

Changing Trend in Clinical Spectrum of Salmonella Typhi in Children

Fatima Tahira,¹ Rani Saba Urooj,² Sameen Bint Ali,³ Afshan Zia,⁴ Tabish Raza,⁵ Shahla Latif⁶

Abstract

Objective: To determine the clinical spectrum and outcome of enteric fever in children.

Methods: It was a descriptive cross-sectional study conducted in Services Hospital, Lahore from 1 January 2021 till 31st July 2021. It included all patients in the age group of 1-18 years who were clinically suspected to have enteric fever. Non-probability consecutive sampling was used. Clinical features and their outcome were recorded on a predesigned proforma. Blood cultures were obtained from all patients and tested microbiologically by standard procedure.

Results: This study included 355 patients. 200 were male and 155 were females. 45 patients were from 1-2 years, 2-5 yrs (83), 6-10 yrs (95) and 11-18 yrs (132). Fever (100%) was seen in all patients followed by anorexia (91%), abdominal pain (85%), vomiting (63%), diarrhea (56%), constipation (28%) and cough (30%). 25% cases presented with high fever on first day of illness. Common physical findings were coated tongue (77%), splenomegaly (49%) and bradycardia (42%). Complications were present in 5% of cases. Blood culture was positive in 36 (10%) patients. Among them 25 patients showed extensive drug resistance.

Conclusion: A change in clinical spectrum of salmonella typhi is manifesting over last few years. It has now been seen in infants and classical step ladder pattern of typhoid fever is rarely seen. Cough along fever is notably present in enteric fever. Drug resistance is a major threat and introduction of TCV vaccine in our EPI schedule for infants and children can reduce the disease burden.

Key words: Clinical spectrum, Outcome, Enteric fever

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Introduction

Enteric fever is a common public health problem in developing countries.¹ The main causative organism is *S. Typhi*, which is a gram-negative rod. However, *Salmonella Paratyphi A* and rarely *S. Paratyphi B* and *Paratyphi C* have also been seen as the cause of this illness. In 2017, statistics collected from all over the world showed that 14.3 million people were sufferers of typhoid fever during that year² that caused

135.9 thousand deaths with main bulk (69.6%) from South Asia.² Enteric fever is widespread in poor income regions in South Asia, including Pakistan, because of lack of clean drinking water and dirty hygienic and sanitation services.^{3,4} During a recent study in Karachi, a high incidence of enteric fever has been reported in children in Pakistan, with rates as high as 1000 cases per 100000 child per year.⁵

The transmission of this illness is through orofecal route and its incubation period varies from 7-14 days and can be as short as 3 days and can extend up till 30 days depending upon the infecting dose. The organism after reaching the lymphoid tissue of the small bowel, involves the Payer's patches which get swollen, and then ulcerate and finally gets healed. Approximately 5% of the patients become chronic carriers especially when gall bladder is involved and release bacteria in feces commonly and rarely in urine after clinical resolution.⁶

Enteric fever involves a varied clinical presentation

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ranging from low-grade fever, malaise, to a more severe disease involving pain in abdomen, high grade fever, decrease oral intake, jaundice, coated tongue, body aches, hepatosplenomegaly. In children, constipation may occur after diarrhea. The clinical picture is more diverse in children under five years of age. If no complications occur, the symptoms and physical findings gradually resolve within 2-4 weeks.

Earlier on typhoid fever was used to be treated by ampicillin, chloramphenicol and co-trimoxazole (first line drugs). Over last two decades *S. typhi* Genotype Hn58 has evolved in various parts of the world which is resistant to first line drugs; multi drug resistant (MDR) typhoid fever.⁷ In 2016, a new strain of salmonella typhi HN58 which is resistant to all five drugs, ampicillin, chloramphenicol, co-trimoxazole, ceftriaxone and quinolones was found in Pakistan. This resistant strain has been labeled as extended drug resistant strain (XDR Typhoid fever).⁸ Its first epidemic was reported in November 2016 in Hyderabad which next year got evolved to Karachi. More than 10,000 cases were reported in July 2019 in Hyderabad and Karachi. This resistant strain (XDR salmonella) is gradually spreading to other cities and it has also been isolated in Pakistani travelers to other countries as well.⁹

Few studies have been conducted regarding clinical spectrum of typhoid fever with XDR salmonella strain in Lahore.¹⁰ Local literature is also scarce on out come and clinical response following antimicrobial use in this group of resistant typhoid fever. This study will help to understand clinical behavior and response to therapy of XDR *S. typhi* Hn58.

Methods

It was a descriptive cross-sectional study conducted in Pediatric Department and Pathology Department of Services Hospital, Lahore from 1st January 2021 till 31st July 2021. After ethical approval from hospital authority, all the patients in the age group of 1 to 18 years with clinically suspected enteric fever were included in this study. Non- probability consecutive sampling was used. Case definition of suspected typhoid fever is a patient with documented fever (38°C and above) for at least 5 days prior to presentation, with rising trend in clinic and having no other focus to explain the cause of the fever (e.g. UTI, pneumonia, abscess etc.) OR a clinically compatible case that is epidemiologically linked to a confirmed case of typhoid fever.¹¹ A detailed account of clinical features were recorded on a Proforma, especially designed for this purpose.

All patients were subjected to detailed history and examination. Blood cultures were done in all patients after taking proper aseptic measures. Salmonella strains were tested for their sensitivity to eight antimicrobial agents by disc diffusion method and were incubated at 37°C for at least 7 days.

All patients were given treatment in the form of IV fluids, anti-pyretics, anti- emetics as and when needed. Empirical treatment started with cephalosporins (Oral Cefixime or IV Ceftriaxone) until blood culture results were available. Patients were switched to IV cephalosporins or fluoroquinolones, if there were no clinical signs of improvement after 5 days of treatment or any signs of complications appear. Final antibiotic regime depends on the culture and sensitivity report. Outcome was determined in the form of completely cured, referred and expired. The data was recorded in SPSS version 20 and Data has been summarized using percentages and frequencies.

Results

This study included 355 patients. Out of these 200 were male and 155 were females shown in table 1. Among them 45 were from 1- 2 years of age, 83 were from 3-5 years of age, 95 were from 6 to 10 years of age and 132 were from 11-18years of age. The age distribution is shown in figure 1 below.

Table 1: Gender Distribution

Gender	No. of patients	Percentage
Male	200	56%
Females	155	44%

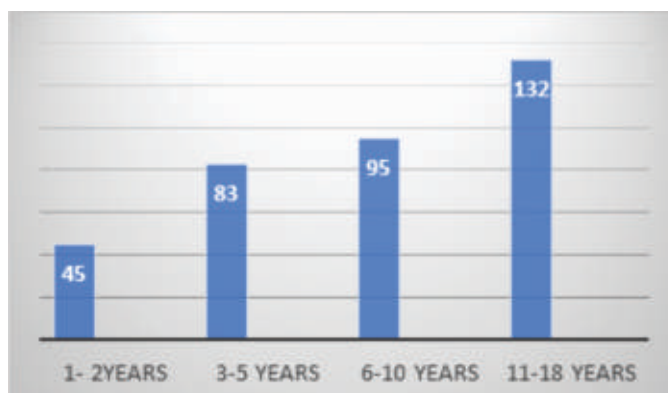


Figure 1: Age Distribution

The most common presenting symptom in our study was fever (100%). High fever >101°F on first day of illness was seen in 25 % case (107/355case). Second common feature was anorexia which was seen in (91%) followed by abdominal pain (85%), vomiting (63%),

diarrhea (56%) and constipation (28%). Cough was a prominent feature in (30%). Least common presenting symptoms were headache (14%) and rash (2.8%) The most common physical finding was coated tongue (77%) followed by splenomegaly (49%) and bradycardia (42%). Least common findings were rose spots (4%) and acute abdominal pain (14%). Complications at the time of admission or during treatment in hospital, were seen in eighteen patients (5%). Adynamic ileus was present in fifteen patients (4%), shock at the time of presentation was present in two patients (0.5%) and intestinal perforation in one patient (0.2%).

Positive blood cultures were seen in 10% of cases and all isolates showed salmonella typhi. All culture positive cases were resistant to ampicillin and chloramphenicol while sensitivity to ceftriaxone was 22% and to ciprofloxacin was 8% (MDR). However, sensitivity to azithromycin, meronem and imipenem was 100%.

Antibiotic sensitivity pattern of culture positive cases has been shown in table 2.

All patients enrolled in the study completed their course of illness successfully. They were being monitored for their signs and symptoms and were given treatment

Table 2: Antibiotic Sensitivity Pattern of Culture Positive Cases

Antibiotic	Sensitive no. of patients	Percentage
Meronem	36	100%
Imipenem	36	100%
Azithromycin	36	100%
Ceftriaxone	8	22%
Ciprofloxacin	3	8%
Chloramphenicol	0	0%
Ampicillin	0	0%

accordingly. All patients were cured, including those who developed complications and were discharged back home with no mortality.

Discussion

In under developed countries, enteric fever has become a big challenge. In recent past, its clinical behavior is changing which has made its clinical diagnosis difficult. In our study at Pediatric Department SIMS Lahore, we have also found a change in its clinical spectrum. Due to its varied clinical manifestations, it is often found to be confused with other infections. Previously typhoid fever used to be considered a disease of toddlers and older children as payers' patches were not well developed in infants thus infants were taken as not a victim of salmonella infection. In our study 45 cases were 1-2

years old. Decreasing trend of breast feeding and injudicious use of weaning foods may be the reason. Our study showed increased incidence of infection in boys. Same results were obtained from other disease prevalent areas.¹²⁻¹³ Although there is no scientific reason for this, however most relevant explanation could be relatively more outdoor contact, consuming eatables from out, and activities, and attitudes of boys resulting in increased risk for S. Typhi infections in low-income countries.¹³ Another reason could be more healthcare seeking for boys by parents.

In our study we found that increase number of cases were reported during the months of April till September with highest number of cases with rainfall as compared to winter season. It has been seen that wet weather conditions and rainfall has major impact on the occurrence of typhoid.¹⁴ Sanitary and drainage system of slums is at worst situation in rainy season.

In our current study, Fever was seen in all (100%) patients. 25% cases (107/355) presented with high fever >101 F on first day of illness. Typical step ladder pattern was not described by most of the patient. Similar results were seen in studies conducted in Karachi and India.^{15,16} Other clinical features that are commonly found in enteric fever are anorexia, vomiting, diarrhea, constipation, headache and abdominal pain. We noted anorexia in 325 (91%) patients and headache in 13% cases that was consistent with results of study done in Srinagar.¹⁷ Diarrhea was seen in 100(28%) patients which is consistent with the results obtained from another study conducted in India,¹⁶ however abdominal pain was found in 14 cases (18.4%) and Vomiting was seen in 225 (63%) patients that was in contradiction to the similar study conducted in India.¹⁶ Constipation was seen in 28% cases in our current study that was in contradiction to study conducted in Canada.¹⁸ This can be due to undue restrictions imposed by general practitioners and family taboos in our country. Similarly, coated tongue was found in 77% of cases that is a higher percentage as compared to a study done in Gujrat in India.¹⁹ In the same way splenomegaly was found in 49% of cases that is again a higher percentage as compared to another study conducted in India.²⁰ This depicts higher degree of bacteremia and septicemia in our study cases. These results showed that enteric strain is evolving and changing its spectrum over time.

Clinical outcome was measured as defervescence (decline of fever), improvement in oral feeding, and deve-

lopment of any complication, mortality or discharge time from hospital. Complications were seen in only 5% of patients and was seen in those with XDR and those who belong to under 10 years age group. All patients were given treatment initially with cephalosporins, however those who did not responded over 5 days or developed complications or culture and sensitivity showed resistance to cephalosporins were shifted to second or third line antibiotic depending on the culture and sensitivity report. All patients in this study were recovered and discharged. Similar results were obtained from a previous study conducted in Pakistan regarding mortality due to typhoid.²¹ However, a study conducted in Vietnam reported 2% mortality secondary to *S. Typhi* among hospitalized patients.²²

Blood culture was positive in only 10% of patients (35 cases). This relatively lower percentage of culture positivity could be due to the prior use of antibiotics before sending the blood cultures. All culture positive cases were resistant to first line treatment of enteric fever. This is in contradiction to previous studies where sensitivity to ceftriaxone and quinolones was high²³. However, sensitivity to ceftriaxone was only 22% and to ciprofloxacin was 8% (11 cases MDR typhoid fever) and azithromycin, meronem and imipenem were 100% sensitive (24/35 cases XDR Typhoid fever). A study conducted in Bangladesh showed 100% sensitivity to azithromycin.²⁴ This alarming and new trend in antimicrobial resistance in *S. Typhi* demands a rapid action at the international level. If no action will be taken we will be left with only few antibiotic choices for the effective treatment of enteric fever, which will not only raise the cost of treatment but will also, increase the mortality and complications of the disease.

This study puts emphasis on the use of vaccination and other protective measures in our country. In 2019, a mass TCV immunization campaign was conducted for children aged 9 months to 15 years of age in Sindh province and in 2020 in Punjab as well. It is a high time to introduce this vaccine in our vaccination program for all children at 9 months of age in other parts of the country. It will be effective in decreasing the disease burden.

Conclusion

Enteric fever is a very common infection in Pakistan. With the rise of XDR cases, it is time to take urgent measures at national level such as clean drinking water,

environmental hygiene, and sanitation to deal with this public health problem. Vaccination of children against typhoid fever is another short term solution. Blood culture yield can be increased by drawing sample prior to administration of antibiotics. Significant emphasis should be put on the introduction of TCV vaccine in our EPI schedule for infants and children to reduce the disease load.

Conflict of Interest:

None

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Authors Contribution

F.T: Conceptualization of Project, Data Collection, Literature Search, Writing of Manuscript, Drafting, Revision

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F.T, T.R, S.L: Literature Search

F.T, A.Z, S.A.B: Drafting, Revision

F.T, R.S.U: Writing of Manuscript