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Original Research Article

Current perspectives of enteric fever: a hospital based study of 185 culture positive cases from Ahmedabad, India

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ABSTRACT

Background: Enteric fever is endemic in Ahmedabad and its diagnosis and treatment is fraught with problems. The last two decades have seen a change in clinical pattern of enteric fever with emergence of multi drug resistant strains. Hence, the study was carried out with the aims to study the clinical profile, hematological features, sensitivity pattern, response to antimicrobials and outcome of culture proven enteric fever.
Methods: This was a retrospective study carried out at a tertiary care teaching hospital at Ahmedabad, India from January 2014 to December 2016.
Results: Out of the 185 study patients, 35.8 % were less than 5 years of age. Of the total 185 isolates, 160 (86.4%) were *Salmonella typhi* while 25 (13.6%) were *Salmonella paratyphi* A. Following sensitivity patterns were recorded: cotrimoxazole (93%), chloramphenicol (93%), ampicillin (96.2%), nalidixic acid (98.4%), cephalosporins (100%) and azithromycin (70.8%). Leukocytosis was seen in significant number of patients less than 5 years of age as compared to more than 5 years. 91.9% patients were treated by ceftriaxone as a monotherapy with defervescence time of 3.8 days and no mortality.
Conclusions: Effective vaccination strategy targeting children less than 5 years can decrease the burden of this disease. Presence of fever without focus and leukocytosis in less than 5 years suggests possibility of enteric fever. Salmonella have once again become sensitive to first line antibiotics like ampicillin, cotrimoxazole and chloramphenicol. There is a good rate of sensitivity to nalidixic acid but high rate of resistance against azithromycin in this part of the country. Ceftriaxone as a monotherapy is quite effective in the treatment.

Keywords: Antibiotic sensitivity, Blood culture, *Salmonella*

INTRODUCTION

Enteric fever is an infectious disease caused by *Salmonella enterica serotype typhi* or *paratyphi* A/B. Though it is a preventable disease, it is a major global threat to public health. According to most recent estimates (published in 2014), approximately 21 million cases and 2, 22,000 typhoid related deaths occur annually worldwide.[1] Ochiai LR et al, in their review of disease burden due to enteric fever from five Asian countries reported a higher incidence of typhoid fever from India, Indonesia and Pakistan.[2] Enteric fever is endemic in India. Reported data for the year 2013 shows 1.53 million cases and 361 deaths.[3]

There is a wide spectrum of clinical presentation of enteric fever and hence clinical diagnosis is often fraught with problems. Blood culture is considered as the gold standard for the diagnosis and gives information about antibiotic sensitivity of the isolate. However, the lack of laboratory facilities, poor awareness amongst health care professionals, administration of prior antibiotics and cost

factor are hurdles in this diagnostic approach. The Widal test has suboptimal sensitivity and specificity, requires careful interpretation and gives appropriate results only after 7 days of illness.[4]

By the end of 1990s, *salmonella enterica* developed resistance simultaneously to all first line drugs like chloramphenicol, cotrimoxazole and ampicillin.[5] Also according to various studies, there is significant increase in Nalidixic acid resistant salmonella typhi (NARST).[6,7] Cephalosporins such as ceftriaxone and cefixime are recommended as first line drugs but studies are required to study defervescence and relapse rates. Azithromycin which is recommended as a second line drug also, needs to be studied, as there is limited experience of its clinical use in enteric fever.[8,9]

Thus, enteric fever raises several issues in diagnosis and treatment. There is a continuous need to study the sensitivity patterns and emergence of resistant organism as well as clinical response to antibiotic therapy. Hence, a retrospective study was done in our hospital.

The objective of the study was to study the frequency and sensitivity pattern of *Salmonella typhi* and *paratyphi.* To study clinical, laboratory and radiological profile of culture proven enteric fever. To study response to antimicrobials and outcome of patients of culture proven enteric fever.

METHODS

This retrospective observational study was carried out at a tertiary care teaching hospital at Ahmedabad, India. The records of all the indoor culture positive cases of *Salmonella* in children until 14 years of age during a period of three years from January 2014 to December 2016 were obtained from medical record department. Institutional scientific and ethical committee approved the study. Cases were diagnosed as enteric fever if presented with fever (temperature >38 degree Celsius) and their blood culture yielded *Salmonella typhi* or *paratyphi.* Case records were analyzed for clinical data, laboratory parameters, ultrasonography findings and treatment details. Patients who took discharge against medical advice were not included in the study. Statistical analysis was done using IBM SPSS (Statistical programme for social sciences) 20.0 version. The variable definitions used in this study were:

- Leucopenia: Total WBC count < 4000 cells/cu mm
- Leukocytosis: Total WBC count > 11,000 cells/cu mm
- Eosinopenia: Absence of eosinophils in peripheral smear
- Thrombocytopenia: Platelet count < 1,50,000/cu mm
- Serum transaminase (ALT) was considered elevated if its value was above normal (15-45 IU/L)
- Serum widal was considered positive if *salmonella typhi* O or H titer >1:160 or *Salmonella paratyphi* AH or BH >1:160.
- Blood culture: 2-5 ml of blood was collected by sterile venipuncture technique and inoculated in BD BACTEC Peds PlusTM/F culture vials (containing enriched Soybean-Casein Digest broth and resins). The culture vials were then incubated at 37 degree Celsius in the BACTEC 9050 fluoroscent series system and monitored regularly for the presence of microorganisms. Microorganisms produce carbon dioxide by metabolizing the substrate in a culture bottle. This increases fluorescence of a vial sensor, which is monitored by the instrument. The bottles in which growth is seen is further sub-cultured on agar plates (MacConkey agar, Blood agar and Chocolate agar) and incubated in an incubator for 24 hours. Salmonella produces colourless colonies on MacConkey agar plates. The colonies are subjected to biochemical reactions for identification and species differentiation. Antibiotic sensitivity was done by standard disc diffusion method using following antibiotic discs (sulfamethoxazole-trimethoprim, ampicillin, chloramphenicol, nalidixic acid, ciprofloxacin, ofloxacin, levofloxacin, ceftriaxone, cefotaxime, cefepime, cefixime and azithromycin). Antibiotic sensitivity testing was performed in accordance with the clinical and laboratory standards institute (CLSI) guidelines by Kirby-Bauer disc diffusion method.
- Ultrasonography reports were studied for the presence of hepatomegaly, splenomegaly, mesenteric lymphadenopathy, acalculous cholecystitis, ascites, biliary sludge and cholelithiasis.

RESULTS

During this period, 185 children had blood culture positive enteric fever. Of these 185 children, 112 were male and 73 were female with the male: female ratio 1.53:1. The age ranged from 1 year to 14 years with mean age of 7.2 years. 11.3% were less than 2 years, 24.5% were between 2 to 5 years, 44.8% were between 5 to 10 years and 18.9% were between 10 to 14 years.

Fever was present in all the patients. The median duration of fever prior to admission was 7 days, the range being 1 to 60 days. High-grade fever was seen in 94.6 % and chills in 72.4%. Abdominal pain, vomiting, cough and loose stools were the most common associated symptoms seen in 84.7%, 47.6%, 54.6% and 30.3% patients respectively. Hepatosplenomegaly was seen in 21.1% patients. Only hepatomegaly was seen in 54.6% while only splenomegaly was seen in 22.2% (Figure 1).

Seven patients had history of enteric fever in the past. Of these four, were culture proven while no details were available for the rest. It was disheartening to note that only three patients in the whole study had history of typhoid immunization.

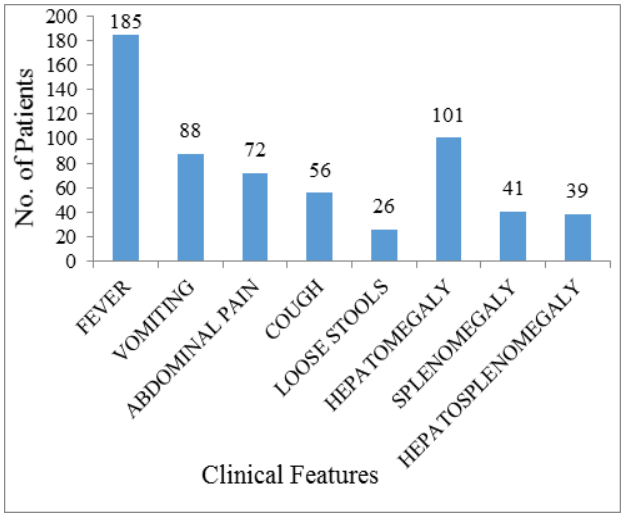

Figure 1: Clinical features of enteric fever.

The mean white blood cell count was 7815/cumm with a range from 2300/cumm to 20,610/cumm. 82.7% patients had normal WBC counts. 5.9% had leucopenia and 11.4% had leukocytosis. It was noted that there was leukocytosis in significant number of patients less than 5 years as compared to more than 5 years by using chi square test ($p < 0.001$). Absolute eosinopenia was seen in 16.2 % patients. The mean platelet count of the study patients was 2,60,481/cumm with a range from 22,000/cumm to 7,48,000/cumm. Thrombocytopenia was seen in 8.6%. ALT was elevated in 14.6% patients. Widal test was done in 125 out of 185 patients. The mean duration of fever at which Widal test was done was 9.4 days. Widal test was positive in 65 (52%) patients out of 125 culture positive patients.

Ultrasound examination of abdomen was done in 88 patients out of the 185 study patients. The mean duration of fever when ultrasound was performed was 10 days. The following ultrasound findings were reported hepatomegaly (37.5%), splenomegaly (37.5%), mesenteric lymphadenopathy (14.7%), bowel wall thickening (11.3%), ascites (10.2%), acalculous cholecystitis (9%), biliary sludge (9%) and cholelithiasis (1.1%).

Out of the 185 study patients, 160 (86.4%) were positive for *Salmonella typhi* while 25 (13.6%) had *salmonella paratyphi* A. The cultures were sent after a mean period of 7.64 days after the onset of fever, the range being 1 to 60 days. Twenty-eight (15.1%) patients had received antibiotics before approaching the institute. The table shows sensitivity patterns of isolates year wise over the study period (Table 1).

Table 1: Year wise sensitivity pattern of the *salmonella enterica* isolates.

Antibiotic sensitivity	2014		2015		2016		2014-16
	***S. typhi* 23n (%)**	***S. par* A 4n (%)**	***S. typhi* 79n (%)**	***S. par* A 8n (%)**	***S. typhi* 58n (%)**	***S. par* A 13n (%)**	**Overall *Salmonella enterica* 185n (%)**
S to TS	23(100)	4(100)	72(91.1)	8(100)	52(89.6)	13(100)	172(93)
S to CH	20(86.9)	4(100)	73(92.4)	8(100)	55(94.8)	12(92.3)	172(93)
S to AMP	22(95.6)	4(100)	75(94.9)	8(100)	56(96.5)	13(100)	178(96.2)
S to NA	22(95.6)	4(100)	78(98.7)	8(100)	57(98.3)	13(100)	182(98.4)
S to CEPH	23(100)	4(100)	79(100)	8(100)	58(100)	13(100)	185(100)
S to AZM	12(52.17)	2(50)	59(74.7)	6(75)	42(72.4)	10(76.9)	131(70.8)

S=sensitive, TS=Trimethoprim-sulfamethoxazole, CH=Chloramphenicol, AMP=Ampicillin, NA=Nalidixic acid, CEPH=Cephalosporins, AZM=Azithromycin

Out of 185 children, majority of children were treated with ceftriaxone (91.9%). Ceftriaxone was used as a monotherapy in the dose of 100 mg/kg/day. Fifteen children received other antibiotics which included cefixime (6), cefotaxime (3), amoxicillin-clavulanic acid (4) azithromycin (1), and ampicillin (1).

The mean period of receipt of ceftriaxone after hospitalization was 6.7 days. The patients who received ceftriaxone received cefixime at 20 mg/kg/day after discharge to finish total antibiotic course of 14 days. The mean time of defervescence defined as number of days from the day of onset of antibiotic treatment in the hospital to the disappearance of fever was 3.8 days.

The mean duration of hospital stay in our study was 6.9 days. There was no mortality in our study series. Complications were noted in 25.4% patients. The common complications were hepatitis (13.5%), thrombocytopenia (7%), pancytopenia (3.7%), bronchitis (3.2%) and myocarditis (1.6%).

Serious complications like septic shock, neuropsychiatric manifestations, osteomyelitis, gastrointestinal bleeding or

perforation were not seen in any of our patients. Relapse of enteric fever was seen in four patients.

DISCUSSION

This study is one of the largest retrospective studies on enteric fever in pediatrics. Other large series include R Ganesh et al, J Gavhane et al and Walia et al.[7,10,11]

In our study, we noted that of the total patients, 11.3% were less than 2 years, 24.5% were between 2 to 5 years, 44.8% were between 5 to 10 years and 18.9% were between 10 to 14 years. R Ganesh et al in their study of enteric fever at Chennai noted 17.8% patients less than 2 years, 32% between 2 to 5 years, 33.5% between 5 to 10 years and 15.8% more than 10 years.[7] The comparison shows that there is maximum incidence of enteric fever between 5 to 10 years of age. In addition, in the preschool age (below 5 years), the incidence is quite high in both the studies. Brooks et al stated in his study that preschool children have 8-9 times more risk for salmonella infection than older persons do in enteric fever endemic areas.[12] Our study shows high incidence (35.8%) of enteric fever below 5 years. This suggests that our region is endemic for enteric fever. The high disease burden in preschool children highlights the importance of vaccine at early age and improvement in water supply and sanitation facilities.

Table 2: Prominent clinical features in culture positive enteric fever in various studies.

Clinical features	Our series (%)	Jog et al (%)	R Ganesh et al (%)	Gavhane et al (%)
Abdominal pain	84.7	33.6	-	10
Vomiting	47.6	42	49	10
Cough	54.6	-	-	22
Loose stools	30.3	31	29	10
Hepatomegaly	54.6	15.9	71	-
Splenomegaly	22.2	7.5	34	-
Hepatosplenomegaly	21.1	12.6	-	70

Fever was a common clinical presentation seen in all our patients similar to studies done by other authors.[7,10,11,13] Table 2 shows the clinical features of enteric fever seen in our series in comparison with other published studies. The incidence of vomiting and loose stools in our study is comparable with other studies. However, there was high incidence of abdominal pain and cough in comparison with other studies.

Most of our cases had normal total leukocyte counts similar to earlier studies.[4,7,10] Leucocytosis (11.4%) and leucopenia (5.9%) in our study is comparable to other studies. However, leucopenia is less as compared to IAP report (20-25%).[4] It was noted that there was leukocytosis in significant number of patients less than 5 years as compared to more than 5 years by using chi square test ($p < 0.001$). Though it is mentioned in literature that leukocytosis makes the diagnosis of enteric fever less probable, in children less than 5 years with fever and leukocytosis, enteric fever should be considered as one of the possibility.[4] Absolute eosinopenia was seen in 16.2% cases. Various studies show absolute eosinopenia in the range of 0-80%.[4,7,10] This can be attributed to baseline high eosinophil counts seen in many children in eastern Ahmedabad due to parasitic infestations or pollutants from nearby chemical industries. Thrombocytopenia in our study is less (8.6%) as compared to IAP report (10-15%) and Gavhane et al (30%).[4,7] ALT elevation is comparable to other studies.[7]

Table 3 shows comparison of laboratory parameters of our study with other studies. Positive Widal test was seen in 52% patients which is comparable to study by Jog et al (48.4%).[5] Ultrasound findings in our study were similar to other studies.[14,15]

In our study, 13.6% isolates were *S paratyphi* A which was less than that reported in literature (20%).[16] Walia et al and Jog et al had reported 19.4% and 40% incidence of *S. paratyphi* A in New Delhi and Mumbai respectively.[5,6] This suggest that with proper vaccination strategy with Vi antigen vaccine; the disease burden can be brought under control to a large extent in this part of the country. The sensitivity pattern of isolates obtained in the study show 100% sensitivity to cephalosporins which is in accordance with other studies.[5,10,17] Sensitivity to cotrimoxazole, chloramphenicol and ampicillin was 93%, 93% and 96.2% respectively which is similar to other studies by Gavhane et al (98%) and Jog et al (96%).[5,10] High sensitivity to above drugs indicate that salmonella has once again become susceptible to first line antibiotics. High nalidixic acid resistance that is a surrogate marker of fluoroquinolone resistance noted in other studies was not noted in our study. R Ganesh et al noted 56-73% resistance, Jog et al noted 79% and Walia et al noted 56.9-88.9% resistance to nalidixic acid.[5,7,11] However, in our study, we noted only 1.6% resistance (3 out of 185 isolates) to nalidixic acid. This concludes that nalidixic acid resistance is not high in salmonella enterica organism in the Gujarat region and fluoroquinolones can

be used. But they should not be used in pediatric age group as it is not approved by Drug Controller General of India to be used under 18 years of age unless the child is resistant to all other recommended antibiotics and is suffering from life threatening infection.[8] Azithromycin is recommended as a second line drug in uncomplicated enteric fever.[8,18] Sensitivity to azithromycin in our study was 70.8%. This high level of resistance in salmonella against azithromycin in this region can be due to overuse of azithromycin for common illnesses. However, still studies are required to evaluate the in vitro and in vivo efficacy of azithromycin.

Table 3: Prominent laboratory parameters in culture positive enteric fever in various studies.

	Our series (2014-16)	Gavhane J et al	Ganesh R et al	Kundu et al- IAP report
No. of cases	185	98	316	
WBC count in normal range	82.7%	80.62%	Most cases	Most cases
Leucocytosis	11.4%	12.24%	12%	-
Leucopenia	5.9%	7.14%	8%	20-25%
Absolute eosinopenia	16.2%	0%	72%	70-80%
Thrombocytopenia	8.6%	30%	-	10-15%
ALT elevation	14.6%	40%	14%	-

In majority of children, ceftriaxone was used as a monotherapy and was highly effective in terms of clinical improvement in both uncomplicated and complicated cases of enteric fever. Hence, the study suggests that ceftriaxone can be used as a monotherapy in the treatment of enteric fever.

CONCLUSION

Enteric fever continues to be a major public health problem and is endemic in this region of India. Effective vaccination strategy targeting children less than 5 years can decrease the burden of this disease. Presence of fever without focus and leukocytosis in less than 5 years should alert the pediatrician about possibility of enteric fever. Salmonella is an easy to culture organism and hence blood culture should always be collected before starting antibiotics. Salmonella have once again become sensitivite to first line antibiotics like ampicillin, cotrimoxazole and chloramphenicol. There is a good rate of sensitivity to nalidixic acid in this part of the country. However, there is also a high rate of resistance against azithromycin. Ceftriaxone as a monotherapy has been quite effective in the treatment of enteric fever. Combination therapy does not provide any added benefit.

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