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ORIGINAL RESEARCH

Clinical Profile, Laboratory Parameters and Drug Sensitivity Pattern of Enteric Fever in Children: Experience of a Tertiary Care Centre

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ABSTRACT

Background and Objectives: Enteric fever (typhoid and paratyphoid fever) has remained a major public health concern in developing countries including India. Wide variation in clinical presentations makes its diagnosis on clinical ground alone a daunting task. Emergence of strains with polymicrobial resistance is a matter of serious public health concern. This study was conducted in a tertiary care setting to study the myriad clinical manifestations, laboratory parameters & antibiotic sensitivity pattern of typhoid fever in children. **Methods:** This hospital based prospective observational study was conducted at department of Pediatrics N.M.C.H Patna, Bihar, India over 2 years from August 2019 to July 2021 including consecutively admitted children of 1-15 years of age with fever for >3 days and isolation of S. typhi from blood culture. **Result:** Over the study period, 87 children were enrolled in this study. Mean age of the study population was 4.12± 1.41 years. Mean weight was 14.36± 3.35 Kg. Males (51) outnumbered females (36) with a male: female ratio of 1.4:1. Duration of hospital stay (days) was 6.14 ± 3.98. Relative bradycardia was an uncommon finding with only 11 (12.6%) children exhibiting it. Total duration of fever was up to 1 week in 16 (18.4%), 1-2 weeks in 57 (65.5%) and >2 weeks in 14 (16.1%). Common symptoms were malaise (72.4%), chills (62.1%), vomiting (59.8%) and pain abdomen (51.7%). Diarrhoea (42.5%) was more common than constipation (24.1%). Coated tongue was seen in only 17 (19.5%). Incidence of MDRTF was 31 (35.6%). Quinolones were sensitive in nearly 50% cases only. Cefuroxime was inferior to cefixime when considered as an effective oral drug for treatment of enteric fever (sensitivity of 65% vs 85%). Parenteral 3rd generation cephalosporins were sensitive in nearly 90% cases. Emergence of resistance to these drugs in nearly 10% raises serious concerns. No drug was found to be sensitive in all cases with 3 cases showing resistance to even Meropenem. Azithromycin continues to remain a highly sensitive drug (91.9% sensitivity). Amikacin remains a good second line agent with sensitivity in nearly 83.9% cases. **Conclusion:** Fever, malaise, anorexia, vomiting, chills, headache, coated tongue, diarrhoea and organomegaly are the common clinical manifestations of enteric fever. No laboratory finding is consistently associated with enteric fever. Re-emergence of strains with high sensitivity to previously used first line antibiotics chloramphenicol (62%) and co-trimoxazole (56%) was found. Emergence of MDRTF strains remains an area of much concern. Cases with resistance to all antibiotics except for 2-3 drugs demands heightened interest in robust preventive measures including effective vaccines.

Key words: Blood culture, enteric fever, typhoid fever, resistance, multi drug resistant, Salmonella typhi.

INTRODUCTION

Typhoid fever also known as "Enteric fever", is a generic term that refers to both typhoid and paratyphoid fever. It is one of the most common causes of fever in children with variable presentations and significant difference in the signs and symptoms compared to adults.[1] Infact, assessment of any child presenting with fever without an obvious focus is a challenge to most of the Paediatricians. To determine the etiology and plan the management in the first few days might be difficult but expected from the treating physician. As parents become very anxious if fever

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persists beyond 48 hours, most paediatricians have the tendency to start some antibiotics before having any real clue about the etiology despite being aware of the act that most of these fevers might just be of viral etiology. However, if the child is suffering from enteric fever, this initial antibiotic might modify the course of the disease and pose significant difficulty in interpretation of further lab investigations.

Enteric fever is a common infectious disease presenting as an acute multisystem febrile illness caused by gram negative bacteria of several serovar-S. enterica serotype typhi (formerly Salmonella typhi). Other Salmonella serotypes, particularly S. enterica serotype paratyphi A, B, or C and occasionally typhimurium is the causative agent in some cases.[2] In contrast to the developed countries where its incidence has decreased considerably with improvements in food handling and water/sewage treatment, enteric fever continues to be a major public health problem in developing countries particularly the Indian subcontinent[3,4]. Diagnosis of enteric fever on clinical grounds alone is not recommended as the presenting features are diverse and mimic those observed with other common febrile illnesses. Definite diagnosis requires isolation of the bacterium (S. typhi or paratyphi) from culture of blood, stool, urine, rose spot, bone marrow or gastrointestinal secretions. Bacteria can be isolated from blood in 80-97% of cases before use of antibiotics.[5] Prompt recognition with timely &appropriate antibiotics and other supportive measure can considerably reduce both morbidity and mortality and is important for a favourable outcome.

In 1972, a major epidemic of drug-resistant typhoid fever was first reported and since then resistance to all the first line drugs (chloramphenicol, co-trimoxazole & ampicillin) has been reported. These were called as Multi Drug Resistant typhoid fever (MDRTF).[6] Subsequently, increasing frequency of resistance has been reported from all parts of the world, more so from developing countries.[7] Gradually some strains developed resistance to fluoroquinolones & even 3rd generation cephalosporins, which is a matter of great concern.[8] In endemic areas such as India, classical signs and symptoms of enteric fever are not always seen[9]. This has been attributed to the widespread and indiscriminate use of antimicrobials. Unusual manifestations pose great risk as it leads to diagnostic dilemma and delay in diagnosis. With this background, we decided to study the clinical presentations, laboratory parameters and drug sensitivity of enteric fever in a tertiary care setting, which most often caters to complicated cases and cases unsuccessfully treated elsewhere.

Aim and Objectives

1. To study patient profile, clinical & laboratory manifestations of typhoid fever.
2. To evaluate sensitivity pattern of S.typhi to the commonly used antibiotics

MATERIALS AND METHODS

Study setting: Pediatrics OPD and IPD at NMCH, Patna, Bihar, India

Study duration: 2 years from August 2019 to July 2021.

Type of study: Hospital based prospective observational study.

Sample size consideration: As average number of cases of blood culture positive S. typhi was approx. 40 per year in our hospital. So, the expected population size was 80 in 2 years. Considering confidence level of 95% and Confidence interval of 5% the minimum sample size derived was approx. 60.

Inclusion criteria: Children between 1-15 years of age presenting to OPD or IPD of our hospital with fever for more than 3 days with suspicion of enteric fever on the basis of history, clinical exam & relevant laboratory reports were screened for eligibility in this study and investigated for the possibility of enteric fever. Other focus of infection like respiratory, nervous, cardiac and genitourinary were subsequently ruled out on the basis of clinical or laboratory findings. Children who were blood culture positive for S. typhi were included in final analysis.

Exclusion criteria: Children with negative blood culture or growth of an organism other than S. typhi, and cases diagnosed as enteric fever only on clinical ground or widal tests were excluded.

Study technique: After obtaining written informed consent, we enrolled cases in this study. All such children were subjected to thorough physical examination and focused history taking from guardians to document pertinent factors. Information so obtained and data regarding baseline characteristics, demographic features, presenting symptoms, laboratory results were entered in a structured proforma.

Data analysis: Pertaining data was first entered in Microsoft excel sheet and analysed using SPSS Software version 20 software. Results were presented as mean, median, interquartile range, standard deviation or percentage as appropriate. Dichotomous events were compared by Chi-Square test and continuous variables were compared by Student t-test. P value less than 0.05 was considered as significant.

RESULT

Over the study period, we enrolled 87 children in this study. Mean age of the study population was 4.12± 1.41 years. Mean weight was 14.36± 3.35 Kg. Males (51) outnumbered females (36) with a male: female ratio of 1.4:1. Duration of hospital stay (days) was 6.14 ± 3.98. Table 1 depicts general characteristics of our study population. Most of the children were of 5-10 years, of rural background and lower middle-class strata. 23 (26.4%) had a past history of typhoid fever.

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Table 1: General characteristics of the study population.

Parameter	Number (n=87)	Percentage
Age:		
<5 years	27	31.1%
5-10 years	39	44.8%
10-15 years	21	24.1%
Background:		
Rural	48	55.2%
Urban	39	44.8%
Socio-economic status		
Upper class	10	11.5%
Upper middle	8	9.2%
Middle	13	14.9%
Lower middle	25	28.7%
Lower	31	35.6%
Water supply source		
Municipality	20	22.9%
Borewell	31	35.6%
Handpump	27	31.1%
Others	9	10.4%
Past history of typhoid fever	23	26.4%
History of ingestion of unhygienic food in preceding 2 weeks	51	58.6%

Temperature pattern: Relative bradycardia was an uncommon finding with only 11 (12.6%) children exhibiting it. Total duration of fever was up to 1 week in 16 (18.4%), 1-2 weeks in 57 (65.5%) and >2 weeks in 14 (16.1%). Peak temperature recorded was 99-101deg F in 23 (26.4%), 101-103 deg F in 47 (54.1%) and >103deg F in 17 (19.5%) children.

Clinical features: The most common symptom after fever was malaise (72.4%), chills (62.1%), vomiting (59.8%) and pain abdomen (51.7%). Diarrhoea (42.5%) was more common than constipation (24.1%). Coated tongue was seen in only 17 (19.5%). Important clinical sign was isolated hepatomegaly in 13 (14.9%), isolated splenomegaly in 10 (11.8%) and hepatosplenomegaly in 29 (33.3%).

Table 2: Clinical features of the study group

Parameter	Number (n=87)	Percentage
Fever	87	100%
Chills	54	62.1%
Malaise	63	72.4%
Delirium/altered sensorium	7	8.1%
Headache	27	31.1%
Vomiting	52	59.8%
Pain abdomen	45	51.7%
Constipation	21	24.1%
Diarrhoea	37	42.5%
Cough	19	21.8%
Joint pain	9	10.4%
Relative bradycardia	11	12.6%
Dehydration	39	44.8%
Coated tongue	17	19.5%
Abdominal tenderness	15	17.2%
Hepatomegaly alone	13	14.9%
Splenomegaly alone	10	11.8%
Hepatosplenomegaly	29	33.3%
Chest signs on auscultation	12	13.8%
Meningeal signs	5	5.7%
Complications	4	4.6%

Laboratory findings: No laboratory finding was consistent for typhoid fever. Though eosinopenia was found in 51 (58.6%), yet it was not a consistent finding as 14.9% had eosinophilia and the rest 26.4% had normal

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eosinophils count. Surprisingly, even widal test which is given much importance by some clinicians, was positive in only 65% cases and the rest had negative widal test even when truly suffering from enteric fever.

Table 3: laboratory parameters of the study group

Laboratory parameter	Number (n=87)	Percentage
Haemoglobin		
<11 gm/dl	53	60.9%
>11 gm/dl	34	39.1%
Leukocytes		
Normal count	23	26.4%
Leukopenia	41	47.1%
Leucocytosis	23	26.4%
Neutrophils		
Normal count	31	35.6%
Neutropenia	39	44.8%
Neutrophilia	17	19.5%
Eosinophils		
Normal count	23	26.4%
Eosinopenia	51	58.6%
Eosinophilia	13	14.9%
Platelets count		
Normal	55	63.2%
Decreased	32	36.8%
Widal test		
Positive	57	65.5%
Negative	30	34.5%

Antimicrobial sensitivity pattern: In the present study, antibiotic sensitivity testing was done in all culture positive cases for the drugs commonly used in typhoid fever. Ampicillin, chloramphenicol, co-trimoxazole were considered the first line drugs in past and resistant to all these three drugs is known as multidrug resistant typhoid fever (MDRTF). In this study, incidence of MDRTF was 31 (35.6%). Quinolones were effective in nearly 50% cases only. Oral 3rd generation cephalosporines were highly effective drugs. Cefuroxime was inferior to cefixime when considered as an effective oral drug for treatment of enteric fever (65% vs 85%). Parenteral 3rd generation cephalosporins were sensitive in nearly 90% cases. Emergence of resistance to these drugs in nearly 10% raises serious concerns. Alarmingly, no drug was found to be sensitive in all cases. Infact, 3 cases showed resistance to even Meropenem. Azithromycin continues to remain a highly sensitive drug (>90% sensitivity). Amikacin remains a good second line agent with sensitivity in nearly 85% cases.

Table 4: Antimicrobial sensitivity pattern of enteric fever

Drug	Sensitive (Number)	Percentage
Ampicillin	19	21.8%
Cotrimoxazole	49	56.3%
Chloramphenicol	54	62.1%
Ciprofloxacin	44	50.6%
Ofloxacin	41	47.1%
Levofloxacin	53	60.9%
Cefixime	74	85.1%
Cefuroxime	57	65.5%
Cefotaxime	75	86.2%
Ceftriaxone	78	89.6%
Azithromycin	80	91.9%
Meropenem	84	96.5%
Amikacin	73	83.9%

DISCUSSION

Typhoid fever remains a common infectious disease presenting as acute febrile multisystem illness. The present study has detailed analysis of 87 cases of blood culture positive enteric fever in terms of symptoms, clinical signs, investigations and in vitro antibiotics sensitivity/resistance pattern.

In our study, 69% children were above 5 years age and only 31% were below 5 years. This is similar to most of the studies where enteric fever has been

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reported to be more common beyond 5 years of age.[10] This higher incidence in school going children can be explained from the fact that school going children are more likely to contract the bacterium from contaminated food or drinking water. They are also exposed to various food items from street vendors which is mostly unhygienic. These factors make them more vulnerable to exposure to typhoid bacilli. Fever was more of remittent or intermittent type and classical stepladder rise of temperature was not seen. The shortest duration of fever observed was 5 days in one patient who was admitted on day 3 of fever, and longest duration was 18 days. Relative bradycardia was an uncommon finding with only 11 (12.6%) children exhibiting it. Total duration of fever was up to 7 days in 16 (18.4%), 1-2 weeks in 57 (65.5%) and >2 weeks in 14 (16.1%). Similar finding has been reported by Ranganatha et al[11] and others. Defervescence of fever coincided with other clinical features of response to treatment.

In the present study 60% children studied had anaemia with haemoglobin less than 11gm%. The lowest haemoglobin level found was 6.4gm% in a 1.6-year-old male child who also had a concomitant iron deficiency anaemia. The lowest TLC noted was 2200/cu mm and highest TLC noted was 18400/cu mm. There is no specific pattern in blood counts which could be considered as hallmark of typhoid fever. This is in agreement with the findings of IAP task force report.[12] Widal test was done in all cases and it was considered positive if there was atleast 2-fold or more rising titre or a titre of atleast 1:120 or more for H antigen OR 1:120 or more for O antigen. Among the 87 culture positive cases, only 57 (65%) cases showed a positive reaction which is lesser as compared to 89% as reported by Sudharshan[13]. This can be attributed to prior intake of antibiotics before presentation to us. Ampicillin, chloramphenicol and co-trimoxazole were considered the first line drugs in past and resistant to all these three drugs is known as multidrug resistant typhoid fever (MDRTF). In our study, first line drug Ampicillin was sensitive in only 21% cases, but Chloramphenicol was sensitive in in 62% cases and Co trimoxazole in 56% cases which indicate re-emergence of sensitivity to these 2 first line drugs. However, 35.6% cases were MDRTF which is comparable to the studies of Geetika D et al[14] and Gopal et al[15] and it corroborates with the trend of increasing sensitivity to chloramphenicol and cotrimoxazole. Quinolones as a group, were sensitive in around 50% of children studied only. The lesser sensitivity of ciprofloxacin and ofloxacin may be attributed to their frequent, unjustified as well as underdose usage in diarrhoea and other common childhood ailments by quacks and some clinicians alike, thereby resulting in emergence of resistance. Levofloxacin is less commonly misused in children, so it might have retained its sensitivity to some extent.

We also found Azithromycin to be sensitive in 91.9% cases, and to our great relief it was sensitive in all cases which were resistant to all first line drugs plus quinolones plus cephalosporins. However, this is a matter of great concern that there was sizable number of such cases which were resistant to this extent (6.9%). Amikacin was sensitive in 83.9% cases which is worrisome given its near 100% sensitivity reported in most of the earlier studies. Surprisingly there were 3 (3.5%) cases which were resistant to even Meropenem which is considered to be the most effective drug against S. typhi. To add to our worry was 1 patient who was sensitive to only Azithromycin, cotrimoxazole & chloramphenicol and resistant to all other drugs including Meropenem. This means than the alarm bell is ringing loud[16] and there needs to be a heightened focus on robust preventive measures, especially conjugate vaccines before we come across more cases with such high degree drug resistance.

CONCLUSION

Fever, malaise, anorexia, vomiting, chills, headache, coated tongue, diarrhoea and organomegaly are the common clinical manifestations of enteric fever. No laboratory finding is consistently associated with enteric fever. Even widal test can be negative in one-third cases with proven enteric fever. We found re-emergence of strains with high sensitivity to previously used first line antibiotics chloramphenicol (62%) and co-trimoxazole (56%). The emergence of MDRTF strains remains an area of much concern. Most importantly, there were even cases with resistance to all antibiotics except for 2-3 drugs. This poses a serious public health concern and demands heightened interest in robust preventive measures including effective vaccines.

Limitation: There were few limitations to our study. First (and perhaps the most important), it's a single centre study with a low sample size. Second, Nalidixic acid sensitivity test was not done, which is considered as surrogate marker of quinolones sensitivity/resistance. Third, Bacteriophage typing facility was not done to differentiate between S. typhi and S. paratyphi A,B,C. Fourth, most of the patients didn't turn up for follow up, so, we couldn't study relapse rates of treatment.

Conflict of interest: None to declare

Financial disclosure: the authors declare that present study has not received any financial assistance

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