Sulfamethoxazole-Trimethoprim Versus Ampicillin in Treatment of Acute Invasive Diarrhea in Adults

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Twenty-seven Navajo adults with moderate to severe acute inflammatory diarrhea were hospitalized and randomly given ampicillin or sulfamethoxazole-trimethoprim. All patients had invasive diarrhea as defined by sheets of fecal leukocytes, seen on methylene blue wet-slide preparations, and significant clinical symptoms, including postural hypotension from dehydration or fever (temperature greater than 100°F [or 37.8°C]). Patients were followed daily for 5 days in the hospital. Responses of symptoms in all 13 patients who were given sulfamethoxazole-trimethoprim were comparable to or better than those 14 patients randomly assigned to receive ampicillin. Nineteen (73%) of the 27 patients had culture-proven shigellosis, 6 of whom had ampicillin-resistant *Shigella* isolates. All isolates were susceptible to sulfamethoxazole-trimethoprim in vitro. The eight patients with culture-proven shigellosis treated with sulfamethoxazole-trimethoprim responded as well as the eight patients with ampicillin-susceptible infections treated with ampicillin. Three of the eight patients successfully treated with sulfamethoxazole-trimethoprim had ampicillin-resistant organisms. The three patients with ampicillin-resistant organisms who were treated with ampicillin appeared to do less well; one was a clinical and bacteriological failure at 72 h and subsequently improved after sulfamethoxazole-trimethoprim therapy. As predicted by in vitro susceptibility studies and by studies in children, sulfamethoxazole-trimethoprim was highly effective in treating adult patients with shigellosis and appears to be the treatment of choice in areas where ampicillin resistance among *Shigella* is common.

Until the development of ampicillin resistance among *Shigella* in recent years, ampicillin has been the highly effective treatment of choice in acute shigellosis. For ampicillin-susceptible *Shigella* infections, ampicillin therapy significantly reduced the duration and severity of the illness, and fecal shedding of *Shigella* in children and adults, when compared with either oral kanamycin or placebo (3, 14). However, in recent years, many *Shigella flexneri* and *Shigella sonnei*, the two most common strains that cause shigellosis in the United States, have become resistant to ampicillin (9, 10). Sulfamethoxazole-trimethoprim (SXT) is effective in vitro against ampicillin-resistant strains of *Shigella* (4). SXT has been found to be effective in treating children with acute shigellosis (2, 6, 7), but no controlled trials in adults have appeared. In this prospective, double-blind study, we have examined the efficacy of ampicillin or SXT randomly administered to 27 patients who required admission to the Fort Defiance Indian Hospital for inflammatory diarrhea suggesting shigellosis.

MATERIALS AND METHODS

Patients. Adult patients with moderate to severe acute inflammatory diarrheal illnesses requiring hos-

pitalization at the Fort Defiance Indian Hospital between September 1976 and August 1978 were considered for study. All patients gave written informed consent. Competent Navajo translators were used when necessary. All patients had inflammatory diarrhea as demonstrated on the methylene blue or Gram stain for fecal leukocytes. Several had profuse blood-streaked diarrhea. All patients admitted to the study had either postural hypotension (diastolic blood pressure drop of 5 mmHg or more, or systolic drop of greater than 20 mmHg) or fever (greater than 100°F [or 37.8°C]) or both. Patients were excluded from study if they had a history of allergy to penicillin or sulfa drugs, had a history of hemolytic anemia, were pregnant, or were breast-feeding.

Treatment. Drug assignment was based on a table of random numbers before the start of the study. Ampicillin, 500 mg orally four times a day, was given to those with even random numbers, and SXT (800 mg of sulfamethoxazole and 160 mg of trimethoprim) was given twice daily by mouth to those assigned to odd random numbers. Antibiotics were continued for 5 days.

Laboratory data. Fresh cup stool specimens were examined within 15 min on methylene blue and inoculated onto salmonella-shigella and eosin-methylene blue agars, and onto selenite enrichment broth for subsequent subculture onto eosin-methylene blue and salmonella-shigella agars. These specimens were obtained before antibiotic therapy and at least twice

more during hospitalization, over the 5 subsequent days. *Shigella* isolates were tested in vitro for susceptibility to SXT and ampicillin by disk diffusion on Mueller-Hinton agar, and SXT susceptibilities were confirmed by agar dilution. In addition, two representative coliform isolates were examined in the Sereny test for invasiveness (11).

Clinical data. Each day a physician who did not know the antibiotic administered recorded the following data for the previous 24 h: maximum temperature, number of loose bowel movements (with or without gross blood), nausea, vomiting, anorexia, abdominal pain, headache, myalgias, and malaise.

Clinical improvement was defined as greater than 50% reduction in symptom count, with each of the above symptoms represented by 1.

Statistical analyses were done using Student's *t* test.

RESULTS

As shown in Table 1, 27 patients met the criteria for admission to the study; 14 were randomly assigned to receive ampicillin, and 13 were assigned to receive SXT. The ages, sex distribution, and duration of illness were comparable in the treatment subgroups. Responses in terms of reduction in fever and number of loose stools over the 5 days of daily follow-up are shown in Fig. 1. Fever and diarrhea in the SXT group were significantly reduced within 24 h ($P < 0.001$ for both symptoms). Significant reductions in fever and diarrhea in the ampicillin-treated group occurred 1 day later, within 48 h.

Of the 27 patients, 19 had culture-proven shigellosis. Seventeen had *Shigella flexneri*, and two had *Shigella sonnei*. Of these 19 patients, 6 had ampicillin-resistant *Shigella*. All *Shigella* isolates were susceptible to SXT (minimum inhibitory concentrations less than 20 and 1 μ g of sulfamethoxazole and trimethoprim per ml, respectively). The responses of fever and diarrhea in these treatment subgroups are shown in Fig. 2. Responses of the eight patients with documented shigellosis given SXT were comparable to those of the eight patients with ampicillin-susceptible *Shigella* who were treated with ampicillin. However, the three patients with ampi-

cillin-resistant *Shigella* who were treated with ampicillin appeared to respond more slowly.

Two patients were quite ill at the end of 48 to 72 h, necessitating breaking of the blind treatment code. Both patients were receiving ampicillin, and both were changed to SXT; they subsequently improved. One of these two had a subsequently documented ampicillin-resistant organism. Two other patients with ampicillin-resistant organisms treated with ampicillin recovered uneventfully within 3 days. The three patients with ampicillin-resistant organisms treated with SXT showed significant clinical improvement within 24 h and had completely recovered by day 2 of therapy.

The results of the stool cultures are shown in Fig. 3. Although the numbers were small, there was again a tendency toward prolonged culture positivity in the ampicillin-resistant shigellosis treated with ampicillin. In contrast, none of the 25 cultures obtained after the first day from the 16 patients treated with SXT or ampicillin (who had ampicillin-sensitive isolates) were culture positive. The two patients who had positive stool cultures for *Shigella* after 48 h had both received ampicillin. One was the patient mentioned above who had an ampicillin-resistant organism and who failed on ampicillin therapy. The other patient had an ampicillin-susceptible organism and recovered uneventfully.

DISCUSSION

Shigellosis is a major problem in areas throughout the world where sanitation is poor, including the United States. Resistance to ampicillin and sulfonamides, the only two antibiotics of proven efficacy in adults, in recent years has become quite common. The fact that 6 (32%) of our 19 isolates were ampicillin resistant reflects its widespread occurrence among *Shigella* (4, 9, 10). Among the few potentially effective antimicrobial agents to which these *Shigella* remain susceptible in vitro at this time is SXT. Over a 2-year period at the Fort Defiance Indian Hospital, we treated 27 adults who required

TABLE 1. Number and characteristics of study treatment groups

Treatment	Stool culture ^a	No. of patients	M/F	Mean age (yrs) (range)	Duration of illness (days)	Admission stools per day	Admission temp (°F/°C)
Ampicillin	<i>Shigella</i> (AS)	8	2/6	53 (22-68)	1.8	6.3	101.9/38.8
	<i>Shigella</i> (AR)	3	1/2	64 (47-76)	1.8	13.7	101.7/38.7
	Negative	3	2/1	33 (29-49)	3.8	13.3	100.7/38.2
SXT	<i>Shigella</i>	8	3/5	54 (18-79)	1.2	7.6	102.7/39.3
	Negative	5	3/2	66 (43-89)	2.5	9.4	102.5/39.2

^a AS, Ampicillin susceptible; AR, ampicillin resistant.

FIG. 1. Mean ($\pm$ standard deviation) maximal daily temperature and daily stool responses of all patients with inflammatory diarrhea to ampicillin (A, $\bullet$, $n = 14$) or to SXT ($\times$, $n = 13$) over the 5-day treatment period.

hospitalization for invasive diarrhea. Our results demonstrate that SXT is at least as effective as ampicillin in the treatment of patients with acute inflammatory diarrhea. It is also as effective as ampicillin in treating ampicillin-susceptible shigellosis and is superior in patients infected with ampicillin-resistant *Shigella*.

Nelson et al. have demonstrated that SXT is superior to ampicillin in treating infants and children requiring hospitalization for shigellosis (7) and in ambulatory children with shigellosis (6). A theoretical advantage of SXT over ampicillin is the maintenance of normal anaerobic colonic flora during treatment (13; R. L. Guerrant, S. J. Wood, L. Krongard, R. A. Reid, and R. H. Hodge, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 18th, Atlanta, Ga., abstr. no. 295, 1978).

This study demonstrates the efficacy of SXT in treatment of acute shigellosis in adults iden-

tified early with the aid of the fecal leukocyte examination. The methylene blue examination for fecal leukocytes, when done promptly with a fresh cup specimen, is an extremely sensitive test for the rapid, presumptive diagnosis of shigellosis in a setting where inflammatory colitis due to shigellosis is common as in this population (5; J. M. Hughes, J. D. Rouse, F. A. Barada, and R. L. Guerrant, Am. J. Trop. Med. Hyg., in press). Eight (30%) of our 27 patients with acute inflammatory diarrhea had negative initial cultures for *Shigella*. Based on the known sensitivity of only 60 to 70% of stool cultures that are positive in acute symptomatic shigellosis (8), a majority of these patients probably had shigellosis with false-negative initial stool cultures. None had invasive *Escherichia coli* or other recognized invasive pathogens. One of these in-

FIG. 2. Mean ($\pm$ standard deviation) maximal daily temperature and daily stool responses of the 19 patients with documented shigellosis to SXT ($\times$, $n = 8$), of those with ampicillin-resistant shigella infections to ampicillin (AR, $\circ$, $n = 3$), and of those with ampicillin-susceptible shigella infections (AS, $\bullet$, $n = 8$), over the 5-day treatment period.

FIG. 3. Percent of patients with shigellosis with positive stool cultures on SXT (x); on ampicillin with ampicillin-resistant organisms (AR, O); and on ampicillin with ampicillin-susceptible organisms (AS, ●). Total numbers of stool cultures obtained at each time are given in parentheses.

dividuals had a family member with a simultaneous similar illness that was documented shigellosis by culture. Examination for fecal leukocytes in patients suspected of having shigellosis facilitates initiation of antimicrobial therapy early in the course of the illness and thereby prompt reduction in symptoms and excretion of the pathogen. Lacking evidence of shigellosis, other potentially invasive pathogens should be considered which might require different or no antimicrobial therapy, such as *Campylobacter fetus* subsp. *jejuni* or *Salmonella* infections, respectively. *C. fetus* subsp. *jejuni* infections are being increasingly recognized throughout the world, including the United States, and should be sought using specially selective media (1).

SXT is as effective as ampicillin in the treatment of moderately severe ampicillin-susceptible *Shigella* infections in adults, and appears to be effective in treating patients with ampicillin-resistant shigellosis. Therefore, SXT appears to be the drug of choice for symptomatic shigellosis in areas where ampicillin resistance is common.

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