

Original Research Article

Assessment of clinical profile, antibiotic sensitivity and prescription pattern in blood culture positive enteric fever among pediatric and adult patients admitted in a tertiary care hospital: a prospective study

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ABSTRACT

Background: Asterion Introduction: Enteric fever is a major concern in developing country. It is predominantly caused by serovars *typhi* and *paratyphi* of *Salmonella enterica*. Recently, an upsurge in antimicrobial resistant strains has worsened the management of enteric fever. So, aim of present study is to evaluate the clinical profile, antibiotic sensitivity and prescription pattern in blood culture proven cases of enteric fever in pediatric and adult patients.

Methods: Single centre, prospective study was conducted at a tertiary care hospital. Demographic and clinical details of blood culture proven enteric fever admitted in hospital were collected over the period from August 2016 to November 2018.

Results: Total 58 blood cultures grew *Salmonella* spp. , amongst them 84.48 % had growth of *Salmonella typhi*. Blood culture was sent after a mean period of 9 days and 10 days of fever in pediatric and adult patients respectively. All isolates of *S. paratyphi* A were pansusceptible, whereas 36.73 % isolates of *S. typhi* were multidrug resistant and nalidixic acid resistant. 68.97% patients received antibiotics before admission. The difference between mean time to defervescence in patients who received ceftriaxone and those who received more than one antibiotic was not statistically significant. (*P* value 0.87)

Conclusion: Blood cultures are the important diagnostic tool to identify multidrug resistant *Salmonellae*. Study showed that combination therapy was not statistically superior and awareness of local antimicrobial susceptibility pattern significantly helps for better management of the patients.

Keywords: Adults, Blood culture, Enteric fever, Pediatrics

INTRODUCTION

Enteric fever is caused by *Salmonella enterica* serotype *typhi*, and serotypes *Paratyphi* A/B, and C. The above two serotypes are classified clinically as *typhoidal* *Salmonella* strains. *S. typhi*, and *S. paratyphi* A/B are

human restricted pathogens whereas *S. paratyphi* C involves animals as well. The disease is a major public health problem, especially in the developing countries like India. There were 2.16 million episodes of enteric fever worldwide, resulting in 216 000 deaths in 2000. Amongst them, developing Asian countries

comprised more than 90% of this morbidity and mortality.¹ India has an annual incidence of 493.5/100,000 persons per year and in a recent systematic review, the pooled estimates of annual incidences of typhoid and paratyphoid fever in India was 377 (178-801) and 105 (74-148) cases in 100,000 person per year, respectively.^{2,3} In the developed countries like United States, majority of cases of enteric fever are related with travel history to endemic area. The rate of enteric fever is 10 per 1 million travellers, arriving from Asian countries whereas it increases to 89 per 1 million travellers from India.⁴

In developing countries like India, diagnostic protocol is not followed by majority of practitioners. Lots of patients are still treated empirically without any confirmative investigation. There are various diagnostic methods available for confirmation of enteric fever. Widal test which is the most commonly used diagnostic test, has significant limitations in its sensitivity, specificity and interpretation.⁵ Typhidot which is a rapid-dot enzyme immunoassay (EIA), is also frequently utilised and has the advantage of giving a faster result. Blood culture is the gold standard with specificity of 100% and sensitivity of 40% to 80%.⁶ In addition, sensitivity pattern of antibiotics for a isolate is available too. But majority times, blood cultures are not sent because of reasons like cost factor, ignorance on part of clinicians about their relevance, reluctance on part of the patient and unavailability of standard laboratories.

The appropriate and timely administration of antibiotics reduces the mortality and shortens the duration of fever from 3-4 weeks to 3-5 days.⁷ The most frequently used antibiotics to treat *Salmonella enterica* are third or fourth generation cephalosporins along with macrolides like azithromycin.⁸ The emergence of widespread resistance to the commonly used antibiotics has led to difficulty in the management of the disease.

So, primary objective of the study was to analyze the sensitivity pattern of the blood culture proven enteric fever cases along with the prescription pattern of the treating clinician. The secondary objective was to study the clinical and laboratory parameters of patients along with previous antibiotic consumption history.

METHODS

A single centre, prospective study was conducted at is a 200-bed tertiary-care hospital with approximately 20000 annual admissions in a catchment area of 20 lakh persons. The hospital has centralized electronic medical and laboratory record databases that use unique identification numbers. The hospital pathology laboratory has standardized blood culture techniques that use fully automated blood culture system.

Patients admitted in a tertiary care hospital, who had blood culture positive for bacteria causing enteric fever

during the period of August 2016 to November 2018 were enrolled in study. Inclusion criteria were patients whom age ranging from 0-18yrs for pediatrics and 18-80yrs for adults. Second, patients admitted in hospital with clinically suspected enteric fever and under antibiotic therapy were enrolled in study. Patients admitted with proven infectious disease other than enteric fever and having co-infection were excluded from the study. Any patient with multiple positive laboratory records obtained was excluded. Informed consent was obtained from the patients or their relatives in paediatric patients. A detailed case record form was used to collect the data of the patients. Data includes patients' demographic details, previous medical history, sign & symptoms, clinical examination, laboratory investigations, details of treatment given to the patients in hospital and after discharge, diagnosis and patient outcomes.

Antimicrobial sensitivity testing at Microbiology laboratory based on Clinical and Laboratory Standards Institute guidelines. Antimicrobial sensitivity of ampicillin, chloramphenicol, cotrimoxazole, ciprofloxacin, cefixime, and ceftriaxone were observed. The statistical t test was utilized to determine the significance. *P* values less than 0.05 were considered statistically significant.

The study was approved by the Institutional Ethics Committee.

RESULTS

A total of 58 patients were found to be having blood culture positive for *Salmonella enterica* serotype *typhi* and *paratyphi A/B* during the study period. Out of 58 patients, 27 were under paediatric age group and 31 were adult patients.

Among paediatric patients, 20 were male and 7 were female patients. While, in adult patients, 20 were male and 11 were females (Figure 1). The age of the patients ranged from 1 year to 53 years and the mean age was 22.4 years.

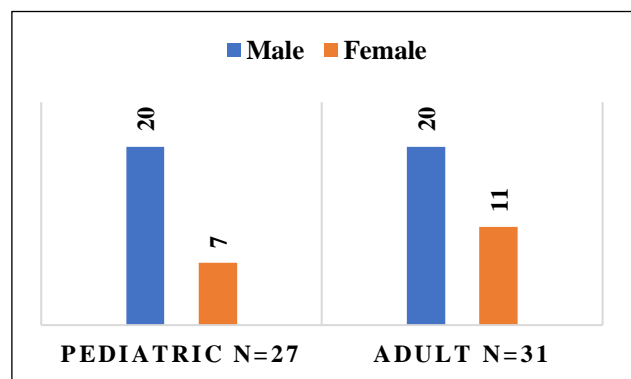


Figure 1: Age and gender wise distribution of blood culture proven Enteric fever cases.

The commonest reason for hospital admission was fever. Amongst paediatric patients, 44.45% had fever ranging from six to ten days whereas 33.34% and 22.23% patients had fever duration of one to five days and more than ten days respectively. Similarly, in adult patients, 41.93% had duration of fever from six to ten days whereas 32.26% and 25.81% had duration of fever of more than ten days and one to five days respectively (Table 1).

Table 1: Percentage of duration of fever during hospital admission.

Duration of fever	Paediatric patient	Adult patient
1-5days	33.34%	25.8%
6-10 days	44.45%	41.93%
>10 days	22.23%	32.26%

The percentage of patients having chills associated with fever in paediatric and adult age group were 48.15% and 25.81% respectively. Overall 39.66% patients were suffering from abdominal pain at the time of admission. The percentage of patients suffering from vomiting in paediatric age group was 62.96% whereas in adults was 32.26%. Patients complaining of loose stools and constipation were 32.76% and 12.07% of total patients respectively. All except five patients, received initial treatment from general practitioners before getting admitted at tertiary care hospital. The past history of enteric fever was present in only three patients. None of the patients had received vaccination for enteric fever anytime in their life. The relative bradycardia was evident only in two patients. Hepatomegaly was present in 18.6% while splenomegaly was seen in 8.6% patients. Hepatosplenomegaly was noticeable in 14.2% patients (Table 2). None of the patients developed complications like perforation, gastrointestinal bleeding or acute mental changes.

Table 2: Clinical profile of Enteric fever.

Clinical features	Percentage
Fever with chills	48.15%(P), 25.81%(A)
Vomiting	62.96%(P), 32.26%(A)
Abdominal pain	39.66%
Loose stools	32.76%
Constipation	12.07%
Relative bradycardia	3.45%
Hepatomegaly	14.2%
Splenomegaly	8.6%
Hepatosplenomegaly	14.2%
Leucopenia	19%
Leucocytosis	5.17%
Eosinopenia	84.3%
Thrombocytopenia	17.24%
Raised liver enzymes	51.86%(P), 61.3%(A)
Past history of enteric fever	5.17%

Leucopenia (defined as a total WBC count < 4000 / cmm) was present in 19% of the patients whereas 80% had normal counts. Leucocytosis (defined as WBC count > 11000 / cmm) was present in three patients. The mean white blood cell (WBC) count was 5846 / cmm with a ranging from 1278 / cmm to 13600 / cmm. Absolute eosinopenia (0% eosinophils) was seen in 84.3% patients. 17.24% manifested thrombocytopenia (defined as platelet count <1.5 lacs / cmm). The liver enzymes - aspartate and alanine aminotransferase were raised in 61.3% of adults and 51.86% of paediatric patients.

The blood cultures were sent after a mean period of 9 days and 10 days of fever in paediatric and adult patients respectively. Amongst the paediatric patients, 22 had blood culture positive for *Salmonella typhi* whereas 5 had blood culture positive for *Salmonella paratyphi A*. Similarly, in adult patients, 27 had blood culture positive for *Salmonella typhi* and 4 had *Salmonella paratyphi A* in their blood cultures (Figure 2).

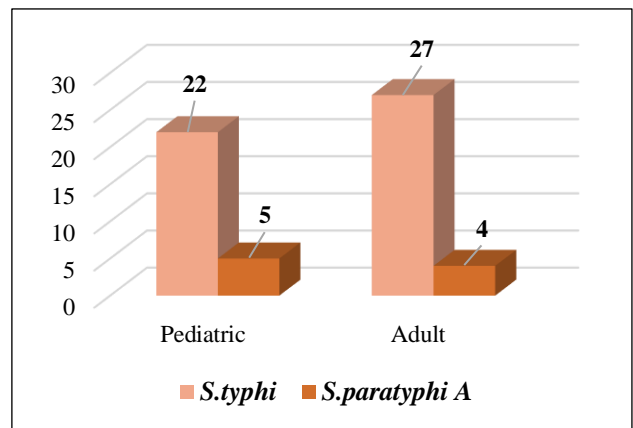


Figure 2: Age wise distribution of number of Salmonella spp. isolated from blood cultures during study period.

All the isolates of *Salmonella paratyphi A* were sensitive to ampicillin, chloramphenicol, trimethoprim - sulfamethoxazole, third generation cephalosporin like ceftriaxone, azithromycin and antibiotics of higher classes.

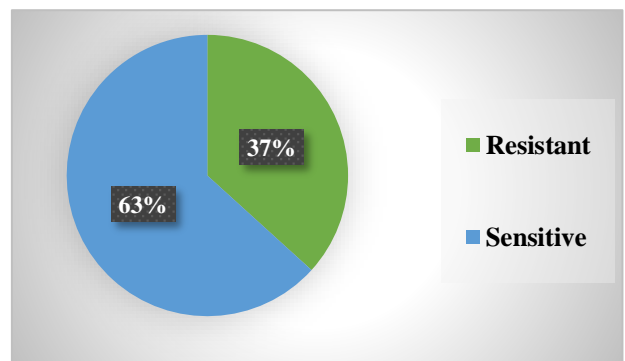


Figure 3: Percentage of ceftriaxone resistance among Salmonella spp. isolated from blood cultures.

The 63.27% isolates of *Salmonella typhi* were sensitive to all the above-mentioned antibiotics whereas 36.73% isolates were only sensitive to fourth generation cephalosporins, beta lactam - beta lactamase inhibitors, carbapenems and azithromycin. (Figure 3) These isolates were multi drug resistant and also resistant to nalidixic acid.

The IgM Typhidot was done in 44.83% of the patients. Total 19 patients were typhidot positive but in 7 patients; it was negative despite of blood culture being positive. Widal test was done only in 9 out of total patients. It was positive (defined as *S. typhi* O antigen >120 and either *S. typhi* H or *S. paratyphi* H antigen titres >120) in all of them. The mean duration of fever at which widal test was positive was 11.6 days.

The number of patients who received antibiotics before admission was 40(68.97%). These antibiotics were beta lactams like cefuroxime, cefixime, amoxicillin - clavunate, quinolones like ofloxacin and azithromycin. A combination of antibiotics was used in 17 (29.31%) patients. During hospitalization 29 out of 58 (50%) patients received combination of two antibiotics. The most common combination utilised was ceftriaxone and azithromycin. The proportion of patients who received only one antibiotic during their hospital stay was 36.21% and there were 13.79% patients who received more than two antibiotics during indoor stay (Table 3).

Table 3: Percentage of antibiotic consumption among paediatric and adult patients before and after hospital admission.

Before admission	Percentage of antibiotic consumption
One antibiotic	68.97%
Combination of antibiotics	29.31%
No antibiotic	1.72%
After admission	
One antibiotic	36.21%
Two antibiotics	50%
>2 antibiotics	13.79%

The only reason for change of antibiotics during treatment was persistence of fever. The most common antibiotic used was ceftriaxone (72.41%). The other antibiotics used were meropenem, imipenem, ofloxacin, doxycycline, metronidazole, ceftriaxone - sulbactam, cefoperazone - sulbactam and amoxicillin - clavulanate. At the time of discharge, 44.83% patients received azithromycin, 36.21% patients were given third generation oral cephalosporins and equal percentages were discharged on a combination of antibiotics. The other antibiotics advised on discharge were quinolones, carbapenems and beta lactam - beta lactamase inhibitors.

The overall mean time to defervescence after hospital admission was 5.74 days. Patients who received ceftriaxone only showed mean defervescence time of 5.68 days whereas in those who received more than one antibiotic during their course of hospital stay was 5.95 days. The difference between the two was not statistically significant (*p* value 0.87) and the 95% confidence interval was -3.48 to 2.94. Similarly in those, who had blood culture positive for *Salmonella typhi*, the mean defervescence time was 5.86 days whereas in cases of *Salmonella paratyphi* A, it was 4.20 days. The difference between them was not clinically significant (*p*value 0.53) and the 95 % confidence interval was -3.59 to 6.91 (Table 4).

Table 4: Mean of defervescence time observed based on treatment and Salmonella spp. isolated from blood culture.

Based on treatment given	Time of defervescence	p-value
Only Ceftriaxone	5.68 days	0.87
>one antibiotic	5.95days	
Based on <i>Salmonella</i> spp. isolates		
<i>S. typhi</i>	5.86days	0.53
<i>S. paratyphi</i> A	4.20days	

DISCUSSION

Present study included only those who had blood culture positive for *S. typhi* or *paratyphi* A. who were widal positive along with those who had positive blood culture.^{9,10} The study patients who had positive blood culture but this study was retrospective.¹¹ There was another large series retrospective study consisted of 50 patients as compared to 58 in present study but all the patients in their study were more than 12 years of age whereas present study included both paediatric as well as adult patients.^{10,12} The mean age of patients and present study was 24.5 years and 22.4 years respectively. In the retrospective studies the mean age was 21.7 years and 18.2 years respectively.^{11,13}

The signs and symptoms of the patients in the present study were similar to those found in earlier studies.^{10,11,13} The relative bradycardia was present only in very few patients, on the same lines as it was in other studies.^{10,11} However in study nearly two third of patients had pulse rate within normal range despite fever.¹³ As compared to study, hepatomegaly and splenomegaly were present in lesser number of patients.¹⁰ Leucopenia was found in 19% of the patients whereas normal WBC was present in 80% of patients. In study conducted, 21% had leucopenia.¹⁰ In present study, there was presence of leucocytosis in three patients, which can cause diagnostic dilemma. Absolute eosinopenia was present in 84.3% of our patients as compared to seen in 77% of patients, in study So absolute eosinopenia can be one of the indicators for enteric fever.¹¹ The platelet counts can be

normal or mildly reduced in enteric fever. It was well studied that myeloid maturation arrest occurs along with a decrease in the number of erythroblasts and megakaryocytes and an increased phagocytic activity of histiocytes in the bone marrow causing bone marrow suppression.¹⁴ In present study, 17.24% patients had thrombocytopenia whereas in studies, it was present in 30.9% and 14.8% respectively.^{10,13} The liver enzymes are frequently raised two to three times of the normal range. On the lines of the other studies, they were increased in 61.3% and 51.86% of adults and children respectively.

Blood culture is the most sensitive method of diagnosis but the inherent limiting factors are low grade bacteremia and prior receipt of antibiotics.¹⁵ In present study, 84.48% patients had growth of *Salmonella typhi* and the rest had *Salmonella paratyphi A*. Similarly, in studies conducted, 80% of patients had growth of *Salmonella typhi* and 20% had *Salmonella paratyphi A*.^{10,13} Conversely, in the retrospective study, 40% of the isolates were *S. paratyphi A*.¹¹ The rampant misuse and abuse of antibiotics has led to the emergence of multidrug resistance *Salmonella* species. This has caused a great deal of misery and agony to both the clinicians as well as the patients. There was no significant difference in antimicrobial susceptibility of *Salmonella typhi* and *Salmonella paratyphi A* in the study conducted, though having maximum resistance to chloramphenicol, ampicillin and amoxicillin. In present study, all the isolates of *S. paratyphi A* were susceptible including ampicillin, chloramphenicol, trimethoprim - sulfamethoxazole, third generation cephalosporins, quinolones and azithromycin whereas the 36.73% of the isolates of *S. typhi* were multidrug and nalidixic acid resistant, being sensitive only to 4th generation cephalosporins, beta lactam - beta lactamase inhibitors, carbapenems and azithromycin. Observe did not any resistance to third generation cephalosporins unlike present study. However, they did elaborate high prevalence of nalidixic acid resistance. Even in the study, all the isolates were sensitive to third generation cephalosporins despite of presence of some nalidixic acid resistant strains.¹³ So, clearly there seems to be a difference in sensitivity patterns in present study as compared to other studies. The emergence of multidrug resistance along with nalidixic acid and third generation cephalosporins resistance in *S. typhi* should serve as a wake up call for the clinicians.

The antibiotics are prescribed very frequently in the community. Many time patient's self - medicate. In present study, 68.97% patients had consumed antibiotics prior to admission and 17 patients had received a combination of antibiotics. This indicates that blood cultures should be sent in all the suspected cases of enteric fever. Even if the patients have received prior antimicrobials. Also in study 46.2% patients had received antibiotics before hospitalization.¹¹

The most common antibiotic used in present study was ceftriaxone. Half of the patients received combination of

two antibiotics, most common being ceftriaxone and azithromycin. There were 13. 79% patients whose antibiotic prescription was changed more than once. The reason was persistent fever. It has been shown that defervescence takes anywhere from 3 to 6 days after initiation of therapy.¹⁶ The difference between mean defervescence time in those patients, who received ceftriaxone only and those who received more than one antibiotic in combination was not statistically significant. Similarly, in the study, there was no significant difference in time to defervescence in the above mentioned groups. So, it's very important for the clinicians to have patience and wait for the required time for defervescence in the sensitive strains. Similarly, the unnecessary change of antibiotics should be avoided.

The main limitation of the present study was small sample size. Further studies are required with enrolment of more patients. The antibiotics received by the patients prior to admission could have impacted the time to defervescence. The small sample size could have affected the comparison of efficacy of the antibiotics.

CONCLUSION

The emergence of multidrug resistance along with nalidixic acid and third generation cephalosporins resistance in *S. typhi* indicate a necessity for practising stringent antimicrobial stewardship. Blood culture which is the most sensitive method for diagnosis of enteric fever should be done for all patients. Antibiotics can be started on suspicion of enteric fever but it should be deescalated once the blood culture report is available.

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