Enteric Fever in Mumbai – Clinical Profile, Sensitivity Patterns and Response to Antimicrobials


Abstract
Aims: Enteric fever is endemic in Mumbai and its diagnosis poses several problems. Our main aim was to study the clinical profile, haematological features of culture proven typhoid cases, the antimicrobial susceptibility pattern of the isolates and the time to defervescence with the treatment received.

Material and Methods: This was a retrospective chart review of all cases of culture proven enteric fever carried out at a tertiary care private hospital in Mumbai over the period January 2003 to September 2005.

Results: Culture positivity in our study was 52.6%. Sixty one percent of the isolates were Salmonella typhi while 39% were Salmonella paratyphi A. An absolute eosinopenia was seen in 76.9% of the patients. Before being admitted to the hospital, 46.2% received antibiotics. The mean time to defervescence in patients who received prior antibiotics was 4.5 days while that in those who did not receive prior antibiotics was 5.1 days.

Conclusions: A high culture positivity despite prior or ongoing antibiotic treatment was seen. Absolute eosinophil count of 0% could be an important marker of typhoid. High prevalence of nalidixic acid resistance, a marker of resistance to fluoroquinolones was observed. Combination treatment was not found to be superior to treatment with a single antibiotic. ©

INTRODUCTION
Enteric fever is a systemic illness caused by Salmonella enterica serotype typhi or paratyphi A/B. In India the disease is endemic with an incidence ranging from 102 to 2219 per 100,000 population.1 It results in considerable morbidity, absenteeism and resource utilization.

Diagnosis of enteric fever is fraught with problems. History, physical findings and fever pattern are suggestive but can neither confirm nor exclude typhoid. Blood culture is the ‘gold standard’ for diagnosis and also gives information about antibiotic sensitivity of the isolate; however the cost of cultures, lack of “culture of cultures” and administration of prior antibiotics are impediments in this diagnostic approach. The Widal test is very commonly used in Indian set up but has very variable sensitivity and specificity and problems in interpretation. Therapy of enteric fever is becoming more complicated and expensive with time. By the end of 1990s, Salmonella enterica developed resistance simultaneously to all first line drugs like chloramphenicol, cotrimoxazole and ampicillin.

Fluoroquinolones when first introduced in early 1990’s were very effective but the past decade has seen a progressive increase in the MICs of ciprofloxacin and high incidence of clinical failure to quinolones. The beta lactams such as cefixime and ceftriaxone are now being increasingly used but these are expensive drugs and are associated with a long time to defervescence and high rates of relapse. There have also been sporadic reports of high-level resistance to ceftriaxone in S. typhi and S. paratyphi.2 Experience with new drugs such as azithromycin is at present scanty.5-7

To sum up, enteric fever raises several issues of diagnosis and treatment. There is a scarcity of studies in literature addressing these issues. Hence a retrospective review of patients of enteric fever at our hospital was carried out to solve some of these pertinent clinical problems.

Aims and Objectives
The primary aim of the study was to study the sensitivity patterns of S. enteritica and response to antimicrobial therapy. The secondary aims were to study the clinical and laboratory profile of patients with culture proven enteric fever.

MATERIAL AND METHODS
This was a retrospective chart review of all cases of enteric fever carried out at a tertiary care private
hospital in Mumbai, India. The records of all patients discharged from our hospital between January 2003 and September 2005 with a diagnosis of enteric fever, typhoid fever or paratyphoid fever were assessed for suitability for inclusion in our study. These records were retrieved from the Medical Records Section of the hospital after going through the computer records using ‘enteric fever, typhoid fever or paratyphoid fever’ as discharge diagnosis in the search criteria. Only culture proven cases of enteric fever were included in the study. Others were considered as clinically diagnosed typhoid and were excluded from the study. They were used to calculate the culture positivity. Clinical, laboratory and treatment information was extracted from the medical records on a detailed proforma and analyzed. The two-sample t test was used to compare continuous variables and the chi square test was used to compare categorical variables. A p value of less than 0.05 was considered significant.

The Ethics Committee of the hospital had no objection for retrospective data analysis, as the data collected was based on routine clinical practice. Further, the committee had no objection to publish a paper based on this retrospective data, provided the patient identify was not revealed.

**RESULTS**

A total of 226 patients received a discharge diagnosis of enteric fever/ typhoid fever/ paratyphoid fever during the period January 2003 to September 2005. Out of these 226, 119 (52.6%) were culture proven cases of enteric fever and were included in the analyses.

Seventy-four of the 119 study patients were male and 45 were female. The age ranged from 7 months to 66 years, the mean age being 21.7 years.

All patients had fever prior to admission; the median duration of fever prior to admission was 7 days, the range being 2 to 90 days. High-grade fever was seen in 66.3% and chills were present in 57.9%. Vomiting, abdominal pain and loose stools were the most common associated symptoms seen in 42%, 33.6% and 31% patients respectively. Only two patients complained of constipation. None of the patients had relative bradycardia. Hepatosplenomegaly was seen in 12.6% patients. Only hepatomegaly was seen in 15.9% while only splenomegaly was seen in 7.5% patients. Seven patients gave history of enteric fever in the past. Only 1 of these 7 was culture proven, 2 were culture negative and no details were available for the rest.

The mean white blood cell (WBC) count was 6358/cumm with a range from 1050/cumm to 15,120/cumm. Eighty five percent had the WBC count within the normal range (4000 –11000/cumm) while 11.4% patients had leucopenia (WBC count < 4000/cumm). Leucocytosis (WBC count >11000/cumm) was seen in only 4 patients. Absolute eosinopenia (0% eosinophils) was seen in 76.9% patients. The mean platelet count of the study patients was 2,04,800/cumm (range 31,000 to 4,88,000). Thrombocytopenia (platelet count < 1.5 lacs/cumm) was seen in 25.9%. Hyperbilirubinemia (> 1 mg/dl) was seen in 28.7% while the ALT was elevated (> 60 IU/ml) in 43% patients.

Seventy-three of the 119 study patients (61%) were positive for *Salmonella typhi* while the rest had *Salmonella paratyphi* A. The 73 isolates of *Salmonella typhi* included 70 from blood culture, 2 from bone marrow and 1 from stool culture. All the *Salmonella paratyphi* A were isolated from blood cultures. The cultures were sent after a mean period of 11 days after the onset of fever. Table 1 shows the sensitivity pattern of the isolates year wise over the study period. There is no significant difference between the year wise antimicrobial susceptibility patterns of that of *S typhi* and *S paratyphi* A. Data for azithromycin is not included as sensitivity to azithromycin was not tested during the study period. None of the isolates of *Salmonella paratyphi* A showed block resistance to ampicillin, chloramphenicol and cotrimoxazole.

Widal test results were available for 64 of 119 patients. Widal test was positive (defined as S. typhi O antigen >120 and either S. typhi H or S. paratyphi H antigen titres >120) in 24 of 64 patients (48.4%). The mean duration of fever at which Widal test was positive was 10.7 days (95% CI 8.3, 13.1 days).

Fifty-five patients (46.2%) received antibiotics before being admitted to the hospital. Beta lactams (cefuroxime, cefadroxyl, cefixime, ceftriaxone, amoxycillin, cefotaxime, amoxycillin-clavulanate) were taken by 20 patients before admission while quinolones were used in 14 patients. Three patients gave history of having taken azithromycin. Twelve patients had taken a combination of antibiotics including beta lactams, quinolones, aminoglycosides, azithromycin and chloramphenicol. Data on the duration of prior antibiotic use was available only in 20 of the 55 cases and the mean duration of prior antibiotic use was 11 days (95% CI 8.3, 13.1 days).

### Table 1: Year wise sensitivity pattern of the *Salmonella enteritica* isolates

<table>
<thead>
<tr>
<th>Year</th>
<th>S. typhi</th>
<th>S. paratyphi A</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>S to A, CH, TS</td>
<td>28 (96)</td>
</tr>
<tr>
<td></td>
<td>S to NA</td>
<td>9 (31)</td>
</tr>
<tr>
<td></td>
<td>S to ceftriaxone</td>
<td>23 (96)</td>
</tr>
<tr>
<td></td>
<td>15 (100)</td>
<td>2 (13)</td>
</tr>
<tr>
<td></td>
<td>7 (30)</td>
<td>100%</td>
</tr>
<tr>
<td>2004</td>
<td>S to A, CH, TS</td>
<td>15 (100)</td>
</tr>
<tr>
<td></td>
<td>S to NA</td>
<td>2 (13)</td>
</tr>
<tr>
<td></td>
<td>S to ceftriaxone</td>
<td>5 (25)</td>
</tr>
<tr>
<td></td>
<td>17 (85)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2005</td>
<td>S to A, CH, TS</td>
<td>16 (100)</td>
</tr>
<tr>
<td></td>
<td>S to NA</td>
<td>25 (21)</td>
</tr>
<tr>
<td></td>
<td>S to ceftriaxone</td>
<td>114 (96)</td>
</tr>
</tbody>
</table>

*S = sensitive, A = ampicillin, CH = chloramphenicol, TS = TMP-SMX, NA = nalidixic acid*
antibiotic use was 3.9 days (range 1 to 10 days).

Ceftriaxone was the most common antibiotic used to treat patients in hospital; 74 of 119 patients (62.1%). A combination of ceftriaxone (2 gm bd IV) and azithromycin (500 mg od PO) was used in 16 patients (13.4%). Rest of the patients (25%) received various other antibiotics singly or in combination. The mean duration of receipt of antimicrobials after hospitalization was 11 days.

The mean time to defervescence defined as time period in days from the day of onset of the antibiotic treatment in the hospital to the disappearance of fever was calculated for various patient groups. The mean time to defervescence in the group of patients who had received antibiotics prior to admission was 4.5 days (95% CI 3.9, 5.1 days) while in the patients who did not receive prior antibiotics was 5 days (95% CI 4.3, 5.7 days), p 0.2 (NS).

The overall mean time to defervescence when ceftriaxone alone was used as therapy was 4.2 days. It was 4.2 days in 2003, 4.4 days in 2004 and 4.2 days in the year 2005 (p = 0.84). The mean time to defervescence in the patients who received ceftriaxone in hospital did not differ significantly between those that had received prior antibiotics and those who did not receive prior antibiotics (4.4 days versus 5 days respectively).

The mean time to defervescence in those patients who received a combination of ceftriaxone and azithromycin was 5.1 days and did not differ significantly from those who received ceftriaxone alone (p 0.06).

**DISCUSSION**

This study is one of the largest retrospective studies on enteric fever. Other large series include those by Chowta et al. and Walia et al.8 Most of the clinical symptoms and signs reported by us are similar to those reported earlier.1,4 Very prolonged fever lasting more than 90 days, seen in 2 of our patients was unusual for enteric. This may have been due to an additional cause operating in the earlier part of illness. Relative bradycardia and constipation considered to be salient features of enteric were not seen/very infrequently seen in our study. Few other studies have also found these to be inconsistent features of enteric fever.1 Four patients in our study had leucocytosis, a laboratory finding that is believed to cast a doubt on its being a differential diagnosis for pyrexia. Conversely, absolute eosinopenia, (seen in 77% of our patients) can be used as a pointer of enteric when a complete blood count is done in a patient with fever. Deshmukh et al in their study on paediatric patients with bacteriologically and/or serologically diagnosed typhoid fever found absolute eosinopenia in 71.4% of patients.10 Leucopenia, eosinopenia, thrombocytopenia and anaemia in enteric can be attributed to the myeloid maturation arrest, decrease in the number of erythroblasts and megakaryocytes and increased phagocytic activity of histiocytes in the bone marrow.11

As many as 46.2% patients in our study received antibiotics either single or in combination for as long as 10 days before being admitted to the hospital. Despite this they were still culture positive. The high yield from blood cultures despite antibiotics could have been as a result of processing of the blood cultures by the BACTEC method, which uses soybean casein digest broth, yeast extract, animal tissue digest, sucrose, hemin, menadione, pyridoxal hydrochloride, sodium bicarbonate and sodium polyanethol sulphonate as a culture medium optimised with cationic exchange resin. The usual perception is that culture positivity falls dramatically with prior use of antibiotics9,10,12 and often dissuades clinicians from sending blood cultures in patients with pyrexia. However results of our study advocate that blood cultures should be sent in suspected enteric fever even if the patient is on antimicrobials.

Interestingly 40% of the isolates in our study were *S paratyphi* A as against 20% in literature.13 This may be a consequence of increasing immunization with the Vi antigen vaccine that does not protect against *S. paratyphi*.14 The sensitivity pattern of the isolates obtained in this study is in accordance with the other studies from India.13,15 There is high prevalence of nalidixic acid resistance and return of sensitivity to chloramphenicol, ampicillin and cotrimoxazole. We did not observe any resistance to third generation cephalosporins as in other studies by Chowta et al., Safdar et al., etc. Chande et al observed resistance to cefotaxime in one isolate in their study from central India.17

The mean fever clearance time with ceftriaxone used as single therapy observed in our study was 4.2 days (95% CI 3.7, 4.7 days) as against 6.1 days in literature.4 No change in the time to defervescence with ceftriaxone over the years was seen in our study (4.2 days in the year 2003, 4.4 days in 2004 and 4.2 days in 2005). Surprisingly, receipt of antibiotic therapy prior to admission was found to have no significant impact on the time to defervescence.

There has been no retrospective/prospective study evaluating the efficacy of combination therapy for enteric fever. Results of our study however suggest that combination therapy may not be superior to single drug therapy, as we did not observe any significant difference in the time to defervescence in those patients who received ceftriaxone alone or in combination with azithromycin.

**Limitations**

The main limitation of this study is its retrospective nature and that it was not protocol driven. Patients were receiving various antimicrobials singly or in combination for varying periods prior to hospitalization, which could impact the time to defervescence. Also the inability of the study to detect a difference in efficacy...
of various antimicrobial regimes chiefly single versus combination therapy may be due to the small sample size.

The efficacy of various antimicrobials in enteric fever can be best studied by a randomized controlled trial in a large number of antimicrobial naïve culture positive patients. However it is virtually impossible to recruit antimicrobial naïve culture positive patients.

With all the limitations notwithstanding this study is the largest study of culture proven typhoid. Some important conclusions which can be drawn from the study include importance of absolute eosinopenia as a diagnostic marker of typhoid, high culture positivity despite receipt of prior antibiotics, high prevalence of nalidixic acid resistance (79%), return of susceptibility to chloramphenicol (96%), 100% sensitivity to ceftriaxone and non superiority of combination therapy versus single agent therapy. Urgently needed are well-designed randomized controlled trials to compare the efficacy of various antibiotics in inpatient and outpatient therapy of enteric fever.

REFERENCES