Numbers in parentheses represent number of patients examined.

[d] ND, Not done.

[e] There were two patients infected with *S. dysenteriae* and two patients infected with *S. flexneri*. There was no significant difference in the relapse rates between the two dose groups ($P = 0.14$, Fisher exact test).

[f] The occurrence of all relapses in the groups under 3 years of age was significant ($P = 0.03$, Fisher exact probability test).

children (3 years of age or under), however, a higher dose of ampicillin is required if prevention of a bacterial relapse is desired. In another study we have found that a dose of 100 mg/kg per day prevented bacteriological relapses in all age groups (3).

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