PROFILE OF CULTURE POSITIVE ENTERIC FEVER IN CHILDREN ADMITTED IN A TERTIARY CARE HOSPITAL

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ABSTRACT

BACKGROUND

According to literature, there are only few studies and also only one Indian prospective study from South India available on culture positive enteric fever, hence this study was undertaken to provide a data about entire profile of culture positive enteric fever in children from South India, particularly Puducherry.

The aims of this study are to assess-

- a) Proportion of culture positive enteric fever cases among children aged 6 months to 18 years, admitted with fever of ≥ 3 days in a tertiary care hospital,
- b) Their clinical and laboratory profile,
- c) Culture sensitivity pattern,
- d) Response to antibiotics,
- e) Complications.

MATERIALS AND METHODS

This was a prospective observational study done between June 2016 and May 2017 at SLIMS, Puducherry. Total study population was 51. They were included in the study after getting informed consent and the following data were collected: a) Age, sex and socioeconomic details; b) Symptoms; c) Signs; d) Laboratory parameters; e) Antibiotic sensitivity pattern; f) Treatment and clinical outcomes. All the data were statistically analysed by using SPSS software.

RESULTS

In our study, 58.82% were < 5 years. The predominant symptoms seen are high grade fever in 51 (100%), vomiting in 27 (52.94%), anorexia in 22 (43.14%) and diarrhoea in 20 (39.22%). The predominant signs seen are isolated hepatomegaly in 34 (66.66%), hepatosplenomegaly in 11 (21.57%) and coated tongue in 10 (19.61%). Majority of the population had normal total counts, high CRP and elevated SGOT and SGPT. Salmonella typhi was the major isolate in Blood Culture and Sensitivity and all strains were sensitive to ceftriaxone. Overall, Mean (SD) time for defervescence of fever was 3.86 (± 2.12) days and Mean (SD) hospital stay duration was 6.84 (± 2.09) days. Only one complication (consolidation) and no death were seen in our study.

CONCLUSION

Enteric fever should be suspected when there is high CRP, normal WBC and Platelet counts in a child with ≥ 3 days fever with isolated hepatomegaly/ hepatosplenomegaly. Blood culture is the gold standard diagnostic test. Antibiotic sensitivity pattern showed re-emergence of strains with high sensitivity to first line antibiotics like Ampicillin, Chloramphenicol and Cotrimoxazole. Nalidixic acid resistance was observed in all isolates. All the cultures were sensitive to Ceftriaxone and it was used as first line intravenous antibiotic for enteric fever with good outcome.

KEYWORDS

Culture Positive Enteric Fever; Clinical and Laboratory Profile; Clinical Outcomes.

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BACKGROUND

Enteric fever is one of the common causes of fever in children with varied presentations. We have observed that many studies are available in general on enteric fever, but only few studies^{1,2,3,4} mentioned about profile of culture positive enteric fever in the medical literature. Since there is paucity of studies^{5,6}

Available on culture positive enteric fever and also only one Indian prospective study¹ from South India, this study was undertaken to provide a data about entire profile of culture positive enteric fever in children from South India, particularly Puducherry. Since culture positive cases can give true picture of entire spectrum and outcome of enteric fever, the study was confined to culture positive enteric fever cases alone.

Aims and Objectives

To assess- a) Proportion of culture positive enteric fever cases among children aged 6 months to 18 years, admitted with fever of ≥ 3 days in a tertiary care hospital; b) Their clinical and laboratory profile; c) Culture sensitivity pattern, d) Response to antibiotics and e) Complications.

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MATERIALS AND METHODS

This was a prospective observational study done during one year (June 2016 - May 2017) at Sri Lakshmi Narayana Institute of Medical Sciences (SLIMS), Puducherry, after Ethical clearance obtained from Ethical Committee, SLIMS, Puducherry. The study population was Children aged 6 months to 18 years admitted with fever of ≥ 3 days in a tertiary care hospital, proved to have culture positive enteric fever. Children with Enteric fever associated with co-infections or those who are managed outside are excluded from the study. Sample size was calculated at power of 80% and alpha error of 0.05; required sample size was 50 based on previous study.⁵

All children presenting with fever of ≥ 3 days were subjected to undergo following investigations: Hb (Haemoglobin), TLC (Total Leukocyte Count), PLC (Platelet count), CRP (C-Reactive Protein), LFT (Liver Function Test), WIDAL, Blood C and S (culture and sensitivity), USG Abdomen and CXR (Chest X-Ray). Once blood culture was positive for salmonella, they were included in the study after getting informed consent and the following data were collected: a) Age, sex and socioeconomic details, b) Symptoms, c) Signs, d) Laboratory parameters, e) Antibiotic sensitivity pattern, and f) Treatment and clinical outcomes.

Investigations detail: Hb, TLC and PLC were done by automated haemogram analyser. CRP was done by Turbidimetry. LFT was done by fully automated analyser. WIDAL was done by tube method. Blood C and S under aseptic precautions, 1 mL of blood was taken using sterile syringe and put into 10 mL of Ox Bile broth to give an optimal dilution of 1:10. Then sample was transported to microbiology lab of the hospital. In the lab, broth was incubated at 37°C in the incubator for 24 hours. Then subculture was done in MacConkey agar. Then appearance of pale, non-lactose fermenting colonies were looked for. If present, battery of chemical tests were done to confirm *S. typhi* and paratyphi growth.

After confirming growth, antibiotic sensitivity was done in Mueller-Hinton agar using Kirby-Bauer technique. A loopful of growth was taken from the agar and inoculated in peptone water. After 10 minutes, this peptone water poured over Mueller-Hinton agar to cover its entire surface. Then antibiotic discs like ampicillin, chloramphenicol, cotrimoxazole, nalidixic acid, ciprofloxacin, ofloxacin, ceftriaxone, piperacillin/ tazobactam and azithromycin are placed which was incubated for 24 hours at 37°C. Then zone of inhibition measured and results were interpreted by Microbiologist. Culture negativity was declared only after 10 days. Microbiologist was blinded. USG Abdomen was done by ultrasound machine and CXR AP/PA View was done by digital x-ray machine. Imaging reports were given by Radiologists and they were blinded.

Treatment Details: Ceftriaxone (75 mg/kg) was started as the initial drug of choice and later if there was no clinical response Ofloxacin (10 mg/kg) and/or Azithromycin (10 mg/kg) were added. Clinical outcomes like response to antibiotics and complications were assessed during hospital stay.

Statistical Analysis

All the data were statistically analysed by using SPSS (Statistical Package for the Social Sciences) software (IBM-SPSS- Statistics 2014, version 22.0). Demographics, clinical and laboratory variables were given in the frequencies with their percentages and mean (SD) of various outcomes of interest as applicable. Differences in the qualitative variables were analysed using chi-square analysis. A "p" value < 0.05 was considered as statistically significant.

RESULTS/ Demography

Figure 1. Number of Target Population and Study Population

Age	Boys	Girls	Total	Chi-Square Test (X ²)	P value
6 months - 2 years	3 (5.88%)	13 (25.49%)	16 (31.37%)	1.529 with 2 degrees of freedom	0.46
> 2 years - 5 years	9 (17.64%)	5 (9.80%)	14 (27.45%)		
> 5 years - 18 years	13 (25.49%)	8 (15.69%)	21 (41.18%)		
Total	25 (49.02%)	26 (50.98%)	51 (100%)		

Table 1. Age and Sex Distribution of Culture Positive Enteric Fever Cases

Age groups were divided into three categories in our study population. More number of children 30 (58.82%) were seen of < 5 years of age. The distribution of total no. of boys and girls were almost equal. There was no statistically significant difference between age and sex groups ($p > 0.05$) (Table 1).

Majority of the study population were from upper middle class 58.82% (30), whereas lower middle class contributes 31.37% (16) and hardly few cases were noticed in upper class and upper-lower class i.e. 5.88% (3) and 3.92% (2) respectively.

In our study, 58.82% were using corporation water and 68.63% had food intake outside.

Clinical Features

Figure 2. Symptoms among Study Population

The predominant symptoms seen are high grade fever in 51 (100%), vomiting in 27 (52.94%), anorexia in 22 (43.14%) and diarrhoea in 20 (39.22%) in the study population (Fig. 2).

Figure 3. Signs among Study Population

The predominant signs seen are isolated hepatomegaly in 34 (66.66%), hepatosplenomegaly in 11 (21.57%) and coated tongue in 10 (19.61%) in the study population (Fig. 3).

Investigations

Blood Culture and Sensitivity: The organism seen in majority of the blood cultures were *Salmonella typhi* [49 (96.08%)], whereas *Salmonella paratyphi* was hardly seen [2 (3.92%)]. The difference was found to be statistically significant ($p < 0.05$).

Figure 4. Antibiotic Sensitivity Pattern of *Salmonella typhi* and *paratyphi*

Antibiotic sensitivity pattern showed ceftriaxone and piperacillin/ tazobactam were sensitive in all study population (100%), contradictory to that all were resistant to nalidixic acid. Primary antimicrobials like ampicillin, chloramphenicol and cotrimoxazole also showed sensitivity in majority of the study population (Fig. 4).

NARST was seen in all 51 (100%) children and MDRST was noticed in 1 (1.96%) child. [NARST- Nalidixic Acid Resistant *Salmonella typhi*; MDRST- Multi Drug Resistant *Salmonella typhi* {Resistance to all three antimicrobials (Ampicillin, Chloramphenicol and Cotrimoxazole)}].

Haemo-globin Levels	Age Groups	No.	%	Mean (SD) Haemo-globin Level in the Study Population	P value
< 11 g/dL	6 months – 5 years	22	43.14%	11.24 (± 1.42) g/dL	< 0.05
< 11.5 g/dL	> 5 years - 12 years	7	13.73%		
< 12 g/dL	> 12 years	0	0%		

Table 2. Haemoglobin Levels Related to Age

Out of 51 children, 29 (56.86%) children were found to have anaemia in the study and the most affected age group is < 5 years (Table 2).

Most of the study population had normal total counts, i.e. in 39 (76.47%), Leucocytosis in 7 (13.73%) and Leukopenia in 5 (9.8%), whereas normal Absolute Eosinophil Count were seen in 47 (92.16%) and Eosinopenia in 4 (7.84%).

Platelet counts were normal in majority of the study population [47 (92.16%)] and few had abnormal counts like thrombocytopenia [3 (5.88%)] and thrombocytosis [1 (1.96%)].

Out of 51 children, 29 (56.86%) underwent Widal test and remaining had fever < 7 days duration, hence not done. Overall, Widal was positive in 15 (29.41%) children.

In this study, CRP was elevated (i.e. positive) in major population [45 (88.24%)] and remaining were negative [6 (11.76%)].

Out of 51, elevated SGOT and SGPT were seen in 34 (66.67%) and 25 (49.02%) children respectively.

USG abdomen was done in 22/51 (43.13%) children and not done in remaining because of social factors. Out of 22 children 10 (45.45%) had Isolated Hepatomegaly, 7 (31.82%) had Hepatosplenomegaly and 5 (22.73%) had normal USG abdomen findings.

Out of 51 children 20 (39.22%) underwent CXR and in remaining it was not done because of social factors. Out of 20 children, 19 (95%) had normal chest x-ray study and only 1 (5%) had consolidation.

Treatment and Clinical Outcomes

IV Antibiotics Received	No. of Patients	Percent	Mean (SD) Time for Defervescence of Fever	Overall Mean (SD) Time for Defervescence of Fever	P value	Mean (SD) Hospital Stay Duration	Overall Mean (SD) Hospital Stay Duration	P value
Ceftriaxone	38	74.51%	3.5 ($\pm$ 1.33) days	3.86 ($\pm$ 2.12) days	> 0.05	6.8 ($\pm$ 2.09) days	6.84 ($\pm$ 2.09) days	> 0.05
Ceftriaxone + Ofloxacin	7	13.73%	5.3 ($\pm$ 4.07) days			8.4 ($\pm$ 3.36) days		
Ceftriaxone + Azithromycin	4	7.84%	5.5 ($\pm$ 2.89) days			9.3 ($\pm$ 2.06) days		
Ceftriaxone + Ofloxacin + Azithromycin	2	3.92%	2.5 ($\pm$ 0.7) days			6 ($\pm$ 0) days		

Table 3. Details of IV Antibiotics among Study Population

In our study, ceftriaxone alone was most preferred antibiotic to treat enteric fever. In combination regime ceftriaxone was initially used, later other antibiotics were added based on poor clinical response i.e. if fever persists for more than 72 hours. There was no statistically significant difference in mean time for defervescence of fever and in mean hospital stay duration between those received ceftriaxone alone and ceftriaxone with other antibiotics (Table 3).

Clinical Outcomes	No.	%	Remarks
Clinically recovered well without complication	50	98.04%	37- received ceftriaxone, Remaining received combination of antibiotics
Complication	1	1.96%	Consolidation, Recovered well after treatment with Ceftriaxone for 5 days
Death	0	0	No death in our study

Table 4. Clinical Outcomes in Our Study

In this study, 37 (72.55%) clinically recovered well without complication with the treatment of ceftriaxone alone (Table 4).

DISCUSSION

This was a prospective, observational study done between June 2016 and May 2017 at a tertiary care hospital, Puducherry. A total of 89 children had culture positive enteric fever, but only 51 were taken up for study based on inclusion and exclusion criteria.

Demography

In our study, 58.82% were < 5 years and 31.37% were < 2 years of age, which was supported by Sinha et al⁷ study from

India, who suggests that typhoid fever is common in 1 - 5 years old children. Infectious Disease surveillance (IDSurv) data by Indian Academy of Paediatrics (IAP) from December 2010 - December 2013 showed 44.6% were < 5 years and 10.7% were < 2 years of age.⁸ In contrast to these findings, one Indian study by Chandrasekhar et al¹ observed more number of children (59.65%) in > 5 years of age. There is no sex predominance seen in our study.

In our study majority of the children [30 (58.82%)] were from upper middle class, which was similar to the study by Chandrasekhar et al¹ where 39 (75%) were from upper middle class.

The major risk factor is food intake outside and contaminated water in the present study. Mogasale et al⁹ also showed contaminated water is an important risk factor in his study.

Clinical Features

In our study, the predominant symptom next to fever was vomiting seen in 27 (52.94%) children, which was similar to the study by Chandrasekhar et al¹ where 47.1% had vomiting as the predominant symptom in study population. Both Jog et al⁴ and Gupta et al³ also observed vomiting as the major symptom in 42% and 33.3% respectively.

Bhutta et al¹⁰ showed anorexia (70%) as the predominant symptom next to fever, which was seen in 43.14% in our study.

The predominant examination finding was isolated hepatomegaly 34 (66.66%) and hepatosplenomegaly was seen in 11 (21.57%) children in the present series. Ramaswamy Ganesh et al⁶ had also observed that hepatomegaly was the predominant sign in their study being present in 71% of the study population. While both Chandrasekhar et al¹ and Gupta et al³ observed hepatosplenomegaly as the most common sign seen in 24 (46%) children and 42 (51.9%) children in their studies

respectively. None in our study had isolated splenomegaly, while Kumar et al² showed splenomegaly as the predominant sign which was seen in 47 (44.3%) children.

Investigations/ Blood C and S Pattern

Majority of the organism was *Salmonella typhi* (96.08%) and remaining was *Salmonella paratyphi A* (3.92%). All the *Salmonella* isolates were resistant to nalidixic acid in our study. This type of Nalidixic Acid Resistant *Salmonella typhi* (NARST) was also reported in the retrospective study by Vidhya Krishna et al⁵ in 92.9% who were resistant to nalidixic acid. Choudhary et al¹¹ in Chennai observed 91.9% resistance to nalidixic acid. Similarly, Gupta et al,³ Jog et al,⁴ Chandrasekhar et al,¹ Ramaswamy Ganesh et al⁶ and Joshi et al¹² have also observed NARST in 82.7%, 79%, 76.9%, 73% and 56% respectively in their studies, which seem to be significant one.

Multi Drug Resistant *Salmonella typhi* (MDRST) were seen in some studies like Chandrasekhar et al¹ (5.8%), Nagshetty et al¹³ (10%) and Manchanda et al¹⁴ (39%), but contrary to that our study showed that there is an emergence of sensitivity to these primary antimicrobials like Ampicillin (98.04%), Chloramphenicol (98.04%) and Cotrimoxazole (98.04%). MDRST was seen in 1 (1.96%) children in our study. Studies by Jog et al,⁴ Gupta et al³ and Joshi et al¹² have also supported our findings of sensitivity to primary antimicrobials.

The important aspect with respect to antibiotic sensitivity in our study was the sensitivity of the culture to ceftriaxone in all the culture positive children. This is similar to the observations by Chandrasekhar et al,¹ Gupta et al,³ Jog et al,⁴ Chowta et al,¹⁵ Singh et al¹⁶ and Malla et al¹⁷ studies.

In addition to that, in our study all *Salmonella* isolates were sensitive to piperacillin-tazobactam. No studies were mentioned about this drug.

Other Laboratory Findings

Anaemia was more in Umar et al¹⁸ study which showed 69.2%, in our study it was 45.1%. Other studies showed lesser proportion than our study as follows: Yaramis et al¹⁹ (38%), Chandrasekhar et al¹ (34.6%) and Gupta et al³ (10%).

In our study, WBC counts were normal in 76.47%. Remaining had WBC count abnormalities, among that leucocytosis (13.73%) were seen > leukopenia (9.80%). This is similar to the observations on culture positive enteric fever by Ramaswamy Ganesh et al⁶ [Leucocytosis (12%) > leukopenia (8%)], Umar et al¹⁸ [Leucocytosis (15.4%) > leukopenia (2%)] and Singh et al¹⁶ [leucocytosis (15.9%) > leukopenia (12%)].

Eosinopenia was present in 7.84% in our study, which was < the previous studies by Jog et al⁴ and Ramaswamy Ganesh et al,⁶ who observed eosinopenia in 76.9% and 72% respectively.

Thrombocytopenia in our study (5.88%) is < that observed by Jog et al⁴ (25.9%), Gupta et al³ (14.8%) and Yaramis et al¹⁹ (10%). But in our study thrombocytosis was present in one child (1.96%) who had iron deficiency anaemia and also none of the previous studies had shown this feature.

Widal was positive in 15 (51.72%) of the 29 who had undergone the test. This is similar to that of other studies by Gupta et al³ (43.2%), Jog et al⁴ (48.4%) and Singh et al¹⁶

(50.7%), whereas Kumar et al² (68.9%), Malla et al¹⁷ (83%) and Chowta et al¹⁵ (88.6%) had shown high percentage of Widal positivity.

In our study, elevated CRP was seen in 46 (90.20%) children, whereas no studies mentioned about CRP.

Elevated SGOT (66.66%) was seen > the elevated SGPT (49.02%) in our study. Similar findings were observed by Chandrasekhar et al,¹ who showed elevated SGOT (73%) > elevated SGPT (69.2%) and Yaramis et al¹⁹ also showed raised level of SGOT (61.3%) > the raised level of SGPT (48.4%). This is contrast to Jog et al⁴ and Gupta et al³ have showed SGPT was elevated in 43% and 31% respectively, which were > elevated SGOT.

USG Abdomen done in 22/51 children, it showed isolated hepatomegaly in 10 (45.45%) and hepatosplenomegaly in 7 (31.82%) in our study. Gall bladder abnormalities were not seen in our study in contrast to Ramaswamy Ganesh et al⁶ study, wherein USG Abdomen revealed gallbladder (GB) hydrops in 6 children, thickening in 8 children, GB sludge in 1 and free fluid abdomen in 13 children.

In our study, CXR was done in 20/51. It showed normal study in 19 (95%) and consolidation in 1 (5%). No studies mentioned about CXR findings.

Treatment and Clinical Outcomes

In the management of enteric fever in our study ceftriaxone was the initial antibiotic of choice in 74.51%, which is similar to that of Gupta et al³ series. But Jog et al⁴ showed only 62.1% of children had ceftriaxone as the initial antibiotic of choice.

Among the combination of antibiotics, 7 (13.73%) children received both ceftriaxone and ofloxacin as the initial antibiotics in our study, while 4 (7.84%) children received both ceftriaxone and azithromycin. Jog et al⁴ study had shown the slightly higher usage of combination of ceftriaxone and azithromycin in 16 patients (13.4%).

In our study, azithromycin was added if fever and toxicity persisted even 72 hours after initiation of ceftriaxone.

All three antibiotics (ceftriaxone, ofloxacin and azithromycin) were given in 2 (3.92%) children in our study. In these 2 children, both ceftriaxone and ofloxacin were started initially and later because of persisting toxicity and fever spikes > 5 days azithromycin was added.

Overall, mean (SD) time taken for defervescence of fever was 3.86 ($\pm$ 2.12) days in our study, which was almost similar to that of Malla et al¹⁷ where mean time for defervescence was 4.7 days.

In our study, mean (SD) time taken for defervescence of fever to ceftriaxone alone was 3.5 ($\pm$ 1.33) days. The mean time to defervescence when ceftriaxone alone was used as therapy in Jog et al,⁴ Gupta et al³ and Malla et al¹⁷ were 4.2 days, 4.3 days and 5 days respectively.

In our study, combination treatment in children treated with ceftriaxone and ofloxacin had the mean (SD) time for defervescence as 5.3 ($\pm$ 4.07) days with ceftriaxone and azithromycin it was 5.5 ($\pm$ 2.89) days, whereas in children who received all 3 antibiotics (ceftriaxone, ofloxacin and azithromycin) it was 2.5 ($\pm$ 0.7) days.

Parry et al²⁰ observed fever clearance times for fluoroquinolones, third generation cephalosporins and azithromycin as 4 days, 7 days and 4 to 6 days respectively.

Overall, mean (SD) hospital stay was 6.84 ($\pm$ 2.09) days in our study. The available studies have not mentioned about the total number of hospital stay days.

In our study only one patient had consolidation and recovered with ceftriaxone, whereas Singh et al¹⁶ observed 4 cases had pneumonia as the complication in his study.

No other complications were noted in our study during the hospital stay. Gastrointestinal complications were observed in Gupta et al³ study who showed melena in 6 children (7.5%) and Kumar et al² also observed gastrointestinal bleed with perforation in one patient in his study. Bhutta et al¹⁰ showed intestinal perforation in 0.5%.

There was no death in our study, while Parry et al²⁰ and Chowta et al¹⁵ showed death in their studies.

CONCLUSION

In our study, 58.82% were < 5 years. High grade fever, vomiting, anorexia and diarrhoea were the common symptoms. Isolated hepatomegaly and hepatosplenomegaly were the common signs. Enteric fever should be suspected when there is high CRP, normal WBC and platelet counts in a child with $\geq$ 3 days fever with isolated hepatomegaly/hepatosplenomegaly. Blood culture is the gold standard diagnostic test. *Salmonella typhi* was the major isolate. Antibiotic sensitivity pattern showed re-emergence of strains with high sensitivity to first line antibiotics like Ampicillin, Chloramphenicol and Cotrimoxazole. Nalidixic acid resistance was observed in all isolates. All the cultures were sensitive to Ceftriaxone and it was used as first line intravenous antibiotic for enteric fever with good outcome. Only one complication (consolidation) and no death were seen in our study.

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