ISSN: 2469-5769

Sarswat et al. Int J Pediatr Res 2018, 4:039
DOI: 10.23937/2469-5769/1510039
Volume 4 | Issue 2
Open Access

International Journal of Pediatric Research

ORIGINAL ARTICLE

Pediatric Nature of Enteric Fever with Emerging Antibiogram: A Cross Sectional Study

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Abstract

Introduction: Typhoid fever is a life-threatening systemic infection occurring in developing countries like India. The presenting signs and symptoms of typhoid fever in children differ from adults. Some studies indicate reemergence of sensitivity of Salmonella with chloramphenicol.

Method: 164 children between 1-12 years of age with suspected enteric fever were enrolled in the study. Out of these, 73 patients were diagnosed as enteric fever and clinical features were compared among different age groups. Antibiotic sensitivity profile was also studied in blood culture positive patients.

Results: Abdominal distension were significantly more commonly seen in children less than 5 years while nausea, constipation and blood in stool were completely absent in this age group. Abdominal pain and headache were significantly more in children more 5 years than compared to it younger group. The sensitivity for classical drugs Chloramphenicol, Ampicillin and Cotrimoxazole was found to be 70%, 80% and 47.5%, respectively. Conclusion: Clinical profile of enteric fever in children differ with age. There is re-emergence of sensitivity of *Salmonella typhi* for chloramphenicol, ampicillin and Cotrimoxazole in blood culture.

Keywords

Salmonella typhi, Clinical profile, Blood culture, Antibiotic sensitivity

Introduction

Typhoid fever is a life-threatening systemic infection occurring in developing areas of the world and continues to be a major public health problem. Over 21 million people worldwide get infected annually with estimated mortality of 2,00,000 people per year [1].

The presenting signs and symptoms of typhoid fever in children differ significantly from those in adults [2]. The common clinical features of typhoid fever are fever, vomiting, diarrhea, cough, hepatosplenomegaly, anemia and thrombocytopenia [3,4].

Salmonella typhi (S. typhi) is the causative agent which is most frequently isolated in the blood during first week of illness. In the wake of emerging multidrug resistant strains of bacteria causing typhoid fever, the disorder is known to be associated with significant morbidity and mortality. It is also recognized that delay in the diagnosis and institution of appropriate therapy may significantly increase the risk of adverse outcome and mortality.

The emergence of multidrug resistance to 1st line drugs like Chloramphenicol, Ampicillin and Cotrimoxazole has been a concern [5,6]. The problem only worsened with the advent of NARST (Nalidixic acid resistant *Salmonella typhi*) making Ciprofloxacin a doubtful drug of choice for treatment of Typhoid fever. Some studies have shown reemergence of sensitivity of Salmonella with chloramphenicol [6-8]. With changing pattern of antibiogram it is necessary to continuously monitor the drug resistance pattern and understand the mechanism involved.

Method

Study design

This was a cross-sectional study, conducted at Hindu Rao Hospital from May 2012 till November 2013. Approval of the study protocol was obtained from the ethical committee of the institute and written informed consent was taken from the parents of all the children.

Citation: Sarswat S, Kumar M, Gupta R (2018) Pediatric Nature of Enteric Fever with Emerging Antibiogram: A Cross Sectional Study. Int J Pediatr Res 4:039. doi.org/10.23937/2469-5769/1510039

Accepted: October 03, 2018: **Published:** October 05, 2018

Participants

Children of 1-12 years admitted in pediatric wards of Hindu Rao hospital with fever of at least 3 days duration suspected/diagnosed of having enteric fever on the basis of clinical examination and laboratory investigations were included in the study. Exclusion criteria: Patients who have already received/receiving antibiotics at the time of admission, patients subsequently diagnosed to have disease other than typhoid fever, patients below 1 year and above 12 years of age.

Sample Size

Using previous studies data [9] by and expecting the positive blood culture rate of 40%, with precision error of estimation (d) = 0.10, and alpha = 0.05, the sample size of 95 cases is needed. At least 40 blood c/s positive patients for *Salmonella typhi*. Sample size was calculated by using the formula for descriptive study ($z^2 \times p \times q)/d^{2.}$

Procedure

The demographics, clinical characteristics of all enrolled patients were recorded on a prestructured proforma. Axillary temperature was recorded keeping thermometer in axilla for 3 minutes and patient with temperature more than 38 degree Celsius was considered to have fever. The following investigations were done in all patients included in the study: Complete Hemogram with absolute eosinophil count, liver function test, blood culture and antibiotic sensitivity pattern of organism grown, Typhidot IgM (ENTEROCHECK-WB, zephyr biomedicals), Widal test. Patients with clinical diagnosis of typhoid fever were initially treated with third generation cephalosporin. The clinical course was closely monitored. The clinical response to therapy was considered inadequate if there was deterioration or no clinical improvement within 5 days of starting specific therapy. Persistence of fever for more than 5 days was taken as a sign to start second line antibiotic. Blood culture was done by automated blood culture system, BACTEC 9120. Antibiotic sensivity testing (AST) was performed as per CLSI (clinical and laboratory standard institute) guidelines [10]. The antimicrobial agents tested were Ampicillin (10 µg), Ceftriaxone (30 µg), Meropenem (10 µg), Chloramphenicol (30 µg), cefuroxime (30 µg), Ciprofloxacin (5 µg), Cotrimoxazole (25 µg), Ciprofloxacin (30 µg), Ofloxacin (30 µg), Amoxiclav (20/10 µg), Gentamycin (10 µg) Hi-Media, Mumbai, India. A standard strain of *E. coli* ATCC 25922 was included as quality control.

Statistical Analysis

Statistical testing was conducted with the statistical package for the social science system version SPSS 17. The comparison of normally distributed continuous variables between the groups was performed using Student's t test. Nominal categorical data between the groups were compared using Chi-square test or Fisher's exact test as appropriate. Non- normal distribution continuous variables were compared using Wilcoxon Rank Sum test. For all statistical tests, a P value of less than 0.05 was taken to indicate a significant difference.

Results

Out of these 164 patients, 73 were found to have blood culture positive and/or Widal positive and/or Typhidot M positive and they constituted the study group. Source of water supply was studied, and it was found that 55 patients (75.34%) were consuming Municipal Corporation Delhi (MCD) water supply while 10.95% that is 8 patients were using candle filters (Table 1). Tanker and boring water were used by 4 and 3 patients respectively. Two patients were using motor and 1 was found to be using aqua guard. Affected patients were divided in two groups < 5 years and > 5 years so that the difference in the presentation of these two age groups can be studied. In our study those < 5 years were 16 (21.9%) and > 5 years were 57 (78.08%). Clinical features were studied in both these age groups and most common symptoms were fever (100%), loss of appetite (87.67%) and weakness (79.45%). That significantly more common in < 5 years was abdominal distension while nausea, constipation and blood in stool were completely absent in this age group (Table 2). Abdominal pain and headache were seen in 81% and 79% of

Table 1: Demographic characteristics.

Parameter	n = 73
Age less than 5 years	16 (21.9%)
Male	54 (74%)
Source of water supply	
MCD	55 (75.4%)
Aqua guard	1 (1.4%)
Filter (candle)	8 (10.9%)
Tanker	4 (5.5%)
Boring	3 (4.1%)
Motor	2 (2.7%)

Data expressed in number (percentage), MCD: Municipal Corporation of Delhi.

Table 2: Comparison of clinical profile in children less than 5 yr and above.

Symptoms	≤ 5 yrs. (n = 16)	> 5 yrs. (n = 57)	P value
Fever	16 (100%)	57 (100%)	-
Step ladder pattern	1 (6%)	18 (32%)	0.054
Loss of appetite	12 (75%)	52 (91%)	0.09
Abdominal pain	9 (56%)	46 (81%)	0.04
Vomiting	7 (44%)	29 (51%)	0.61
Diarrhoea	3 (19%)	7 (12%)	0.68
Headache	6 (38%)	45 (79%)	0.003
Weakness	10 (63%)	48 (84%)	0.058
Abdominal distension	5 (31%)	6 (11%)	0.041
Cough	4 (25%)	9 (16%)	0.46
Constipation	0	5 (9%)	0.58
Nausea	0	12 (21%)	0.057
H/O blood in stool	0	2 (4%)	1

children older than 5 years significantly more compared to 56% and 29% in younger group respectively (Table 2). The most common clinical sign was coated tongue followed by hepatomegaly.

Antibiotic sensitivity profile

The sensitivity for classical drugs Chloramphenicol, Ampicillin and Cotrimoxazole was found to be 70%, 80% and 47.5%, respectively. 100% sensitivity was found for Ceftriaxone. Sensitivity for Amoxiclav, Ciprofloxacin and Meropenem was 82.5%, 87.5% and 95%. Gentamycin and Ofloxacin had 67.5% and 85% sensitivity, respectively (Table 3).

Discussion

Typhoid fever is one of the leading causes of morbidity and mortality across the world [11]. In India typhoid fever is endemic with morbidity ranging from 107-229 per 1,00,000 population [12]. Our study is a single center prospective study of typhoid cases highlighting the clinical features in different age groups, laboratory and antibiotic sensitivity pattern of *Salmonella typhi* isolated from these cases. Out of 73 typhoid patients in our study 74% (54) were male and 26% (19) were females. In a study conducted by Hayat, et al. among 100 clinically diagnosed typhoid patients 75% were males and 25% females. The mean age of presentation was 7.48 years and 57 patients (78.08%) were above 5 years and 16 (21.9%) were below 5 years. A study from a Tertiary care hospital in Chennai, South India showed that 169 (53.48%) out of 316 cases of typhoid fever were > 5 years of age [13]. Similarly, Chandrasekhar, et al. in their study showed that 60% of typhoid patients were above 5 years of age. Chandrasekhar, et al. while studying children with blood culture positive typhoid fever found that 73.1% of the patients were consuming municipal corporation water [14]. In our study 75.34% (n = 55) of the patients were consuming corporation water. The remaining patients were using candle filter water (10.95%) and tanker water (5.47%). Laboratory investigation were remarkable with prominent anemia, thrombocytopenia in 47% , less commonly leukocytosis, neutropenia and eosinophilia (Table 4). These hematological alterations have also been reported in previous study [15]. Other prominent finding was elevated liver enzymes and bilirubin.

Fever was the common clinical presentation seen in all (100%) of our cases as reported by Sinha, et al. [16] and Siddiqui, et al. [17] also. Anorexia (87.65%), abdominal pain (75.34%) and vomiting (47.9%) were the most common clinical symptoms following fever.

In our study, children less than 5 years had different clinical presentation compared to those aged more than 5 years. Abdominal distension (31%), cough (25%) and diarrhea (19%) were more commonly seen in children < 5 years while anorexia (91%), weakness (84%), abdominal pain (81%), headache (79%) and vomiting (51%) were associated more in those > 5 years. There is paucity of data regarding variable clinical presentation in different age groups. In a study done by Chandrashekar, et al., anorexia and diarrhea were the predominant symptoms in children < 5 years while cough was more common in > 5-year group [14]. In our study the average period of hospital stay was 7.17 days whereas in a study conducted by Ganesh R, et al. it was 6.5 days [13].

The definitive diagnosis of enteric fever is possible with isolation of the causative agents. However, the availability of microbiological culture facilities is often limited in the regions where enteric fever is endemic. In addition, cultures can be negative when antibiotics are started before taking blood for culture. Initially chloramphenicol, ampicillin and cotrimoxazole were used for the treatment of typhoid fever. In 1980s there was emergence of resistance to all these drugs and ciprofloxacin was being used, to which resistance developed later. But in last few years there is reemergence of sensitivity to 3 classical drugs chloramphenicol, ampicillin and Cotrimoxazole as stated by various studies [6,18,19]. Indian academy of pediatrics has recommended ceftriaxone as 1st line drug for complicated typhoid fever. In our study sensitivity for ceftriaxone is 100%. Other 2 drugs which showed high sensitivity were Meropenem and Ofloxacin (95% and 85% respectively). The sensitivity for ciprofloxacin was also high (87.5%). Our study has also shown reemergence of sensitivity to classical drugs which was in accordance with previous studies. In our study, sensitivity for Chloramphenicol, Ampicillin and Cotrimoxazole was 70%, 80% and 47.50% respectively. Although Fluoroquinolones were the initial

Table 3: Antibiotic sensitivity testing.

Antibiotic	Sensitivity
Ciprofloxacin	35 (87.5%)
Chloramphenicol	28 (70%)
Cotrimoxazole	19 (47.5%)
Ampicillin	32 (80%)
Cefuroxime	18 (45%)
Ceftriaxone	40 (100%)
Amoxiclav	33 (82.5%)
Ofloxacin	34 (85%)
Meropenem	38 (95%)
Gentamycin	27 (67.5%)

Data expressed in number (percentage).

Table 4: Lab parameter.

Parameter	N = 73
Anaemia	31 (42.46%)
Leukopenia	3 (4.10%)
Thrombocytopenia	34 (46.57%)
Leucocytosis	14 (19.17)
Neutropenia	13 (17.80%)
Eosinopenia	11 (15.06%)
SGOT (> 55 IU/L)	61 (83.56%)
SGPT (> 45 IU/L)	33 (45.20%)
Bilirubin (> 1 mg/dl)	15 (20.96%)

choice of antibiotic in enteric fever, the high prevalence of NARST raises the concern over their usage. We were not able to test for Nalidixic acid sensitivity due to difficulty in procurement of the kit.

Conclusion

Enteric fever varies in presentation with abdominal distension more common in younger children whereas abdominal pain and headache were more common in older children. There is re-emergence of sensitivity of *S. typhi* for Chloramphenicol, Ampicillin and Cotrimoxazole.

Conflict of Interest

None.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standard of institution and with the 1964 Helsinki declaration and its later amendments or comparable standards.

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