

CLINICAL PROFILE AND ANTIMICROBIAL RESISTANCE PATTERNS IN PAEDIATRIC ENTERIC FEVER

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Abstract

Background:

Enteric fever is one of the biggest causes of morbidities in the children especially where there is poor sanitation. The growing spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Salmonella strains makes its management more complicated and a major health problem to the population.

Objective: To identify the clinical picture and antimicrobial

resistance patterns of culture-confirmed enteric fever among pediatric patients.

Methods: The proposed cross-sectional study was carried out within the Department of Pediatrics for a period of six months from December 2024 to May 2025. The patients who were included were pediatric patients who had blood culture-confirmed Salmonella Typhi or Paratyphi infection and were aged 15 years or less. A structured proforma was used to

gather data regarding demographics, clinical features, and laboratory results. The susceptibility test was done by CLSI standards. The SPSS package version 27 was used to analyze data. The continuous variables were represented as mean plus standard deviation or median plus interquartile range, and the categorical variables were in form of frequencies and percentages. Clinical features were correlated with resistance patterns by Chi-square or Fisher exact test with a p-value of below 0.05 being regarded as significant.

Results: There were 378 enrolled children whose mean age was 8.1 +3.4 years; 56% were male. Salmonella Typhi was found to cause 88.1 percent of the isolates. All patients had fever; 63 and 51 per cent reported abdominal pain and vomiting, respectively. Hepatomegaly and splenomegaly were observed in 41% and 32% respectively and 19% had both of them. Strains of MDR were identified in 14.8 percent of cases with XDR strains identified in 43.4. There was a high resistance to first-line antibiotics and fluoroquinolones, but azithromycin (91.8%) and meropenem (98.9) were both very effective. Prolonged fever and organomegaly were significantly related to XDR infections ($p < 0.05$).

Conclusion: XDR Salmonella strains continue to become the cause of pediatric enteric fever, which restricts the possibilities of empirical treatment. Constant monitoring, therapy based on resistance, antimicrobial stewardship, immunization, and enhanced sanitation are the key to achieve disease burden reduction and restrict the transmission of resistant infections among children.

INTRODUCTION

Enteric fever is a worldwide health issue that has remained a leading cause of morbidity and mortality among the general population, especially in the low- and middle-income countries, mainly due to Salmonella enterica serovars Typhi and Paratyphi. Children are particularly exposed to this burden with the highest incidence being witnessed among

children under the age of five years [1]. Ingestion of infected food and water is the primary transmission method that is related to insufficient sanitation, unsafe drinking water, and inappropriate hygiene standards. Pediatric enteric fever is usually associated with high-grade unremitting fever, and may have gastrointestinal symptoms of abdominal pain, diarrhea or constipation, vomiting, and, in severe cases, hepatosplenomegaly, and systemic complications [2].

Enteric fever is still endemic in sub-Saharan Africa and South Asia, even though in a few places, there was the improvement of the public health infrastructure. It is estimated in the world that millions of cases are reported every year; there are significant disparities by region and socio-demographic group. Providing a significant percentage of typhoid and paratyphoid, children under 15 years of age are a focus on the ongoing disease burden in children [3]. In spite of the fact that vaccination and better awareness have helped to reduce the occurrence in some environments, such success is jeopardized by the prevalence of antimicrobial-resistant strains of *Salmonella* which complicate treatment and expose to adverse outcomes [3,4].

Enteric fever has undergone changes in antimicrobial resistance (AMR) over the last decades, with the first-line agents (ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole) becoming resistant, eventually giving way to the appearance of multidrug-resistant (MDR) strains. In relatively recent times, fluoroquinolone and 3rd generation cephalosporin resistance has also increased, leading to extensively drug-resistant (XDR) *Salmonella* Typhi [4]. The patterns of resistance severely reduce treatment choices, in such a way that the expensive reserve antibiotics like carbapenems and macrolides may need to be employed, which is not always easily accessible in settings with limited resources.

Pakistan is one of the countries which have been hit the most by XDR typhoid fever with children bearing a heavy burden. Hospital-based research and surveillance data have recorded alarming increase in culture-confirmed cases particularly in the city and peri-urban regions. In Khyber Pakhtunkhwa including Peshawar, there has been a reported significant prevalence of pediatric enteric fever and children have been found to be highly positive compared to adults [5]. In 2016-2020, tens of thousands of cases were documented in the country, with a significant percentage of them being XDR strains [6]. These strains have proved to be resistant to ceftriaxone that forms a core of empirical therapy thus making clinical treatment more difficult.

The XDR Salmonella problem in Pakistan is a serious menace to child health through perseverance and propagation. The isolates in children have been highly resistant with only a few effective treatment choices; this has escalated the risk of extended disease, morbidity and financial expenditure on treatment [7]. Even though the XDR typhoid has been maintained during the COVID-19 pandemic, probably because of shifts in the healthcare-seeking behavior and practice, there has been a temporary reduction in cases reported, however, XDR typhoid has remained unabated in the post-pandemic period [8]. This tendency indicates the weak character of existing control tools and the necessity of the continuous surveillance.

Knowledge of the clinical picture of pediatric enteric fever in the context of the development of antimicrobial resistance is a necessary tool to help make a diagnosis and introduce empirical treatment in time. Local information on the features and the patterns of susceptibility is of specific significance in endemic areas when the treatment choices frequently precede the availability of culture outcomes. In addition, they can be used in

antimicrobial stewardship efforts, vaccination, and wider public health interventions to help contain the transmission of resistant strains.

Objective:

To identify the clinical profile, and antimicrobial resistance patterns in culture confirmed cases of pediatric enteric fever cases presenting in a tertiary care pediatric department.

METHODOLOGY**Study Design:**

The type of this study was a prospective cross-sectional study, which was carried out in Lady Reading Hospital, Peshawar department of Pediatrics.

Study Duration:

The research was conducted during six months beginning in December 2024 and May 2025 after receiving the permission of the College of Physicians and Surgeons Pakistan (CPSP).

Sample Size:

An estimated frequency of extensive drug resistance of 43.4% [9], with a 95 percent confidence interval and a 5 percent margin of error were used to determine the sample size of 378 patients (OpenEpi software).

Population and Setting of the study:

Both boy and girl children who are under the age of 15 years old and report to the pediatric section with the characteristics reflective of enteric fever were enrolled. Positive blood culture test was done to confirm the diagnosis of either *Salmonella enterica* serovar Typhi or Paratyphi.

Inclusion Criteria:

Patients were included whenever they:

- Were aged ≤ 15 years.
- Has had a history of a minimum of 3 days with fever 38°C and or gastrointestinal symptoms including abdominal pain, diarrhea, vomiting or constipation.
- Had laboratory-proven enteric fever on the basis of positive blood samples.

Exclusion Criteria:

Patients were disqualified when they:

- Had over 72 hours of antibiotic receipt before blood culture sample.
- Had familiarity with chronic systemic illnesses or immunodeficiency disorders.
- Had missing final clinical or laboratory records.

Data Collection Procedure:

A structured and pre-designed pro forma was used to collect data. The demographic data such as age, gender, and residence were collected after the informed consent of parents, or other legal guardians. Clinical data were gathered by use of comprehensive history and physical examination, which recorded the pattern of fever, duration of fever, gastrointestinal symptoms and physical examination including hepatomegaly or splenomegaly. Hospital records were used to obtain laboratory data, such as blood culture reports and antimicrobial susceptibility testing based on Clinical and Laboratory Standards Institute (CLSI) guidelines. Data on previous antibiotic use, treatment taken and in-hospital outcome was also taken. All the data were coded and anonymized and were stored in the secure database, which was cross-checked to maintain accuracy and confidentiality.

Data Analysis:

The analysis of data was done through the SPSS version 27. The continuous variables, including age and duration of fever, were tested as mean + standard deviation, or median + interquartile range respectively based on the type of data. Frequencies and per cent were used to show categorical variables, such as gender, clinical features, Salmonella serotype, and antimicrobial resistance patterns. The proportion of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Salmonella isolates was determined. The Chi-square test or Fisher exact test was used to evaluate associations between the clinical variables and antimicrobial resistance patterns, where necessary. The p-value that was set to be statistically significant was less than 0.05. Tables and figures were used to present results which were understandable and interpretable.

RESULTS

Three hundred and seventy-eight enteric fever pediatric patients were included who had a confirmed blood culture. The study population consisted of a mean age of 8.1 with deviations of 3.4 years with most cases (42.6) falling between the 6-10 years age bracket. It was males who were affected slightly more than females, 56 percent. The majority of the patients belonged to urban or peri-urban regions. Salmonella Typhi was the most abundant isolate with 88.1 percent of cases, and Salmonella Paratyphi was found in 11.9 percent cases (Table 1).

All the patients had fever (100%). The gastrointestinal symptoms were prevalent, and 63 percent reported having abdominal pains and 51 percent reported vomiting. Thirty-one percent and 23 percent of the patients had diarrhea and constipation, respectively. Forty-one percent had hepatomegaly and 32% had splenomegaly, and 19% had hepatomegaly and splenomegaly (Table 2).

Antimicrobial susceptibility tests showed that there are 56 MDR strains (14.8%), and 164 XDR strains (43.4%), which were in line with the earlier national estimates [9]. The resistance to first-line antibiotics and fluoroquinolones was high. The most effective agents were still Azithromycin (91.8%) and meropenem (98.9%) (Table 3).

The duration of fever (>7 days), hepatomegaly, and splenomegaly were significantly related to XDR infections ($p < 0.05$), but the gender was not significantly related to resistance patterns (Table 4).

Table 1: Demographic Characteristics and Microbiological Profile (n = 378)

Variable	Frequency (n)	Percentage (%)
Age Group (years)		
≤5	93	24.6
6–10	161	42.6
11–15	124	32.8
Gender		
Male	212	56.1
Female	166	43.9
Residence		
Urban/Peri-urban	246	65.1
Rural	132	34.9
Salmonella Species		
S. Typhi	333	88.1

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Variable	Frequency (n)	Percentage (%)
S. Paratyphi	45	11.9

Table 2: Clinical Features and Physical Findings (n = 378)

Feature	Frequency (n)	Percentage (%)
Fever	378	100
Abdominal pain	238	63
Vomiting	193	51
Diarrhea	117	31
Constipation	87	23
Hepatomegaly	155	41
Splenomegaly	121	32
Hepatosplenomegaly	72	19

Table 3: Antimicrobial Susceptibility Patterns of Salmonella Isolates (n = 378)

Antibiotic	Sensitive n (%)	Resistant n (%)
Ampicillin	68 (18)	310 (82)
Chloramphenicol	82 (21.7)	296 (78.3)
Trimethoprim–Sulfamethoxazole	89 (23.5)	289 (76.5)
Ciprofloxacin	106 (28.0)	272 (72.0)
Ceftriaxone	210 (55.6)	168 (44.4)

Antibiotic	Sensitive n (%)	Resistant n (%)
Azithromycin	347 (91.8)	31 (8.2)
Meropenem	374 (98.9)	4 (1.1)

Table 4: Association Between Resistance Pattern and Clinical Variables (n = 378)

Variable	Non-XDR n (%)	XDR n (%)	p-value
Fever >7 days	74 (35.7)	112 (68.3)	<0.001
Hepatomegaly	60 (28.9)	95 (57.9)	<0.001
Splenomegaly	48 (23.1)	73 (44.5)	0.002
Male gender	92 (44.3)	120 (45.1)	0.87

Chi-square test applied; p < 0.05 considered statistically significant.

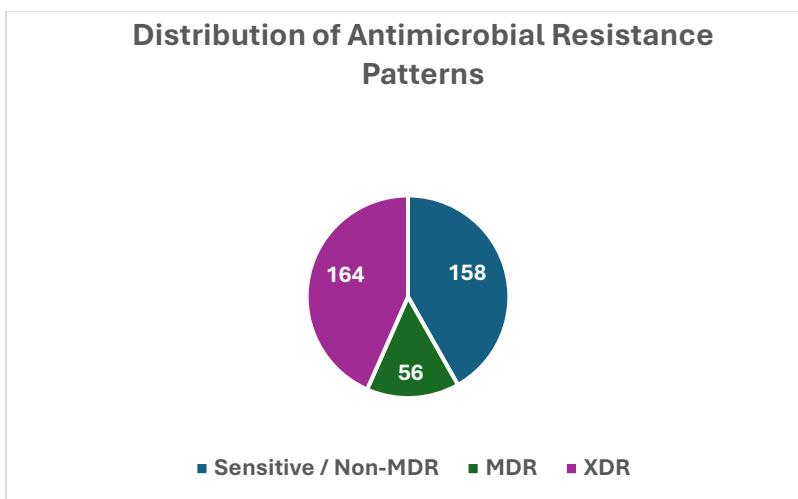


Figure 1: Antimicrobial Resistance Patterns

DISCUSSION

A high rate of extensively drug-resistant (XDR) *Salmonella* strains was found in this prospective study of 378 culturally-confirmed cases of pediatric enteric fever with 43.4 percent of the cases being *Salmonella* XDR and 14.8 percent being *Salmonella* multidrug-resistant (MDR). The most frequent isolate was *Salmonella* Typhi (88.1%), which conforms with global and regional surveillance statistics that reveal its superior representation in pediatric enteric fever [9,10]. Most of the affected children were aged 6-10 years with a minor male dominance as is consistent with other pediatric cohorts in hospitals [11,12]. Fever was a clinical manifestation that was universal, whereas gastrointestinal symptoms included abdominal pain (63%), and vomiting (51%). Hepatomegaly and splenomegaly were also observed in 41% and 32% cases respectively and in 19% of cases both. These results can be compared with the other studies indicating the variable but frequent systemic involvement in the enteric fever of children, especially those with resistant infections [13,14]. It is possible that the high proportion of XDR cases in this study that had long-term fever and organomegaly could pre-determine more severe manifestations of the disease and slow down recovery, as similar pediatric groups have documented [15,16].

The results of antimicrobial susceptibility testing uncovered the high prevalence of resistance to first-line antibiotics (ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole) and fluoroquinolones, which proves that the agents are ineffective to be used in endemic settings empirically [9,17]. Ceftriaxone resistance was also detected in 44.4 percent of isolates, which reflects the severe loss of the efficacy of the third generation cephalosporins, which is in line with the increasing cases of XDR strains in children's populations [10,18]. The use of Azithromycin (91.8% sensitivity) and

meropenem (98.9% sensitivity) was still effective, which justified the inclusion of these two drugs as the most important treatment options in XDR infections [19,20]. However, new reports of decreased azithromycin susceptibility signal the necessity to use it cautiously and implement the most effective antimicrobial stewardship [19].

The comparisons with other studies indicate that XDR prevalence among the given cohort is not lower than the national and regional trends indicating XDR prevalence in pediatric patients of 40-45% on average [9,10,18]. The prevalence of MDR of this study (14.8%) is not as high as some of the previous reports but still clinically relevant [11,12]. On the whole, these trends suggest the further drift in the direction of highly resistant strains, so the significance of the local susceptibility monitoring to inform empirical treatment.

Resistance has a clinical impact as demonstrated by the association of XDR infections with prolonged fever, hepatomegaly, and splenomegaly. These results have been demonstrated in other areas, which suggests that resistant infections are usually characterized by worse ODs, higher rates of complications, and extended hospitalizations [14,16,17]. These statistics demonstrate that there is an urgent need to improve the diagnosis of this disease at an early stage, resistance-based treatment, and preventive measures, including immunisation and other interventions to reduce the disease load in children [19,20].

Limitations

There are a number of limitations in this study. The first, it was carried out in one tertiary care center and, therefore, it might not be applicable to other regions with divergent patient populations or antibiotic prescribing patterns. Second, the molecular characterization of the resistance genes was not carried out and it could not identify the

particular mechanism of MDR and XDR patterns [9,16]. Third, there was no long-term follow-up and post-discharge results and this limits the possibility of relating the resistance patterns to recovery or relapse rates. Lastly, although antimicrobial susceptibility tests were conducted using CLSI guidelines, both lab variability and reporting methods could restrict comparison with other data. Nevertheless, the study remains a valuable and current contribution to the clinical picture and patterns of resistance of endemic childhood enteric fever.

CONCLUSION

This paper has shown that the emergence of extensively drug-resistant *Salmonella* strains has turned pediatric enteric fever into a condition that is difficult to treat using traditional empiric-based interventions. MDR strains are still common, and the first-line antibiotics and fluoroquinolones resistance is widespread. The XDR infections were related to a long-term fever and systemic involvement, which focuses on clinical severity of the resistant infections. Although azithromycin, as well as meropenem are still effective, close stewardship is needed to avoid resistance. Such results underscore the necessity of active antimicrobial surveillance and resistance-based treatment, vaccinations, and water and sanitation to alleviate the burden of disease and prevent the transmission of the resistant enteric fever in children.

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