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 hospitalization 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 suscep-
tibility to SXT and ampicillin by disk diffusion on
Mueller-Hinton agar, and SXT susceptibilities were
confirmed by agar dilution. In addition, two repre-
sentative coliform isolates were examined in the Ser-
eny test for invasiveness (11).
Clinical data. Each day a physician who did not
know the antibiotic administered recorded the follow-
ing 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 ran-
domly assigned to receive ampicillin, and 13 were
assigned to receive SXT. The ages, sex
distribution, and duration of illness were com-
parable 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 ampicil-
in-treated group occurred 1 day later, within
48 h.

Of the 27 patients, 19 had culture-proven shig-
ellosis. Seventeen had Shigella flexneri, and two
had Shigella sonnei. Of these 19 patients, 6 had
ampicillin-resistant Shigella. All Shigella iso-
lates were susceptible to SXT (minimum inhibi-
tory concentrations less than 20 and 1 \( \mu g \)
of sulfamethoxazole and trimethoprim per ml, re-
spectively). The responses of fever and diarrhea in
these treatment subgroups are shown in Fig.
2. Responses of the eight patients with docu-
mented shigellosis given SXT were comparable
to those of the eight patients with ampicillin-
susceptible Shigella who were treated with am-
picillin. 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 treat-
ment code. Both patients were receiving ampi-
cillin, 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 re-
covered 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 am-
picillin and sulfonamides, the only two antibi-
otics of proven efficacy in adults, in recent years
has become quite common. The fact that 6 (32%)
of our 19 isolates were ampicillin resistant re-
ffects 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

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<th>Table 1. Number and characteristics of study treatment groups</th>
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<td>Treatment</td>
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* AS, Ampicillin susceptible; AR, ampicillin resistant.
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.


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

![Graph 1](http://aac.asm.org/Downloaded from http://aac.asm.org on October 11, 2017 by guest)

**Fig. 1.** Mean (± standard deviation) maximal daily temperature and daily stool responses of all patients with inflammatory diarrhea to ampicillin (A, ♦, n = 14) or to SXT (x, n = 13) over the 5-day treatment period.

![Graph 2](http://aac.asm.org/Downloaded from http://aac.asm.org on October 11, 2017 by guest)

**Fig. 2.** Mean (± standard deviation) maximal daily temperature and daily stool responses of the 19 patients with documented shigellosis to SXT (x, n = 8), of those with ampicillin-resistant shigella infections to ampicillin (AR, ◇, n = 3), and of those with ampicillin-susceptible shigella infections (AS, ♦, n = 8), over the 5-day treatment period.
individuals 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 specialty 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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LITERATURE CITED