Spectrum of complications in blood culture positive enteric fever in children aged 1-15 years: A 10-year-experience from a tertiary care centre in Eastern India

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Abstract

Background: Enteric fever is caused by *Salmonella enterica serovar typhi* and *Paratyphi* A, B and C. Blood culture is the gold standard for diagnosis, but is not always feasible due to logistical issues. This may delay definite diagnosis and treatment resulting in increased complications.

Objectives: To document the spectrum of complications involving different organ systems in blood-culture positive enteric cases

Method: This was a single centre retrospective observational study conducted in the Institute of Child Health (ICH), Kolkata, India. The study period was from January 2013 to December 2022. Children aged 6 months to 15 years, admitted in ICH, with a history of fever of any duration, whose blood culture revealed Salmonella species were included. Clinical symptoms, complications and the outcome of treatment were noted. Data were statistically analysed using SPSS software.

Results: Around one third of the total study population presented with complications. Age group of 5-10 years was the most vulnerable for the infection and its complications. Central nervous system (CNS) involvement, hepato-biliary involvement and gastrointestinal (GI) involvement were the common complications.

Conclusions: Enteric fever involved a broad spectrum of complications involving the CNS, hepato-biliary system and the GI system.

(Key words: *Salmonella typhi,* Blood culture, Complications)

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Introduction

Enteric fever is a multi-system infection caused by *Salmonella enterica serovar typhi* and *Paratyphi* A, B and C and annually around 27 million cases are reported worldwide with around 1% mortality[1,2]. Developing countries of Asia are major contributors to overall disease burden[2]. Multidrug resistance, along with poor hygiene and sanitary conditions are the main obstructions to controlling this disease[3]. Diagnosis of enteric fever may be challenging due to its varied presentation[4]. Blood culture is the gold standard for diagnosis and the highest yield is 90% in the 1st week of illness, and 75%, 60% and 25% in the 2nd, 3rd and 4th weeks respectively[5,6]. However, due to inadequate laboratory facilities, cost and technical difficulties to obtain a good culture sample from small children, culture is not frequently done in developing countries. Positivity of blood culture may be further compromised by prior antibiotic usage. Sensitivity and specificity of the Widal test being low, in most cases, treatment is empirical[6].

Studies have found gastrointestinal tract (GIT) complications such as paralytic ileus and intestinal perforation, central nervous system (CNS) complications like encephalopathy and ataxia, pulmonary complications like pneumonia and reactive arthritis in the bones and joints[7-12]. In our experience, a substantial number of cases of enteric fever have delayed presentation and most are inadequately treated resulting in admission with different complications. There are several studies regarding risk factors, epidemiological factors and preventive strategies, with few studies documenting different complications of enteric fever especially from this part of India.

Objectives

To assess the frequency of various complications and treatment outcomes in children admitted with fever and whose blood culture revealed salmonella.

Method

This retrospective study was conducted at the Institute of Child Health, Kolkata from January 2013 to December 2022. Data of seven hundred and twenty children aged 6 months - 15 years were included in the study, all with a history of fever for more than 5 days and blood culture of all the patients revealed Salmonella species. Children were included in the study irrespective of prior antibiotic treatment. In all included patients, age, sex, duration of illness, presenting symptoms were documented and all patients were scrutinized for all possible documented complications of enteric fever with the help of history and examination findings. Complications were defined as conditions aggravating an already existing illness i.e., enteric fever and directly related to the morbidity and mortality of the disease. Wherever required and feasible,

appropriate and relevant investigations were done to document the complications. In addition to routine blood count and blood culture report, data of liver function tests (LFTs), renal function tests (RFTs), abdominal ultrasonography (USG), prothrombin time (PT) / activated partial thromboplastin time (APTT), electrocardiography (ECG), x-ray chest (CXR), echocardiography, cerebrospinal fluid (CSF), computed tomography (CT) and magnetic resonance imaging (MRI) of the patients were collected wherever available.

***Ethical issues**:* Approval for the study was obtained from the Institutional Ethics Committee for Biomedical and Health Research, Institute of Child Health, Kolkata, India (No. ICH/ IECBMHR/ 26/ 2023) dated 01.07.2023 As this was a retrospective study informed consent was not a possibility.

***Statistical analysis**:* Data entry was done in Microsoft Excel and was statistically analysed using SPSS software. Descriptive statistical data like means, medians and standard deviations were calculated for continuous variables. Statistical analysis was performed using Chi-square test to see association between complications and age group, days of illness, anaemia, leucopenia and thrombocytopenia. A p-value less than 0.05 was considered significant.

Results

Table 1 shows the demography of the study population.

Table 1: ***Demography of study population***

Variable	Total patients *(n=720)* *n (%)*	With complications *(n=236)* *n (%)*	Without complications *(n=484)* *n (%)*
Age group (years)			
<5	190 (26.4)	52 (27.4)	138 (72.6)
5-10	383 (53.2)	137 (35.8)	246 (64.2)
>10	147 (20.4)	47 (32.0)	100 (68.0)
Sex			
Male	390 (54.2)	121 (31.0)	269 (69.0)
Female	330 (45.8)	112 (34.0)	218 (66.0)

Mean age of the children was 7.4 ± 3.18 years. We had 59 (8.2%) patients ≤2 years and the youngest patient during the study period was 9 months and 15 days old. Duration of illness was up to 7 days in 285 (39.6%) cases, 8-14 days in 269 (37.4%) cases, 15-21 days in 87 (12.1%) cases and more than 21 days in 79 (10.9%) cases. Around 33% of total patient population had some form of complication. Incidence of complications was highest in the 5-10-year age group followed by the >10-year age group. Treatment was started with injection ceftriaxone as first line in 633 (88%) patients who already had oral antibiotics, while injection ceftriaxone plus oral azithromycin was started in those who did not respond to ceftriaxone till five consecutive days or had been on ceftriaxone for the last few days before coming to hospital. In our study, 128 (17.8%) were vaccinated against typhoid.

Breakup of various complications is depicted in Table 2, showing that major systems involved were CNS and GIT.

Table 2: ***Frequency of involvement of different systems***

Involved system	No of cases	% of complications *(n=236)*	% of total patients *(n=720)*
Central nervous system	79	33.5	11.0
Hepatobiliary	64	27.1	08.9
Abdominal	53	22.5	07.4
Haematological	29	12.3	04.0
Bones and joints	20	08.5	02.8
Respiratory	14	05.9	01.9
Cardiovascular	09	03.8	01.2

Further breakup of various systems is depicted in Table 3. Few cases were seen from other systems like haematological, bones and joints, respiratory and CVS. There were 5 (2.1%) cases of disseminated intravascular coagulation, and 11 (4.7%) cases of haemophagocytic syndrome. Twelve (5.1%) cases had reactive arthritis. 10 (4.2%) had pneumonia and 6 (2.5%) had pleural effusion. Four (1.7%) patients presented with pericarditis and 3 (1.3%) with shock.

Table 3: ***Different complication according to system involvement***

System involved	Number of cases	% of system involved	% of complication *(n=236)*	% of total patients *(n=720)*
Central nervous system (n=79)				
Encephalopathy	37	46.8	15.7	05.1
Cerebellar ataxia	13	16.5	05.5	01.8
Aphasia/dysphasia	11	13.9	04.7	01.5
Meningismus	09	11.4	03.8	01.3
Febrile seizures	09	11.4	03.8	01.3
Hepato-biliary (n=64)				
Enteric hepatitis	56	87.5	23.7	07.8
Coagulopathy	08	12.5	03.4	01.1
Abdominal (n=53)				
Paralytic ileus	16	30.2	06.8	02.2
Intestinal perforation	14	26.4	05.9	01.9
Ascites	13	24.5	05.5	01.8
Haematemesis and melaena	10	18.9	04.2	01.4
Haematological (n=29)				
Thrombocytopenia	17	58.6	07.2	2.36
HLH	11	37.9	04.7	01.5
DIC	05	17.2	02.1	0.6
Miscellaneous				
Reactive arthritis	12		05.1	01.7
Pneumonia	10		04.2	01.4
Pleural effusion	06		02.5	0.8
Pericarditis	04		01.7	0.5
Myocarditis	04		01.7	0.5
Shock	03		01.3	0.5

Discussion

The relative incidence of enteric fever is higher in the younger age group. In our study, mean age of presentation was 7.4 years similar to 7.5 years in the study by Comeau JL, *et al*[13]. In our study, 53.2% cases were aged 5-10 years and 26.4% were aged below 5 years. This age distribution was similar to that in the study by Rangantha A, *et al* where 47% cases were aged 5-10 years. During our study period the youngest patient was 9 months and 15 days old, endorsing the stance of Modi R, *et al*[15] that no age is exempt from typhoid. A meta-analysis by Britto C, *et al*[16] showed that the highest prevalence was in age group 5-9 years, followed by 10-14 years and below 5 years.

In our study 32.8% of patients had complications, 34 having multiple complications. Similarly, a study by Malik AS[7] had complications in around one third of patients. In our study, maximum complications were in the CNS, followed by hepatobiliary, abdominal, haematological, bones and joints, respiratory and cardiovascular in descending order of frequency. Malik AS[7] documented anicteric hepatitis, bone marrow suppression, paralytic ileus, myocarditis, psychosis, cholecystitis, osteomyelitis, peritonitis, pneumonia, haemolysis, and syndrome of inappropriate release of antidiuretic hormone in descending order of frequency. A study by Alshosk M, *et al*[17] on complications of enteric fever showed that 12.4% had abdominal complications. In our study, abdominal complications were third in order, though enteric hepatitis was the commonest complication irrespective of the systems involved in our study.

In our study, enteric encephalopathy was the most frequent neurological complication constituting 5.1% of total cases and 15.7% of total complication and this is similar to the study by Jemni L, *et al*[8]. Out of 79 patients with neurological complication 46.8% had encephalopathy. Although acute cerebellar ataxia is a rare complication, we had 13 patients with this complication constituting 16.5% of total neurological complications. There are many case reports supporting our findings[18,19]. Our study revealed frequency of enteric hepatitis to be 23.7% similar to study by Pramoolsinsap C, *et al*[20]. In our study, of 53 abdominal complications 14 had intestinal perforation which constituted 6% of total complications, significantly higher than the prevalence noted in study by Chalya PL, *et al*[21]. Sinha R, *et al*[10] showed that ascites is an under-reported complication of enteric fever. In our study, we had 13 cases of ascites comprising 24.5% of all abdominal complication and 5.5% of total complications. A similar percentage was reported by Chiu CH, *et al*[22] showing 4% incidence of ascites in enteric fever.

Pericarditis is one of the seldom reported complications. Esmailpour N, *et al*[23] has shown in his study that 4.6% cases had cardiac complications which included myocarditis, pericarditis and pulmonary emboli. We had only 9 cases with cardiac complications that included myocarditis and pericarditis (4 each). Total number of deaths was 9 (3.8% of total complications) among which five died of intestinal perforation, two of myocarditis and 2 died of haemophagocytic lympho-histiocytosis.

Conclusions

Enteric fever led to a broad spectrum of complication involving almost all the systems. The most vulnerable age-group for enteric fever and its complication was 5-10 years. Almost one third of hospital admissions were with complications. Common complications were from CNS, hepatobiliary and GIT.

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