REVIEW 10.1111/j.1469-0691.2011.03552.x

Treatment of typhoid fever in the 21st century: promises and shortcomings

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Abstract

Emergence of multidrug resistance and decreased ciprofloxacin susceptibility (DCS) in *Salmonella enterica* serovar Typhi in South Asia have rendered older drugs, including ampicillin, chloramphenicol, trimethoprim–sulphamethoxazole, ciprofloxacin, and ofloxacin, ineffective or suboptimal for typhoid fever. Ideally, treatment should be safe and available for adults and children in shortened courses of 5 days, cause defervescence within 1 week, render blood and stool cultures sterile, and prevent relapse. In this review of 20 prospective clinical trials that enrolled more than 1600 culture-proven patients, azithromycin meets these criteria better than other drugs. Among fluoroquinolones, which are more effective than cephalosporins, gatifloxacin appears to be more effective than ciprofloxacin and ofloxacin for patients infected with bacteria showing DCS. Ceftriaxone continues to be useful as a back-up choice, and chloramphenicol, despite its toxicity for bone marrow and history of plasmid-mediated resistance, is making a comeback in developing countries that show their bacteria to be susceptible to it.

Keywords: Enteric fever, *Salmonella*, *Salmonella enterica*, serovar Paratyphi A, serovar Typhi, Typhi, typhoid fever

Article published online: 25 April 2011

Clin Microbiol Infect 2011; **17:** 959–963

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Introduction

Typhoid fever is an enteric bacterial infection caused by *Salmonella enterica* serovar Typhi or Paratyphi A. Most cases are caused by Typhi, which is usually written *S. Typhi*. It is transmitted by the faecal–oral route, and most of the world's estimated more than 2 million cases, which result in over 200 000 deaths every year, occur in southern Asian countries with poor sanitation and unclean water [1]. The majority of infections are in children [1]. In the USA, Europe, and other industrialized countries with clean water sources, typhoid fever is rare, but in 1 year, 1996–1997, in the USA there were 293 documented cases, of whom about 80% acquired their infections abroad [2].

Pathogenesis and Transmission

Alone among enteric pathogens, *S. Typhi* infects only humans, is ingested, crosses the intestinal epithelium without initially causing any injury or diarrhoea, and multiplies intracellularly in phagocytes in Peyer's patches, spleen, liver, and bone marrow. After the onset of fever and bacteraemia, a variable proportion of patients, 24–83% as reported in recent clinical studies [3–6], develop diarrhoea, but this is usually not a chief complaint, whereas a minority of patients, 7–27% [3–10], excrete the organisms in stools. After recovery from clinical illness, about 1–4% of patients, predominantly females, become chronic asymptomatic faecal carriers, owing to underlying gall bladder stones, which often become the focus of infection lasting for many years [11]. Enteric infection here is a misnomer, because *S. Typhi* merely uses the intestine as a portal of entry for an inoculum that produces a systemic infection, in which, in a relatively small proportion of patients, organisms are subsequently excreted back into the intestine via the biliary tract. Hyperplastic Peyer's patches in the ileum and proximal colon in some patients lead to mucosal ulceration with bleeding or intestinal perforation. Unlike cholera and shigellosis, in which copious amounts of organisms are shed from intestinal luminal liquid into the environment, typhoid is spread in more subtle, varied patterns. The infrequent and transient excretion of

organisms in stools during acute disease will lead to some transmission in environments with poor sanitation, whereas the larger amount of constant and heavy excretion into the environment comes from the chronic carriers, who are important both in unclean environments, because of water contamination, and in developed countries, where they spread disease by hand and by touching others' food.

Aims of Antimicrobial Treatment

The ideal antimicrobial drug for typhoid fever should be available for oral and intravenous use in adults and children, cause defervescence and clinical improvement in 3–7 days, render blood and stool cultures negative during and after treatment, prevent relapses after treatment, and have a low incidence of side effects and low cost. This treatment will both benefit the patients by curing them and prevent disease in nearby exposed persons by curtailing excretion of pathogens in stools. Prevention of death, which would occur in >10% of untreated patients, owing to complications such as bleeding from intestinal ulcers, intestinal perforation, and shock, is an obvious goal of therapy. Fortunately, death or complication is infrequent when antimicrobial therapy is given before complications occur, as shown by the reports of only four deaths, two non-fatal intestinal perforations requiring surgery and ten cases of intestinal bleeding among more than 1600 patients entered into 20 trials of this review.

Trial Methods

Culture-proven patients were febrile children and adults without complications selected at hospitals by obtaining positive blood cultures in the majority of cases. In a few trials, patients were enrolled on the basis of results of bone marrow or stool cultures. Patients were randomly assigned to drug therapies, and followed for clinical cure on the basis of defervescence and amelioration of symptoms. Most patients were followed up at 1 month after the end of therapy for relapse of symptoms. In most trials, bacteriological cure was tested by obtaining negative blood cultures after therapy. Identification of *S. Typhi* and *S. Paratyphi* A and determination of antimicrobial susceptibilities were carried out with the techniques available at each hospital.

History of Antimicrobial Treatment

Chloramphenicol was the drug of choice for several decades after its introduction in 1948, but has been set aside in many countries because of the emergence of plasmid-mediated resistance and the rare but fatal side effect of bone marrow aplasia. Trimethoprim–sulphamethoxazole and ampicillin were employed to counter chloramphenicol resistance in the 1970s, only to be discarded because of the emergence of plasmid-mediated multidrug resistance that covered all three drugs. In the 1980s, ceftriaxone and ciprofloxacin were shown to be effective against multidrug-resistant strains of *S. Typhi*, and became the drugs of choice. The fluoroquinolones, including ciprofloxacin and ofloxacin, were preferred to ceftriaxone because they were available for oral use and were less expensive. However, in the past decade, strains of bacteria have emerged in Asia that show decreased ciprofloxacin susceptibility (DCS), and patients infected with them have not responded to fluoroquinolone therapy as promptly as previously or have failed to clear organisms in stool cultures [4,5]. Azithromycin was tested in the 1990s, with good results, and can now be regarded as a promising alternative to fluoroquinolones and cephalosporins [9,10,12].

TABLE 1. Summary of features of antimicrobial drugs in use for typhoid fever; rates and prevalences are given as ranges of percentages of treated patients or tested bacterial isolates in the cited trials

Drug	Cure rate[a]	Relapse rate[b]	Resistance prevalence	Duration of therapy (days)	References
Azithromycin	81–100	0	0–71[c]	5–7	3–5,7–10,12
Ceftriaxone	72–97	0–17	0	3–14	7,8,17,18,20,25–29
Chloramphenicol	83–96	0–14	0–88	7–14	12,19,21,25–27,29
Fluoroquinolone (ciprofloxacin, ofloxacin, or gatifloxacin)	64–100	0–12	0[d]	3–7	3–6,9,17–21

[a]Trials did not use uniform criteria for cure, but most required defervescence within 7 days of starting therapy without complications or the need for a change of antimicrobial drug and without positive blood culture at the end of treatment.
[b]Relapses were return of symptoms within 1 month of the end of therapy, but follow-up of patients after hospital discharge was incomplete and sometimes not attempted.
[c]Not applicable, because an MIC of ≥8 mg/L was used by some trials, whereas patients with resistant isolates were treated and cured.
[d]None was resistant with a fluoroquinolone MIC of ≥4–8 mg/L, but the incidence of nalidixic acid resistance and/or decreased ciprofloxacin susceptibility with a ciprofloxacin MIC of 0.12–1 mg/L ranged from 0% to 96%.