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Drug Resistant XDR Typhoid in Children Admitted in a Tertiary Care Hospital

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Author`s Contribution

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ABSTRACT

Objective: To evaluate the prevalence and patterns of drug-resistant typhoid fever, including extensively drug-resistant (XDR) and multidrug-resistant (MDR) strains, among children admitted to a tertiary care Hospital.

Methodology: This descriptive observational study was done at Paediatric department of LUMHS from May 2022-november2022. Children aged 1-12 years, both gender and with confirmed diagnosis of typhoid fever based on positive blood cultures were included. Blood culture samples were collected from pediatric patients presenting with suspected typhoid fever are processed according to standard microbiological techniques. Isolation and identification of Salmonella Typhi are performed using appropriate culture media and biochemical tests. Antimicrobial susceptibility testing was conducted using standardized methods. Drug resistance patterns, including multidrug resistance (MDR) and extensively drug-resistant (XDR) phenotypes, are determined based on susceptibility testing results. MDR was defined as resistance to at least three classes of antibiotics commonly used for typhoid fever treatment, while XDR indicates additional resistance to fluoroquinolones and third-generation cephalosporins, which are frontline treatment options for typhoid fever. Data was entered and analyzed using SPSS version 26.

Results: A total of 43 patients were studied, their mean age was 5.91 years. Boys were 72.15 and girls were 27.9%. Most of the cases 65.1% were consuming tap water. MDR resistance was observed in 9.4% of the cases, while XDR resistance was highly frequent among 83.7% of the patients. Very few cases 16.3% had history of typhoid vaccination. However, MDR and XDR resistance were statistically insignificant according to type of water consumption (p->0.05).

Conclusion: In conclusion, the study revealed alarmingly high prevalence rates of extensively drug-resistant (XDR) typhoid with multidrug-resistant (MDR) strains observed in 9.4% of cases. These findings emphasize the urgent need for comprehensive strategies that address both antimicrobial resistance and vaccination efforts to combat the increasing burden of XDR typhoid in children.

Key words: Salmonella Typhi, XDR, MDR, Water consumption, vaccination

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Introduction

Typhoid fever remains a prevalent public health issue in developing nations, characterized as a systemic infection acquired within communities.[1] It predominantly affects overcrowded areas with limited resources and inadequate sanitation facilities. While individuals of any age can be affected, the higher incidence among children underscores the ongoing transmission within the community.[1,2]

Typhoid fever persists as a significant global health challenge, causing illness and preventable deaths. Reports indicate that approximately 21 million cases of typhoid fever are reported worldwide each year, resulting in an

estimated annual mortality of around 200,000 individuals.[3,4] Typhoid fever poses a significant public health challenge in Pakistan, particularly among the pediatric population, where it is frequently associated with unhygienic practices, consumption of unhealthy street food, and contaminated water sources.[5] If left untreated, typhoid fever can result in mortality rates of 10% or higher. The gold standard for diagnosing typhoid fever is the microbial culture of blood or bone marrow.[6,7]

However, the emergence of antimicrobial resistance poses a significant global challenge in the management of typhoid fever.[6,8] Traditionally, the initial treatment for enteric fever consisted of ampicillin, chloramphenicol, and trimethoprim/sulfamethoxazole. However, the rise of resistant bacterial strains has rendered these drugs ineffective.[9] Furthermore, their use has contributed to the emergence of a multidrug-resistant (MDR) strain, which is no longer susceptible to the aforementioned medications.

Consequently, there has been a shift in prescription patterns towards quinolones and cephalosporins, that worked effectively until an extensively drug-resistant (XDR) strain that was resistant to both medication classes emerged.[9,10] In 2016, Hyderabad had the first outbreak of XDR typhoid, which quickly expanded to surrounding cities in the province of Sindh. Since then, Pakistan alone has reported over 10,000 cases in 2016 by WHO, highlighting the alarming extent of dissemination of this highly resistant strain.[9,11] The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains in numerous countries worldwide has sparked significant apprehension regarding the escalation of antibiotic resistance among pathogens like S. Typhi.[11] Tackling the ongoing progression of antimicrobial drug resistance in Sindh represents a critical public health challenge that requires immediate attention to prevent its local containment and potential spread to urban centers in other provinces of Pakistan.[12,3] Therefore, it is imperative to thoroughly characterize the clinical manifestations of MDR and XDR typhoid fever across various age groups within the pediatric population. This is particularly crucial as the disease predominantly affects children, who exhibit elevated rates of complications and mortality, especially among preschool-aged children.[14] Hence, this study was conducted to evaluate the prevalence and patterns of drug-resistant typhoid fever, including extensively drug-resistant (XDR) and multidrug-resistant (MDR) strains, focusing specifically on children admitted to a tertiary care hospital, which may helpful to develop the treatment strategies and public health interventions aimed at controlling the spread of resistant strains in hospital settings.

Methodology

This descriptive observational study was done at Paediatric department of LUMHS from May2022-november 2022. Children aged 1-12 years, both gender and with confirmed diagnosis of typhoid fever based on positive blood cultures were included. Individuals involving known immunodeficiency conditions, negative blood culture results, previous antibiotic usage within the two weeks before to admission, and suspected or confirmed co-infections with additional organisms were excluded. The guardians or parents of pediatric patients who met the eligibility requirements provided informed consent, after counseling and explaining the study's objectives and the confidentiality of their information. Skilled medical personnel meticulously followed aseptic procedures, utilizing sterilized syringes and needles, during the collection of blood samples. From every individual, around 5–10 milliliters of venous blood were obtained. Heparin or EDTA, two suitable anticoagulants, were added to sterile blood collection tubes before blood samples were taken. To protect patient privacy, the blood specimens have been marked with special identification numbers and these samples were quickly sent to the Hospital lab to ensure they could be processed. Blood culture specimens were taken from children who suspected to have typhoid fever, and they were processed using conventional microbiological methods. Using the proper culture media and biochemical assays, Salmonella Typhi was isolated and identified. Standardized procedures were followed to screen for antibiotic susceptibility. Susceptibility screening findings were used to detect drug resistance patterns, particularly extensively drug-resistant (XDR) and multidrug-resistant (MDR) characteristics. MDR was characterized as developing resistance to a minimum of three kinds of antibiotics routinely prescribed for the treatment of typhoid infection; on the other hand, XDR denotes extra resistance to front-line treatments for typhoid fever, such as fluoroquinolones and third-generation cephalosporins. Using an established study proforma, all demographic data, including outcome factors, were accurately recorded. The information obtained was then analyzed using SPSS version 26, a popular statistical software program. This analytical tool made it easier to thoroughly examine and evaluate the dataset, which made it possible to identify important findings that were relevant to the study's goals as well as patterns and correlations.

Results

The mean age of the patients was 5.91 years with a standard deviation of 3.06 years. In terms of gender distribution, there were 12(28.6%) girls and 30(71.4%) boys. Regarding water consumption sources, the majority (64.3%) reported using tap water, followed by filter plant source (28.6%). Duration of fever varied, with 47.6% of patients experiencing fever for 2-5 days, 50.0% for 6-10 days, and only 2.4% for over 10 days. Concerning typhoid vaccination, 85.7% of patients had not been vaccinated against typhoid fever. The most commonly administered first treatment was Ceftriaxone (88.1%), followed by Ciprofloxacin (4.8%). Table I

Table 1: Demographic information of the patients. (n=42)

Variables		N	%
Gender	Girls	12	28.6%
	Boys	30	71.4%
Water type consumption	Can water	01	02.4%
	Filter plant source	12	28.6%
	Mineral water	01	02.4%
	Null water	01	02.4%
	Tap water	27	64.3%
Duration of fever	2-5 days	20	47.6%
	6-10 days	21	50.0%
	>10 days	01	02.4%
Typhoid vaccination	Yes	06	14.3%
	No	36	85.7%
First treatment	Azithromycin	01	02.4%
	Cefotaxime and gentamycin	01	02.4%
	Ceftriaxone	37	88.1%
	Ciprofloxacin	02	04.8%
	Meropenem	01	02.4%
Age of the patients	Mean±SD	5.91±3.06 years	

According to frequency of culture sensitivity among 42 patients, it has been outlined that the majority of patients (90.5%) exhibited sensitivity to a combination of Meropenem and Azithromycin. Additionally, a smaller proportion of patients showed sensitivity to Meropenem alone (4.8%), as well as to combinations of Ceftazidime, Meropenem, and Sulfamethoxazole (2.4%), and Meropenem, Cefixime, and Azithromycin (2.4%). Figure 1.

MDR resistance was observed in 9.4% of the cases, while XDR resistance was highly frequent among 83.7% of the patients. However, MDR and XDR resistance were statistically insignificant according to patients age, gender and vaccination status (p->0.05). Table II & III

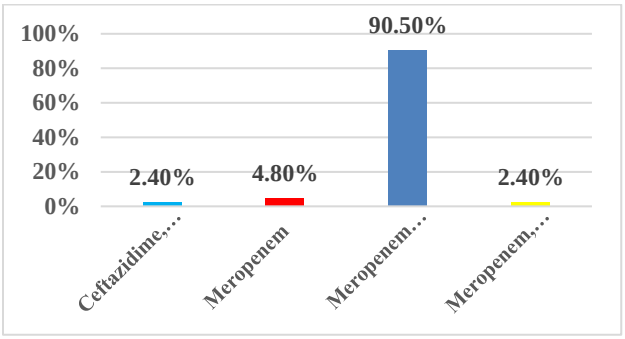

Figure 1. Frequency of culture sensitivity. (n=42)

Table II: MDR and XDR strains in isolated culture. (n=42)

Strains		N	%
MDR	No	38	90.5%
	Yes	4	9.5%
	Total	42	100.0%
XDR	Yes	36	85.7%
	No	6	14.3%
	Total	42	100.0%

Table III: MDR and XDR strains in isolated culture in accordance to age, gender and vaccination. (n=42)

Variables		MDR			XDR		
		Negative	Positive	p-value	Negative	Positive	p-value
Age groups	1-3 years	7	2	**0.510**	3	6	**0.245**
		16.7%	4.8%		7.1%	14.3%	
	4-6 years	12	1		2	11	
		28.6%	2.4%		4.8%	26.2%	
	7-10 years	16	1		1	16	
		38.1%	2.4%		2.4%	38.1%	
	>10 years	3	0		0	3	
		7.1%	0.0%		0.0%	7.1%	
Gender	Girls	11	1	**0.868**	1	11	**0.486**
		26.2%	2.4%		2.4%	26.2%	
	Boys	27	3		5	25	
		64.3%	7.1%		11.9%	59.5%	
Typhoid vaccination	No	33	3	**0.520**	5	31	**0.857**
		78.6%	7.1%		11.9%	73.8%	
	Yes	5	1		1	5	
		11.9%	2.4%		2.4%	11.9%	

Discussion

Typhoid fever remains a significant public health concern, particularly affecting children and young adults.[15] The emergence of antimicrobial resistance poses a significant challenge in effectively treating typhoid fever, leaving healthcare providers with limited options for empiric therapy. This study aims to explore the patterns of drug-resistant typhoid fever, including XDR and MDR strains, in a cohort of 42 cases with positive culture results, characterized by an overall average age of 5.91 years and a male predominance of 71.4%. In the comparison of this study Ashfaq S et al[12] reported that the average age of their study participants was 6.8 years with a standard deviation of 3.1 years, with largest proportion, 44.1%, fell within the age range of over 5 to 10 years and males comprised 54.5% of the study population, while females made up 45.1%.[12]

In the study by Akbayram S et al[16] reported that patients average age was 10.6 ± 4.2 years, with majority of males 52 compared to females 47, out of all 90 patients. In aligns to this study Ali A et al[17] also indicated that out of 197 patients, 118 (59.9%) were male and 79 (40.1%) were female, with an average age of 19.58 ± 13.82 years for the entire group. Average age of above study is higher compared to this study and this difference mays because of difference in selected age range in the study.

In this study regarding water consumption sources, the majority (64.3%) reported using tap water, followed by filter plant source (28.6%). Duration of fever varied, with 47.6% of patients experiencing fever for 2-5 days, 50.0% for 6-10 days, and only 2.4% for over 10 days. Concerning typhoid vaccination, 85.7% of patients had not been vaccinated against typhoid fever. In the support of this study Dudeja N, et al[18] reported that apart from the WASH factors, insufficient food hygiene practices are linked to the prevalence of enteric fever among children in low-income urban areas. According to a previous study by Farooqui A et al[19] reported that the residents of the village resided in impoverished and unsanitary conditions lacking adequate water supply, sewage disposal systems, and other essential amenities. They relied on water from a nearby well as their sole drinking water source. Laboratory analyses revealed the presence of a multidrug-resistant strain of Salmonella enterica serovar Typhi in all well water samples, 65% of household water samples, and 2% of food items. Additionally, 22% of clinical stool samples tested positive for Salmonella enterica serovar Typhi.[19]

In this study according to frequency of culture sensitivity among 42 patients, it has been outlined that the majority of patients (90.5%) exhibited sensitivity to a combination of Meropenem and Azithromycin. Additionally, a smaller proportion of patients showed sensitivity to Meropenem alone (4.8%), as well as to combinations of Ceftazidime, Meropenem, and Sulfamethoxazole (2.4%), and Meropenem, Cefixime, and Azithromycin (2.4%). Consistently, Saleem S et al[20] reported that the sensitivity for meropenem and azithromycin was 100%, while for ciprofloxacin, it was 53.7%. In accordance to this study Ahmad M et al[21] demonstrated that the sensitivity of Cefixime was 27.4%, ceftriaxone sensitivity was in 38.7% of the patients and sensitivity of the Azithromycin was in 96.7% patients, while meropenem was sensitive among 100% of the cases.

Furthermore, in this study MDR resistance was observed in 9.4% of the cases, while XDR resistance was highly frequent among 83.7% of the patients. However, MDR and XDR resistance were statistically insignificant according to patients age, gender and vaccination status (p->0.05). In the comparison of this study Khan MZ et al,[22] found that within all bacterial isolates of enteric fever, 54.1% were extensively drug-resistant (XDR), 20% were positive for extended-spectrum beta-lactamase (ESBL), and 18.5% were multidrug-resistant (MDR). Likewise, Zakir and colleagues recorded a higher prevalence of XDR typhoid fever cases in their research, particularly noting a rise in occurrences among males and individuals aged between 0 and 10 years.[23] The current state of antimicrobial surveillance in Pakistan is notably inadequate and demands immediate attention to understand and predict future trends in antimicrobial resistance.[10] This study possesses several potential limitations like limited study sample size, which could significantly affect the statistical reliability of the findings. Nevertheless, conducting further extensive studies is recommended to address this alarming issue.

Conclusion

Study findings underscored a higher prevalence of extensively drug-resistant (XDR) typhoid, with 9.4% of cases showing multidrug-resistant (MDR) strains. These results highlight the pressing necessity for comprehensive approaches targeting antimicrobial resistance and vaccination initiatives, particularly focusing on addressing the escalating challenge posed by XDR typhoid among children.

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