# Treatment of Salmonella enteritis and its effect on the carrier state

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*Summary: During an outbreak of Salmonella enteritis, 113 symptomatic and asymptomatic patients were assigned to different treatment groups: 43 received ampicillin; 41 were given trimethoprim-sulfamethoxazole; and 29 received no specific therapy. During the four-week observation period no statistically significant benefit from treatment with either ampicillin or trimethoprim-sulfamethoxazole was apparent in relation to duration and severity of symptoms or duration of the carrier state. However, the impression that trimethoprim-sulfamethoxazole might have shortened the period of fecal Salmonella excretion in the few asymptomatic patients may warrant further controlled studies.*

*There was no significant alteration in hematological or biochemical values, or urine constituents, in patients receiving trimethoprim-sulfamethoxazole. Side effects probably attributable to this drug developed in only 5% of the 41 patients.*

*It is concluded that uncomplicated salmonellosis is best treated without using currently available chemotherapeutic agents.*

Infection by Salmonella serotypes other than *S. typhosa* usually produces only a brief clinical illness with few sequelae other than continued fecal excretion of the organism after apparent recovery from the illness. During this period, which may last many months,[1] infected patients are a potential source of spread of infection, especially in enclosed environments. Since treatment of carriers with commonly used antibiotics whose *in vitro* antibacterial spectrum includes the Salmonella genus is usually unrewarding, an agent capable of eradicating the carrier state would be of immense value in limiting the spread of Salmonella infection.

An antimicrobial preparation containing trimethoprim and sulfamethoxazole became available recently for clinical trial in Canada. This was supplied as Septrin by Burroughs Wellcome & Co. (Canada) Ltd.; each tablet contains 80 mg. trimethoprim and 400 mg. sulfamethoxazole. These agents act synergistically by blocking sequential steps in the folate metabolism of susceptible bacteria.[2] Trimethoprim-sulfamethoxazole has been used successfully in the treatment of genitourinary and bronchopulmonary* infections caused by various organisms, brucellosis,[4] and gram-negative septicemia unresponsive to previous treatment with appropriate antibiotics (for references, see*). Preliminary studies from Nigeria[5] and Uganda[6] reported its success in the treatment of typhoid fever, and a recent extensive trial of the combined drugs in treatment of patients whose blood clot cultures were positive for *S. typhosa* revealed that trimethoprim-sulfamethoxazole was much superior to chloramphenicol in the rapidity and uniformity of relief of toxicity. The *in vitro* activity of this combination against other members of the Salmonella genus suggested that salmonellosis also should respond to treatment with trimethoprim-sulfamethoxazole,[8] and a recent outbreak of this infection provided an opportunity to compare the efficacy of Septrin and other forms of therapy.

## Materials and methods

An outbreak of uncomplicated Salmonella enteritis at the Victoria General Hospital, Halifax, involved nearly 200 people—mainly student nurses, dietary workers and inpatients. *Salmonella typhimurium* (var. Copenhagen, phage type 49) was the responsible organism in over 90% of the patients studied and was traced to its source in contaminated poultry. *S. saint-paul* was recovered from the stools in nine cases and *S. blockley* in three.

Many persons infected early in the outbreak had been treated with ampicillin by their physicians. When the extent of the outbreak was recognized, subsequent patients, including 33 who were asymptomatic, were allocated to a group which received one tablet of Septrin three times a day for seven days or to a group to which no specific treatment was given. No patient with a history of allergy to sulfonamides was given Septrin. No patient was admitted to the study who was known to have malignant disease, pre-existing gastrointestinal disturbance, or any immunological disorder, who was receiving other antibiotic or corticosteroid medication, or who

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*For references, see: Proceedings of a Conference on The Synergy of Trimethoprim and Sulphonamides, London May 9, 1969: *Postgrad Med J* 45 (suppl), Nov. 1969. Genitourinary infections: pp. 56-61, 61-64, 65-71, 71-75, 77-80, 81-83. Bronchopulmonary infections: pp. 86-88, 89-90, 91-94. Gram-negative septicemia; p. 53.

was unlikely to be available for the first four weeks after entry to the trial. Patients who were being treated with ampicillin and who fulfilled the criteria were included: they received at least 2 g. ampicillin daily for five to 28 days as prescribed by their own physicians.

Of the 113 patients studied, 43 received ampicillin, 41 trimethoprim-sulfamethoxazole, and 29 no specific therapy. The majority (81) were female; ages ranged from 16 to 71 years (mean: 28.5 years). Following the initial positive stool culture, the majority of the patients provided two stool specimens weekly for four weeks or until three consecutive cultures were negative.

Since Septrin had only recently been approved for clinical trial in Canada, patients in this group had the following investigations performed the day after its completion: urinalysis, leukocyte count, packed-cell volume, blood urea nitrogen, serum bilirubin, alkaline phosphatase and SGOT. Biochemical estimations were performed with a Technicon SMA 12/60 AutoAnalyzer.

## Results

The numbers and percentages of patients with positive stool cultures at the end of each week after Salmonellae had been identified in stool cultures are listed in Table I.

In relation to the total number of patients, percentages of positive stool cultures in those receiving specific therapy (Fig. 1) declined in linear fashion (the slopes of the curves for patients receiving ampicillin and trimethoprim-sulfamethoxazole were $-0.145 \pm 0.034$ and $-0.154 \pm 0.034$ respectively). In untreated patients a similar linear decline occurred during the first two weeks and a more abrupt fall in the third and fourth weeks (the slope of the four-week curve was $-0.281 \pm 0.042$). Intergroup differences at each of the four weeks were not statistically significant ($P > 0.05$), although logit transformation [9] of the proportions shows that interaction between type of treatment and time is significant ($P < 0.025$). A basically similar pattern was observed in symptomatic patients, whose infection was characterized by fever, diarrhea or abdominal cramps (Fig. 2). Since only six asymptomatic patients received no specific therapy, the apparent benefit derived from treatment with trimethoprim-sulfamethoxazole (Fig. 3) cannot be shown to be statistically significant.

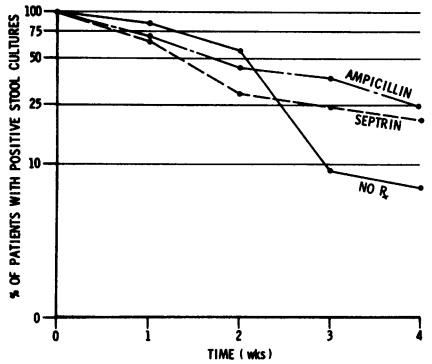


FIG. 1—All patients. Ampicillin, 2 g. daily for five to 28 days; Septrin (trimethoprim, 80 mg., and sulfamethoxazole, 400 mg.) tab. 1, three times a day for seven days: No Rx = no specific therapy.

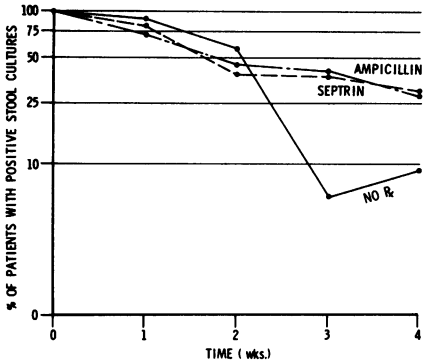


FIG. 2—Symptomatic patients (80). The apparent increase at four weeks in "untreated" patients with positive stool cultures is due to the inclusion of one patient whose stools had not been cultured in the preceding two weeks (Table I).

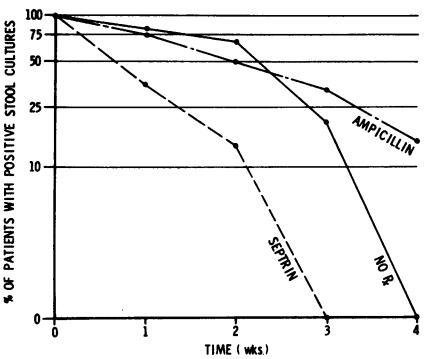


FIG. 3—Asymptomatic patients (33).

Mean values of laboratory investigations before and after treatment with trimethoprim-sulfamethoxazole are shown in Table II. In only one patient with initially normal packed-cell volume (39.5%) did the value fall below normal during treatment (to 36%). Leukopenia was not observed. SGOT values were elevated in three patients before therapy; they increased in two (57 to 87, and 60 to 88 I.U. per ml.) and decreased in one (64 to 50 I.U.). In one other patient whose pre-treatment SGOT value was 35 units per ml., this increased to 70 I.U. In two patients the serum bilirubin level rose from 0.3 and 0.8 to 1.0 and 1.2 mg. per 100 ml. respectively, and in one it remained constant at 1.4 mg. per 100 ml. In no patient with normal initial values of blood urea nitrogen or serum alkaline phosphatase was the post-treatment value above the normal limit. Urinalysis after treatment showed neither urinary casts nor significant degrees of albuminuria.

Of the 41 patients treated with trimethoprim-sulfamethoxazole, one had a pruritic rash during treatment, and one a Candida infection after completion of the seven-day course—an incidence of 4.9% adverse reac-

**TABLE I**
**Results of stool cultures in the different treatment groups**

| *Treatment group* | *Patients* | *Weeks after first positive stool culture* 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| No specific therapy (29 patients) | Asymptomatic..... | 6 | 6 | 5 | 5 |
| | with positive stools..... | 5 (83%) | 4 (67%) | 1 (20%) | 0 |
| | Symptomatic..... | 23 | 17 | 17 | 22 |
| | with positive stools..... | 21 (91%) | 10 (59%) | 1 (6%) | 2 (9%) |
| Ampicillin (43 patients) | Asymptomatic..... | 13 | 12 | 12 | 13 |
| | with positive stools..... | 10 (76%) | 6 (50%) | 4 (33%) | 2 (15%) |
| | Symptomatic..... | 30 | 29 | 27 | 29 |
| | with positive stools..... | 21 (70%) | 13 (45%) | 11 (41%) | 8 (28%) |
| Trimethoprim and sulfamethoxazole (41 patients) | Asymptomatic..... | 14 | 14 | 13 | 14 |
| | with positive stools..... | 5 (36%) | 2 (14%) | 0 | 0 |
| | Symptomatic..... | 27 | 23 | 24 | 27 |
| | with positive stools..... | 22 (81%) | 9 (39%) | 9 (38%) | 8 (30%) |

TABLE II
**Hematological and biochemical values in 41 patients treated with trimethoprim-sulfamethoxazole**

| | Normal values | Mean values Before treatment | After treatment |
|---|---|---|---|
| Packed-cell volume..... | >37% | 40.9 (4)* | 40.4 (5) |
| Leukocytes..... | 5,000-10,000/c.mm. | 6700 (2) | 7000 (2) |
| SGOT..... | 10-50 I.U./ml. | 33 (3) | 38 (3) |
| Serum bilirubin..... | 0.1-1.0 mg./100 ml. | 0.6 (2) | 0.6 (3) |
| Blood urea nitrogen..... | 10-20 mg./100 ml. | 15 (3) | 16 (3) |
| Serum alkaline phosphatase | 30-85 I.U./ml. | 51 (4) | 48 (3) |

*Figures in parentheses indicate number of patients with abnormal values.

tions probably due to the drug. Two other patients complained of nausea during treatment; since this is a common symptom in salmonellosis, its significance in these cases cannot be determined.

## Discussion

Persistent fecal excretion of salmonellae by asymptomatic subjects is a source of further spread of infection. Although it has long been recognized that "It is notoriously difficult to clear salmonella carriers by antibiotic treatment, . . . the idea still persists that when administered during the attack of enteritis itself an antibiotic discourages subsequent carriage of the organism."[10] Studies by Dixon[11] and Aserkoff and Bennett[12] demonstrated this proposition to be unfounded; they showed that the organisms persist longer in patients treated with the antibiotics most commonly used (ampicillin, chloramphenicol, neomycin and streptomycin) than in untreated patients. A further hazard of antibiotic therapy is the *in vivo* acquisition of antibiotic resistance by an infecting strain which initially was susceptible to multiple antibiotics,[12] which allows dissemination of resistant organisms.

Ampicillin, in the dosages used in the present study, did not result in a significantly decreased proportion of patients with positive stool cultures during any of the first four weeks of treatment and, therefore, was of no value in limiting the duration of the carrier state in either symptomatic or asymptomatic patients—a conclusion similar to that of Aserkoff and Bennett.[12] Treatment with trimethoprim-sulfamethoxazole similarly showed no statistical advantage over purely supportive therapy. (Its effect on organism resistance was not determined.) However, on the basis of the small number of asymptomatic patients studied, the impression that trimethoprim-sulfamethoxazole was of some benefit in reducing the length of fecal carriage of salmonellae in such patients may warrant further controlled studies. One formerly persistent carrier of *S. saint-paul* was described recently[3] whose stool cultures, positive for 25 years, became negative after he received two Septrin tablets daily for five weeks.

Neither duration nor severity of symptoms was apparently influenced by specific therapy.

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## Résumé

### *Le traitement de l'entérite à Salmonella et son effet sur l'état de porteur de germes*

Au cours d'une épidémie d'entérite à Salmonella, nous avons réparti 113 malades, symptomatiques et asymptomatiques, entre divers groupes différents au point de vue médication: 43 ont reçu de l'ampicilline, 41 triméthoprim-sulfaméthoxazole) et 29 furent laissés sans traitement spécifique. Durant la période d'observation de quatre semaines, nous n'avons pas noté que le traitement (ampicilline ou triméthoprim-sulfaméthoxazole) ait eu une action notable sur le plan statistique, au point de vue durée et sévérité des symptômes, ou sur la durée de l'état de porteur de germes. Cependant, l'impression que le trimethoprim-sulfaméthoxazole a pu abréger la période d'excrétion fécale de Salmonella chez les quelques malades asymptomatiques pourrait justifier une étude plus approfondie du médicament.

Chez les malades recevant le triméthoprim-sulfaméthoxazole, il n'existant aucune modification sensible des paramètres hématologiques ou biochimiques, ni des analyses d'urine. Des réactions secondaires, probablement attribuables à ce triméthoprim-sulfaméthoxazole, ne se sont manifestées que chez 5% des 41 cas.

Nous croyons donc pouvoir conclure qu'il est préférable de ne pas traiter les cas de salmonellose non compliquée par les agents chemothérapeutiques actuellement sur le marché.

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*Serratia marcescens*
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