

Clinical profile and Outcome of Enteric Fever in hospitalized children aged 6 months to 2 years

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Abstract

Background : Enteric fever is a common endemic disease in Bangladesh.¹ Enteric fever caused by *Salmonella typhi* (typhoid fever) is a major therapeutic consideration of all prolonged illnesses with pyrexia in pediatric practices particularly in developing countries like Bangladesh.²

Objectives : To evaluate the clinical profile and outcome of enteric fever in hospitalized children aged 6 months to 2 years

Methods: This was a prospective study conducted in the paediatric medicine unit of Dhaka Shishu Hospital during the period of November 2003 to August 2004. Forty children (age 6 months to 2 years) with specific criteria for diagnosing enteric fever enrolled in this study. Statistical analysis was done using the SPSS. All the data were expressed in percentage, mean or standard deviation. Anova test was used as the test for significance.

Results : The clinical features, laboratory data, response to treatment were studied in 40 cases of enteric fever (diagnosed by prefixed criteria). Majority of the patients belonged to the age group between 9 months to 2 years. Fever was the main presenting feature in all the cases (100%). Other associated features were anorexia (95%), vomiting (85%), diarrhea (80%), abdominal distension (75%), cough (70%), pallor (70%) and lethargy (50%). Of the signs, high temperature 101°F (95%), coated tongue (92.5%), tachycardia (90%), toxic appearance (87.5%) and anemia (70%) were the commonest features while hepatomegaly was present in 37.5% of cases. Typhoid fever was the most frequent (82.5%) enteric fever and the Widal test was significantly positive in 100% of cases. Blood culture was positive in 4 cases only with *S. typhi* in 3 cases (75%) and *S. paratyphi A* in 1 case (25%) and all isolated organisms were sensitive to Ceftriaxone and Ciprofloxacin. The outcome of the study population was assessed in terms of improved, cured, failure of treatment, complications and relapse. Cure rate was high (82.5%) in the study group. In the remaining 17.5%, the patients were considered improved. No case of relapse was recorded during the follow-up period of these patients. Failure of improvement or deterioration of clinical condition after treatment was not noted in this study. Complications were minimal in the study population and none of the patients died in this study.

Conclusion: Contrary to the popular belief and west-oriented teaching, typhoid is certainly common in infants and young children in countries of the Third World and younger children are more likely to present with a non-specific febrile illness which makes the diagnosis difficult and as such adequate knowledge of the clinical presentations of this age group is essential for effective diagnosis and treatment.

Introduction

The World Health Organization has estimated that at least 12.5 million cases of enteric fever occur annually worldwide.³ Though it is endemic all over the world the incidence has decreased markedly in developed countries. Enteric fever predominantly occurs in the developing countries where water supplies are substandard and sanitary conditions remain poor.⁴ It is a systemic syndrome⁵ and also a severe systemic form of Salmonellosis. The following organisms are responsible for enteric group of fevers:

1. *Salmonella typhi*
 2. *Salmonella paratyphi A*
 3. *Salmonella schottmuelleri* (formerly *S. paratyphi B*)
 4. *Salmonella hirschfeldii* (formerly *S. paratyphi C*).⁶
- Infection by *S. typhi* causes typhoid fever whereas infection by the other three causes paratyphoid fevers.⁷

In developing countries, *S. typhi* is often the most common *Salmonella* isolate³ of the paratyphoid fevers, those caused by *S. Paratyphi A* are the commonest.⁸

It is endemic in Bangladesh because of our primitive sanitation systems which favors the transmission of the disease⁹ It still remains as a significant cause of morbidity and mortality in Bangladesh with increasing evidence of emergence of multi-drug resistant strain of *Salmonella typhi*.²

The age incidence of typhoid fever varies widely in different studies in various countries. Some studies showed that the incidence of typhoid fever peaks between 5 and 12 years.¹⁰ In Malaysia, the average age at presentation was 91.3 (range 6-159) months.¹¹ In a study in Taiwan, out of 71 children diagnosed to have typhoid fever 83% were between 5-15 years.¹⁰ Hospital-based studies have suggested that peak incidence in children is 5 to 15 years of age. This is in contrast to the first community-based data on typhoid disease conducted by ICDDR, Dhaka; which indicates that overall incidence of typhoid fever was 3.9 cases per 1000 population per year; in children <5 years the rate was 18.7 per 1000 children per year. Children <5 years of age had an 8.9-fold increased likelihood of infection when compared all others. Among children less than 5 years of age, 85% of cases occurred between 2 and 4 years of age; 4.0% occurred during the first year of life and 27% occurred in the second year.¹² These findings are

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similar to those of the recent community based study of typhoid incidence in Dehli, India.¹³ A hospital based retrospective and prospective study was done in Kolkata, India to ascertain which particular age group is more affected and as such should be the target age group for an immunization program. This study showed that children between 2-3 years of age are the most susceptible age group (35.6%) and thereby are the highest risk group against Typhoid infection as compared to other age groups.¹⁴ These results corroborate the findings of an earlier study of Bangladesh amongst hospitalized patients which shows 6(16.2%) out of 37 patients in the age group of 2-3 years are more susceptible to this infection.¹⁵ No age is exempt but typhoid fever is less common in children under 2 years.¹⁶ Therefore in this study patients of 6 months to 2 years were selected.

The classical features of typhoid fever are mainly found in school-age children and young adults. When *S. typhi* is isolated from young children the presentation is often atypical.¹⁷ No doubt the clinical picture in paediatric typhoid is remarkably different from what is often seen in grownups.¹⁸ Definitive diagnosis of enteric fever requires certain laboratory investigations, but a single test may not have sufficient sensitivity to make a confident and rapid diagnosis in endemic areas. Although the clinical features of enteric fever are not distinctive and there is considerable diversity in its clinical spectrum in different age groups of patients; yet it may be possible to make a presumptive clinical diagnosis of typhoid fever with a combination of clinical features so that a rapid diagnosis may be made.⁹

Therefore it is important to study the common clinical spectrum of enteric fever that favors its diagnosis. In this study we have tried to evaluate the clinical profile and outcome of hospitalized children aged between 6 months to 2 years suffering from enteric fever.

Materials and methods

This was a prospective study from November 2003 to August 2004 conducted at the paediatric medicine unit of Dhaka Shishu (children) Hospital. Forty (40) febrile children (suspected enteric fever) were included in this study.

The **Inclusion Criteria** was-

- Age : children 6 months to 2 years of age
- Sex : Both male and female
- fever for more than a week
- suspected enteric fever
- without prior antibiotic therapy

Exclusion Criteria

- Age : Below 6 months and above 2 years of age.
- Patients associated with other febrile illness e.g. dengue, malaria, meningitis, TB etc.
- enteric fever patients with severe complications
- Use of antibiotic prior to inclusion in the study

In this study we had applied the following-**diagnostic criteria for enteric fever**

- **clinically suspected enteric fever**

(persistence of fever for over a week, anorexia, vomiting, diarrhea, abdominal distension, cough, lethargy, coated tongue, toxic appearance, tachycardia, anemia, hepatomegaly)

- supported by **one or both of the following-**

Widal titer- positive (1 : 160 or more for somatic antigen and / or 1 : 320 or more for flagellar antigen)¹⁹ and/or presence of rising titer.

Isolation of *Salmonella typhi* or *paratyphi*

from blood, urine or stool culture.

A thorough history was taken particularly with reference to the symptoms of enteric fever in children of the specified age group. A complete physical examination and necessary laboratory investigations (Widal test/blood, urine or stool culture) were done routinely for all the selected patient. Study patients were treated with one of the following appropriate drugs-Ceftriaxone or Ciprofloxacin. During treatment everyday the hospitalized children were evaluated clinically. The responses to the treatment were noted and the outcome of these hospitalized patients were seen. The outcome of the study population was assessed in terms of improved, cured, failure of treatment, complications and relapse. The following Operational definition were applied in this study-

- **defervescence** : (number of days taken for temperature to return to normal). When the patients core temperature drops below 99.7°F (37.6°C) after initiation of therapy and remains so for at least 3 days without the use of antipyretics.

- **improved** : Patients are considered improved if fever disappeared and signs Symptoms of typhoid fever have partially resolved. After clinical improvement in the hospital, patients are discharged home to complete their therapies and advised for followup up to 14 days

- **cure** : Patients are considered clinically cured if fever disappeared and all signs and

symptoms of typhoid fever resolved. It is also defined as disappearance of fever within 7 days of initiation of treatment with clinical improvement.

- **failure** : Defined as lack of improvement or worsening of signs and symptoms or need to change antibiotic therapy. It is also defined as persistence of fever and /or deterioration of clinical condition or complications leading to fatalities even after 7 days of antibiotic therapy.

- **clinical Relapse** : Return of febrile illness at least 3 days after the patient initially becomes a febrile, in the absence of any new infective focus clinically.

All the cardinal data were collected and recorded systematically in pre-designed questionnaire form. Then analyzed and the values were expressed in percentage, mean or standard deviation (SD). Statistical analyses were done using the SPSS (Statistical Package for Social Sciences) program for personal computers. Anova test was used as the test for significance. P value of <0.05 was considered significant.

Result

Forty (40) patients who full filled the inclusion criteria were included in this study. Then clinical presentations, laboratory data, response to treatment of this forty (40) cases were studied. Considering the age distribution of this study patients showed that majority of the them belonged to the age group between 12 to 24 months 18.18 ± 5.02 months (range, 9-24 months) (Table I). The lowest age was 9 months.

Among this study population the frequent symptoms were fever, anorexia, vomiting, diarrhea, abdominal distension, cough, pallor, and lethargy and the frequent signs were high temperature, coated tongue, tachycardia, toxic appearance, abdominal distension and anemia (Table-II).

Table- I : Age distribution of study population (n = 40)

Age group (months)	No of patients	Percentage (%)	Mean age ± SD
6 months to <12 months	5	12.5	18.18 ± 5.02 months (range, 9-24 months)
12 months to 24 months	35	87.5	

Table-II. Frequency of symptoms and signs of the study population (n=40)

Symptoms	No. of patients	Percentage (%)	Signs	Number of patients	Percentage (%)
Fever	40	100.0	Fever>101°F (38.3° C)	38	95.0
Anorexia	38	95.0	Coated tongue	37	92.5
Vomiting	34	85.0	Tachycardia	36	90.0
Diarrhea	32	80.0	Toxic appearance	35	87.5
Abdominal Distension	30	75.0	Abdominal distension	30	75.0
Cough	28	70.0	Anemia	28	70.0
Pallor	28	70.0	Hepatomegaly	15	37.5
Lethargy	20	50.0	Abdominal tenderness	8	20.0
Malaise	14	35.0	Splenomegaly	4	10.0
Headache	12	30.0	Hepato splenomegaly	3	7.5
Myalgia	10	25.0	Meningismus	2	5.0
Chills	10	25.0	Rales or rhonchi	2	5.0
Abdominal pain	9	22.5	Rose spots	0	0.0
Constipation	8	20.0	Relative bradycardia	0	0.0
Convulsion	1	2.2	Jaundice	0	0.0
			Psychosis	0	0.0

On admission the majority (60%) of this cases were clinically diagnosed as enteric fever by the attending physician of the paediatric medicine unit of Dhaka Shishu (children) Hospital (Table III). Sixteen cases (40%) were clinically diagnosed as Gastroenteritis, Pneumonia, Acute abdomen etc

Table-III Provisional Diagnosis on admission (n = 40)

Provisional diagnosis	No of patients	Percentage (%)
Enteric fever	24	60.0
Gastroenteritis	7	17.5
Anemia	4	10.0
Pneumonia	2	5.0
Acute abdomen	1	2.5
Meningitis	1	2.5
Malaria	1	2.5

Widal test was done in all study patients and positive in 100% of cases. This study also showed that typhoid fever is the most frequent type (82.5) of enteric fever (Table-IV). Results of the Widal test showed that :In typhoid fever the titers were : only T_O was 1 : 160 or more in 12.5%; T_H was 1 : 320 or more in 10%; both T_O & T_H was 1 : 160 in 2.5% while T_O 1 : 160 and T_H 1 : 320 in the majority (37.5%) of cases. In paratyphoid fevers the titers of Widal test were: B_O= 1 : 320 in 2.5% and B_H 1 : 320 in 5% and A_H 1 : 160 in 10% of cases. Rising titer was noted in only 20% of cases (Table-V)

Table-IV. Widal test of study population (n = 40)

No of cases	Widal test significant (n = 40)		
	T _O /T _H	A _O /A _H	B _O /B _H
40	33	4	3
Percentage (%) 100%	82.5	10.0	7.5
Specific type of enteric fever	Typhoid fever	Para typhoid A	Para typhoid B

Table-V. Results of the Widal test (n = 40)

Antigen & Titer	No of patients	Percentage (%)
T _O = 1 : 160	2	5.0%
T _O 1 : 320	3	7.5%
T _H = 1 : 320	3	7.5%
T _H 1 : 640	1	2.5%
T _O = 1 : 160 & T _H = 1 : 160	1	2.5%
T _O = 1 : 160 & T _H 1 : 320	12	30.0%
T _O = 1 : 160 & T _H > 1 : 640	2	5.0%
T _O 1 : 320 & T _H 1 : 320	9	22.5%
B _O = 1 : 320	1	2.5%
B _H 1 : 320	2	5.0%
A _H = 1 : 160	1	2.5%
A _H 1 : 320	3	7.5%
T _O /T _H Rising Titer	8	20.0%

In this study blood, stool and urine culture was send in 26 cases. Among them only 4 (15.3%) cases were blood culture positive (causative organism was isolated) Table VI . Salmonella typhi was the major organism isolated (Table-VII).

Table-VI Results of blood, stool and urine culture(n = 26)

Name of sample	No of patients	Organism isolated	Percentage (%)
Blood	20	4	15.3
Stool	3	0	0.0
Urine	3	0	0.0

Table-VII Profile of isolated Salmonella (n = 4) in blood culture

Organism isolated	No of patients	Percentage (%)
Salmonella typhi	3	75
Salmonellaparatyphi A	1	25

Table-VIII shows that 25% of cases were multi-drug resistant (MDR strains : resistant to Chloramphenicol, Co-trimoxazole and Amoxicillin). None of the isolates were resistant to neither Ceftriaxone nor Ciprofloxacin

Table- VIII Sensitivity pattern of isolated Salmonella

Drugs	Sensitive		Resistant	
	no.	%	no.	%
Ampicillin	1	25	3	75
Amoxicillin	3	75	1	25
Co-trimoxazole	3	75	1	25
Chloramphenical	3	75	1	25
Ceftriaxone	4	100	-	-
Ciprofloxacin	4	100	-	-

In this study majority (85%) of cases were treated with Ceftriaxone and only 15% with Ciprofloxacin. With this therapy in the majority (60%) of cases defervescence occurred within 4 days after starting of treatment (Table-IX). Thirty three patients (82.5%) were cured with appropriate antibiotics while 17.5% were improved and discharged with advice to complete the therapy at home. There were no failure of treatment, no relapse and no death. None of the patients were discharged on risk bond (Table-X).

Table-IX Time-to-defervescence (n = 40)

Duration (days)	No of patients	Percentage (%)	Mean time \pm SD
1 – 4	24	60.0	4 \pm 1.24 days (range, 2 – 6 days)
5 – 7	16	40.0	
> 7	0	0.0	

Table-X Outcome of the study population (n = 40)

Outcome	No of patients	Percentage (%)
Cured	33	82.5
Improved	7	17.5
Failure of treatment	0	0.0
Relapse	0	0.0
DORB		
(Discharged on Risk Bond)	0	0.0
Death	0	0.0

Discussion

This study was conducted to evaluate the clinical profile and outcome of enteric fever in hospitalized children aged 6 months to 2 years. For many years enteric fever is regarded as a disease that affects mainly children of school age and adults.^{20, 12} However, like Saha et al¹⁴ and Sinha et al³ our findings challenge this common view. A series of systematic studies have shown that bacteremic *S. typhi* infection also occurs in children <5 years, including in infants and toddlers <2 years of age. In the present study, the highest incidence was found in the age group of 12-24 months (87.5%). The mean age was 18.18 \pm 5.02 months (the age range being 9-24 months) (table I). There were 5 cases between the age group of 6 months to less than 12 months with an incidence of 12.5% in this age group (table I). Therefore, our study has clearly shown that enteric fever also occurs in infants and toddlers of upto 2 years of age.

The most consistent clinical symptom was fever which occurred in 100% of cases (Table-II). This is comparable with other series.^{13,20} Other major symptoms were anorexia (95%), vomiting (85%), diarrhea (80%) and abdominal distension (75%). Diarrhea was much more common than constipation (80% vs. 20%). This finding was consistent with some previous studies³ that diarrhea is more common in young children with typhoid fever than in adults, leading to a diagnosis of acute gastroenteritis. Cough, a non-specific symptom, but which sometimes may be confused with respiratory tract infection was common and found in 70% cases. Pallor was evident in 70% of cases in this study. It is consistent with another study¹⁸ which states that in typhoid of infancy and early childhood clinical profile include anemia among others. In our study lethargy (50%) and malaise (35%) were found as symptoms. This is similar to the common understanding that fever and malaise misinterpreted as a viral syndrome occurs in infants and young children with typhoid fever. However, our finding are also consistent with the fact that in infants and young children infection by *S. typhi* may present as a rapid septicemic type illness, with respiratory

signs, seizures and meningism¹⁷ In this study, however, respiratory signs (2.5%), seizures (2.5%) and meningism (5%) were far less frequent than anticipated. Other symptoms such as abdominal pain, headache, and chills (but not rigor) were also found among the patients.

Apart from fever, coated tongue (92.5%) and toxic appearance (87.5%) were the most important pointers towards the diagnosis of enteric fever (table-II). Similarly tachycardia was a very common physical finding (90%) while relative bradycardia was not observed in our study. This data is in agreement with the report that relative bradycardia is not a feature of enteric fever in children.²¹ Anemia (70%) as well as abdominal distention (75%) were common in our study population. Abdominal tenderness, which can be diagnostically important in children²² was present in 20% of cases. Hepatomegaly was noted in 37.5% of children which is similar (35%) to that of an Ethiopian study while it was the feature of 42% in South African and 27% in Nigerian children with typhoid fever.²³ In a Bangladeshi study it was shown that palpable liver present in 58% cases and palpable spleen in 33% cases and hepatosplenomegaly in 44.1% cases of children with enteric fever.¹⁰ However, we could only detect splenomegaly in 10% and hepatosplenomegaly in only 7.5% of our study age-group. Meningism was noted in 5% of the present study. The cerebrospinal fluid (CSF) profile was normal in all of them. In this series, there was no single instance of rose spots among the 40 Bangladeshi children with enteric fever who were studied. Absence of rose spots was also reported in another study.⁹ Rose spots are said to be very difficult to detect in dark-skinned children.²⁴

Many investigators believed that there was no typical clinical picture of typhoid fever in young children. Nevertheless, in this study the correct clinical impression of typhoid fever was made on admission in 60% of cases, Sixteen cases (40%) were clinically diagnosed as Gastroenteritis, Pneumonia, Acute abdomen etc (table-III). This is similar to the correct impression of typhoid fever in 55.6% of cases of the Ethiopian series and to the 58% of the Nigerian series.²³

In our study diagnosis was made on clinical impression along with positive Widal test in all 40 cases (including the 4 blood culture positive cases). High positivity of Widal test has been reported by some authors,²⁵⁻²⁶ while others doubt its value.^{35, 150} In our study, the positive Widal test was high (100%). The rising titer was demonstrable in 8(20%) of cases (table-V). Four-fold rise of titer was also noted in the majority (70%) of cases in our study. The Widal test was also positive in the in all the culture proven cases of enteric fever (Table-V). Saha et al laid diagnostic criteria in 1996 for Bangladeshi children. Based on their data, the titers ($T_O > 1:80$ and $T_H > 1:160$) were considered to be significant with 88% sensitivity and 98% specificity respectively.¹⁹

In our study, typhoid fever (82.5%) was the most frequent enteric fever while paratyphoid A was 10% and paratyphoid B was 7.5% only. *Salmonella typhi* is a major cause of enteric fever in Bangladesh. Of the paratyphoid fevers, those cause by *Salmonella paratyphi A* is more common.⁸

Culturing the *Salmonella* strain involved is usually the basis for confirming the diagnosis,³ blood culture being considered the gold standard. Out of 40 cases in our study blood culture was done in 20 cases, stool culture done for 3 cases and urine culture done in 3 cases. Blood culture was positive in only 4 (15.3%). Stool and urine cultures were not positive in any case in our studies (table-VI). The low isolation rate of *Salmonella* from blood culture in our study may be explained partly because only a single culture was done before treatment, and partly because majority of the patients (60%) reported to the hospital

late during the disease (after 7 days of fever). Other studies showed that results of blood culture were positive in 40-60% of the patients seen early in the course of the disease.³ However, our results are similar to the isolation rate (15.33%) as reported in 1990 by Choudhury et al²⁷, although they are less than that reported by others.²³ In our study Culture positive but Widal negative cases were none.

In the present study the majority (85%) of cases were treated with Ceftriaxone and only 15% of cases with Ciprofloxacin (table-VIII) in adequate doses and duration. Treatment was given for 10 days during the hospital stay in this majority of patients.

The outcome of the patient was assessed in terms of defervescence, improved, cured, failure of treatment, complications and relapse. Cure rate was high (82.5%) in the study group (table-X). Bacteriological cure was not assessed in our study. In the remaining 17.5%, the patients were considered improved. After clinical improvement in the hospital, patients were discharged home due to their financial constraints. In this group of patients treatment was given for 7 days during their hospital stay and during discharge they were advised to complete their therapies at home and for followup up to 14 days. No case of relapse was recorded during the follow-up period of these patients. Failure of improvement or deterioration of clinical condition after treatment was not noted in this study.

Conclusion

Contrary to popular belief this study showed that enteric fever is not uncommon under 2 years of age. The clinical finding that was seen in our study was that 95% of young children had anorexia. Similarly vomiting (85%),diarrhea(80%) and cough (70%), Coated tongue (92.5%),toxic appearance (87.5%) was common in young children. However, abdominal pain occurred only in 22.5% and presence of hepatomegaly and splenomegaly was less. Relative bradycardia was not a feature in young children. These findings gave us a correct clinical impression of typhoid fever in young children.

Limitations of the Study

- a) It was a hospital-based study with time limitation.
- b) All cases were not bacteriologically proven enteric fever.
- c) Bacteriological cure was not assessed

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