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NATURE OF ENTERIC FEVER IN PEDIATRIC WITH EMERGING-ANTIBIOTIC SENTIENCE : A CROSS SECTIONAL STUDY

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Abstract

Introduction: Typhoid fever is a life-threatening systemic infection of variable severity caused by Salmonella serotypes that occurs in developing countries such as India. The signs and symptoms of typhoid fever in children differ from those in adults. Few studies suggest renewed sensitivity of Salmonella to chloramphenicol.

Method: 88 children aged 2-10 years with suspected enteric fever were admitted in pediatric ward and pediatric ICU (as per their clinical conditions) were included in the study. Enteric fever was diagnosed in 52 of these patients, and the clinical features were compared in the different age groups. In patients with positive blood cultures, the sensitivity profile to antibiotics was also investigated.

Results: Abdominal distension, sepsis and encephalitis were significantly more common in children younger than 5 years, whereas nausea, constipation, and blood in stool were rare in this age group. Abdominal pain, headache and intestinal perforation were significantly more common in children older than 5 years than in the younger group. Sensitivity to the classical drugs chloramphenicol and ampicillin was 73.33% and 60%, respectively.

Conclusion: the clinical profile of enteric fever in children differs according to age. There is a recurrence of Salmonella typhus sensitivity to chloramphenicol and ampicillin in blood cultures.

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 21.5 million people worldwide get infected annually with estimated mortality of 2,00,000 people per year [1].

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The presenting signs and symptoms of typhoid fever in children differ significantly from those in adults [2]. This is commonly accompanied by weakness , abdominal pain ,constipation, headache, and mild vomiting [4,5] . some patients develop a skin rash with rose colored spots. In severe cases patients may experience confusion [5] without treatment symptoms may last for weeks to months.[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 and Ampicillin 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 N.C. Medical college from June 2022 till march 2023. 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.

Participants

Children of 2-10 years admitted in pediatric ward of N. C. Medical college and 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 2 year and above 10 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 88 cases is needed. At least 52 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 and clinical characteristics of all enrolled patients were recorded on a pre-structured proforma. Axillary temperature was recorded keeping thermometer in axilla for 2-3 minutes and patient with temperature more than 100 degree Fahrenheit was considered to have fever. The following investigations were done in all patients included in the study: Complete Hemogram with absolute eosinophil count, erythrocyte sedimentation rate, liver function test, blood culture and antibiotic sensitivity pattern of organism grown, Typhi-dot 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

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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 sensitivity testing (AST) was performed as per CLSI (clinical and laboratory standard institute) guide- lines [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 29. 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 88 patients, 52 were found to have blood culture positive and/or Widal positive and/or Typhi-dot IgM positive and they constituted the study group. Source of water supply was studied, and it was found that 39 patients (75%) were consuming Haryana urban development authority (HUDA) water supply while 11.53% that is 6 patients were using candle filters (Table 1). Tanker and boring water were used by 3 and 5 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 12 (23.07%) and > 5 years were 40 (76.93%). Clinical features were studied in both these age groups and most common symptoms were fever (100%), loss of appetite (78.84%) and weakness (75%). 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).

T**able 1: Demographic characteristics**

Parameters	**N = 52**
Age<5years	12 (23.07%)
Male	38 (73.07%)
Source of water	
HUDA	39 (75%)
Aqua Guard	1 (1.92%)
Filter (candle)	6 (11.53%)
Tanker	3 (5.76%)
Boring	5 (9.61%)
Motor	2 (3.84%)

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Table 2 comparison of clinical profile in children less than 5years and above

Symptoms	Less than 5 years (N =12)	More than 5 years (N = 40)	P value
Fever	12 (100%)	40 (100%)	--
Step ladder pattern	1 (8.33%)	11 (27.5%)	0.052
Loss of appetite	8 (66.66%)	33 (82.5%)	0.08
Abdominal pain	5 (41.67%)	31 (77.5%)	0.04
Vomiting	5 (41.67%)	23 (57.5%)	0.58
Diarrhea	3 (25%)	6 (15%)	0.65
Headache	4 (33.33%)	30 (75%)	0.004
Weakness	6 (50%)	33 (82.5%)	0.056
Abdominal distension	4 (33.33%)	6 (15%)	0.038
Cough	3 (25%)	7 (17.5%)	0.42
Constipation	0 (0%)	4 (10%)	0.54
Nausea	0 (0%)	8 (12.5%)	0.054
H/o blood in stools	0 (0%)	2 (5%)	1

Abdominal pain and headache were seen in 77.5% and 75% of children older than 5 years significantly more compared to 41.67% and 33.33% 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 Ciprofloxacin, Chloramphenicol, Ampicillin and was found to be 86.66%, 73.33% and 60%, respectively. 100% sensitivity was found for Ceftriaxone. Sensitivity for Amoxiclav, ofloxacin and Meropenem was 76.66 s%, 86.66% and 96.66%. Amikacin and gentamycin had 70% and 66.66% sensitivity, respectively (Table 3).

Table 3: Antibiotic sensitivity testing

Antibiotic	Sensitivity
Ciprofloxacin	26 (86.66%)
Chloramphenicol	22 (73.33)
Ampicillin	18 (60%)
Ceftriaxone	30 (100%)
Amoxiclav	23 (76.66%)
Amikacin	21 (70%)
Ofloxacin	26 (86.66%)
Meropenem	29 (96.66%)
Gentamycin	20 (66.66)

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 112-234 per 1,00,000 population [12]. Our study is a single prospective study of typhoid cases highlighting the

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clinical features in different age groups, laboratory and antibiotic sensitivity pattern of Salmonella typhi isolated from these cases. Out of 52 typhoid patients in our study 73.07% (38) were male and 23.07% (12) 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% (n = 39) of the patients were consuming corporation water. The remaining patients were using candle filter water (11.53%) and tanker water (5.76%). Laboratory investigation were remarkable with prominent anemia, thrombocytopenia 46.15% and 51.92% respectively, 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.

Table 4 : lab parameter

Parameters	**N = 52**
Anaemia	24 (46.15%)
Leukopenia	3 (5.76%)
Thrombocytopenia	27 (51.92%)
Leucocytosis	10 (19.23%)
Neutropenia	11 (21.15%)
Eosinopenia	13 (25%)
SGOT (>55IU/L)	31 (59.61%)
SGPT (>45IU/L)	25 (48.07%)
Bilirubin (>1mg/dl)	12 (23.07%)

Fever was the common clinical presentation seen in all (100%) of our cases . Anorexia (78.84%), abdominal pain (69.23%) and vomiting (53.84%) 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 (33.33%), cough (25%) and diarrhea (25%) were more commonly seen in children < 5 years while anorexia (82.5%), weakness (82.5%), abdominal pain (77.5%), headache (75%) and vomiting (57.5%) 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 and ampicillin were used for

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the treatment of typhoid fever. In 1980s there was emergence of resistance to these drugs and ciprofloxacin was being used, to which resistance developed later. But in last few years there is reemergence of sensitivity to classical drugs chloramphenicol and ampicillin as stated by various studies [6]. 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 (96.66% and 86.66% respectively). The sensitivity for ciprofloxacin was also high (86.66%). Our study has also shown reemergence of sensitivity to classical drugs which was in accordance with previous studies. In our study, sensitivity for Chloramphenicol and Ampicillin was 73.33% and 60% respectively. Although Fluoroquinolones were the initial 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 and Ampicillin

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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