ORIGINAL ARTICLE

Retrospective Cohort Study of Typhoid Fever in Paediatric Patients at a Tertiary Care Hospital in Karachi

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Abstract

Background: *Salmonella enterica serotype Typhi (S. typhi)* is responsible for causing Typhoid fever which is estimated to cause tens of millions of cases worldwide. Pakistan is currently experiencing an outbreak of extensively drug-resistant (XDR) typhoid.

Objective: To document the frequency and clinical features of XDR typhoid and determine the utility of our treatment approach with ceftriaxone in the face of expanding resistance to this drug and document sensitivity patterns of *S. typhi* against other antibiotics.

Methods: This retrospective cross-sectional study was conducted at the Paediatric ward and Intensive Care Unit of Liaquat National Hospital for 1 year (September 2021 to August 2022). Children aged 1 to 12 years who were diagnosed with typhoid fever were included in the study. Infants (below 1 year), suspected cases of typhoid fever without positive cultures, and cases of typhoid fever presenting in the outpatient department were excluded. SPSS v26 was used for data analysis. An independent t-test was applied for mean comparison while a chi-square/fisher-exact test was applied to check the association. P≤0.05 was considered as significant in all cases.

Results: 86 cases of typhoid fever were included in the study. Mean age of the cohort was 6.012 (±3.068) years, having 15 (17.4%) MDR typhoid and 71 (82.6%) XDR cases. Fever was a common feature in all patients. Leukopenia was observed in 25.6% of cases. None of the cases showed sensitivity to ciprofloxacin. All 71 XDR cases were sensitive to meropenem and azithromycin. A significant difference was observed in terms of loose motions (p=0.005), cough (p=0.01) and seizures (p=0.03) between both groups.

Conclusion: As resistance against commonly used antibiotics is emerging; organisms may show susceptibility to less commonly used first-line drugs. Ceftriaxone no longer appears to be an effective drug in the majority of cases of typhoid fever, by increase in extensively drug-resistant typhoid. Carbapenems and azithromycin are better choices for these patients; however, these should be used judiciously in an evidence-based manner.

Keywords: *Antibiotic resistance, antibiotic sensitivity, typhoid fever, multi-drug resistant, extensively drug-resistant.*

INTRODUCTION

The organism *Salmonella enterica serotype Typhi (S. typhi)* is responsible for causing Typhoid fever in humans. *S. typhi* is primarily transmitted through the fecal-oral route, and typhoid fever is endemic in low- and middle-income countries due to the consumption of unsafe drinking water and poor sanitation and hygiene [1]. 14.3 million cases of enteric fever (out of which 9 million for typhoid fever) occurred globally in 2017, with 135.9 thousand deaths due to the same, out of which South Asia had a significant chunk of 69.6%. In Pakistan, only 20% of the population has access to safe drinking water. Therefore, it is not surprising that typhoid fever is the most common bacteremic illness in children of Pakistan [2].

The clinical presentation of typhoid fever is marked by fever as a prominent symptom and is often accompanied by an array of symptoms like fatigue, headache, nausea, *etc.* that may be difficult to distinguish from other diseases like malaria, dengue, and chikungunya [3]. Moreover, the lack of early diagnostic tests often contributes to improper therapy and a prolonged course of illness [4].

The most dreaded and fatal complication of typhoid fever is intestinal perforation, however, typhoid-related fatality has reduced significantly in the post-antibiotic era; it is still estimated to be 1% [5]. The overuse and self-prescription of antibiotics, which is a common issue in South Asia including Pakistan, contributes to antibiotic resistance and questions the sensitivity of blood cultures done afterward [6].

Since the discovery of chloramphenicol as a treatment for *S. typhi* in 1948, the organism has been challenging the treatment approach every few years. It has become resistant to the aforementioned commonly used drug [7]. Pakistan is currently experiencing an outbreak of extensively drug-resistant (XDR) typhoid and can spread

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globally. The current XDR *S. typhi* clone is resistant to five classes of antimicrobials (chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, fluoroquinolones, and third-generation cephalosporins) [8]. However, it is sensitive to carbapenems and azithromycin [9].

The studies evaluating antibiogram of typhoid fever are giving the good news of sensitivity to some of the first-line antibiotics such as cotrimoxazole, which may be due to the decreased use of these drugs but at the same time also reporting emerging resistance to meropenem and azithromycin [10, 11].

A study by Anjum *et al.* conducted at the National Institute of Child Health Karachi reported that 2.63% of their cases (n=76) were resistant to azithromycin, while no case of meropenem resistance was found [12]. However, another study from Pakistan and one from Indonesia have reported meropenem resistance among their typhoid fever patients [13, 14].

Although the CDC has provided guidelines for treating XDR *S. typhi*, a holistic treatment strategy for typhoid fever still needs to be developed for Pakistan [15]. The National Institute of Health (NIH) Pakistan has published an advisory for the prevention and treatment of typhoid fever, suggesting a cautious use of sensitive antibiotics [16].

However, the question of empiric treatment remains, as the culture results become available in 48 to 72 hours, and a trial of ceftriaxone on a sick, hospitalized patient during this time is less likely to work with the increasing number of XDR typhoid cases in Pakistan. Some clinicians are trying to find ways to overcome this dilemma with the availability of rapid tests, such as the rapid test for detecting ceftriaxone resistance [17].

There is an increased flow of children affected by XDR typhoid fever in our department, so we intended to document the frequency and clinical features of XDR typhoid fever and to find out the utility of our treatment approach with ceftriaxone in the face of expanding resistance to this drug. Moreover, we wanted to document the sensitivity patterns of *S. typhi* against other antibiotics. This study will increase our understanding of XDR *S. typhi* among 1-12 years old children, and thereby enabling better treatment.

MATERIAL AND METHODS

This retrospective cross-sectional study was carried out at the Paediatric ward and Intensive Care Unit (ICU) of Liaquat National Hospital, from September 2021 to August 2022. Liaquat National Hospital is a 700-bed tertiary care hospital in the center of Karachi and is a non-profit organization serving all socioeconomic classes. Children aged 1-12 years, with a confirmed diagnosis of typhoid fever, admitted in the ward or ICU with any outcome, *i.e.* discharged, leave against medical advice (LAMA), or expired, were included in the study. Children below 1 year of age, suspected cases of typhoid fever without positive blood culture, and cases of typhoid fever presenting in the outpatient department were excluded from the study. The sample size was estimated by taking 88.9% XDR frequency [18] among *S. typhi* at 95% confidence interval and 7% margin of error, which was 78.

Study Protocol

Ethical approval for the study was sought from the hospital's ethical review committee (REF letter No: App # 1015-2024-LNH-ERC). A laboratory-confirmed case of typhoid fever was defined as a patient whose blood culture was positive for *S. typhi* (BACTEC/BACT-ALERT). Blood culture bottles were incubated in the BACTEC automated system. The positive flagged bottles from the system were sub-cultured on blood agar, chocolate agar and MacConkey agar. The suspected Salmonella non-fermenting colonies were identified by biochemical reaction and serology. The authors extracted data from patient files and the hospital's electronic record on a structured Performa for cases fulfilling the inclusion criteria. Patient demographics, signs and symptoms with duration, lab parameters, treatment(s) given, duration of hospital stay, complications, if any, and outcome were recorded.

Antibiotic susceptibility of *S. typhi* against meropenem, azithromycin, ceftriaxone, cefixime, ciprofloxacin, trimethoprim-sulfamethoxazole and ampicillin was also recorded from blood culture reports. Cases were stratified as either multi-drug resistant (MDR) or extensively drug-resistant (XDR). Those isolates of *S. typhi*, which showed resistance to chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole, were classified as MDR. MDR *S. typhi* with additional resistance to fluoroquinolones and third-generation cephalosporins were classified as XDR.

Statistical Analysis

Data analysis was done by using IBM SPSS Statistics version 26. Mean and standard deviation were computed for quantitative variables. Frequency and percentage were calculated for qualitative variables. An independent t-test was applied for mean comparison while the chi-square/fisher exact test was used to check the association between qualitative variables, considering $p \leq 0.05$ as significant.

RESULTS

Eighty-six (86) blood culture-confirmed cases of *S. typhi* were identified among pediatric patients presenting to Liaquat National Hospital, over one year. The mean age of patients was 6.012(±3.068) years, with a minimum age of 1 year and a maximum of 12 years. 39.5% of children were less than five years old, and 60.5% were more than five years old. There were 15 (17.4%) cases of MDR typhoid, and 71 (82.6%) XDR cases identified in the studied cohort (**Fig. 1**).

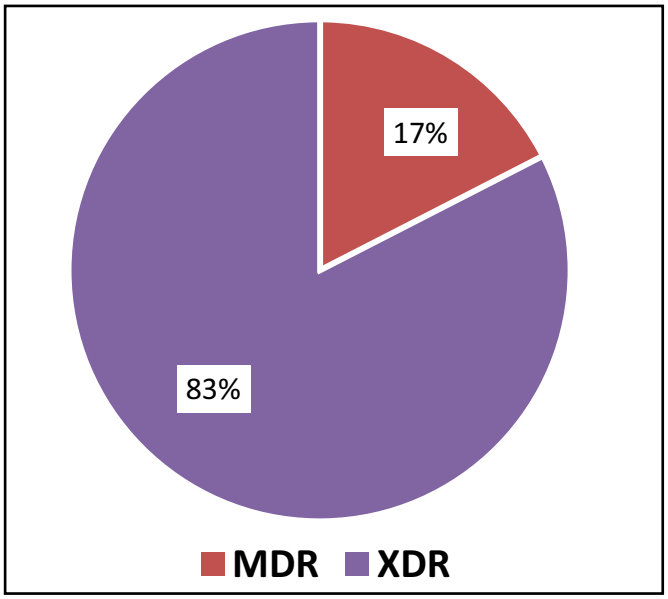

Fig. (1): Pie chart showing the percentage of MDR *versus* XDR Typhoid fever cases based on blood culture (n=86).
(**MDR:** multi-drug resistant; **XDR:** extensively drug-resistant)

Fever was the presenting complaint in all patients. The mean duration of fever was 8.3(±5.978) days, and 69.8% of patients had fever for more than five days. The comparison of fever duration among MDR and XDR is shown in Fig. **(2)**. The second most common presenting complaints were loose motions and vomiting. A detailed comparison is given in Table **1**.

In all typhoid fever patients, mean hemoglobin level was 10.06(±1.66) g/dl, WBC count was 7.89 x 10^9(±4.90) cells/µl and platelets were 175.88 x 10^9 (±99.93) cells/µl.

Table 1: Clinical spectrum of typhoid fever (n=86).

SYMPTOMS	ALL PATIENTS n(%)	MDR cases n(%)	XDR cases n(%)	p-value
Lethargy	4(4.7)	1(6.7)	3(4.2)	0.542
Anorexia	25(29.1)	2(13.3)	23(32.4)	0.212
Vomiting	35(40.7)	6(40)	29(40.8)	0.952
Abdominal pain	29(33.7)	4(26.7)	25(35.2)	0.525
Loose motions	35(40.7)	11(73.3)	24(33.8)	*0.005
Constipation	1(1.2)	1(6.7)	0(0)	0.174
Blood in stool	4(4.7)	1(6.7)	3(4.2)	0.542
Cough	7(8.1)	4(26.7)	3(4.2)	*0.016
Body swelling	16(18.6)	1(6.7)	15(21.1)	0.284
SIGNS				
Hepatomegaly	12(14)	0(0)	12(16.9)	0.115
Splenomegaly	11(12.8)	2(13.3)	9(12.7)	1.000
Abdominal Rigidity	4(4.7)	0(0)	4(5.6)	1.000
COMPLICATIONS				
Encephalopathy	1(1.2)	0(0)	1(1.4)	1.000
Seizures	2(2.3)	2(13.3)	0(0)	*0.029
Pneumonia	2(2.3)	0(0)	2(2.8)	1.000
Cholecystitis	1(1.2)	0(0)	1(1.4)	1.000
Hepatitis	16(18.6)	1(6.7)	15(21.1)	0.284
Generalized oedema	6(6.9)	1(6.6)	5(7.0)	0.958

**Significant at p<0.05*

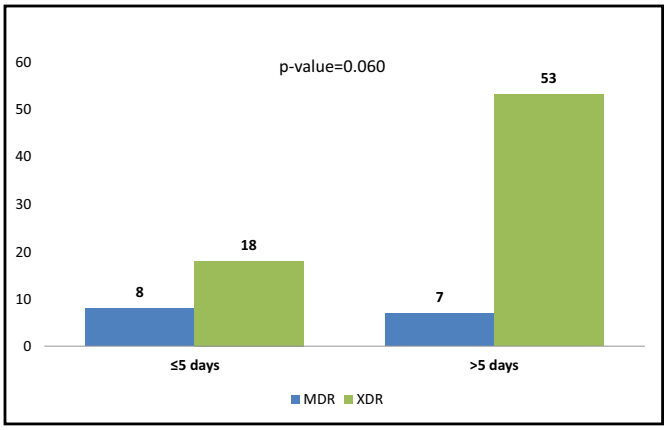

Fig. (2): Frequency of fever duration among MDR and XDR typhoid fever patients (n=86).
(**MDR:** multi-drug resistant; **XDR:** extensively drug-resistant)
(**MDR** *versus* **XDR** p=0.060)

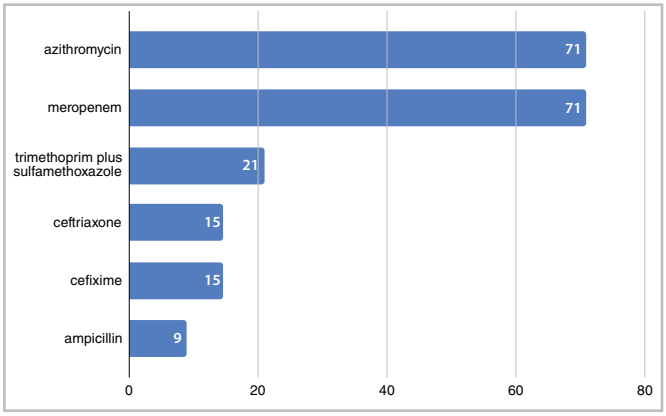

Fig. (3): Graphical representation of drug sensitivities among typhoid patients (n=86).

Leukopenia, a WBC count of less than 5000 x 109 cells/µl, was observed in 25.6% of the cases, and the trend was not significantly different in MDR and XDR groups, 20% and 26.8% respectively. A unique complication of coronary artery aneurysm was found in one of our patients having XDR typhoid fever.

According to blood culture reports, none of the cases showed sensitivity to ciprofloxacin. Among the 15 MDR cases, 9 were sensitive while 6 were resistant to first-line antibiotics (ampicillin, trimethoprim-sulfamethoxazole, chloramphenicol) and all were sensitive to ceftriaxone. In the XDR group, all (71) cases were found to be sensitive to meropenem and azithromycin, but 14 cases also showed sensitivity to trimethoprim-sulfamethoxazole. The individual frequency of sensitivity for each drug is depicted in Fig. **(3)**.

In our study, we found two groups based on the treatment regimen, first (T1) who received ceftriaxone initially and later changed or continued the same treatment according to blood culture sensitivity (n= 41; 47.7%). The second group T2 (n=59; 68.6%) included those patients who received meropenem or azithromycin from the beginning and those who were switched to these antibiotics from ceftriaxone. Typhoid fever patients requiring admission

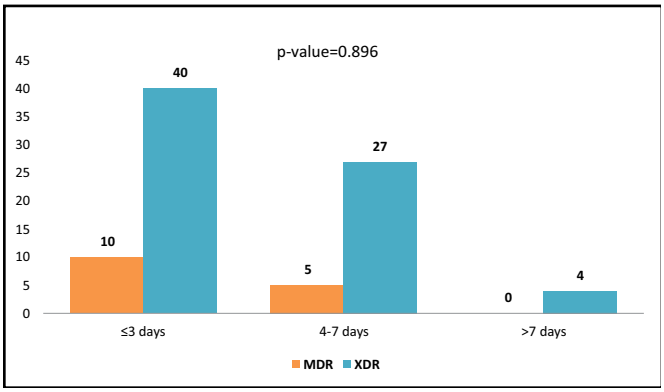

Fig. (4): Frequency of hospital stay duration among MDR and XDR typhoid fever patients (n=86).
(**MDR:** multi-drug resistant; **XDR:** extensively drug-resistant)
(**MDR** *versus* **XDR** p=0.896)

to the hospital usually have complications or cannot tolerate oral medicine. Hence intravenous treatment was initially prescribed to most patients and switched to oral-sensitive antibiotics as soon as the condition was stabilized.

The mean length of hospital stay was 3.209(±2.18) days, and 50% of patients had a hospital stay of less than 3 days. All the patients were discharged when fever defervescence was achieved. The duration of hospital stay was compared between MDR and XDR as shown in Fig. **(4)**.

82(95.3%) patients were discharged home and only 4 got LAMA (leave against medical advice). There was no mortality reported.

DISCUSSION

Typhoid fever is most prevalent in children below 15 years of age. In our study, the mean age was 6.012 (±3.068) years, like the study by Anjum *et al.* [12] conducted in children from NICH Hospital Karachi, which reported a mean age of 5.7± 2.81 years. However, the mean duration of fever was 8.3±5.978 days in our setup but 19.04±8.39 days in their study. One possible reason for the longer fever duration in the population studied at NICH Hospital Karachi could be that inadequate treatment was received because the infecting organism was resistant to the commonly used antibiotics. The other possibility can be different health-seeking behaviors of people presenting to the two hospitals: the former is a private sector hospital and the latter is a public sector.

In a large multi-center study from Karachi (SEAP project) comprising 78% of children under 15 years old, the frequency of XDR typhoid showed a drastically increasing trend from 4% in 2016 to 74% in 2019. Our study, comprising data from September 2020 to August 2021, showed a frequency of 82.6% XDR typhoid cases among the studied cohort [2]. This could be explained by the progressive trend in the prevalence of the XDR variant of typhoid fever in Karachi. Several interconnected factors are causing the high prevalence, such as overuse and misuse of antibiotics, poor sanitation and hygiene, population density and urbanization, travel and migration, inadequate healthcare infrastructure, environmental factors, genetic adaptation of bacteria and gaps in public health response in controlling typhoid fever.

Among the symptoms of typhoid fever, we have observed that anorexia and abdominal pain were more common in XDR typhoid, and malaise and diarrhea occurred more frequently in MDR typhoid. Frequency of vomiting was similar for both groups. In a study by Herekar *et al.* [19] all of the above symptoms were present more commonly in XDR cases than MDR and drug-sensitive groups. This difference in observation could be due to different inclusion criteria of the two studies as Herekar *et al.* [19] included all age groups and out-patient cases as well.

We have found hepatomegaly in 14% of our patients while splenomegaly in 12.8%, which is close to the findings of Shahid *et al.* [20] who have reported 9% and 3% respectively. In another study, hepatomegaly was found in 38.2% of cases and splenomegaly in 21.1% [12]. A study from Nepal also compared the features of hepatomegaly and splenomegaly in typhoid fever and found variable results [21]. There are multiple factors that can modify the severity of typhoid fever, such as the duration of illness, age, previous exposure or vaccination history, virulence of the infecting strain, and quantity of the inoculum ingested [22]. Thus, the patients in these studies might vary in severity of typhoid, thereby presenting with varied signs and symptoms.

Hepatitis was the most common complication found in our cases with a frequency of 18.6%, and encephalopathy was present in 1.2% of cases. One unique complication found in only one of our patients was coronary artery aneurysm. Although less common, the literature lists infections as one of the aetiologies of coronary artery aneurysms [23].

In a recent study by Chaudhry *et al.* [18] leucocytosis was found among 16% of their enteric fever patients, and 88.9% among these belonged to the XDR category. In line with this, 20.9% of our cases also showed a WBC count of more than 12000 x 10^9 cells/µl and 77.7% of these were XDR. It is well-known that, in the first week of typhoid fever, the number of circulating white blood cells reduces, with eosinopenia and relative lymphocytosis [24]. The recovery phase is marked by neutropenia which is characterized by increased margination in blood vessels and defective granulopoiesis in the bone marrow. However, in cases of complicated typhoid fever neutrophilic leucocytosis may develop [24].

The current practice in Pakistan is the initiation of therapy with a cephalosporin in patients with clinical suspicion of typhoid fever. However, based on common knowledge and our findings, this will be ineffective if the infecting strain is XDR. In our study, we observed that 47.7% of our patients received ceftriaxone empirically but after the culture results it was found to be sensitive in just 17.7%

of patients. Qamar *et al.* [1] have previously discussed that oral treatment option for XDR typhoid is limited to azithromycin only. Therefore, a possible strategy for hospitalized patients should be to use meropenem and a combination of ceftriaxone and azithromycin for clinically stable patients till the blood culture reports become available, and a more targeted approach can be used [1]. We observed a similar treatment pattern in our department.

In the present study, no resistance to meropenem was found, but Ali Shah *et al.* [13] have previously reported 48% resistance which points to the fact that overuse of this drug may also render it useless against this tricky organism. Research about new drugs, such as Tebipenem as an oral alternative for treating typhoid is currently underway [25]. Treatment with meropenem and azithromycin is costly and therefore use of preventive measures like the availability of safe drinking water for the public and typhoid vaccine must be ensured.

Pakistan, with the help of the Global Alliance for Vaccines and Immunization (GAVI), became the first country to introduce the WHO-approved vaccine for typhoid in its routine expanded immunization program in 2019. A single dose of the typhoid vaccine provides long-term immunity; therefore, it is expected to reduce the burden of this disease from the already overwhelmed health sector in developing countries [26].

We have not found any significant difference in the mean duration of hospital stay among XDR and MDR groups (p-value= 0.896); this could be explained by the possible skill of the clinicians in detecting and adequately treating XDR typhoid cases and also because most of the people presenting to a private sector hospital want to save the costs of hospitalization and prefer to get discharged as soon as the patient is out of danger. In many cases, intravenous antibiotics are continued from home, which is one of our study's limitations. We have not noted the outpatient follow-up of these patients after discharge, and we have not compared the cost of treatment between the different groups.

As this is a retrospective study, we had certain limitations related to data availability. One limitation is that the vaccination status of these children against typhoid was not available. By knowing the vaccination status, we could have determined the effectiveness of vaccination campaigns in the country. Moreover, we did not inquire about the prior use of antibiotics before presentation which could have altered the clinical spectrum of the disease and associated factors.

CONCLUSION

As resistance against commonly used antibiotics is emerging, organisms may be susceptible to less widely used first-line drugs that must be investigated. Ceftriaxone no longer seems to be an effective drug in the face of extensively drug-resistant typhoid. Carbapenems and azithromycin can be used in diagnosed cases of XDR. However, overuse of antibiotics should be avoided in all cases.

Therefore, education among the population about safety and hygiene, rational use of antibiotics, condemnation of self-medication and advocacy of preventive vaccines is the need of the hour not only for controlling the epidemic of difficult-to-treat typhoid fever but also other deadly infectious diseases.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were following the ethical standards of the institutional and/ or national research committee and the Helsinki Declaration. Ethical approval was obtained from the Institutional Ethical Review Committee of the Liaquat National Hospital Karachi (REF Letter No: App # 1015-2024- LNHERC).

CONSENT FOR PUBLICATION

Written informed consent was taken from each participant of the study.

AVAILABILITY OF DATA

The data set may be acquired from the corresponding author upon request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

DD conceptualized the study and together with HK designed the study protocol. SN, SYS and RG were involved in data collection. DD and MGK carried out the formal data analysis. MF prepared initial draft of the manuscript with support from all authors. All authors, especially HK and SA provided critical feedback and helped shape the final draft. MF is the corresponding author on behalf of all other authors. The manuscript was reviewed and approved by all authors.

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