REVIEW ARTICLE:

CURRENT TRENDS IN THE MANAGEMENT OF TYPHOID FEVER

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INTRODUCTION

Typhoid 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 level. In UK, there is approximately one case per 100,000 population per year. Each year, world over, there are at least 13-17 million cases of typhoid fever, resulting in 600,000 deaths. Eighty % of these cases and deaths occur in Asia alone. In South East Asian nations, 5% or more of the strains of bacteria may already be resistant to several antibiotics.[1] Antibiotics resistance, particularly emergence of multidrug resistant (MDR) strains among s*almonellae* is also a rising concern and has recently been linked to antibiotics use in livestock. Many *S typhi* strains contain plasmids encoding resistance to chloramphenicol, ampicillin and cotrimoxazole, the antibiotics that have long been used to treat enteric fever. In addition, resistance to ciprofloxacin also called nalidixic-acid-resistant *S typhi* (NARST) strains either chromosomally or plasmid encoded, have 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 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 a combination of cefotaxime and amikacin. This study re-emphasizes the changing pattern, and role of quinolones 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. Hundred 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 cotrimoxazole, 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 typh*i. 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 typhimuriu*m) is an AIDS defining criteria in HIV positive patients. HIV positive patients are more prone to develop enteric fever and its frequent relapses.

Anti-microbial Therapy: (Schedule of various antibiotics is given in Table 1).

Chloramphenicol: 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 can be treated with the same drug. (Table 1).

Ampicillin & Cotrimoxazole: Given the increased mortality associated with resistance to chloramphenicol and the rare chloramphenicol-induced bone marrow toxicity, Ampicillin and Trimethoprim-sulphamethoxazole (TMP-SMZ) became the mainstay of treatment.[8] The recent emer-

Table 1: Anti-microbial therapy

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

gence of multidrug resistant strains of *S typh*i, with resistance to Ampicillin and Cotrimoxazole has diminished the efficacy of these drugs.[9] 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 (e.g. 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 and 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.[10] 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.[11] Ciprofloxacin has also been found to be highly effective therapy for infections due to MDR *S typhi* and *S paratyph.*[12] Certain caveats should be entered here regarding the quinolones. Resistance to ciprofloxacin of *S typhi* appears to be increasing, especially in the Indian subcontinent.[13] 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.[14] 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 (10–15 mg/kg divided twice daily for 7–10 days).[14]

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.[15,16] Excellent response rates have been reported with ceftriaxone when administered for 5 to 7 days, but the relapse rate remains incompletely defined.[16] These drugs should be reserved for quinolone resistant cases. It is recommended to treat with ceftriaxone for 10-14 days.

Other antibiotics: Several small studies have reported successful treatment of typhoid fever with aztreonam, a monobactam antibiotic.[17] 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.[18] 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.[19,20] The main advantage of aztreonam and azithromycin is that they can be used in children and in pregnant or nursing females.

Use of gluococorticosteroids 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%).[21] 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 fever with altered mental status or shock. Steroid treatment beyond 48 hours may increase the relapse rate.[22] Corticosteroids are administered for severe toxemia and fever and may produce a dramatic response in the patient with profound septicaemia. 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.

Antipyretics: 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.[23]

Supportive measures are important in the management of typhoid fever, such as oral or intravenous hydration, tepid baths 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.

Prophylaxis

Three types of typhoid vaccines are available.

(i) Phenol-inactivated vaccine;(ii) Live, attenuated *S typhi* strain, Ty21a; (iii) Purified Vi capsular polysaccharide vaccine. Each of these vaccines offer 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 travelers to areas of high risk. There are little data available regarding the protective efficacy of the oral vaccine for travelers. The purified capsular Vi vaccine has significantly fewer adverse effects than the killed whole cell parenteral vaccines. Its efficacy has not been established in travelers, 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 typh*i, 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.[24] 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 consid-

ered 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.

Table 2: Typhoid vaccines.

Vaccine	Dosage	Route
Killed whole vaccine	0.5 ml 2 times, one week apart Revaccination every year	Subcutaneous
Vi CPS	0.5 ml Revaccination at 3 years	Subcutaneous
Ty 21 a	One capsule on days 1,3,5,7 Revaccination at 3 years	Oral

Management of 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 nor-floxacin are more effective and have become the treatment of choice in eradicating the carrier state. **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.

However, in cases of anatomic abnormality (e.g. Biliary stones) eradication of carrier state cannot be achieved by antibiotic therapy alone but will require 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 Dosage schedule of various antibiotics is given in Table 3.

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 astomosis 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.[25] Thus, an effective, well-tolerated typhoid vaccine could help control both endemic and epidemic disease. Dose of typhoid vaccines is given in Table 2.

Table 3: Drug treatment of typhoid carriers.

Drugs	Dosage Duration in days mg/Kg/day	Route
Ampicillin	100mg/kg, tid /qid	Oral
Amoxycillin + Probenicid	30 mg/kg	Oral
Co- trimoxazole	4-20mg/kg bid	Oral
Ciprofloxacin	1500 mg bid	Oral
Norfloxacin	800 mg bid	Oral

CONCLUSION

Management of typhoid fever continues to pose a challenge, even more than a century after the microorganism was first isolated by Gaffkey, a German in 1884. Because of the non-availability of a reliable rapid diagnostic test, the diagnostic skills of the treating physician were of importance in the past and even now the underdeveloped areas. A concerted effort involving clean water supply, proper sanitary 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 refining treatment.

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