

Failure of Ciprofloxacin to Eradicate Convalescent Fecal Excretion after Acute Salmonellosis: Experience during an Outbreak in Health Care Workers

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Objective: To determine the efficacy of ciprofloxacin therapy in eradicating convalescent fecal excretion of salmonellae after acute salmonellosis.

Design: Randomized, placebo-controlled, double-blind trial of ciprofloxacin, with prospective follow-up of nonparticipants.

Setting: An acute care community hospital experiencing an outbreak of salmonellosis.

Patients: Twenty-eight health care workers developed acute infection with *Salmonella java*; 15 participated in a placebo-controlled trial of ciprofloxacin, beginning on day 9 after infection.

Interventions: Eight patients were randomly assigned to receive ciprofloxacin, 750 mg, and 7 patients to receive placebo; both were administered orally twice daily for 14 days. Nonparticipants who received therapy were placed on the same ciprofloxacin regimen.

Measurements and Main Results: Study participants had follow-up stool cultures every 3 days initially and then weekly for 3 weeks; nonparticipants were followed until three consecutive cultures were negative. All eight ciprofloxacin recipients showed eradication of *S. java* from stool cultures within 7 days of beginning therapy (compared with 1 of 7 placebo recipients), and their stool cultures remained negative up to 14 days after discontinuing therapy ($P < 0.01$). However, 4 of 8 relapsed; their stool cultures became positive between 14 and 21 days after therapy. In addition, 3 of 3 hospitalized patients treated with ciprofloxacin who did not participate in the controlled trial also relapsed. Thus, the total relapse rate was 7 of 11 (64%; 95% CI, 31% to 89%). In 4 of these 7 patients, relapse was associated with a longer duration of fecal excretion of salmonellae than that of the placebo group. Relapse could not be explained on the basis of noncompliance, development of resistance, or presence of biliary disease.

Conclusions: Despite its excellent antimicrobial activity against salmonellae and its favorable pharmacokinetic profile, ciprofloxacin at a dosage of 750 mg orally twice daily had an unacceptably high failure rate in patients with acute salmonellosis and may have prolonged fecal excretion of salmonellae. The late occurrence of relapses indicates the need to obtain stool cultures up to 21 days after therapy to document fecal eradication in acute salmonellosis.

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Enteric infection with nontyphoidal salmonellae is an increasing problem in the United States (1), especially in the Northeast (2). Acute salmonellosis accounts for 20 000 hospitalizations and 500 deaths annually, resulting in annual health care costs estimated at \$50 billion for the United States alone (1). Lost wages and decreased productivity because of absenteeism due to illness may push the total cost even higher.

After acute infection, convalescent fecal excretion of nontyphoidal salmonellae may last several weeks (3). This poses a special problem for infected food handlers and health care workers who, under current regulations, are excluded from work while their stool cultures are positive for salmonellae in order to prevent secondary transmission (4). The exclusion of infected health care workers from patient care activities has resulted in major disruptions in hospital services and short-term nursing shortages, thereby compounding the acute effects of hospital outbreaks (5, 6).

Acute salmonellosis in otherwise healthy persons usually takes the form of a self-limited enterocolitis not requiring specific therapy. The current practice of withholding antibiotics in otherwise healthy persons with salmonellosis is based on evidence that intestinal carriage lasts longer in persons receiving antimicrobial agents than in those not treated. In two studies, treatment with ampicillin and chloramphenicol prolonged the fecal excretion of salmonellae (7, 8); however, patients were not randomly assigned to treatment regimens, and these studies were retrospective.

The need for more effective antimicrobial therapy for salmonellosis has been highlighted by the dramatic increase in the number of cases in the United States (9) and by the therapeutic difficulties posed by multi-resistant strains (10). The fluoroquinolones are a new class of antimicrobial agents with excellent in-vitro activity against salmonellae (11). Ciprofloxacin is a currently licensed fluoroquinolone with several potential advantages for treating salmonellosis: First, extremely high drug levels are achieved within the gastrointestinal lumen after oral administration; second, the minimal inhibitory concentration of ciprofloxacin for most salmonellae is extremely low ($< 0.1 \mu\text{g/mL}$); third, ciprofloxacin penetrates intracellularly, which may be important for eradicating intracellular pathogens such as salmonellae (12). In addition, the drug is concentrated in the biliary tract, a known site of persistent infection during chronic carriage of salmonellae. Previous studies have suggested that oral ciprofloxacin is effective therapy for acute diarrhea, including that due to salmonellae (13-

15), and that the drug also could be used to eradicate the chronic carrier state of *Salmonella typhi* (16).

A large outbreak of salmonellosis afforded the opportunity to evaluate ciprofloxacin therapy for eradicating convalescent excretion. The outbreak setting enabled us to study many infected persons who were otherwise healthy; whose date of infection was known; and whose motivation, compliance, and completion rate for the study were likely to be excellent. We describe our experience using ciprofloxacin as therapy for salmonellosis during an outbreak among health care workers.

Patients and Methods

Location

The outbreak occurred in an acute care community hospital of 340 beds in Rhode Island with both internal medicine and family practice housestaff. The hospital has an obstetrics unit and a newborn nursery, an active oncology service, a clinic for persons with human immunodeficiency virus (HIV) infection, and a large geriatric population.

Case-Finding

On 26 October 1988, a noon teaching conference was held at the hospital; on the following day, several conference attendees reported to the employee health nurse that they had developed vomiting and diarrhea within 24 hours of the luncheon meeting. In the subsequent investigation, a case was defined as the acute onset of abdominal pain or diarrhea after attendance at the conference, with at least one of the following symptoms: fever, headache, nausea, or vomiting. A detailed epidemiologic questionnaire evaluating food consumption and clinical symptoms was administered to all 33 conference attendees.

Laboratory Investigation

Stool specimens were obtained from all affected persons and were cultured on blood, eosin-methylene-blue, and xylose-lysine-deoxycholate agar plates within 24 hours of submission. *Salmonella* species were identified by standard biochemical techniques. Serotyping and biotyping of the outbreak strain was done by the Rhode Island Department of Health and confirmed by the Enteric Diseases Laboratory at the Centers for Disease Control. Antimicrobial sensitivities of salmonella isolates were assessed by disk-diffusion susceptibility testing using the method of Kirby-Bauer; minimum inhibitory concentrations were determined by the tube-dilution method. Attempts to isolate plasmid DNA were made using two methods (17, 18).

Study Design

A protocol describing a randomized, double-blind, placebo-controlled trial of ciprofloxacin was evaluated by the institutional review board within 24 hours by special request and approved. Written informed consent was obtained from all participants. Pregnant women and persons receiving previous antimicrobial therapy were excluded from the study. Participants were randomly assigned to receive either oral ciprofloxacin (Miles Pharmaceuticals Inc., West Haven, Connecticut), 750 mg, or oral placebo (supplied by Miles Pharmaceuticals), twice daily for 14 days. Stool cultures were done at entry into the study and every 72 hours during the 14 days of the trial. Stool specimens were then obtained at 7, 14, and 21 days after the completion of drug therapy. Patients were considered culture negative and allowed to return to work when salmonella was not isolated from three consecutive stool specimens obtained 24 hours apart. Intermittent excretion was considered as culture positive until three consecutive cultures were negative. Both the participants and the investigators were blinded to the medications received. A questionnaire was administered at entry and completion to ascertain epidemiologic data, presence of

underlying diseases, concomitant medications, compliance, and adverse reactions.

Statistical Methods

The two-tailed Fisher exact test was used to test differences in food consumption and in clinical characteristics of ciprofloxacin and placebo recipients. The Student *t*-test was used for determining the significance of differences between means. The Wilcoxon rank-sum test was used for determining the significance of differences between the placebo and ciprofloxacin treatment curves up to day 35. Significance was defined as $P < 0.05$. A 95% confidence interval (CI) is given when appropriate.

Results

Epidemiologic Investigation

Of the 33 conference attendees, 28 met the case criteria. Within 4 days of the luncheon, 27 persons had become acutely ill (median incubation period, 10 hours [range, 7 to 84 hours]); one person receiving trimethoprim-sulfamethoxazole for an antecedent urinary tract infection became ill after 21 days. Illness was strongly associated with eating lasagna ($P < 0.01$; relative risk, 11.4), and the attack rate for persons who ate lasagna was 100% (28 of 28). Consumption of salad or canned soda was also associated with illness ($P < 0.05$, relative risk, 2.2; $P < 0.01$, relative risk, 0.08, respectively). The food served at the conference had been purchased at a local restaurant and brought to the hospital immediately before the luncheon.

Four persons were hospitalized because of dehydration due to severe diarrhea and vomiting. There was one case of secondary transmission, probably due to person-to-person spread. Within 24 hours of recognition of the outbreak, all employees who had attended the luncheon were removed from work except for two house officers who were not ill at the time. An 89-year-old woman was admitted because of an acute cerebrovascular accident, and 35 days after admission she developed a nosocomial urinary tract infection with *S. java*, the outbreak strain. She had been admitted and examined by an exposed but well house officer who subsequently developed *S. java* infection. During her hospitalization, the patient never had fever or diarrhea, nor was a Foley catheter inserted. Two urine cultures done after admission were negative for salmonellae. The patient had not consumed any food from outside the hospital. Because *S. java* is such a rarely encountered serotype, it seems likely that the patient acquired the infection from the infected house officer. No apparent secondary cases occurred among household members of any affected persons.

Laboratory Studies

The infecting organism was identified as *S. paratyphi* B, bioser *java*, and was isolated from stool specimens from the 28 persons meeting the case criteria. All initial stool cultures showed a virtually pure growth of *S. java* with only scant growth of normal enteric flora. The outbreak strain was sensitive to all antibiotics tested, including ampicillin, chloramphenicol, third-generation cephalosporins (cefotaxime, ceftriaxone), trimethoprim-

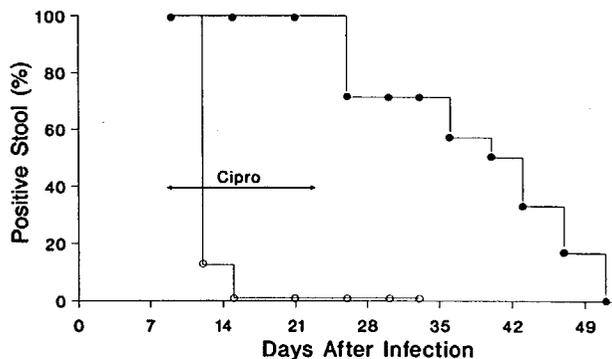


Figure 1. Percentage of study participants with stool cultures positive for *S. java* by days after infection. (○ = ciprofloxacin recipients; ● = placebo recipients; ↔ = duration and timing of ciprofloxacin therapy.)

sulfamethoxazole, and aminoglycosides (gentamicin, tobramycin). The minimum inhibitory concentration for ciprofloxacin was 0.05 $\mu\text{g}/\text{mL}$. All *S. java* isolates tested were serum-resistant. No plasmid DNA was detected despite several attempts at isolation.

Ciprofloxacin Trial

Fifteen persons participated in the study, which began on day 9 after onset of illness. Eight persons were randomly assigned to receive ciprofloxacin, 750 mg, and 7 persons to receive placebo; both drug and placebo were administered orally twice daily for 14 days. Results of the controlled study are shown in Figure 1. All participants had positive stool cultures at entry. Within 72 hours of beginning the trial, only 1 of 8 ciprofloxacin recipients had a stool culture positive for *S. java* compared with 7 of 7 placebo recipients. Within 7 days, all 8 ciprofloxacin recipients had stool cultures negative for *S. java* compared with 1 of 7 placebo recipients ($P < 0.005$). Stool cultures from the ciprofloxacin recipients remained negative for *S. java* during the remainder of the 14-day course. Stool cultures in 4 of 7 placebo recipients were positive at 5 weeks after infection. The treatment curve is significantly different from the placebo curve ($P < 0.01$, Wilcoxon rank-sum test).

Between 14 and 21 days after completing therapy, four of eight ciprofloxacin recipients had stool cultures positive for *S. java*. Relapse was not associated with clinical symptoms. The minimum inhibitory concentration for ciprofloxacin (0.05 $\mu\text{g}/\text{mL}$) was unchanged for the pretreatment and post-treatment isolates. Of the four ciprofloxacin recipients who relapsed after therapy, two stopped excreting *S. java* within 1 week and the other two had positive stool cultures for another 49 and 51 days, respectively. All persons who relapsed had an ultrasonographic examination of the gallbladder and none had cholelithiasis. Ciprofloxacin recipients who relapsed did so after a mean of two negative cultures; the 4 patients who did not relapse had a mean of 5 stool cultures obtained while not receiving antibiotics.

For placebo recipients, the mean duration of salmonella excretion was 38 days and the last placebo recipient to become culture negative did so 51 days after infection. Because of concern about the late relapses in

patients treated with ciprofloxacin, placebo recipients were asked to submit an additional specimen once *S. java* was no longer recovered from three stool cultures and all later cultures remained negative. Six placebo recipients remained in the group after day 40 because one patient withdrew from the study and took a 1-month course of ciprofloxacin.

Table 1 shows the clinical characteristics of the two study groups. There was no significant difference in the frequency of symptoms at entry into the study or in drugs used before the study between the ciprofloxacin and placebo recipients. The number of participants missing one dose was the same in both groups, and there was no significant difference in the number of doses missed. Side effects associated with ciprofloxacin therapy were minor; however, five of eight patients receiving ciprofloxacin noted a mild increase in diarrhea at the beginning of therapy but this did not require withdrawal of ciprofloxacin. No ciprofloxacin recipients reported central nervous system symptoms such as difficulty in concentrating or dizziness. There was no significant difference between the two groups for any of the characteristics listed in Table 1.

Results among Nonstudy Patients

Of the 13 persons who did not participate in the study, 4 received ciprofloxacin therapy. Three were hospitalized because of the severity of their illness and were treated with ciprofloxacin, 750 mg orally twice daily for 14 days, beginning on day 3 of illness. All 3 patients, between 7 and 14 days after completing therapy and after two negative cultures while not receiving antibiotic therapy, had a culture that was positive for *S. java*. In 1 patient, stool cultures remained positive for 35 days. In the other 2 patients, stool cultures were still positive 76 days after relapse. One person received a 1-month course of ciprofloxacin and all subsequent stool cultures remained negative. The patient, a woman with sickle trait, eventually had a cholecystectomy for persistent right upper quadrant pain with recurrent nausea and vomiting; stool cultures immediately before sur-

Table 1. Clinical Characteristics of Participants in a Randomized, Placebo-Controlled Trial of Ciprofloxacin for Treating Acute Salmonellosis

Characteristic	Ciprofloxacin Group (n = 8)	Placebo Group (n = 7)
Men, n(%)	6 (75)	2 (28)
Age, y	29 \pm 3.3*	30 \pm 3.2*
Incubation period, h	17.8 \pm 3.7*	11 \pm 3.7*
Symptoms at entry, n(%)		
Nausea	1 (12)	1 (14)
Diarrhea	2 (25)	2 (28)
Fatigue	6 (75)	5 (71)
Subjects missing one dose, n(%)	5 (63)	5 (71)
Doses missed, n	3 \pm 2*	1.4 \pm 0.5*
Side effects of study drug, n(%)		
Nausea	2 (25)	0
Vomiting	1 (12)	0
Diarrhea	5 (63)	1 (14)

* Mean \pm SD.

gery were positive. She received peri-operative ciprofloxacin; cultures of bile and gallbladder, as well as all subsequent stool cultures, were negative. Pathologic examination showed only mild chronic cholecystitis. One nonhospitalized person received a 5-day course of oral ciprofloxacin, 750 mg twice daily, beginning on day 7 after infection, and four follow-up stool cultures done between 2 to 35 days after therapy were negative for *S. java*.

Nine persons did not receive antimicrobial therapy. Two were men not employed by the hospital and for whom follow-up data are not available. The 7 remaining persons included 1 man and 6 women; one woman was 20 weeks pregnant at the time of infection. The mean age for these 7 persons was 38.7 years (range, 25 to 59 years). Their mean duration of salmonella excretion was 58 days (range, 18 to 84 days). The pregnant woman had follow-up stool cultures during the remainder of her pregnancy. Her stool culture immediately before delivery was negative, and specimens from the infant at birth were negative.

The hospital employees whose job descriptions included direct patient contact were excluded from work until three consecutive stool cultures done 24 hours apart were negative for salmonella. This posed substantial staffing problems for the residency program. The total direct cost related to the outbreak, including the cost of hospitalizations, lost wages, and all follow-up stool cultures was \$101 288. The cost per case for the 26 hospital employees was \$3896.

Discussion

Ciprofloxacin therapy in healthy hospital workers infected with *S. java* during a food-borne outbreak was associated with rapid elimination of the organism from stool but late bacteriologic relapse in 7 of 11 (64%; CI, 31% to 89%) patients who were treated. Relapses could not be explained by the development of resistance to ciprofloxacin or by noncompliance, and ultrasonographic examination showed no evidence of biliary tract disease in these persons. Although we did not measure serum or fecal drug levels, poor absorption or low drug levels within the gastrointestinal lumen would seem unlikely (19, 20). The mean serum level of ciprofloxacin after a 750-mg oral dose is 2 to 3 $\mu\text{g/mL}$ (12), which is over 40 times the minimum inhibitory concentration for the outbreak strain. Although relapse may have occurred because treatment was started somewhat later in the course of illness for the study participants receiving ciprofloxacin, the three hospitalized persons who were treated beginning on day 3 of illness also relapsed. Thus, these data indicate that the efficacy of ciprofloxacin in permanently eradicating salmonella infection may be limited and that follow-up cultures need to be obtained at least 3 weeks after completing therapy to adequately assess elimination of the organism.

The high relapse rate in our patients treated with ciprofloxacin could be due to their having received a large inoculum. Unfortunately, neither the lasagna nor its ingredients were available for subsequent culture to prove this hypothesis. The short incubation period (10 hours) and the nearly pure growth of *S. java* in all

patients' initial stool cultures suggest that the inoculum received was quite large. The incubation period for the four study participants who received ciprofloxacin and relapsed was 12.8 hours (range, 9 to 21 hours) compared with 22.8 hours (range, 8 to 39 hours) for those who did not relapse, but this difference is not statistically significant ($P > 0.05$). The incubation period for the placebo recipients was 11 hours (range, 7 to 18 hours). Another possible explanation for the high relapse rate may be that the duration of therapy (14 days) was too short. Another potential cause of the lack of permanent eradication would be if the infecting strain of *S. java* possessed particular virulence characteristics promoting persistence. The outbreak strain was serum-resistant, highly sensitive to antibiotics, and plasmidless, but these individual traits are not known to directly prolong convalescent excretion. Differences in follow-up may have led to preferential detection of relapse in patients treated with ciprofloxacin. This group had a 21-day follow-up period, at the beginning of which all patients were culture negative and during which stool culture positivity was not suppressed by antibiotic therapy. Placebo recipients (all of whom were still excreting *S. java* after completing their medication regimen) did not have a 21-day follow-up from the date of their first negative stool culture, and this may have caused us to miss late relapses in the placebo group. This is unlikely, however, because placebo recipients were asked to submit a fourth specimen once three consecutive negative stool cultures were obtained, and all additional specimens were negative. Of the seven patients treated with ciprofloxacin who relapsed, only one did so after three negative cultures while not receiving antibiotic therapy; the others relapsed after a mean of two negative cultures. In untreated patients with salmonellosis, three consecutive negative stool cultures have a predictive value of 95% for true eradication of the organism; for treated patients, the predictive value is considerably lower at 78% (3, 21).

Previous investigators have also noted relapses after ciprofloxacin therapy for acute salmonellosis. In a study of adult patients with acute diarrhea who were treated with ciprofloxacin, 500 mg orally twice daily for 5 days, stool cultures were negative in all 10 patients with salmonella within 48 hours of beginning therapy and remained negative for up to 3 weeks after therapy (13). However, in a later study, 16 adults with acute salmonellosis treated with the same dose had negative stool cultures while on therapy; however, 4 had bacteriologic relapse 1 to 3 weeks after completing therapy (15). In another study in which 9 patients with salmonellosis were treated, relapse occurred in 2 (22). The *Salmonella* species causing infection were not identified in these studies. Relapses in one study (15) could not be explained by the development of resistance, because all post-treatment isolates remained equally susceptible to ciprofloxacin.

In none of these previous studies (13-15) was the duration of salmonella excretion after relapse determined. In our study, four of the seven patients who relapsed after ciprofloxacin therapy had a longer duration of positive stool cultures than those not treated. At the time when the last placebo recipient became culture

negative, five of the seven treated patients who had relapsed were still positive and were thus unable to return to work. These data suggest that ciprofloxacin therapy may have prolonged fecal salmonella excretion; however, our observations on the natural history of relapse are limited by the secondary interventions (cholecystectomy and a second course of antibiotic therapy) in the two patients with the longest duration of salmonella excretion.

That a longer duration of therapy may be more effective can be inferred from a study in which 11 of 12 chronic carriers of *S. typhi* treated with ciprofloxacin, 500 mg orally twice daily for 28 days, were cured of infection (16). Two patients who chose to complete a 28-day course of ciprofloxacin, 750 mg twice daily, had negative stool cultures at follow-up up to 1 month after therapy. However, both patients began therapy during the late convalescent rather than the acute phase of infection. Although clinical studies have shown the efficacy of ciprofloxacin for treating patients with typhoid fever (22, 23) and the carrier state of *S. typhi* (16), this experience with *S. typhi* cannot necessarily be extrapolated to infection with the nontyphoidal salmonellae.

Ciprofloxacin has an excellent spectrum of activity against many of the organisms in the family *Enterobacteriaceae* and has been used successfully in treating travelers' diarrhea (14), acute diarrhea (15), and salmonella bacteremia in immunocompromised patients (24, 25). Salmonellosis occurs with an appreciable frequency in HIV-infected persons (26), a group for whom ciprofloxacin constitutes a logical therapeutic choice (27). However, the data from our study indicate that caution must be exercised in using ciprofloxacin as therapy for acute enterocolitis due to salmonella infection. The unacceptably high relapse rate and the possible prolongation of fecal excretion are markers of potential failure for our dosage regimen. The late occurrence of relapses in our study indicates that follow-up stool cultures should be done 3 or more weeks after completing therapy to evaluate the efficacy of therapy. The role of ciprofloxacin in treating acute salmonellosis, as well as the optimal dose of drug and duration of therapy, remain to be determined.

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