Current Trends in the Management of Typhoid Fever

Lt Gen SP Kalra AVSM Bar*, **Lt Col N Naithani**†, **Col SR Mehta** vsm‡, **Sqn Ldr AJ Swamy****

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Introduction

Typhoid (cloudy) fever is a systemic infection, caused mainly by *Salmonella typhi* found only in man. It is characterized by a continuous fever for 3-4 weeks, relative bradycardia, with involvement of lymphoid tissue and considerable constitutional symptoms. In western countries, the disease has been brought very close to eradication levels. In the UK, there is approximately one case per 100,000 population per year. Each year, the world over, there are at least 13-17 million cases of typhoid fever, resulting in 600,000 deaths. 80% of these cases and deaths occur in Asia alone. In South East Asian nations, 5% or more of the strains of the bacteria may already be resistant to several antibiotics [1].

Antibiotics resistance, particularly emergence of multidrug resistant (MDR) strains among *Salmonellae* is also a rising concern and has recently been linked to antibiotic use in livestock. Many *S typhi* strains contain plasmids encoding resistance to chloramphenicol, ampicillin and co-trimoxazole, the antibiotics that have long been used to treat enteric fever. In addition, resistance to ciprofloxacin also called nalidixic-acid-resistant *S typhi* (NARST) strain either chromosomally or plasmids encoded, has been observed in Asia. A significant number of strains from Africa and the Indian subcontinent are MDR type. A small percentage of strains from Vietnam and the Indian subcontinent are NARST strains [2].

The changing pattern of multi drug resistance in typhoid fever was studied in Delhi in 1993 [3]. Out of 76 patients, 12 patients responded to a combination of chloramphenicol and gentamicin, 51 to ciprofloxacin while the remaining 9 responded to combination of cefotaxime and amikacin. This study re-emphasizes the changing pattern, and role of quinolone especially ciprofloxacin in the management of drug resistant typhoid fever, but at the same time indicates that ciprofloxacin is not the drug of choice in all cases of typhoid fever and resistance to it may be seen in some cases, where other drugs have to be used.

100 children (consecutive) with positive blood culture for *S typhi* were studied for clinical profile in Ahmedabad in 2000. 80% *Salmonella* isolates were resistant to amoxycillin, chloramphenicol and co-trimoxazole, but all were sensitive to ciprofloxacin and ceftriaxone [4]. In another study from Rourkela in 2000, out of 5410 blood samples 715 samples, were found positive for *S typhi*. The number of MDR strains of *S typhi* constituted almost 16.1% of the total isolates. In this study, chloramphenicol sensitivity was found quite high (86.5%) and ceftriaxone showed 100% sensitivity. Resistance to ciprofloxacin was found in 2.5% cases [5].

In the extended typhoid epidemic that affected more than 24,000 people in Tajikistan from 1996 through 1998, more than 90% of the organisms were MDR and 82% were resistant to ciprofloxacin. This is the first reported epidemic of quinolones-resistant typhoid fever [6]. Atypical and varied presentations often confuse the picture in enteric fever. Neuropsychiatric manifestations in particular, often may be mistaken for encephalitis, meningitis, cerebral malaria, psychosis, etc [7]. Recurrent salmonellosis (usually *S typhimurium*) is an AIDS defining criterion in HIV positive patients, though for reasons unknown this is rarely due to *S typhi*. HIV positive patients are more prone to develop enteric fever and its frequent relapses.

Diagnosis

Laboratory diagnosis of typhoid fever is based on three principles :

Isolation of organism

Detection of microbial antigen

Titration of antibody against causative organism

Definitive diagnosis of enteric fever requires the isolation of *S typhi* or *S paratyphi*. Cultures of blood, stool, urine, rose spots, the blood mononuclear cell-platelet fraction, bone marrow, and gastric or intestinal secretions may each be useful in establishing the diagnosis. The duodenal string test is especially useful as a noninvasive technique to sample duodenal

*Commandant, AMC Centre and School, Lucknow-2, †Associate Professor, Department of Medicine, ‡Professor and Head, Department of Medicine, Armed Forces Medical College, Pune - 411 040, **Graded Specialist (Medicine), 12 Air Force Hospital, Gorakhpur.

secretions. A positive culture for *S typhi* or *S paratyphi* is obtained in more than 90% of patients if blood, bone marrow and intestinal secretions are all performed [8]. The sensitivity of blood culture alone is only 50 to 70% [9] probably because small quantities of *S typhi* (i.e. <15 organisms/ml) are typically present in the blood of patients with typhoid fever. Oxgall media cultures may increase the sensitivity from blood but not from bone marrow cultures. Because almost all *S typhi* organisms in blood are associated with the mononuclear cell-platelet fraction, centrifugation of blood and culture of this fraction can reduce the time for isolation of the organism but does not increase the sensitivity.

The sensitivity of bone marrow culture is 90% and, unlike blood culture, is not reduced by up to 5 days of prior antimicrobial therapy [8,9]. In some patients with negative results on bone marrow cultures, duodenal string cultures have been positive. One study found that in children the combination of blood and duodenal string culture was as sensitive as bone marrow culture [10]. Children also have a higher incidence of positive stool cultures than adults do (60% versus 27%). Therefore, ideally in adults and children, blood, bone marrow, stool, and duodenal string cultures should all be performed.

A number of serologic tests, including the classic Widal test, have been developed to detect *S typhi* antigen or antibody. None of these tests is sufficiently sensitive, specific, or rapid enough for clinical use. DNA probes for *S typhi* and other *Salmonellae* have been developed, but these tests are not commercially available and may

not be as specific as culture.

Treatment

Supportive measures are important in the management of typhoid fever, such as oral or intravenous hydration, tepid bath and sponging and appropriate nutrition and blood transfusions, if indicated. More than 90% of patients can be managed at home with oral antibiotics, a reliable caretaker, and close medical follow-up for complications or failure to respond to therapy.

Anti-microbial agents (schedule of various antibiotics is given in Table 1).

In the pre-antibiotic era, the mortality rate from typhoid fever was as high as 15%. The introduction of treatment with chloramphenicol in 1948 greatly altered the disease course, decreasing mortality to <1% and the duration of fever from 14-28 days to 3-5 days. Chloramphenicol remained the standard treatment for enteric fever until the emergence of plasmid-mediated resistance to the drug in 1970's. A high relapse rate (10-25%), a high rate of continued and chronic carriage, bone marrow toxicity, and a high mortality rate in some series from the developing world are other concerns with chloramphenicol. Relapse may follow an otherwise uneventful course and should be treated with the same drug [2].

Given the increased mortality associated with resistance to chloramphenicol and the rare chloramphenicol-induced bone marrow toxicity, ampicillin and trimethoprim-sulphamethoxazole (TMP-

Table 1

Anti-microbial therapy

Antibiotic	Route	Adult dosage/day	Dosage:mg/kg/day	Duration (in days)
First-line antibiotics :				
Chloramphenicol	Oral, IV	500 mg qid	50 mg/kg in 4 doses @	14
Trimethoprim-Sulfamethoxazole	Oral, IV	160/800 mg bid	4-20 mg/kg: in 2 doses	14
Ampicillin/Amoxycillin	Oral, IM, IV	1000-2000 mg qid	50-100 mg/kg: in 4 doses	14
Second-line antibiotics:				
Fluoroquinolones				
Ciprofloxacin	Oral/IV	500 mg bid/200 mg bid	NA	10-14
Norfloxacin	Oral	400 mg bid	NA	10
Pefloxacin	Oral, IV	400 mg bid	NA	10
Ofloxacin	Oral	400 mg bid	NA	14
Cephalosporins				
Ceftriaxone	IM, IV	1-2 gm bid	50-75 mg/kg: in 1-2 doses	7-10
Cefotaxime	IM, IV	1-2 gm bid	40-80 mg/kg: in 2-3 doses	14
Cefoperazone	IM, IV	1-2 gm bid	50-100 mg/kg: in 2 doses	14
Cefixime	Oral	200-400 mg od/bid	10 mg/kg: in 1-2 doses	14
Other antibiotics:				
Aztreonam	IM	1 gm/bd-qid	50-70 mg/kg: 2-4	5-7
Azithromycin	Oral	1 gm od	5-10 mg/kg:1	5

@ Dose of chloramphenicol may be reduced to 25 mg/kg after defervescence.

SMZ) became the mainstay of treatment [11]. The recent emergence of multidrug resistant strains of *S typhi*, with resistance to ampicillin and trimethoprim has diminished the efficacy of these drugs [12]. In 1989, MDR *S typhi* emerged. These bacteria are resistant to chloramphenicol, ampicillin, trimethoprim-sulphamethoxazole (TMP-SMZ), streptomycin, sulfonamides and tetracycline. This resistance is also plasmid encoded. In areas with a high prevalence of multidrug-resistant *S typhi* infection (eg. Indian subcontinent, Southeast Asia, and Africa), all patients suspected of having typhoid fever should be treated with quinolone or third-generation cephalosporin until the results of culture sensitivity studies become available.

Quinolones are highly active against *Salmonellae* in vitro, effectively penetrate macrophages, achieve high concentrations in the bowel and bile lumina, and thus have potential advantages over other antimicrobials in the treatment of typhoid fever [13]. Ciprofloxacin has proved highly effective; in two trials, no *S typhi* carriers emerged, a fact that, if sustained in other studies, indicates a major advantage for use of the quinolone antibiotics [14]. Ciprofloxacin has also been found to be highly effective therapy for infections due to MDR *S typhi* and *S paratyphi* [15]. Certain caveats should be entered here regarding the quinolones. Resistance to ciprofloxacin of *S typhi* appears to be increasing, especially in the Indian subcontinent [16]. Other quinolones, including ofloxacin, norfloxacin and pefloxacin, have been effective in small clinical trials. Short-course therapy with ofloxacin (10 to 15 mg/kg divided twice daily for 2 to 3 days) appears to be simple, safe, and effective in the treatment of uncomplicated MDR typhoid fever when the strain is susceptible to nalidixic acid. However, patients infected with relatively quinolone-resistant *S typhi* strains (resistant to nalidixic acid and a minimal inhibitory ciprofloxacin concentration of 0.125 to 1 mg/dl) who receive short-course quinolone therapy (i.e. <5 days), may not demonstrate clinical recovery and could require repeated or alternative treatment [17]. Therefore, all *S typhi* isolates should be screened for nalidixic acid resistance and tested against a clinically appropriate quinolone. Patients with nalidixic acid-resistant strains should be treated with higher doses of ciprofloxacin (i.e. 10 mg/kg twice daily for 10 days) or ofloxacin (10 to 15 mg/kg divided twice daily for 7 to 10 days) [17]. Third generation cephalosporins such as cefotaxime, ceftriaxone, and cefoperazone have been used successfully to treat typhoid fever, with courses as short as 3 days showing similar efficacy to the usual 10 to 14 days regimens [18,19]. Excellent response rates have been reported with ceftriaxone when administered for

5 to 7 days, but the relapse rate remains incompletely defined [19]. These drugs should be reserved for quinolone resistant cases. It is recommended to treat with ceftriaxone for 10-14 days. Several small studies have reported successful treatment of typhoid fever with aztreonam, a monobactam antibiotic [20]. This antibiotic has been shown to be more effective than chloramphenicol in clearing the organism from the blood and was associated with fewer adverse reactions. However, a prospective clinical trial in children in Malaysia was discontinued because of a high failure rate with aztreonam [21]. Azithromycin, a new macrolide antibiotic administered in a dose of 1 gram once daily for 5 days is also useful for the treatment of typhoid fever, although the disease takes longer to defervesce [22,23]. The main advantage of aztreonam and azithromycin is that they can be used in children and in pregnant or nursing females.

The use of glucocorticosteroids has been advocated for the treatment of severe typhoid fever based on a randomized, double blind, placebo-controlled trial carried out in Indonesia. This study showed a significant reduction in mortality in patients with severe typhoid fever (ie. associated delirium, obtundation, stupor, coma, or shock) treated with chloramphenicol and dexamethasone as compared with chloramphenicol-treated control patients (case-fatality rate, 10% versus 56%) [24]. Although the case fatality rate in the control group was high and the study has never been repeated, on the basis of this study, dexamethasone, 3 mg/kg intravenously, followed by eight doses of 1 mg/kg every 6 hours, should be considered for the treatment of severe typhoid with altered mental status or shock. Steroid treatment beyond 48 hours may increase the relapse rate [25]. Corticosteroids are administered for severe toxemia and fever and may produce a dramatic response in the patient with profound sepsis. The wide experience with corticosteroid treatment has failed to show any adverse effects, although the potential for masking intestinal perforation is always present. Corticosteroids are thus best reserved for patients with severe illness. Good nursing care plays a major role in the recovery from typhoid fever. The pyrexia can be managed with tepid baths and sponging. Salicylates and antipyretics should be avoided, because they cause severe sweating and lower the blood pressure.

Carriers

A chronic carrier is one who continues to discharge *S typhi* in either urine or stool for longer than 1 year. About 1-4% of patients who develop chronic carriage of *Salmonella* following enteric fever, can be treated for 6 weeks with an appropriate antibiotic. Treatment with amoxicillin and trimethoprim-sulphamethoxazole

are effective in eradication of long-term carriage, with cure rates of greater than 80% after 6 weeks of therapy. The quinolone antibiotics, such as ciprofloxacin and norfloxacin are more effective and have become the treatment of choice in eradicating the carrier state [26]. However, in cases of anatomic abnormality (eg. biliary or kidney stones) eradication of carrier state cannot be achieved by antibiotic therapy alone but also requires surgical correction of the abnormality. In persons with gallstones or chronic cholecystitis, cholecystectomy eliminates the carrier state in 85%. However, this procedure is recommended only for those cases whose profession is not compatible with the typhoid carrier state, such as food handlers and health care providers [2]. Long-term suppressive antimicrobial therapy should be considered for patients with persistent carriage in whom no anatomic abnormality can be identified or who relapse after cholecystectomy. Dosage schedule of various antibiotics is given in Table 2.

Table 2

Drug treatment of typhoid carriers

Antibiotic	Daily dose	Route	Dose	Duration (Days)
Ampicillin or Amoxycillin + Probenicid	100 mg/kg 30 mg/kg	Oral	tid/qid	6-12 weeks
Co-trimoxazole	4-20 mg/kg	Oral	bid	6-12 weeks
Ciprofloxacin	1500mg	Oral	bid	4 weeks
Norfloxacin	800 mg	Oral	bid	4 weeks

Recurrent *Salmonella* bacteremia in persons with Acquired Immunodeficiency Syndrome

In persons with AIDS and a first episode of *Salmonella* bacteremia, 1 to 2 weeks of intravenous antimicrobial therapy followed by 4 weeks of oral quinolone therapy (eg. ciprofloxacin, 500 to 750 mg twice daily) should be administered in an attempt to eradicate the organism and decrease the risk of recurrent bacteremia [27]. Persons who relapse after 6 weeks of antimicrobial therapy should receive long-term suppressive therapy with a quinolone or trimethoprim-sulfamethoxazole. Quinolones and zidovudine have a synergistic antibacterial effect against *Salmonella*, administration of both drugs may dramatically decrease the risk of recurrent infection [28,29]. Although data are lacking, because of its efficacy in the prevention of *Pneumocystis carinii* infection, trimethoprim-sulfamethoxazole may be a good choice for long-term suppressive therapy for salmonellosis if the organism is susceptible [30].

Role of surgery

Most surgeons agree that elimination of peritoneal spillage and endotoxaemia by surgery offers the best

hope of survival. However, the extent of surgery remains controversial. A prospective study compared the result of 3 operations, simple closure, wedge excision of ulcer and anastomosis or segmental resection and anastomosis. The risk of reperforation and mortality rate were compared. The risk of reperforation and mortality rate was highest (2 and 13 of 21 respectively) in those who had wedge resection and lowest (0 & 9 of 25 respectively) in those who had segmental resection and anastomosis. The risk of reperforation and mortality was 0 and 9 out of 18 respectively in the simple closure group. Segmental resection and anastomosis seems to be the best treatment for typhoid perforation [31].

Vaccines

Three types of typhoid vaccines are available :

Phenol-inactivated vaccine; Live, attenuated *S typhi* strain, Ty21a; Purified Vi capsular polysaccharide vaccine.

Each of these vaccines offers 55% to 85% protection for 3 to 5 years. The main differences relate to their side effects. Local pain at the injection site and mild to moderate systemic reactions are commonly encountered with the phenol-inactivated vaccine. The live-attenuated oral vaccine may cause mild gastrointestinal distress, but because of its low toxicity and ease of administration it should be used for travellers to areas of high risk. There are little data available regarding the protective efficacy of the oral vaccine for travellers. The purified capsular Vi vaccine has significantly fewer adverse effects than the killed whole cell parenteral vaccines. Its efficacy has not been established in travellers, but it is used as an alternative to the oral typhoid vaccine. Lin et al report an efficacy of more than 90% for a new typhoid vaccine with the capsular polysaccharide of *S typhi*, Vi conjugated to nontoxic recombinant *Pseudomonas aeruginosa* exotoxin A (Vi-rEPA). Two injections of this vaccine, given 6 weeks apart, prevented blood-culture positive typhoid fever during a period of 27 months in 5525 children, 2 to 5 years old in Dong Thap Province of Vietnam, where typhoid is highly endemic [32].

An effective typhoid vaccine could have a substantial effect during outbreaks in locations where water and sewage-disposal systems are inadequate. There has been growing concern, especially in the face of MDR strains such as those seen in Tajikistan [6], that vaccination against typhoid fever is not currently considered as part of the usual response to epidemics. In the 1970s, vaccination proved to be a successful intervention in Thailand. There was a rapid decline in blood-culture-confirmed typhoid fever. A low level of confirmed cases was sustained for at least 7 years after

the institution of a program of annual immunization for children 7 to 12 years old with a heat and phenol - inactivated whole-cell vaccine [33]. Thus, an effective, well-tolerated typhoid vaccine could help control both endemic and epidemic disease. Dose of typhoid vaccines is given in Table 3.

Table 3

Typhoid fever vaccines

Vaccine	Age	Route	Dosage	Revaccination
Killed whole-cell vaccine	5 years	subcutaneous	0.5 ml (0.25 ml for children < 10y) x 2 times, 4 weeks apart	3 years
Vi CPS	2 years	subcutaneous	0.5 ml	3 years
Ty21 a, live	6 years	oral	1 capsule every other day, total of 3 capsules	5 years

Conclusion

Management of typhoid fever continues to pose a challenge, even one hundred years after the micro-organism was first isolated by Gaffkey, a German in 1884. The absence of a reliable rapid diagnostic test, will test the diagnostic skills of the treating physician. A concerted effort involving clean water supply, sanitary faeces disposal, effective vaccination and early diagnosis and prompt treatment of cases and carriers will be required to control the disease. Therapeutic strategies will have to take into account the local antibiotic sensitivity patterns of *S typhi* while defining treatment.

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