Research Article

Clinical profile of enteric fever: a prospective study of fifty enteric fever patients

Ashish Kakaria[1],*, Dilip Asgaonkar[2], Meenakshi Narkhede[3]

[1]Registrar, [2]Professor, Department of Internal Medicine, TNMC, Mumbai, Maharashtra, India
[3]Associate Professor, Department of Internal Medicine, SBHGMC, Dhule, Maharashtra, India

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*Correspondence:
Dr. Ashish S. Kakaria
E-mail: ashish_kakaria@yahoo.com

ABSTRACT

Background: The protean manifestations of enteric fever make this disease a true diagnostic challenge. Untreated, typhoid fever is a grueling illness that may progress to delirium, obtundation, intestinal hemorrhage, bowel perforation, and death within 1 month of onset. Survivors may be left with long-term or permanent neuropsychiatric complications. This is a prospective study of fifty confirmed enteric fever adult patients done in Kasturba Hospital Mumbai.
Methods: Fifty enteric fever patients with clinical and laboratory diagnosis were included in the study. They were admitted in wards with the aim of documenting the epidemiological pattern, clinical picture, therapeutic response and complications of Salmonella. Their history and detailed physical examination were recorded and tests including antibiotic sensitivity and resistance were done.
Results: In the study incidence of fever 100%, chills 26%, vomiting 44%, diarrhea 28%, abdominal pain 64%, headache 26%, and signs as splenomegaly 36%, hepatomegaly 42%, rose spots 6%, relative bradycardia 34% were reported. Anemia, leukocytosis and leukopenia and elevated liver enzymes were found in 42.9%, 10%, 21% and 45% respectively. Incidence of Salmonella Typhi, Salmonella Paratyphi was 80% and 20% respectively. There was no mortality in the study.
Conclusion: Clinical presentation, signs and symptoms of Typhoid fever patients are varying. For the confirmatory diagnosis in addition to a high index of suspicion, Widal test and blood culture are required. For the proper treatment of Typhoid fever in view of emergence of resistant strains of S. Typhi antibiotic sensitivity and resistance test should be done whenever facilities available.

Keywords: Salmonella, Typhoid, Paratyphoid, Blood culture, Enteric fever

INTRODUCTION

According to an estimate of US Centers for Disease Control and Prevention, there are 21.6 million typhoid cases annually, with the annual incidence varying from 100 to 1000 cases per 100,000 populations. Enteric fever is not a notifiable disease throughout India and hence the correct incidence is not known. Limited studies in the country reveal more than 3 lakh cases and more than 650 deaths (approx.) annually.[1] It is a potentially fatal multisystemic illness caused primarily by *Salmonella Enterica,* subspecies *enterica* serovars *Typhi* and, to a lesser extent, related serovars paratyphi A, B, and C. The illness occurs in all parts of the world where there is contaminated water supply and sanitation. The disease presents as a clinical dilemma as illness resembles several other infections and because of emergence if drug resistant organisms. Undiagnosed and undertreated cases may result in serious complications. We undertook this study with the aim of documenting the epidemiological pattern, clinical picture, recent trends, complications and therapeutic response of Salmonella.

METHODS

This study is a prospective study of fifty adult (age >12 years) patients done in Kasturba Hospital Mumbai during the period of January 2005 to January 2006. Inclusion criteria:

- Significant Widal titre (S. typhi O antigen >120 and either S. typhi H or S. paratyphi H antigen titres >120) or
- A repeat fourfold rise in Widal test titer () or
- Positive blood culture for Salmonella typhi and/ or Salmonella paratyphi organisms.

Exclusion criteria

- Patients with respiratory tract infection (tuberculosis, pneumonia)
- Patients with urinary tract infections
- Patients with malaria
- Immunocompromised patients (AIDS)
- Patients who had already vaccinated with typhoid vaccine.

As per the inclusion criteria's mentioned above patients with history of fever in outpatient department were admitted in medical wards. On the day of admission documentation was made of all the known symptoms and signs of enteric fever[2] and recorded in a proforma. 15 ml of venous blood was withdrawn with aseptic technique and collected for biochemical, serological tests and blood culture and antibiotic resistance and sensitivity tests. Hemogram (CBC), smear examination for malarial parasite, renal function test (blood urea, serum creatinine), bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), and urine examination along with Widal test, blood culture, and antibiotic sensitivity and resistance test were done. Widal test was performed using serum samples of patients with a slide agglutination test which measures agglutinating antibodies against the lipopolysaccharide 'O' and protein flagellar 'H' antigens of S Typhi and Para Typhi A and B. Serial dilution of sera starting at a dilution of 1:40 were made with 0.9% saline and examined for visible agglutination. Appropriate positive and negative sera were included. Antibacterial susceptibility was done on Mueller Hinton agar by the Kirby-Bauer disc diffusion technique. In view of current high incidence of MDR Salmonella (defined as resistance to chloramphenicol, ampicillin and sulphamethaxazole) oral ciprofloxacin 15 mg/kg/day was initiated to patients as our hospital policy and if culture reports showed nalidixic acid resistance we stopped ciprofloxacin and started intravenous ceftriaxone 50-75mg/kg/day in divided doses. Defervesence was defined as the number of days required for the fever to subside after starting of antibiotic. All the patients were followed up till 8 weeks after discharge for relapse or complications. 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.

RESULTS

Mean age of patients included in the study was 24 ±5 yrs with maximum cases between 15-30 yrs age group. The male to female ratio affected was 1.2:1. Low socioeconomic group (55%) was commonly affected. Students (36%) and unskilled workers were more affected than professionals (14%) (Table 1). Maximum cases (44%) were reported during rainy season followed by summer (32%). Fever (100%), abdominal pain (64%), anorexia (36%), headache (26%) & chills (26%) were most common symptoms among study participants (Table 2). Step ladder pattern of fever was seen only in 16% of cases. In clinical signs incidence of coated tongue (22%), relative bradycardia (10%), splenomegaly (36%) and hepatomegaly (42%) was seen (Table 3).

Table 1: Sociodemographic characteristics.

Character	Number	Percentage
Total cases	50	100
Gender		
Male	28	56
Female	22	44
Age group (in years)		
< 14	10	20
15-30	25	50
31-45	12	24
46-60	2	4
>60	1	2
Occupation		
Student	18	36
Unskilled	13	26
Skilled	5	10
Housewife	8	16
Professional	6	12

Table 2: Incidence of symptoms.

Symptoms	Present	Absent
Fever	50 (100)	0 (0)
Chills	13 (26)	37 (74)
Headache	13 (26)	37 (74)
Constipation	5 (10)	45 (90)
Diarrhoea	14 (28)	36 (72)
Abdominal pain	32 (64)	18 (36)
Vomiting	22 (44)	28 (56)
Black stools	0	50 (100)
Myalgia	8 (16)	42 (84)
Cough	5 (10)	45 (90)
Anorexia	18 (36)	32 (64)

Table 3: Incidence of signs.

Signs	Present	Absent
Coated tongue	11 (22)	39 (78)
Relative bradycardia	17(34)	33(66)
Splenomegaly	18 (36)	32 (64)
Hepatomegaly	21(42)	29 (58)
Rose spots	3 (6)	47 (94)
Altered mentation	(0)	(100)

In this study, haemoglobin<10gm/dl was found in 42.9% of cases. Leucopenia (WBC count < 4000/cumm) & leucocytosis (WBC count > 11000/cumm) was seen in 21% & 10% patients respectively. Thrombocytopenia (platelet count<1.5lacs/cumm) was seen in 30.9%. Hyperbilirubinemia (> 1 mg/dl) was seen in 28.7% while the ALT was elevated (> 60 IU/ml) in 45% patients. A single estimation of significant titre of Widal test was suggestive of Typhoid fever in 80% cases (Table 4). Among the Widal positive cases blood culture was positive in 18 (36%) (Table 5). Incidence of S Typhi was 80% and S. Paratyphi A was 20% (Figure 1).

Table 4: Results of Widal test titer.

Widal test titre	Patients (n=50)	Percentage (%)
TO		
Normal	06	12
2 fold	04	8
4 fold (>1:160)	22	44
8 fold (>1:320)	18	36
TH		
Normal	03	06
2 fold	07	14
4 fold (>1:160)	23	46
8 fold (>1:320)	17	34
AH		
Normal	22	44
2 fold	18	36
4 fold (>1:160)	04	08
8 fold (>1:320)	06	12

Table 5: Relation of Blood culture and Widal test.

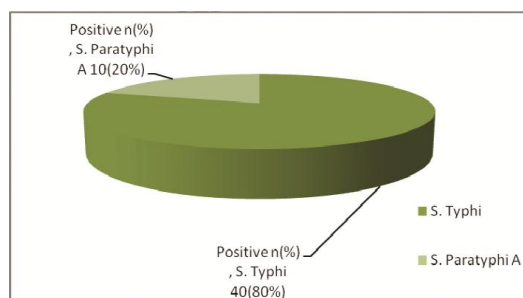| Blood culture	Widal test		Total
	Positive	Negative	
Positive	18(36)	6(12)	24
Negative	26(52)	0(0)	26
Total	44(88)	06(12)	50

Figure 1: Detection of S. Typhi and S. Paratyphi A in 50 patients.

Chloramphenicol and ciprofloxacin resistance was seen in 66% and 22% of cases respectively in the present study. Maximum resistance for chloramphenicol, amoxicillin, and ampicillin was seen as compared to ceftriaxone and ciprofloxacin (Table 6). One patient had resistance to ceftriaxone and received oral azithromycin 1gm daily for 7 days. There was no significant difference between antimicrobial susceptibility patterns of S. typhi and S. paratyphi A.

Table 6: Antibiotic sensitivity.

Antibiotic	Sensitivity n (%)	Resistance n (%)
Amoxycillin	14 (28)	36 (72)
Chloramphenicol	17 (34)	33 (66)
Ampicillin	21 (42)	29 (58)
Cotrimoxazole	19 (38)	31 (62)
Nalidixic acid	15 (30)	35 (70)
Ciprofloxacin	39 (78)	11 (22)
Ceftriaxone	49 (98)	1 (2)

The mean time to defervesence in the group of patients who had received antibiotics prior to admission was 4.8 days (95% CI 3.8,5.2 days) while in the patients who did not receive prior antibiotics was 5 days (95% CI 4.3,5.8 days), p0.2 (NS). The overall mean time to defervesence with ceftriaxone used as therapy was 4.7 days. Average duration of treatment was 12 days with ciprofloxacin and 10 days with Ceftriaxone. The duration of illness prior to hospitalization was 4 to 6 days and the illness lasted for 14 to 20. No relapse was observed among the follow up cases for 8 weeks after discharge from hospital

DISCUSSION

Although the disease is not common in industrialized countries, it remains an important and persistent health problem in countries like India with inadequate sanitation and unsafe water supply. Five cardinal features of Typhoid according to Manson's Tropical Diseases, third edition are fever, relative bradycardia, toxemia, splenic enlargement and rose spots.[3] The first three followed by abdominal distension, pea soup diarrhea and intestinal

hemorrhage should confirm the diagnosis of the disease. Unfortunately in its new edition the paragraph on diagnosis does not include clinical features at all. Though some studies have shown that clinical diagnosis is not always useful, other studies confirm the persistence of these clinical features of Typhoid fever.[4, 5, 6]

In this study cases admitted were throughout the year showing the endemecity of the disease. Maximum numbers of cases were admitted during May-September (56%) (Table 7). Maximum number of cases was observed in the summer and monsoon seasons. The logical risk factors associated with this seasonality of enteric fever episodes include the consumption of unhygienic beverages in the summer months. Also, the ground water-table level sets progressively lower, become more stagnant, and its quality deteriorates increasing the likelihood of people ingesting viable *Salmonellae* in drinking water. The drainages and over-packed rubbish dumps in Mumbai, especially following rainfall, also contribute to the higher incidence. It is hence imperative to ensure safe tap-water supply, and to identify and treat chronic carriers of the implicated bacteria.

Table 7: Month wise distribution of cases.

Month	No. of cases	Percentage (%S)
January	04	8
February	03	6
March	03	6
April	04	8
May	06	12
June	05	10
July	06	12
August	05	10
September	06	12
October	02	4
November	03	6
December	03	6
Total	50	100%

The male to female ratio affected was 1.2:1. Incidentally, this slight preponderance of infections in males probably could be due to the fact that females are brought less frequently to hospitals because of various social, financial and religious bars in our male dominated society and also due to the fact that male goes outside more, takes outside food more frequently than female. The population affected most was of low socioeconomic group which possibly as a result of poor sanitation and overcrowding. All the patients in this study came with fever, and, the duration of fever varied from 3 days to 3 weeks. Maximum cases presented in the 2nd week. The stepladder fever pattern that was once the hallmark of typhoid fever occurred in as few as 16% of cases which was 12% in study by Gupta SP.[5] In most contemporary presentations of typhoid fever, the fever had a steady

insidious onset. Relative bradycardia at the height of the fever is a good clue for the typhoid fever; however, it was present in a small number of cases. Few other studies have also found these to be inconsistent features of enteric fever YK Joshi.[6] Rose spots are pink, blanching erythematous maculopapular lesions approximately 2-4 mm in diameter that appear in crops on the chest and abdomen; they appear during the second week and resolve in 2 to 5 days reported in 5-30% of cases[7]. Rose spots were present only in (6%) which could have been missed due to dark complexion of population in our study. Majority of the symptoms and signs in our study did not have very high predictive accuracy. Symptoms like fever, headache, chills had very high sensitivity and positive predictive value but lacked specificity. Similarly abdominal distention, vomiting, constipation, altered mentation, caecal gurgling and abdominal tenderness on palpation had very high specificity but low positive predictive value and sensitivity. Though various studies have repeatedly emphasized the persistence of these clinical features[8,9] none have given objective data on the value of individual symptoms and signs. Hence diagnosis of enteric fever by symptoms and signs has to be additionally supported by laboratory results. In this study, haemoglobin<10gm/dl was found in 42.9% of cases. Leucopenia, thrombocytopenia and anemia in typhoid 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.[10] In this study, 80% (40) had typhoid fever and 20% (10) patients had paratyphoid fever on the basis of significant Widal titers and isolation of Salmonella in blood culture. In a similar study done by *Krishnan P et al* in Chennai, 70% of isolates were Salmonella typhi and 30% were Salmonella paratyphi A, which was in accordance with our study.[11] The mean duration of illness at presentation was 10.2±4.3 days and the shortest and longest durations were 6 and 18 days respectively.

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. Standard treatment with chloramphenicol or amoxicillin is associated with a relapse rate of 5-15% or 4-8% respectively, whereas the newer quinolones and third generation cephalosporins are associated with higher cure rates.[12] 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. In the present study chloramphenicol resistance was seen in 66% (33).

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 quinolones antibiotics. Ciprofloxacin has also been found to be highly effective therapy for infections due to MDR *S typhi* and S paratyphi.[14] Certain caveats should be entered here regarding the quinolones. Resistance to ciprofloxacin of *S typhi* appears to be increasing, especially in the Indian subcontinent.[15] 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.[16] 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] Ciprofloxacin resistance was seen in 22% (11) in our study.

Excellent response rates have been reported with ceftriaxone when administered for 5 to 7 days, but the relapse rate remains incompletely defined.[18] These drugs should be reserved for quinolone resistant cases. It is recommended to treat with ceftriaxone for 10-14 days. [19] In third generation cephalosporins we tested for ceftriaxone and found it to be 98% sensitive for S. typhi and S. Paratyphi. Only one patient who had resistance to ceftriaxone received oral azithromycin 1gm daily for 7 days. Azithromycin, a new macrolide antibiotic administered in a dose of 1 gram once daily for 5 -7 days is also useful for the treatment of typhoid fever, although the disease takes longer to defervesence.[2,20] The main advantage of azithromycin is that they can be used in children and in pregnant or nursing females.

This study also emphasizes that in areas (e.g. Indian subcontinent, Southeast Asia, and Africa), with a high prevalence of MDR S. Typhi all patients suspected of having typhoid fever should be treated with quinolones or third-generation cephalosporin until the results of culture sensitivity studies become available.

CONCLUSION

- For the prevention of disease in developing countries like India public education measures should be to encouraged regarding the need for thorough hand washing before eating and preparing/handling foods and sanitary disposal.
- In the diagnosis of typhoid fever though none of the clinical symptoms and sign have very high accuracy, diagnostic criteria's may be helpful when combined with high index of suspicion and relevant laboratory investigations.
- Widal test is very commonly used in Indian set up but has variable sensitivity and specificity and

therefore has problems in interpretation. As a gold standard blood culture should be done for the definitive diagnosis and proper treatment pertaining to the antibiotic sensitivity and resistance of the isolate.
- Multidrug resistant typhoid cases, resistant to first line drugs, namely chloramphenicol, cotrimoxazole and ampicillin are reported since 1990. Currently, newer fluoroquinolones and third-generation cephalosporins should be the drugs of choice for the treatment of typhoid fever.
- Management of typhoid (cloudy) fever continues to pose a challenge, even one hundred years after the microorganism was first isolated by Gaffkey, a German in 1884.

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