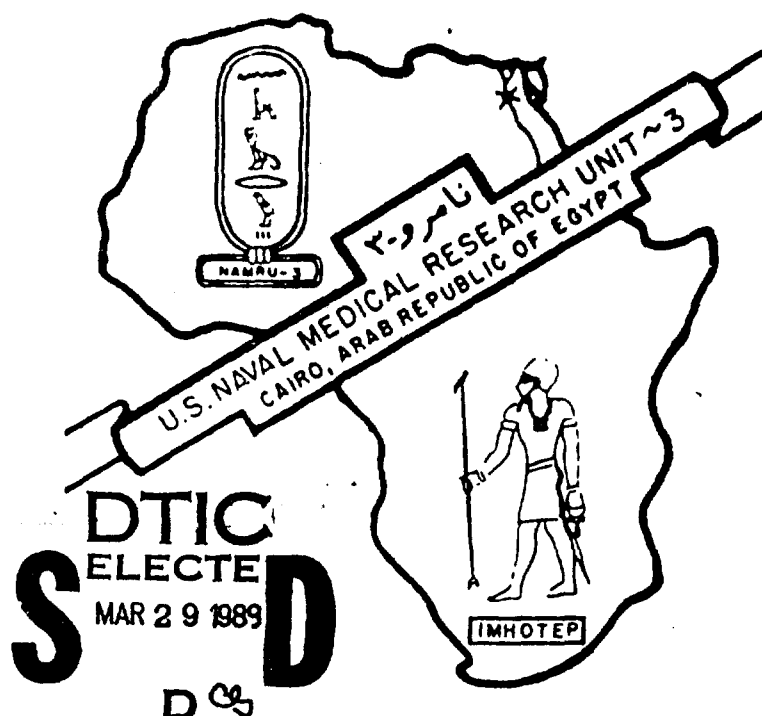


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EMPIRICAL TREATMENT OF SHIGELLA DYSENTERY WITH
TRIMETHOPRIM: FIVE-DAY COURSE VS. SINGLE DOSE

BY

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19. the two dosage schedules of trimethoprim, we concluded that both treatment regimens are effective for the treatment of Shigella dysentery.

* Forlanini Fever Hospital, Ministry of Health, Mogadishu, Somalia.

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EMPIRICAL TREATMENT OF *SHIGELLA* DYSENTERY WITH TRIMETHOPRIM: FIVE-DAY COURSE vs. SINGLE DOSE

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Abstract. Fifty-three adults hospitalized with *Shigella* dysentery were empirically treated with trimethoprim (200 mg) twice/day for 5 days, a single dose of trimethoprim (600 mg), or placebo in a randomized double-blind trial. During the first 24 hr of therapy, there was a reduction in the number of stools in 18/21 (86%) of patients treated with the 5-day regimen (trimethoprim-5) and 13/15 (87%) of patients treated with a single dose (trimethoprim-1), compared with 7/17 (41%) of the placebo group ($P < 0.025$, both comparisons). The mean number of stools passed in the first 24 hr of therapy was 10.6, 10.8, and 21.3 stools in the trimethoprim-5, trimethoprim-1, and placebo groups, respectively. The mean ($\pm$ SD) change in number of stools from baseline among treated patients during the first 24 hr was -4.9 (6.6) and -6.3 (6.3) for the trimethoprim-5 and trimethoprim-1 groups, respectively, compared with an increase of $+2.4$ (14.8) for the placebo group. There was a clinical failure at 48 hr in 9% of the trimethoprim-5 patients and 13% of trimethoprim-1 patients compared with 70% of placebo patients ($P < 0.005$, both comparisons). Although we were unable to demonstrate a difference in efficacy between the two dosage schedules of trimethoprim, we conclude that both treatment regimens are effective for the treatment of *Shigella* dysentery.

The treatment of bacterial infections with single-dose antibiotic therapy offers many potential benefits. Studies of single-dose therapy for urinary tract infections have revealed less toxicity¹⁻³ and a decreased emergence of resistant strains.⁴ Single-dose regimens also are less expensive, and because the entire regimen can be given under supervision, compliance approaches 100%. Single-dose therapy of shigellosis has previously been demonstrated to be effective, both clinically and bacteriologically, for tetracycline^{5,6} and clinically for ampicillin.⁷

The treatment of shigellosis remains a problem because of increasing resistance to commonly prescribed drugs. Sulfonamides were the drug of choice in the 1940s; however, increasing resistance led to their replacement by tetracycline. Similarly, the development of widespread tetracycline resistance in the 1960s led to its re-

placement by ampicillin and, subsequently, to the replacement of ampicillin by trimethoprim-sulfamethoxazole in the 1970s.⁸⁻¹⁰ The frequent occurrence of resistance to sulfamethoxazole^{9,11,12} and the lack of synergy when the *Shigella* strain is resistant to sulfamethoxazole^{11,13,14} suggests that the therapeutic effect of trimethoprim-sulfamethoxazole in many instances may be derived primarily from trimethoprim.

The efficacy of a 5-day course of trimethoprim in shigellosis has been previously demonstrated.¹⁵ To evaluate the efficacy of a single dose of trimethoprim in *Shigella* dysentery, we conducted a randomized double-blind placebo controlled trial comparing the efficacy of trimethoprim single-dose (trimethoprim-1) to a 5-day regimen of trimethoprim (trimethoprim-5).

MATERIALS AND METHODS

All subjects (≥ 10 years old) with acute diarrhea seen at the Forlanini Infectious Disease Hospital in Mogadishu, Somalia, from April through June 1984 were admitted to the study.

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Diarrhea was defined as ≥ 4 stools in the preceding 24 hr with at least one associated symptom of nausea, vomiting, or abdominal pain. Patients who were pregnant, had known trimethoprim allergy, refused hospital admission, had diarrhea of > 10 days duration, did not have *Shigella* isolated from stool, or had trimethoprim-resistant *Shigella* isolated from their stool were excluded from the study. All patients gave informed consent. All subjects had a baseline history and physical examination, which was repeated daily. Subjects gave a stool specimen prior to treatment and were randomly assigned to one of three groups. The trimethoprim-5 group received trimethoprim (200 mg) twice a day for 5 days, the trimethoprim-1 group received trimethoprim, 15 mg/kg or a maximum of 600 mg as a single dose, and the placebo group received an identical appearing placebo. Treatment was begun immediately after a stool was obtained for culture.

As the culture and antimicrobial susceptibility of *Shigella* isolates were determined (usually at 48 hr), each subject was evaluated without knowledge of the treatment regimen as to the need for antibiotic intervention. The code was broken for subjects who were clinically unchanged or worsening, or who had not had a reduction in stool number $\geq 50\%$. If the code was broken because of a lack of response, this was considered a treatment failure. Subjects in the placebo and trimethoprim-1 group were begun on trimethoprim, 200 mg, twice daily for 3 days, while those patients in the trimethoprim-5 group were continued on their regimen if the *Shigella* isolate was sensitive to trimethoprim. Clinical data was recorded blind.

Clinical scores were determined by giving 1 point for each of the following symptoms: fever, chills, headache, dizziness, nausea, vomiting, anorexia, myalgias, or malaise; 2 points for an oral temperature $\geq 100^\circ\text{F}$; 1 point for the presence of orthostatic blood pressure or pulse changes; and 1, 2, or 3 points for mild, moderate, or severe abdominal pain. Orthostatic changes were defined as an increase in pulse of ≥ 20 and/or a decrease in systolic blood pressure of ≥ 15 mmHg or a decrease in diastolic blood pressure of ≥ 5 mmHg after standing for 1 min. A clinical response was defined as a reduction in the clinical score of $\geq 50\%$.

Patients received oral rehydration salts and intravenous fluids according to the ward routine.

A follow-up stool was obtained 5 days after initiation of therapy.

Microbiology

Stools were examined for bacterial and protozoal enteric pathogens before and after completion of treatment. Stools were plated at the patient's bedside onto MacConkey's (MAC), *Salmonella-Shigella* (SS), Hektoen enteric, and xylose-lysine-deoxycholate agars and into *Campylobacter* enrichment.¹⁶ All stools were cultured on selective media for *Campylobacter* and *Yersinia*, and all plates were examined for *Aeromonas*, *Salmonella*, *Shigella*, *Plesiomonas*, *Vibrio*, and *Yersinia* using standard methods.¹⁷⁻²¹ *Shigella* isolates were identified by slide agglutination in grouping and typing antisera (Difco, Detroit, Michigan) and biochemically with the API 20E system (Analytab Products, Plainville, New York). Five pretreatment *Escherichia coli* colonies from bedside or laboratory MAC plates were assayed for enterotoxin activity.^{22, 23}

Initial and post-treatment stools were examined for protozoal parasites microscopically by direct smear (wet mount). Stools, stained and preserved in merthiolate-iodine-formalin solution were reexamined for *Entamoeba* and *Giardia* at NAMRU-3 after ether extraction and centrifugation.²⁴ Direct fecal smears were also examined for red and white blood cells. The presence of fecal leukocytes was confirmed by examination of air-dried smears stained with Loeffler's methylene blue. After examining five fields, results were graded as follows: negative = < 1 leukocyte/oil immersion field, 1+ = 1-5, 2+ = 6-10, 3+ = 11-20, and 4+ = 21+ leukocytes/field.

Quantitative stool cultures were performed on initial and post-treatment specimens to monitor trimethoprim-associated changes in the total number, species, and antibiotic susceptibility of resident aerobic gram-negative flora and to determine the relative number of *Shigella* present. Quantitative counts per gram of stool were done by serial dilutions onto MAC agar plates and incubated for 48 hr. For *Shigella* determinations, no detectable growth meant $< 10^3$ organisms/g of stool, and was considered 10^2 in data analysis. Five colonies were selected from plates with the highest dilution showing growth and stored in nutrient agar stabs for later identification by API 20E and trimethoprim susceptibility testing.



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Antibiotic susceptibilities to trimethoprim and other antibiotics were determined by disc diffusion.²⁵ Minimal inhibitory concentrations (MIC) of trimethoprim, sulfamethoxazole, and trimethoprim-sulfamethoxazole in combination (1:20) were determined by the agar dilution method with Mueller-Hinton agar (Mueller-Hinton II, BBL Microbiology Systems, Cockeysville, Maryland) and a Steers replicator.²⁷ *E. coli* (ATCC 25922) and *Staphylococcus aureus* (ATCC 25923) strains served as controls for both the disc diffusion and agar dilution procedures. The MIC of trimethoprim, sulfamethoxazole, and trimethoprim-sulfamethoxazole were determined for all strains of *Shigella*. Trimethoprim-susceptible strains were defined as those with MIC ≤ 4 $\mu\text{g/ml}$; sulfamethoxazole- and trimethoprim-sulfamethoxazole (1:20)-susceptible strains were defined as those with MIC ≤ 100 $\mu\text{g/ml}$, respectively.²⁸ Fractional inhibitory (FIC) indices < 1.0 were considered indicative of trimethoprim-sulfamethoxazole synergy^{28, 29} and demonstrated that an individual *Shigella* isolate had enhanced susceptibility to the combined drugs at a ratio of 1:20.

Statistical analysis

The Kruskal-Wallis analysis of variance was used to test for differences among groups. Tests for differences between proportions were done using the χ^2 method with Yate's correction unless an expected cell frequency was < 5 . In these instances, Fisher's exact test was used. Spearman's ranking method was used for all correlation analyses.

RESULTS

A total of 53 patients met the criteria for study admission. There was no statistically significant difference between groups in regard to age, sex, weight, duration of diarrhea before treatment, pretreatment antibiotics, or number of stools in the 24 hr prior to study entry (Table 1) ($P > 0.05$ for all comparisons). All patients were moderately-to-severely ill with a mean number of stools of 18.9, 17.1, and 15.9 stools for the 24 hr prior to study admission for the placebo, trimethoprim-1, and trimethoprim-5 groups, respectively. Orthostatic changes were evident in 88.7% of patients, fever in 41.5%, fecal leukocytes were 3+ or 4+ in 94.2%, and visible blood was seen

in the stools of 98.2%. There were no statistically significant differences in these variables between groups or in the mean number of *Shigella* per gram of stool (Table 2).

There were 29 exclusions. Twenty patients were excluded because their stool culture did not grow *Shigella*; three patients had a *Shigella* isolate resistant to trimethoprim; two patients were pregnant; two patients would not enter the hospital; one patient was not admitted because the hospital was full; and one patient left the hospital to be seen by a tribal healer and did not return.

All *Shigella* isolates, by study criteria, were sensitive to trimethoprim. Thirty-four of 54 (62.9%) isolates (one study admission was infected with two *Shigella* serotypes) were resistant to sulfamethoxazole (MIC > 100 $\mu\text{g/ml}$), and 25 of 54 (46.3%) were resistant by disc diffusion (disc concentration = 300 μg). Synergy between trimethoprim and sulfamethoxazole was noted in all 20 *Shigella* strains that were sensitive to sulfamethoxazole by both MIC and disc diffusion, and in the 9 isolates with MIC > 100 $\mu\text{g/ml}$ but sensitive by disc diffusion. None of the 25 isolates resistant by both MIC and disc diffusion methods exhibited synergy.

Direct fecal smears and MIFs were negative for *G. lamblia* and *E. histolytica* trophozoites in all of the 52 specimens examined. In one patient in the trimethoprim-5 group and one patient in the trimethoprim-1 group an *E. coli* was isolated that produced heat stable (ST) enterotoxin. Although these patients had the longest and third longest time to last loose stool, both had clinical responses by 24 hr. Both heat stable-positive *E. coli* isolates were trimethoprim-sensitive by disc diffusion. No other enteric pathogens were isolated.

During the first 24 hr of therapy, 18/21 (86%) of the patients in the trimethoprim-5 group and 13/15 (87%) of the patients in the trimethoprim-1 group had a reduction in the number of stools relative to the 24 hr prior to therapy. Fewer patients in the placebo group (7/17) (41%) showed a reduction ($F < 0.011$ for both comparisons). The mean reduction in stool numbers during this period was 4.9 (± 6.6) for the trimethoprim-5 group and 6.3 (± 6.3) for the trimethoprim-1 group. In the placebo group, there was a mean increase in stool numbers of 2.4 (± 14.8) ($P = 0.036$ for trimethoprim-1 vs. placebo, $P = 0.055$ for trimethoprim-5 vs. placebo).

During the first 24 hr of therapy, there were

TABLE 1

Characteristics of 53 patients with shigellosis receiving placebo, trimethoprim single-dose, or trimethoprim five-day regimen*

Patient characteristics	Placebo (n = 17)	Trimethoprim	
		Single dose (n = 15)	Five day (n = 21)
Mean ($\pm$ SD) age in years	3.2 (17.2)	36.5 (18.5)	33.2 (16)
Male:female ratio	1.0	2.0	0.9
Mean ($\pm$ SD) weight in kg	49.0 (13.9)	52.1 (9.1)	48.0 (13.5)
Mean ($\pm$ SD) duration of diarrhea before treatment, days	2.5 (1.4)	3.1 (2.3)	2.6 (1.4)
Mean ($\pm$ SD) No. of stools in 24 hr before therapy	18.9 (8.4)	17.1 (8.1)	15.9 (8.7)
Percent self-treated with antibiotics prior to admission	82.4	60.0	85.7

* No significant differences between groups ($P > 0.05$ for all comparisons).

10.6 (± 6.9), 10.8 (± 8.7), and 21.3 (± 13) stools passed in the trimethoprim-5, trimethoprim-1, and placebo groups, respectively ($P = 0.009$ for trimethoprim-5 vs. placebo, $P = 0.006$ for trimethoprim-1 vs. placebo). During the second 24 hr both treatment groups continued to show a reduction in number of stools passed compared with the placebo group (Table 3).

After 48 hr of therapy, 14/21 (66.7%), 10/15 (66.7%), and 4/17 (23.5%) in the trimethoprim-5, trimethoprim-1, and placebo groups, respectively, had shown a clinical response ($P = 0.020$ for trimethoprim-5 vs. placebo, $P = 0.036$ for trimethoprim-1 vs. placebo). Of the 4 patients in the placebo group who responded, 3 had quantitative *Shigella* counts of $< 10^3$ /g of stool. Conversely, 4/7 nonresponders in the trimethoprim-5 group and all nonresponders in the trimethoprim-1 group had *Shigella* counts $> 10^5$ /g of stool.

In the placebo group, 12/17 patients had the code broken at 48 hr and were treated with trimethoprim. This represents a 70% failure rate in the placebo group. In the trimethoprim-1 group the code was broken for 2/15 patients and in the trimethoprim-5 group in 2/21 patients, representing failure rates of 13% and 9%, respectively.

There were no significant differences between the trimethoprim-5 and trimethoprim-1 patients for any of the outcome variables, which included clinical response at 24 and 48 hr, number of stools or reduction in number of stools at 24 and 48 hr, time to last loose stool, or likelihood of a positive follow-up stool culture at 5 days after beginning treatment with trimethoprim.

The presence of fever prior to study entry was not associated with any outcome variable, whereas patients with orthostatic changes took longer to last loose stool in both treatment groups ($P = 0.05$, Spearman's rank).

The mean quantitative counts of *Shigella*/g of stool were 8.9×10^4 , 4.8×10^5 , and 6.1×10^4 , respectively, for the placebo, trimethoprim-1, and trimethoprim-5 groups ($P > 0.25$). High log counts of *Shigella*/g of stool were associated with a decreasing likelihood of a positive clinical response at 48 hr ($P < 0.05$, Spearman's correlation) in the trimethoprim-1 and trimethoprim-5 groups. Among placebo patients, high *Shigella* counts were associated with a longer duration of illness before presentation, high numbers of stools passed in the 24 hr prior to study entry, and a poor clinical response at 24 hr ($P < 0.05$; Spearman's correlation).

TABLE 2

Comparison of severity of illness at admission for three shigellosis treatment groups*

Number (percent) with clinical signs and symptoms	Placebo (n = 17)	Trimethoprim	
		Single dose (n = 15)	Five day (n = 21)
Orthostatic changes	15 (88.2)	13 (86.7)	19 (90.5)
Fever	7 (41.2)	6 (40.0)	8 (38.1)
Fecal leukocytes (> 10 /field)	15 (93.8)†	13 (92.9)†	21 (100.0)
Visible blood in stools	17 (100.0)	14 (93.3)	21 (100.0)
<i>Shigella</i> /g of stool (mean)	8.9×10^4	4.8×10^5	6.1×10^4

* No significant differences between groups ($P > 0.05$ for all comparisons).

† One missing observation.

TABLE 3
Comparison of clinical responses in three shigellosis treatment groups

Outcome variables	Placebo (n = 17)	Trimethoprim		P of difference vs. placebo	
		Single dose (n = 15)	Five day (n = 21)	Single dose	Five day
No. (%) of treatment failures*	12 (70)	2 (13)	2 (9)	<0.005	<0.001
No. (%) of patients with a reduction in stools at:					
24 hr	7 (41.2)	13 (86.7)	18 (85.7)	0.022	0.011
48 hr	10 (58.8)	14 (93.3)	20 (95.2)	0.030	0.009
Mean ($\pm$ SD) No. of stools after beginning therapy:					
0-24 hr	21.3 (13.0)	10.8 (8.7)	10.6 (6.9)	0.006	0.009
25-48 hr	15.6 (13.0)	6.0 (4.9)	6.0 (7.1)	0.017	0.007
Mean reduction ($\pm$ SD) in No. of stools during first 24 hr of treatment†	-2.4 (14.8)	6.3 (6.3)	4.9 (6.6)	0.036	0.055
No. (%) of patients with a positive clinical response at 48 hr	4 (23.5)	10 (66.7)	14 (66.7)	0.036	0.020

* Code broken at 48 hr.

† (n stools in 24 hr prior to treatment) (n stools in first 24 hr of treatment).

Prior to study entry, 77% of patients took antibiotics. Only 1 patient was self-treated with an antibiotic to which the subsequent *Shigella* isolate was susceptible. There was no significant difference between groups in the proportion of patients self-administering antibiotics ($P > 0.09$).

Follow-up cultures at 5 days after beginning therapy revealed a bacteriologic cure in 13/14 (92.9%) patients in the trimethoprim-1 group. In the one subject with a positive follow-up culture, the initial and follow-up isolates were sensitive to trimethoprim. In the trimethoprim-5 group, there were 14 negative follow-up examinations; in 4 cases a follow-up stool was not available. There were 3 bacteriologic failures at 5 days. Persistence of *Shigella* in the placebo group could only be evaluated in the 5 cases in which the code was not broken; 2/5 had positive cultures at 5 days. Relapses, defined as a recurrence of symptoms or diarrhea, occurred in 3/21 (14.3%) of the trimethoprim-5 and 0/15 (0%) of the trimethoprim-1 ($P = 0.18$). The relapses were of <24 hr duration and did not require retreatment in 2 of the 3 cases. There were no preliminary or outcome variables associated with likelihood of relapse in treated patients.

Side effects were minimal in all three groups. In the trimethoprim-5 group, 6 patients had symptoms felt to be related to therapy; 4 with headache, 1 with abdominal cramps, and 1 with dizziness. In the trimethoprim-1 group, there was 1 patient in whom headache may have been re-

lated to therapy. In the placebo group, there were 3 patients with headache, and 1 with nausea and malaise attributed to treatment.

DISCUSSION

Shigellosis remains one of the most common causes of diarrhea in the world today. It has been estimated that approximately 20% of patients with diarrhea worldwide who are admitted to a hospital have shigellosis.³⁰ An inexpensive, easily administered therapeutic regimen of low toxicity would be advantageous for the treatment of shigellosis. A single-dose regimen is less expensive than the standard 5 days of therapy and is easily administered with the ability to ensure essentially complete compliance. Studies of single-dose therapy for urinary tract infections also have revealed a decrease in toxicity as well as a decrease in the level of induced bacterial resistance when compared to conventional 7- to 10-day regimens.^{1, 2, 4}

Previous studies of tetracycline have revealed that a 2.5 g single dose is effective in the treatment of shigellosis.^{5, 6} However, this regimen may be associated with a significant amount of nausea and vomiting. Furthermore, many strains of *Shigella* are currently resistant to tetracycline (98% in the present study). Ampicillin has been shown to be clinically effective as a single dose (100 mg/kg) in the treatment of shigellosis, but a high incidence of bacteriologic failures has been noted

in both children and adults.⁷ This is epidemiologically important as it allows continued spread of the disease. In addition, the high level of resistance to ampicillin (87% in the present study) makes this drug a poor choice for single-dose therapy.

Single-dose trimethoprim has not been adequately evaluated in the treatment of shigellosis. Consequently, we chose to conduct a randomized double-blind placebo controlled trial of trimethoprim. Trimethoprim was evaluated rather than trimethoprim-sulfamethoxazole, because an epidemiologic survey of this area in 1983 showed 81% of the *Shigella* strains were resistant to sulfamethoxazole, with no evidence of synergy with trimethoprim in the resistant strains. This lack of synergy between trimethoprim and sulfamethoxazole when the organism is highly resistant to sulfamethoxazole has been found by other studies^{11, 13, 14, 31} and was reconfirmed in the present study; no synergy was noted in 25/25 *Shigella* strains resistant to sulfamethoxazole by both disc diffusion and agar dilution methods. In addition, a number of studies have revealed decreased toxicity with trimethoprim as compared to the combination of trimethoprim-sulfamethoxazole.^{32, 33}

This study demonstrated that a single dose of trimethoprim is as effective as a standard 5-day course of trimethoprim in the treatment of shigellosis and that both regimens were superior to placebo. Both treatment regimens were superior to placebo in decreasing the number of stools passed in the first and second 24 hr after the institution of therapy, and in the number of clinical responses obtained at 48 hr (Table 3). In the placebo group the code was broken at 48 hr because of a lack of response in 70% of the patients, while in the two treatment groups the code was broken in only 11%. Comparing the trimethoprim-5 and trimethoprim-1 groups, there were no significant differences for any of the outcome variables (Table 3).

The common use of nonprescription antibiotics in Mogadishu was a concern as a possible source of bias in our results. In this study, 77% of the patients took antibiotics prior to study entry; however, there was no difference among study groups. Capsules of the commonly available antibiotics were shown to the patients and 43% identified tetracycline as the antibiotic they had taken. Most pretreated patients had taken only 2 or 3 capsules prior to study entry. One patient in the trimethoprim-5 group had taken 3 tablets of a sulfa drug the preceding day and

had a *Shigella* cultured from his stool sensitive to sulfamethoxazole. This was the only patient who took an antibiotic prior to study entry to which the causative agent of his diarrhea was susceptible. Trimethoprim alone is not available, and trimethoprim-sulfamethoxazole is rarely used because it is 4-5 times more expensive than ampicillin, sulfa drugs, chloramphenicol, or tetracycline. The determination of quantitative *Shigella* counts was helpful in explaining some of the clinical inconsistencies: placebo responders and trimethoprim treatment failures. In the placebo group, 75% of those who had clinical responses had very low *Shigella* counts in their stools ($< 10^3$ *Shigella*/g of stool). These patients may have had either mild infections or were in the process of spontaneously clearing their infections. In contrast, 75% of the nonresponders in the trimethoprim treatment groups had *Shigella* counts $> 10^5$ /g of stool.

In the present study, only 3 of 57 (5%) *Shigella* isolates were resistant to trimethoprim. However, we suspect, as with other antibiotics, that resistance to trimethoprim will develop as already has been documented in many areas of the world.³⁴ Ongoing monitoring of *Shigella* sensitivities should be conducted.

We conclude that a single dose of trimethoprim is as effective as a standard 5-day course of trimethoprim in the treatment of shigellosis, and that both regimens are superior to placebo. In areas of the world where the resistance of *Shigella* strains to sulfamethoxazole is high and only minimal synergy between trimethoprim and sulfamethoxazole can be expected, a single dose of trimethoprim would provide an inexpensive, minimally toxic, easily administered therapeutic regimen with virtually complete compliance for the treatment of shigellosis.

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