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Original Research Article

A study of clinico-diagnostic profile and antibiogram in children with enteric fever in a tertiary care hospital

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ABSTRACT

Background: Enteric fever remains a major concern in developing countries caused by *Salmonella typhi*. Recently, an upsurge in antimicrobial resistant strains has complicated the management. The present study was undertaken to evaluate the clinical profile, compare typhidot test with blood culture and determine antimicrobial susceptibility pattern.
Methods: Single centre descriptive study was conducted by enrolling children who presented with fever and who were either blood culture positive for *S. typhi* or typhidot positive. The clinico-laboratory data and antibiogram was studied.
Results: Out of 76 cases, blood culture was positive in 35 (46%) cases. Typhidot test showed 92.11% positivity. Abdominal pain (78%), vomiting (68%), hepatomegaly (68%) and splenomegaly (43%) were most commonly observed. The sensitivity for classical drugs chloramphenicol, ampicillin and cotrimoxazole was 88.57%, 74.28% and 77.14%. High susceptibility to ceftriaxone (97.14%) and high resistance to ciprofloxacin (55.14%) was observed.
Conclusions: Prompt diagnosis of enteric fever is essential for appropriate management therefore, important to have conventional tests like typhidot test. There is re-emergence of sensitivity to the classical drugs. Ceftriaxone as monotherapy is quite effective. Effective vaccination strategy and hygienic practices can decrease the burden of this disease.

Keywords: *S. typhi*, Blood culture, Typhidot test, Antibiotic susceptibility

INTRODUCTION

Enteric fever is an acute infection characterized by prolonged fever following the ingestion and subsequent invasion of *Salmonella* enteric serovar *Typhi* (*S. typhi*), a human-restricted pathogen. A related but milder disease is caused by *S. paratyphi* A followed by *S. paratyphi* B/C.

It contributes majorly to the burden of morbidity as it is a disease of unfortunate environmental hygiene, sanitation and poor public health standards, causing an estimated 12 to 21 million cases and 1.4 to 2.1 lakhs death worldwide each year.[1-3] The Indian subcontinent bears the brunt of the disease both in terms of absolute case numbers and drug-resistant strains. From the recent systemic review, the pooled estimates of incidence were 377 cases and 105 cases per 100,000 person per years for typhoid and paratyphoid respectively, with incidence being highest in children between 2 to 5 years.[4]

While blood culture is gold standard for diagnosing enteric fever, it is positive in only about 30-40% of cases. Diagnosis based on clinical criteria poses problems since enteric fever mimics many febrile illnesses. Hence, clinicians routinely depend on antigen testing methods such as Widal test and typhidot test to confirm the diagnosis of enteric fever.[5]

Most of the enteric cases can be managed at home with oral antibiotics and good nursing care. For severe cases with persistent vomiting, severe diarrhea, inability to take oral feeds, abdominal distension and encephalopathy, parenteral antibiotic is needed preferably in a hospital.

Third generation cephalosporins, both oral (cefixime and cefpodoxime proxetil) and injectables (ceftriaxone and cefotaxime) are recommended for first line treatment of enteric fever. Fluoroquinolones are broadly regarded as the most effective drug for the treatment of typhoid fever. But unfortunately, few strains of *Salmonella* have shown reduced susceptibility to fluoroquinolones. The nalidixic acid resistant *S. typhi* (NARST) is a major marker of reduced susceptibility to fluoroquinolones.

Due to growing antibiotic resistance seen during the management of enteric cases, *Salmonella* and its various species are required to be periodically tested for sensitivity and resistance patterns, to guide the clinical management at the local level.[6]

The present study was undertaken with the objectives to discuss the current status of enteric fever in children including its clinical profile, blood culture positivity of *S. typhi* and to determine antimicrobial susceptibility patterns. This study also directed the key problems with diagnosis of enteric fever, resistance patterns and future directions.

METHODS

This descriptive study was conducted in the pediatric department of Geetanjali medical college and hospital from January 2020 to June 2021.

Inclusion criteria

Of all the children who presented with fever aged up to 18 years and who were either blood culture positive for *S. typhi* or typhidot positive were included in the study. Also all eligible children were consecutively enrolled in the study after taking prior informed consent from the parents were included.

Exclusion criteria

Patients who had already received antibiotics at the time of admission, patients subsequently diagnosed with co-infection and non-consent patients.

Using previous studies data and expecting the prevalence rate of 5%, with precision error of estimation (L) 5%, the sample size was calculated by using the formula for descriptive study,

$$\text{sample size}=\frac{(Z^2\times P\times Q)}{L^2}=76.$$

The study was approved by the institutional ethics committee of GMCH (ref. no. GU/HREC/EC/2019/1752).

Demographic profile, relevant information of individual patient was collected using a well-structured proforma by interviewing the parents/attendant. A detailed clinical history, a thorough clinical examination and laboratory investigations at the time of admission and during the course of hospital stay was performed in all cases and the findings were recorded.

Peripheral blood samples were collected and were sent for typhidot and blood culture at the time of admission. Samples were cultured by an automated method (Bact/ALERT 3D; Biomeriux).

The laboratory confirmed typhoid cases were studied with respective of its clinico-diagnostic profile and antimicrobial susceptibility.

All the children were treated with appropriate antibiotics according to the drug sensitivity report and the drug efficacy was judged primarily by the patient's clinical response with particular attention being given to the number of days of treatment required to make the patient afebrile. Finally, children were discharged afebrile with advice for follow-up in case any febrile illness reoccurred.

Statistical analysis

Data was entered into MS excel software. Statistical analysis was performed using the statistical packages for social sciences (SPSS) version 21 IBM corporation. Descriptive statistics were used. Chi square test done for sensitivity and specificity for typhidot test with comparing to gold standard blood culture method.

RESULTS

A total of 76 children were enrolled in the study. It included 50 male (65.79%) and 26 female (34.21%) children showing male predominance. 31 cases were aged between 6-10 years, 20 cases were below 5 years and 25 cases were aged above 10 years (Figure 1). Mean age for typhoid fever in this study was 8.67±3.89 SD years.

Typhoid incidence was found to be more in lower class (43.4%), followed by in middle class (35.5%) and least in upper class (21.1%).

All the 76 cases were presenting with history of fever. As many as 40.8% of cases had fever between 3-6 days prior to admission, 51.3% of cases had fever for 7-10 days and only 6% presented with fever of more than 10 days. Mean duration of fever was 6.9±2.30 SD days. Mean temperature at the time of admission was 101.3 ˚F (101.3±0.97 SD). Overall, all patients had a temperature of more than 99˚F and less than 104˚F.

Abdominal pain and vomiting were the most common symptoms seen in 75% and 68.42% of cases respectively. Symptoms like anorexia (56.58%), headache (43.42%), diarrhea (36.84%), constipation (18.42%) and cough (40.79%) were also seen in children. On examination 68.42% had hepatomegaly and 43.42% had splenomegaly. Very few patients had complications in form of GI perforation (3.95%), hepatitis (6.58%), bronchitis (7.89%), encephalopathy (2.63%) and myocarditis (1.31%).

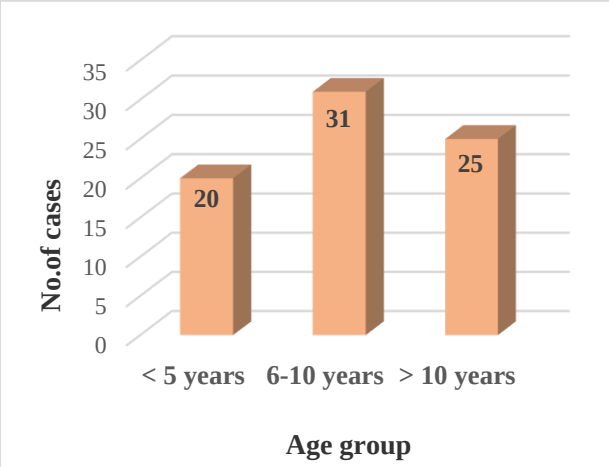

Figure 1: Distribution of study population according to age group.

Most of the patients had normal leukocyte count in this study. Leukopenia (WBC count <4000/cmm) was present in 36.84% of patients. Leukocytosis (WBC count >11000/cmm) was present in 15.79% of patients. The liver enzyme SGPT was raised in 6.58 percentages of patients.

Out of 76 patients enrolled in this study, 70 patients had positive typhidot test (92.11%). Blood culture was positive in 46% cases in our study. Out of 35 blood culture positive cases, typhidot test was positive in 29 cases. The comparison of typhidot test with blood culture is shown in Table 1. The sensitivity of typhidot test was found to be 82.85%. Only 14.47% children were immunized with typhoid vaccine (TCV).

Table 1: Comparison of typhidot test with blood culture.

Typhidot test	Blood culture		Total
	Positive	Negative	
Positive	29	41	70
Negative	6	0	6
Total	35	41	76

Antibiogram showed 97.14% isolates were susceptible to ceftriaxone and cefixime, 88.57% were to chloramphenicol, 77.14% to cotrimoxazole, 82.85% to azithromycin, 74.28% to ampicillin and 57.14% to ciprofloxacin. Isolates resistant to all the three first line antibiotics are MDR isolates seen in 11.42% cases.

Defervescence of fever shows the clinical response to the treatment (Table 2). The mean duration of defervescence of fever was 4.3 days. (4.34±1.56 SD).

The patients with a presumptive clinical diagnosis of typhoid fever were initially treated with ceftriaxone. Cases not responding to ceftriaxone with no defervescence in fever for 7 days were started with azithromycin. On discharge, the child was started on oral cefixime or azithromycin to make a total duration of antibiotic of 14 days.

Table 2: Response to treatment.

Fever defervescence (days)	No. of cases	Percentage
2-3	25	32.9
4-5	35	46.1
6-7	12	15.8
>7	4	5.2

DISCUSSION

Typhoid fever is an endemic communicable disease with high incidence in developing countries. It continued to be an important cause for high grade pyrexia in our country. Though it was common infection in children, it was difficult to diagnose because of its nonspecific symptoms and signs. However, it was necessary to diagnose early to initiate appropriate antibiotic therapy because delay in treatment may lead to several morbidities and even death.

This study was primarily carried out to evaluate various clinico-diagnostic and antibiotic sensitivity pattern in children. 76 cases with laboratory-confirmed typhoid fever were included.

In this study maximum incidence of typhoid fever was seen in age group 6-10 years (40.79%) followed by children above 10 years of age (32.89%), and children less than 5 years of age (26.32%). The mean age found was 8.6 years (SD 3.84). Similar results have been reported in previous studies.[5,7,8] Overall, the incidence of typhoid fever was high among school going children. Highest incidence of typhoid fever in this age group can probably be attributed to outside food eating practices and consuming contaminated drinking water.

The high disease burden in school children highlighted the importance of vaccine at early age and improvement in hygiene. In our study only 14.4% children were immunized with typhoid vaccine because of lack of awareness and poor socio-economic status. Although all immunized children recovered early without any complications. The study consisted 50 male (65.79%) and 26 female (34.21%) children. The male:female ratio in the study group was 2:1, having male predominance

which was similar to other studies.[8-10] However this could be attributed to the fact that male child in rural area are given more liberty and preference for school and street-food consumption. Maximum patients belonged to the lower socioeconomic status (43.4%), followed by 35.5% patients from the middle class and 21.1% from upper class which was consistent with other studies.[8,11] This may be explained by differences in drinking water sources and poorer hygienic conditions amongst the lower socioeconomic class.

The purpose of this study was to assess the importance of some clinical and laboratory features in the diagnosis of enteric fever.

Fever was present in all our patients. 100% is the reported incidence quoted in the study by Jha et al and Devaranavadagi et al.[6,8] Most of the patients (36.84%) had temperature ranging between 101-102˚F with mean temperature of 101.3 ˚F (SD 0.97). In this study mean duration of fever was 6.9 days which is consistent with other studies.[6,9]

Most of the signs and symptoms of the patients in the present study were similar to those found in earlier studies. The comparison of prominent clinical features of typhoid fever in our series with various studies is shown in Table 3.

The most common symptom apart from fever was abdominal pain (75%) and then vomiting (68.42%) which was consistent with other studies.[10] Contradictory to this, few studies reported anorexia as the most common symptom next to fever.[8,12] Symptoms like headache (43.42%), cough (40.79%), diarrhea (36.84%) and constipation (18.42%) were in agreement with the above studies.[6,7,9,11,12]

Even though 100% of cases presented with fever only 22.3% children had a toxic look and 7.89% had altered sensorium. This may be because this study was done in a tertiary centre and these children presented to us late in the course of the disease. Our data showed that most common clinical findings were hepatomegaly (68.4%) and abdominal tenderness (59.2%). The rarity of enteric hepatitis had been stressed by several authors. Most of our cases had normal total leukocyte counts similar to earlier studies.[5,13] Leucocytosis (15.8%) and leucopenia (36.8%) in our study was comparable to other studies.[8] However, leucopenia was more as compared to IAP report (20-25%).[14] SGPT elevation was comparable to other studies.[5,15] Complications were seen in 19% cases in the present study, lower than that reported by Malini et al.[16] This can be explained by the high index of suspicion, immunization and the prompt institution of treatment with appropriate antibiotics. Out of the complication's hepatitis, bronchitis and gastrointestinal perforation were in accordance with other studies.[5,17]

In our study typhidot test was positive in 70 out of 76 cases. The sensitivity of typhidot test was found to be 82.85%, which is comparable to most of the other studies conducted as even their sensitivity ranged from 80 to 90%.[18-21] Typhidot fulfills one of the standard ideal diagnostic test as it did not usually miss the diagnosis when compared to blood culture. However, six blood culture positive cases had negative results in typhidot assay. These six false negative results may be due to covering of the IgM antibody by IgG antibodies during the second week of fever.

Blood culture was positive in 46% of cases (n=35 out of 76) in the present study. In other studies the culture positivity varied from 10% to 80%.[5,9,18,22-24] Blood cultures actually turn out to be cheaper and more cost effective in the long run, as positive cultures suggest the sensitive antibiotics and unequivocally establish the diagnosis of typhoid. Limiting factors for blood culture are low grade bacteremia, volume of blood obtained for culture and prior receipt of antibiotics decreasing the culture positive cases. Analysis of the observations in this study, indicated that although blood culture was the gold standard for diagnosis of typhoid fever, typhidot test was a quick diagnostic alternative in the developing countries due to its high sensitivity and specificity. Typhidot will be particularly helpful in areas where facilities for doing a blood culture is not available.

The antibiogram of *S. typhi* had been going through significant alterations over a period of time. Although multidrug resistance looks to be tapering at one end, there have been widespread reports of NARST (nalidixic acid resistant *S. typhi*) all around world that were responsible for decreased susceptibility to ciprofloxacin resulting in treatment failures and complications in enteric fever.[25-28]

In the present study, antibiotic sensitivity testing was done in all culture positive cases. Table 4 shows comparison of antibiotic sensitivity in our series with various studies.

Table 3: Comparison of prominent clinical features in typhoid fever in various studies (%).

Clinical features	Our study	Jha et al (2019)	Gautam et al (2019)	Devaranavdagi et al (2017)	Ganesh et al (2010)	Laishram et al (2016)
Fever	100	100	100	100	100	100
Abdominal pain	78	45	39.6	18	-	69.3
Vomiting	68.42	60	62.9	44	49	26.53
Cough	40.79	35	-	10	-	26.5
Anorexia	56.5	75	-	61	-	81.6

Continued.

Clinical features	Our study	Jha et al (2019)	Gautam et al (2019)	Devaranavdagi et al (2017)	Ganesh et al (2010)	Laishram et al (2016)
Headache	43.3	51	-	12	-	76.5
Diarrhea	36.84	53	32.7	16	29	37.7
Coated tongue	52.6	70	-	49	-	81.6
Toxic look	22.3	-	-	68	16	-
Hepatomegaly	68.4	53	14.2	44	71	77.5
Splenomegaly	43.4	63	8.6	21	34	38.7
Relative bradycardia	6.5	23	3.4	-	-	-
Rose spot	5.2	0	-	-	-	0

Table 4: Comparison of antibiogram in various studies (%).

Antibiotics	Our study	Jeeyani et al (2017)	Jha et al (2019)	Devaranavadagi et al (2017)	Sarswat et al (2018)	Dahiya et al (2019)
Ampicillin	74.28	96.2	40	70	80	81
Chloramphenicol	88.57	93	80	84	70	95
Ceftriaxone	97.14	100	90	100	100	100
Cefixime	97.14	100	83	100	-	100
Cotrimoxazole	77.14	93	73	-	47.5	93
Ciprofloxacin	55.14	-	51	87	87.5	-
Azithromycin	82.85	70.8	91	60	-	95

Lower sensitivity of azithromycin in our study may be due to misuse and overuse of this drug in common respiratory illness.[29] Contradictory to which a study done by Mishra et al reported 100% sensitivity to azithromycin.[28] The least sensitivity was shown by ciprofloxacin (57.14%). Emergence of this decreased susceptibility of fluoroquinolones was a matter of concern in southeast countries of Asia. The lesser sensitivity of ciprofloxacin may be due to their frequent, unjustified and underdose usage in diarrhea and other childhood illnesses, resulting in resistance. Ampicillin, chloramphenicol, cotrimoxazole were considered the first line drugs in past and resistant to all these three drugs was considered as multidrug resistant typhoid fever. Incidence of MDR isolates in this study was 11.4%. The rampant misuse and abuse of antibiotics had led to the emergence of multidrug resistance *S. typhi*.

As per current recommendations, ceftriaxone was used to treat all the patients diagnosed with enteric fever. In those patients who were discharged before 14 days, therapy was completed with cefixime. The advantage of cefixime was its good safety profile, cost effective and available in oral form. All the blood culture positive patients responded well to empirical third generation cephalosporine. The mean value for fever defervescence was 4.23 days (SD 1.56). Earlier studies also reported similar range of the fever defervescence duration.[6,11,30]

The study was limited because of its smaller sample size. If more children would have been enrolled in the study a more detailed picture of clinical features and laboratory features could be obtained. Large scale prospective evaluation of typhidot test in endemic populations should be done to find the exact usefulness of typhidot test.

CONCLUSION

Though enteric fever is a major health concern in pediatric population, it can be prevented with proper public health measures and effective vaccination strategy targeting children less than 5 years. The manifestations are diverse but presence of fever without focus and normal to low leukocyte count is more common which should alert the pediatrician about possibility of enteric fever. *Salmonella* is an easy to culture organism and hence blood culture should always be collected before starting antibiotics. Ceftriaxone as a monotherapy has been quite effective in the treatment of enteric fever. Emergence of multidrug resistance along with nalidixic acid resistance in *S. typhi* indicates rationale antibiogram. Thus, there is a need for continuous microbiological surveillance and demands robust preventive measures.

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