

# A Critical Analysis of the Management of Typhoid Fever in a Tertiary care hospital in India

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## ABSTRACT

Enteric fever is endemic in many parts of the third world. In India, it is the fifth most common infectious disease. With increasing resistance to fluoroquinolones and re-emergence of chloramphenicol, the policy of empirical treatment of typhoid fever (TF) needs to be rationalized. This study was carried out to compare the prescription pattern of typhoid fever for two successive years, to study the change in trend in the prescription pattern, to rationalize prescription and to check the rationality of the use of drugs. A retrospective analysis of the management of all the cases of TF during the year 2002 & 2003 was carried out at Kasturba hospital, Manipal. Prescriptions of all the case records of in – patients diagnosed as TF were collected through a specifically designed proforma and analysed. A total number of 96 cases were admitted in 2002 and 90 in 2003. Ceftriaxone emerged as the most commonly used antibiotic in both the years. Fever was seen in almost all the cases. Number of cases with widal tested as positive were 33 in 2002 and 42 in 2003. Number of cases resistant to cephalosporins were nil in both the years. Cephalosporins continue to be used commonly. Use of ciprofloxacin has declined. Widal test continues to be carried out commonly though it is of little practical value and easily misinterpreted. Re-emergence of chloramphenicol is a welcome sign.

**Keywords:** *Typhoid fever, Tertiary care, Cephalosporins*

Enteric fever is caused by salmonella typhi and paratyphi bacilli and is endemic in many parts of the third world. The incidence is highest in South-central and Southeast Asia (>100 cases per 100000 population per year) and associated with a high rate of complications. Atypical clinical findings make an early diagnosis difficult [1]. High fever, toxemia, constipation during first week of fever, diarrhoea during second week of fever, mild splenomegaly and leucopenia/neutropenia, complicated by encephalopathy, intestinal haemorrhage and perforation during third week of fever are the typical manifestations of typhoid fever (TF) [2].

Credible measures of disease incidence are necessary to guide typhoid fever control efforts [3]. The gold standard of treatment for enteric fever now, amongst other drugs, is a 4-fluoroquinolone or a third generation cephalosporin, especially in multidrug resistant states [4, 5]. An estimated 600,000 deaths from enteric fever occur annually throughout the world [6].

Enteric fever continues to be a major public health problem, especially in the developing countries of the tropics. The sensitivity pattern of *S. typhi* is changing

and there is re-emergence of sensitivity to chloramphenicol but rising resistance to ciprofloxacin [7].

The emergence of antibiotic-resistant strains of bacteria is closely linked to the irrational use of antibiotics in treating human infections, especially ciprofloxacin [4].

Ampicillin, chloramphenicol and co-trimoxazole had been the first line drugs for treating typhoid fever, but with emerging resistance in the 70s and 80s, they fell in disuse. There is a change in the antibiogram of *S. typhi* now with re-emergence of sensitivity to chloramphenicol, ampicillin and co-trimoxazole and development of resistance to quinolones. With increasing resistance to fluoroquinolones and the possibility of re-emergence of sensitivity to chloramphenicol among salmonellae, the policy of empirical treatment of enteric fever needs to be rationalized [8].

Hence the need of a critical analysis of the pharmacotherapy of typhoid fever in a tertiary care setup (Kasturba hospital, Manipal). This study was carried out to compare the prescription pattern of

**Table 1.** Demographic profile

Parameters	2002		2003	
	Males	Females	Males	Females
Total no. of cases	96		90	
Gender wise distribution	28(29.16%)	68(70.83%)	28 (31.1%)	62 (68.88%)
Avg. age of presentation (yrs)	22	21.5	33	31
Avg. duration of drugs(days)	10.41		10.62	
Avg. duration of hospital stay (days)	7.89		7.63	
No. of pediatric admissions	12.5%(12)		16.67%(16)	

**Table 2.** Utilization in Individual Drug Group

Drug Name	2002 No. of patients treated (n)	2002 %	Percent recovery %	2003 No. of patients treated (n)	2003 %	Percent recovery %
Ceftriaxone	46	48	46 (100%)	36	40	36 (100%)
Cefipime	14	15	14 (100%)	09	10	09 (100%)
Ciprofloxacin	09	09	03 (33%)	05	06	01 (20%)
Ofloxacin	14	15	13 (92%)	17	19	17 (100%)
Sparfloxacin	02	02	01 (50%)	03	03	03 (100%)
Amoxicillin	03	03	01 (33%)	08	09	04 (50%)
Cotrimoxazole	02	02	02 (100%)	03	03	03 (100%)
Gentamicin	06	06	04 (66%)	06	07	05 (83%)
Chloramphenicol	00	00	0	03	03	03 (100%)

**Table 3.** Microbiological findings

	2002	2003
Widal test +ve	34.37% (33)	43.75% (42)
Blood culture +ve	11.45% (11)	8.33% (8)
Sensitivity to all antibiotics	4.16% (4)	7.29% (7)
Resistance to cephalosporins	Nil	Nil

typhoid fever for two successive years and thereby study the change in trend in the prescription pattern, rationalize prescription and check the rationality of the use of drugs.

## MATERIALS AND METHODS

A retrospective analysis of the management of all the cases of TF during the year 2002 & 2003 was done at our hospital. Permission was obtained from the Institutional Ethics Committee (IEC) to carry out a drug utilization study and from the medical superintendent (MS) of our hospital to study all the files of typhoid cases for the year 2002 & 2003 from the medical records section. All types of patients i.e. adults, children, geriatric age group were included in the study. Both males and females were included in the study. Diagnosis of patients was based on clinical features, widal test and blood culture. Recovery was based on a 48 hr fever free interval after the completion of a course of antibiotics. Prescriptions of all the case records of in – patients diagnosed as TF were collected through a specifically designed proforma and analysed. The mode of presentation of clinical course, treatment history, laboratory investigation reports, antibiotic administered response to therapy and the complications were recorded.

## RESULTS

### A. Demographic profile: (Table 1)

The most significant finding in the demographic section is the gender difference in the incidence of typhoid fever. Out of the 96 cases in 2002, more than 50% i.e. 68 cases were females. A similar observation

was seen in 2003. Out of the 90 cases, 62 cases were females.

### B. Drug utilization pattern and percent recovery: (Table 2)

Among the drugs used for the treatment ceftriaxone emerged as the most commonly used in both the years, the incidence being 48% in 2002 and 40% in 2003. The percent recovery is maximum for cephalosporins (100%) considering the number of patients treated with them and least for ciprofloxacin indicating the high rate of resistance against *S.typhi*. Percent recovery is 100% for cotrimoxazole and chloramphenicol also but the number of patients treated is very few. Ofloxacin has also shown a good 92% recovery rate. The criteria for recovery is clinical and it is a 48 hr fever free interval after the culmination of a course of antibiotics.

### C. Microbiological findings: (Table 3)

Widal test was found to be positive only in 33 cases in 2002 and 42 cases in 2003. Even blood culture which is a reliable test is positive only in 11 cases in 2002 and 8 cases in 2003. In both 2002 and 2003 not a single case was found to be resistant to cephalosporins.

### D. Clinical features: (Table 4)

Fever was seen in almost all the cases. The number of cases with hepatosplenomegaly were 28 (29.16%) in 2002 and 33 (34.37%) in 2003. Only hepatomegaly was seen in eight (8.33%) cases in 2002 and in 13 cases (13.54%) in 2002 and only splenomegaly in ten (10.41%) cases in 2002 and eight cases (8.33%) in 2003. Twenty four patients (25%) underwent sonography of the abdomen in 2002 and 20 patients (20.83%) in 2003.

Table 4. Miscellaneous

	2002	2003
Ultrasound abdomen	25% (24)	20.83% (20)
Hepatosplenomegaly	29.16% (28)	34.37% (33)

## DISCUSSION

Definitive treatment of typhoid fever (enteric fever) is based on susceptibility. Until susceptibilities are determined, antibiotics should be empiric, of which there are various recommendations. But treatment should not be delayed for confirmatory tests since early and prompt treatment drastically reduces the risk of complications and fatalities. Antibiotic therapy should be narrowed once more information is available. The 2003 World Health Organization (WHO) guidelines recommend treatment with fluoroquinolones and cephalosporins as the 1<sup>st</sup> line agents for both complicated and uncomplicated cases of typhoid fever based on the culture and sensitivity [9]. The protocol used for the treatment in our study matches with the WHO recommendations. Cephalosporins are used in 63% of the cases in 2002 and in 50% of the total cases in 2003. This is followed by the fluoroquinolones which have been used in 26% of the cases in 2002 and in 28% of the cases in 2003. The most recent professional guideline for the treatment of typhoid fever in south Asia was issued by the Indian Association of Pediatrics (IAP) in October 2006. Although these guidelines were published for pediatric typhoid fever, the authors feel that they are also applicable to adult cases. For empiric treatment of uncomplicated typhoid fever, the IAP recommends cefixime and, as a second-line agent, azithromycin. For complicated typhoid fever, they recommend ceftriaxone. Aztreonam and imipenem are second-line agents for complicated cases. We, the authors believe that the IAP recommendations have more validity than the WHO recommendations for empiric treatments of typhoid fever since quinolone resistance is high in this part of the world [10]. A recent Cochrane review of antimicrobial treatment of typhoid fever concludes that there is little evidence to support administration of fluoroquinolones to all cases of typhoid and that satisfactory cure rates can be achieved in drug sensitive cases with first line agents such as chloramphenicol [11]. Chloramphenicol has been used only in 3% of the cases in 2003 and not used in 2002. But we welcome the reemergence of chloramphenicol to treat typhoid fever in our setup.

Cephalosporins continue to be used commonly (48% & 40%) but this cannot be considered as a good sign because of the fear of impending resistance to them which has already been reported in some places [12]. Imipenem and meropenem may be the next possible alternatives to drug resistant anti-salmonella isolates [13]. But fortunately not a single case has been treated with these drugs in our study. As per the literature ofloxacin is supposed to be more potent than ciprofloxacin for gram positive organisms like chlamydia, mycoplasma and mycobacterium leprae [14]. But the response to ofloxacin seems to be good against S.typhi (a gram negative bacilli) in our setup

considering the fact that its use is more compared to ciprofloxacin. (Table 1) There have been reports in literature of resistance to nalidixic acid and ciprofloxacin but not to ofloxacin [15]. The use of ciprofloxacin has definitely declined (9% & 5%) reassuring the fact that its resistance is widespread. Therfall and Ward [16] have reported that S.typhi with decreased resistance to ciprofloxacin is endemic in several Asian countries, and incidence of such strains has increased in travelers from the Indian subcontinent. They suggested 3<sup>rd</sup> generation cephalosporins such as ceftriaxone or cefotaxime as possible alternatives and in their study it was assured that all strains were sensitive to these drugs. Prolonged antibiotic therapy of 10.41 days in our days is justified since this may eliminate the carrier state and this match with the IAP recommendations [10]. As per the literature blood culture is positive in 90% in the first week of fever and in 75% in the second week [17]. But to our surprise only 11.45% in 2002 and 8.33% in 2003 were positive by culture. It could be possible that patients have taken some antibiotics prescribed by local doctors before coming to the hospital which has resulted in poor response to blood culture. Widal antigen test continues to be carried out commonly even though the fact is that it is of little practical value and easily misinterpreted [17]. The popularity of widal test in the diagnosis of enteric fever is undeserved, considering its fallacies and shortcomings [18]. The incidence of ultrasound abdomen is only 25% & 20% in 2002 & 2003 respectively. But it has been shown that ultrasound can be a non-invasive, economical and a reasonably sensitive tool for diagnosing typhoid when serology is equivocal and cultures are negative [19]. Hence ultrasound can be considered more often compared to widal test.

In three cases chloramphenicol has been used in 2003 which is a sign of its reentry in the prescription. The long period of absence may have resulted in the reemergence of the sensitivity of S.typhi against it. With respect to gender, TF was found to be more in females compared to males and the age of presentation was also higher in females compared to males in both the years studied.

To conclude, the prescriptions for typhoid fever in our study were found to be rational with respect to dose, strength & duration of treatment. Polypharmacy is found to be low (number of drugs per prescription is less than 3). The use of ciprofloxacin has reduced considerably reassuring the fact that ciprofloxacin resistance is widespread. The widespread use of cephalosporins is not a good sign and re-emergence of chloramphenicol is a welcome sign. Response to ofloxacin seems to be good and hence can be prescribed more often.

Rapid diagnosis, institution of appropriate antibiotic treatment, adequate rest, antipyretics, hydration, and

correction of fluid-electrolyte imbalance are some of the measures necessary along with the antibiotics. Adequate nutrition like a soft, easily digestible diet should be continued unless the patient has abdominal distension or ileus. Close attention to hand washing and limitation of close contact with susceptible individuals during acute phase of infection must be strictly followed. Regular follow-up and monitoring for complications and clinical relapse (this may include confirmation of stool clearance in non-endemic areas or in high risk groups such as food handlers) can be fruitful. Our advice to travelers traveling to endemic areas include avoidance of undue exposure to possible infection through food and water (contaminated water, salads, street foods), use of bottled water whenever possible, otherwise use only boiled water. Two typhoid vaccines are available, both with proved efficacy of 60-80%, and should be taken at least two weeks before travel [11].

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