ORIGINAL ARTICLE

Extensive Drug Resistant Typhoid in Pediatric Age Group

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ABSTRACT

Objective: To determine the frequency of extensively drug-resistant (XDR) *Salmonella Typhi* among pediatric patients with suspected enteric fever admitted to a tertiary care hospital.

Study Design: Cross-sectional descriptive study.

Place and Duration of Study: This study was conducted at the Department of Pediatric Medicine, Bolan Medical Complex Hospital, Quetta, from July 2021 to December 2021.

Material and Methods: A total of 137 children aged 1–15 years with clinically suspected typhoid were enrolled through sequential non-probability sampling. Blood samples (3–5 ml) were processed using the Bactec Peds Plus system. *Salmonella* serovars were confirmed through biochemical and serological tests. Antimicrobial susceptibility was assessed using the Kirby-Bauer method per CLSI 2013 criteria. XDR was defined as resistance to five key antibiotics. Data were analyzed using SPSS v26.0; associations were evaluated using the Chi-square test with significance at $p < 0.05$.

Results: Out of 137 children (mean age 6.5 ± 3.1 years), 91 (66%) had positive blood cultures, and 48 (35%) were found to have XDR *Salmonella Typhi*. The age group most affected was 6–10 years (45%). A significant association was found between positive blood culture and XDR typhoid ($p < 0.001$). Gender and age group were not significantly associated with XDR status.

Conclusion: XDR typhoid fever poses a significant threat to the pediatric population. High prevalence in culture-confirmed cases highlights the need for timely diagnosis, effective antimicrobial use, and implementation of preventive strategies such as vaccination, sanitation, and safe water access.

Key Words: *Typhoid fever, XDR Salmonella Typhi, Drug resistance, Pediatrics, Pakistan*

INTRODUCTION

Enteric fever, which is a major public health problem, especially in low- and middle-income nations in Asia, Africa, and South America, includes typhoid and paratyphoid fevers. The bacteria that cause this illness include *Salmonella enterica serotypes Typhi*, which causes typhoid fever, and *Salmonella enterica serotypes Paratyphi A, B, or C*, which causes paratyphoid fever.[1] This is due to the fact that low-income countries often struggle with inadequate sanitation and a lack of access to safe drinking water.[2] According to the WHO, there are approximately 21 million cases of enteric fever

and 161,000 related deaths each year.[3] In Pakistan there has been estimated a highest rate of Typhoid with 493.5 per 100,000 cases in 2018.[4] The worldwide proliferation of multidrug-resistant (MDR) *Salmonella* and the rise of extensively drug-resistant (XDR) Salmonella highlight the necessity for better diagnostic tests and the creation of new treatment approaches to replace existing antibiotics. In Pakistan there is radically increase in cases after a new XDR Typhi outbreak in Sindh province.[4] XDR was first reported in Sindh where in 2019, a vaccination campaign was launched with the aim of vaccinating 10 million children of age between 9 months and 15 years.[5]

Despite the availability of antibiotics as the primary treatment for enteric fever, the emergence of extensively drug-resistant (*XDR*) *Salmonella Typhi* has posed a significant challenge to effective management, particularly in children. This study was therefore conducted to address this gap by determining the frequency of XDR *Salmonella Typhi* in children with suspected typhoid fever. The findings aim to inform local treatment protocols and guide preventive health strategies such as vaccination and improved sanitation.

MATERIAL AND METHODS

IRB was issued by Medical superintendent Bolan Medical Complex Hospital without date and number.

This cross sectional study was conducted at the Pediatric Medicine Department, Bolan Medical Complex Hospital, Quetta from July 2021 to December 2021. A total of 137 pediatric patients, aged 1 to 15 years and clinically suspected to have typhoid fever, were enrolled using a sequential non-probability sampling technique. The sample size was calculated using the WHO sample size calculator with a confidence level of 95%, a target accuracy of 8%, and an expected prevalence of 65%.[6]

Inclusion criteria: Children aged between 1 and 15 years, of both genders, who were clinically suspected of having typhoid fever were included in the study.

Exclusion criteria: Patients with a confirmed diagnosis of malaria, those presenting with pyrexia of unknown origin, and those who had received antibiotics within 72 hours prior to presentation were excluded from the study.

Methods: The study was approved by the hospital's ethics committee and the College of Physicians and Surgeons Pakistan (CPSP). 137 children with clinically probable typhoid infection, ages 1 to 15, were enrolled. Informed consent was obtained from guardians, in accordance with the Helsinki Declaration guidelines. Venous blood samples (3–5 ml) were collected aseptically before the initiation of therapy. Samples were transported within an hour to the microbiology department at Bolan Medical College Hospital and inoculated into Bactec Peds Plus culture bottles. The cultures were incubated at 37°C for 7 days. Subcultures were then performed on MacConkey agar plates. Serological agglutination testing using monovalent and polyvalent antisera was done to confirm *Salmonella* serovars.

Antimicrobial susceptibility testing was conducted using the Kirby-Bauer disc diffusion method on Mueller-Hinton agar with eight antibiotic discs: ampicillin (10 µg), imipenem (10 µg), co-trimoxazole (25 µg), ciprofloxacin (5 µg), ceftriaxone (30 µg), meropenem (10 µg), and azithromycin (15 µg). Discs were incubated Descriptive statistics were calculated to determine the frequency of extensively drug-resistant (XDR) typhoid, as per the study objective. Quantitative variables such as age, height, weight, and duration of illness were expressed as mean ± standard deviation. Qualitative variables included gender, fever intensity (high/low grade), abdominal pain (mild/moderate/severe), hygiene (good/bad), socioeconomic status (upper/middle/lower), blood culture result (positive/negative), and XDR typhoid status (yes/no). The population was stratified by age and gender. Effect modifiers, including socioeconomic status, length of hospital stay, residence, height, weight, and age, were assessed for associations using the Chi-square test, with a p-value of <0.05 considered statistically significant.

RESULTS

A total of 137 children were enrolled in the study, including 79 boys (58%) and 58 girls (42%). The median age was 6.5 years (IQR: 4–10 years). The median height was 112 cm (IQR: 100–122 cm), and the median weight was 21.2 kg (IQR: 16–26 kg).

TABLE 1: Distribution of patients according to gender and anthropometric data (n=137)

Variable	Frequency	Percentage
Gender		
Boys	79	58.0
Girls	58	42.0
Variable	Median	IQR
Age (years)	6.5	4–10
Height (cm)	112	100–122
Weight (kg)	21.2	16–26

Of the 137 children, 94 (69%) presented with high-grade fever and 43 (31%) had low-grade fever. Abdominal pain was reported in varying intensity: mild in 20 (15%), moderate in 55 (40%), and severe in 62 (45%) patients. Good hygiene practices were observed in only 47 (34%) of the children.

Positive blood cultures were found in 91 (66%) patients. Among these, 48 exhibited resistances to multiple drugs and fulfilled the criteria for XDR typhoid. Thus, the overall frequency of XDR typhoid among the total sample was 35%.

Stratification by age revealed that 62 (45%) children belonged to the 6–10 years age group, 58 (42%) to the 2–5 years age group, and 17 (13%) to the 11–15 years age group

TABLE 2: Distribution of patients according to different variables *(n=137)*

Variables	Frequency	Percentage
Intensity of Fever:		
High grade	94	69
Low grade	43	31
Intensity of Abdominal Pain:		
Mild	20	15.0
Moderate	55	55.0
Severe	62	45.0
Personal Hygiene:		
Good	47	34
Bad	90	66
Blood Culture:		
Positive	91	66
Negative	46	34
Extensive Drug Resistance:		
Yes	48	35
No	89	65
Socioeconomic Status:		
Upper	37	27
Middle	39	28
Lower	61	45
Age group:		
2-5 years	58	42
6-10 years	62	45
11-15 years	17	13

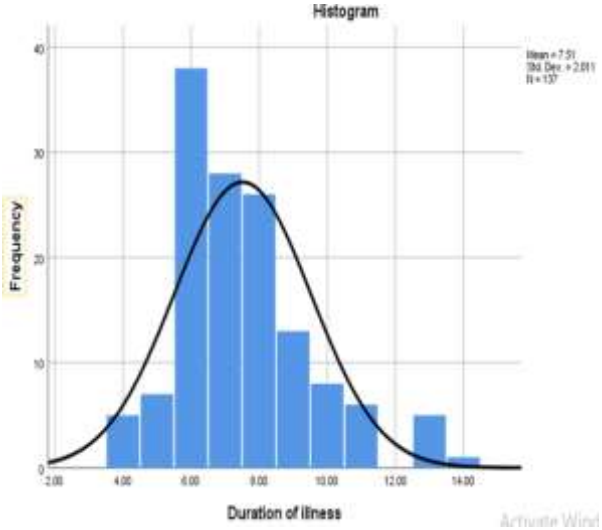

Fig 1: Graphical Representation of mean -MEAN length of stay in hospital (*n=196)*

There was significant relationship found between blood culture positivity and extensive drug resistance. Out of 91 positive blood cultures, 48 were extensive drug resistance. Similarly, there was also insignificant relationship between gender and extensive drug resistance. Likewise, there was no significant relationship found between age stratification with positive blood culture and extensive drug resistance. Although more number of patients managed to fall in between age groups 6-10 years of category (table 3). Although the rate of positive blood culture in males were found high as compare to females, however no significant relationship was found statistically (table 4). The mean length of hospital stay in patients in our study was 7.51 ± 2.01 days (fig 1).

TABLE 3: Frequency distribution of demographic variables in children with respect to extensively drug-resistant (XDR) typhoid among 91 positive blood culture patients

Variable	XDR Typhoid Yes (n=48)	XDR Typhoid No (n=43)	X^2	p-value
Gender			0.70	0.40
Male	30	28		
Female	18	15		
Age Group (years)			1.64	0.44
2–5	21	16		
6–10	19	24		
11–15	8	3		

DISCUSSION

To our understanding, this study represents the inaugural investigation into the primary widespread XDR typhoid outbreak globally, as well as the documentation of mortality and morbidity rates in Pakistan.[7]

The primary cause of complications and fatalities appears to be the delay in the commencement of suitable antibiotic treatment. The prevalence of XDR typhoid has surged to critically high levels, posing a potential threat of becoming virtually untreatable and resulting in elevated rates of illness and death in Hyderabad.

Less than 15 years old was the target age range in our study for instances of enteric fever. Comparable studies have shown that in endemic countries, children under the age of 15 are more likely than adults over that age to get typhoid fever.[7-9] Reduced immunity, risky eating practices, and unsanitary environments in public and school settings may all be contributing factors to this. However, other studies have produced contradicting findings, indicating that the age group most likely to be affected was older than 15 years.[10,11]*Salmonella Typhi* was found in 66% of the positive blood cultures in our study. However, a study by Azmat et al. revealed that the *Salmonella Typhi* was detected in 78.7% of blood cultures.[12] There is indeed tremendous increase in the frequency of positive blood culture yielding *Salmonella Typhi*in study conducted by Azmat el al. This marginal increase in the frequency conducted by Azmat et al. may be due to larger age group subjects that were enrolled in the study. Moreover, with respect to gender distribution, males are most commonly affected in study conducted by Azmat et al. Almost similar results were shown in our study showing there is more males affected compared to females who acquired the disease. Although sample collection technique was non-probability consecutive sampling technique that allows every individual to get equal chance of getting enrolled in the study. The targeted age group that was affected in our study was children aged 6-10 years old constituting about 45% of total patients enrolled in the study. Study conducted by Sina et al has also demonstrated the similar results.[13] The reason could be due to poor immune mechanism of children that are highly prone to infection especially with improper sanitation, bad hygiene and less frequent hand washing that needs to be addressed. Creating awareness at basic level in the form of parental counseling may help us mitigate the magnitude of problem and improve the outcome of pediatric population. In our study, out of 91 children with positive blood culture reports, 35% were found to have XDR *Salmonella Typhi* Study conducted by Yousafzai et al in Karachi showed about 63.5% subject that had confirmed XDR *Salmonella Typhi*results.[14] The results of both studies are not indifferent however showing a huge percentage of population has got affected with this illness. Similar results in terms of socioeconomic status were observed. In both study, lower socioeconomic groups tend to affect more than middle and upper socioeconomic. This is definitely due to lack in the provision of basic health care facilities and absence of knowledge and awareness about maintaining good hygiene due to limited number of resources. The spread of the XDR-typhoid fever outbreak in Karachi is attributed to community water supply and consumption habits related to street food. This ongoing outbreak shows no signs of abating and continues to escalate within the city.

Therefore, it is sense to establish regulations that will increase the safety of street food and to upgrade community water supply systems to comply with recommended standards. Additionally, mass immunization campaigns against typhoid fever that target high-risk groups should be prioritized by health authorities. The prevalence of *Salmonella Typhi* in Pakistan can be temporarily reduced by vaccination, but long-term sustainable solutions include ensuring that everyone has access to clean drinking water, installing sanitation systems that lessen fecal contamination of the environment, and advising people not to consume contaminated food.

Addressing clean drinking water provision is crucial not only for Pakistan but also aligns with the United Nations Sustainable Development Goals, underscoring its significance for the health and well-being of populations worldwide.

CONCLUSION

The high frequency (35%) of XDR *Salmonella Typhi* among culture-confirmed cases in this study underscores the growing threat of antibiotic resistance in pediatric typhoid infections. These findings are consistent with other regional studies that report increasing XDR prevalence, particularly in urban areas with poor sanitation

and limited access to clean water. Additionally, vaccination with the typhoid conjugate vaccine (TCV) has the potential to substantially reduce the burden of typhoid fever and could also influence antimicrobial resistance patterns. However, it is crucial to invest in long-term sustainable interventions such as improving access to clean drinking water, enhancing environmental hygiene, and implementing sanitation measures. These efforts are highly recommended to combat the spread of typhoid fever and address its underlying causes effectively.

Conflict of interest: None

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