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FREQUENCY AND OUTCOME OF EXTENSIVE DRUG RESISTANCE (XDR) TYPHOID FEVER IN TERTIARY CARE HOSPITAL SET UP IN LAHORE

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Abstract

Objective: *To determine the frequency and outcome of Extensive Drug Resistance (XDR) typhoid fever in tertiary care hospital set up in Lahore*

Study Design: *Descriptive longitudinal study*

Study place and period*: Department of Pediatrics, Fatima Memorial Hospital, Lahore from 01 May 2025 till 31 July 2025*

Methodology: *Two hundred children were included with typhoid fever. Then blood sample was taken for assessment of antibiotic sensitivity pattern through culture testing. Children were admitted to the hospital and standard treatment was started. Outcome was noted. All the data was recorded in proforma and analysed using SPSS v.25. Extended drug resistance and complete cured were expressed as f (%).*

Results: *The mean age of children enrolled in this study was 7.95 ± 4.10 years Out of 200 children, 109 (54.5%) were males and 91 (45.5%) were females. The mean duration of fever was 6.21 ± 2.22 days. The mean grade of fever was 103.08 ± 0.83 °F. After starting antibiotics treatment, mean hospital say of children was 7.54 ± 2.89 days. On culture testing, out of 200 children, 104 (52%) children had XDR. Out of 200 children, complete cure with treatment was achieved in 180 (90%) cases.*

Conclusion: *The risk of XDR is not negligible in children with typhoid fever. Therefore, it is important to prescribe appropriate antibiotics to prevent and reduce the risk of XDR in children.*

INTRODUCTION

When a pathogenic organism is consumed by food and water tainted by faeces, enteric fever results. Depending on the infectious dose, the incubation period typically lasts between 9.7-21.2 days. [1, 2] The clinical picture might vary from a mild, dry cough, low-grade fever, and malaise to a severe illness with several aftereffects and abdominal pain. Numerous factors affect the severity and clinical prognosis, including the length of the illness prior to the start of appropriate therapy, the choice of antimicrobial treatment, age, prior exposure or immunization history, the virulence of the bacterial strain, the amount of inoculum consumed, and the host's immune status..[3, 4]

The yearly incidence in Pakistan, a lower middle-income nation, is 493.5 per 100,000 people. This rate puts it in the category of nations where typhoid is a major problem. The provinces of Sindh and Punjab have the highest risk of contracting the virus.[5] Children in Lahore who had enteric fever showed a concerning pattern of antibiotic medication

resistance. Azithromycin, meropenem, and imipenem showed the least amount of resistance. Research supports the prompt adoption of customized antibiotic stewardship and infection control measures.[1]

Traditionally, trimethoprim/sulfamethoxazole, ampicillin, and chloramphenicol were used as first-line treatments for enteric fever. However, these medications are no longer effective as resistant microorganisms have emerged as a result of their irrational use. The first reports of this strain date back to 1970, but between 1980 and 1990, resistance to first-line medications spread widely.[6] The prescribing pattern shifted to quinolones and cephalosporins after this, up until the advent of an extensively drug-resistant (XDR) strain that was also resistant to these medications. In 2016, Hyderabad had the first XDR typhoid outbreak, which quickly expanded to other Sindh provincial cities. Since then, more than 10,000 cases have been documented in Pakistan alone, demonstrating the startling scope of this extremely resistant strain's dissemination.[7, 8]

According to a study done in Lahore, 46.1% of children with typhoid fever had prolonged medication resistance.[9] Another study, carried out in Karachi, discovered that 50.5% of children with typhoid illness had prolonged medication resistance. Hospital stays lasted an average of 6 (1–19) days. While 1.5% of children passed away while in the hospital, 98.5% of children were released following full recovery.[10]

The purpose of this study was to ascertain the prevalence and consequences of XDR typhoid fever in the pediatric population. According to limited research, over 50% of typhoid fever cases may have an XDR risk. However, there is limited work done in this regard. Therefore, to establish if the incidence is high in the local setting, we carried out this study to gather evidence in our population and apply the results. We would be able to follow better diagnostic and prognostic methods in the future and also improve our practice and expertise.

METHODOLOGY

After obtaining approval from the Ethical Review Board, this descriptive longitudinal study was done at Paediatrics Department, Fatima Memorial Hospital (FMH), Lahore from May 2025 till July 2025. Using the WHO calculator, sample size (n) was 200 cases that was estimated keeping confidence level at 95%, absolute precision required at 7% along with reported percentage of extended drug resistance i.e. 46.1% in children with typhoid fever.[9] The children were recruited in the study after setting the Non-probabi1ity, consecutive samp1ing technique, as on1y following were recruited.

Inclusion Criteria: Chi1dren of age 1-15 years, both genders, presented with clinical suspicion of typhoid fever were recruited from emergency department. Typhoid fever was confirmed as if there was high grade fever >102°F present for more than three days and confirmed on b1ood cu1ture for Sa1monella typhi as per C1inica1 and Laboratory Standards Institute (CLSI) guideline.[10]

Exclusion criteria: Children already taking antibiotic treatment, with recurrent fever within 3 months were excluded.

Written informed consent was taken from parents / guardians before recruitment. Demographics (name, age, gender, weight, duration of fever, grade of fever on presentation, residence, socioeconomic status, season), were noted. Then blood sample was taken and sent to the laboratory of the hospital for assessment of antibiotic sensitivity pattern through culture testing. Reports were assessed and findings were recorded. XDR was labelled if on blood culture, bacteria detected in the blood had resistance against recommended or most prescribed antibiotics for management of typhoid fever, including 3rd generation cepha1osporins and f1uoroquinolones.[10] Children were started with the standard treatment was given to all children. All the children were followed-up until child was discharged from hospital. Patients were discharged when afebrile and taking oral feed. During stay, if outcome including complete cure and discharge was noted. Complete cure was labelled if fever resolved within 72 hours of treatment and no ever for next 24 hours. All the data was recorded in the proforma.

Data was analysed using software SPSS version 25. Quantitative variables age, weight, duration

of fever, grade of fever, hospital stay were expressed as mean ± standard deviation. Qualitative variables like gender, residence, socioeconomic status, season, extended drug resistance and complete cured were expressed as frequency and percentage. Data was stratified for age, gender, weight, duration of fever, grade of fever, residence, socioeconomic status, and season. Post-stratification, chi-square test was used to compare the frequency of XDR and outcome in stratified groups, keeping P-value ≤ 0.05 as significant.

RESULTS:

In this study, we enrolled total 200 children with typhoid fever, with the mean age of 7.95 ± 4.10 years Out of 200 children, 109 (54.5%) were males and 91 (45.5%) were females. The mean weight of children was 25.89 ± 11.51 kg. Out of 200, 90 (45.0%) were living in rural areas, 75 (37.5%) were from semi-urban areas and 9 (4.5%) were from urban slums. About 107 (53.5%) children were from 1ow socioeconomic class, 90 (45.0%) belonged to middle class families and 03 (1.5%) were from high class families. The mean duration of fever was 6.21 ± 2.22 days. The mean grade of fever was 103.08 ± 0.83 °F. Mostly children presented with typhoid during winter 74 (37.0%) and summer 76 (38.0%), while 33 (16.5%) children presented during spring and 17 (8.5%) during autumn. After starting antibiotics treatment, mean hospital say of children was 7.54 ± 2.89 days. Table-I

On culture testing, out of 200 children, 104 (52%) children had XDR. Figure-1

Out of 200 children, complete cure with treatment was achieved in 180 (90%) cases. Figure-2

Data was stratified for effect modifiers including age, gender, duration and grade of fever at presentation. It was observed that age and gender has no impact on the frequency of XDR, in achieving complete cure and mean duration of hospital stay (p>0.05). Similarly, duration and grade of fever also had no impact on the frequency of XDR, in achieving complete cure and mean duration of hospital stay (p>0.05). Table-II

Table-I: Demographics and clinical history of patients (n = 200)

		Observation
	Age, years	7.95 ± 4.10
	Gender	
	Males	109 (54.5%)
	Females	91 (45.5%)
	Weight, kg	25.89 ± 11.51
	Residence	
	Urban	26 (13.0%)
	Rural	90 (45.0%)
	Semi-urban	75 (37.5%)
	Urban slums	9 (4.5%)
Socioeconomic status		
	Low	107 (53.5%)
	Middle	90 (45.0%)
	High	03 (1.5%)
	Duration of fever, days	6.21 ± 2.22
	Grade of fever, °F	103.08 ± 0.83
	Season	
	Winter	74 (37.0%)
	Summer	76 (38.0%)
	Spring	33 (16.5%)
	Autumn	17 (8.5%)
	Hospital stay, days	7.54 ± 2.89

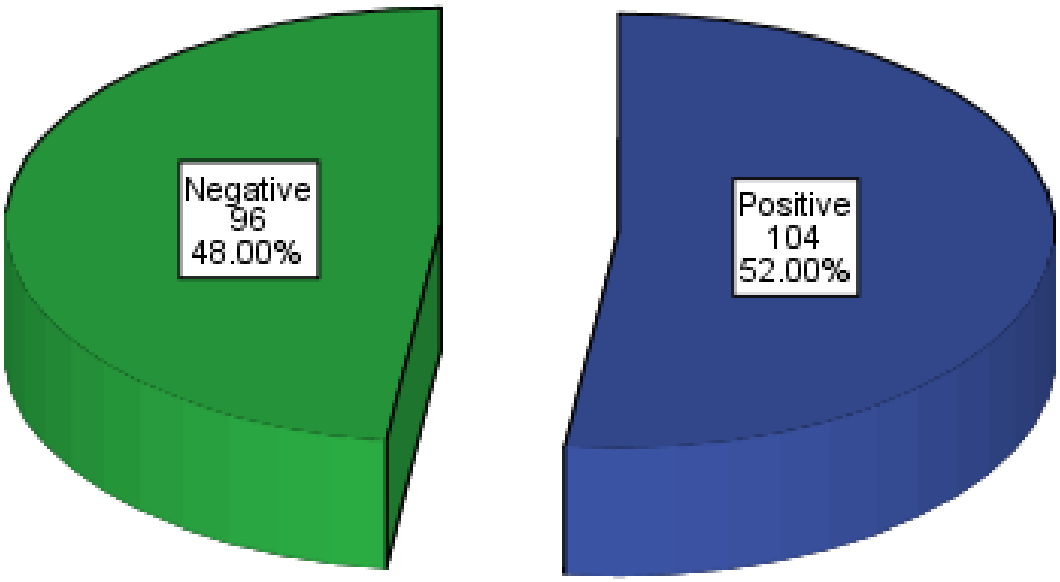


Figure-1: Presence of Extensive Drug Resistance (n = 200)

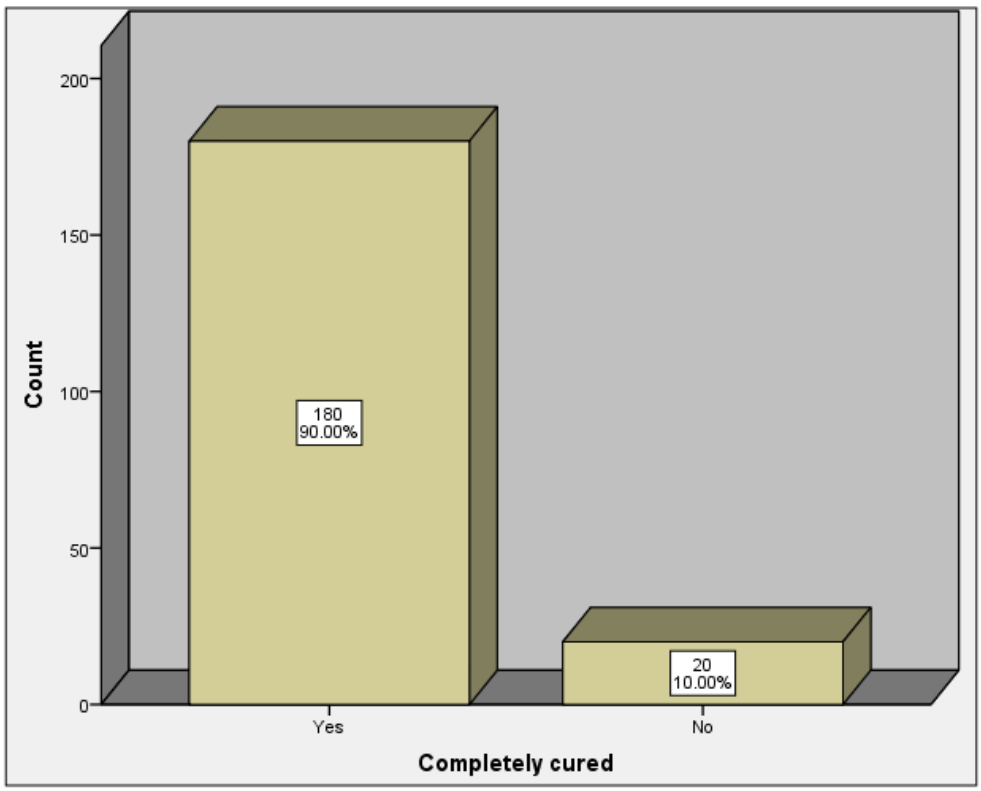


Figure-2: Complete cured achieved with treatment in children with typhoid fever (n = 200)

Table-II: Association of Extensive Drug Resistance and outcomes with effect modifiers

		Extended drug resistance	Completely cured	Hospital stay	p-value, XDR	P-value, Complete cure	p-value hospital stay
		n = 104	n = 180	Mean±SD			
Age, years	<5 years	31 (51.7%)	50 (83.3%)	7.95 ± 2.61	0.953	0.050	0.419
	6-10 years	40 (53.3%)	72 (96.0%)	7.40 ± 3.08			
	>10 years	33 (50.8%)	58 (89.2%)	7.32 ± 2.92			
Gender	Male	57 (52.3%)	99 (90.8%)	7.60 ± 3.07	0.928	0.670	0.764
	Female	47 (51.6%)	81 (89.0%)	7.47 ± 2.68			
Duration of fever	<7 days	56 (50.0%)	100 (89.3%)	7.79 ± 2.84	0.523	0.704	0.161
	≥7 days	48 (54.5%)	80 (90.9%)	7.22 ± 2.95			
Grade of fever	102	32 (51.6%)	55 (88.7%)	7.60 ± 2.88	0.958	0.712	0.468
	103	31 (50.8%)	54 (88.5%)	7.85 ± 2.82			
	104	41 (53.2%)	71 (92.2%)	7.25 ± 2.97			

DISCUSSION:

In this study, we observed XDR in 104 (52%) children who presented with typhoid fever. After starting antibiotics treatment, mean hospital say of children was 7.54 ± 2.89 days. Out of 200 children, complete cure with treatment was achieved in 180 (90%) cases. These results are consistent with recent reports obtained from Pakistan, where one retrospective cohort study conducted in Karachi found that 54% of children with typhoid illness had XDR.[11]

According to research done in Lahore by Zakir et al., 46.1% of children with typhoid fever had XDR.[9] In a study done in Karachi, Herekar et al. discovered that 50.5% of children with typhoid had positive XDR results. Hospital stays lasted an average of 6 (1–19) days. While 1.5% of children passed away while in the hospital, 98.5% of children were released following full recovery.[10] Ashraf et al. discovered that 52.4% of children tested positive for XDR in another investigation. The mean 1ength of hospita1 stay (7.27 ± 1.68 vs. 7.77 ± 2.2 days, p=0.103) did not show any significance between children with or without XDR.[12]

In a similar study, Shah et al. found XDR in 44.9% of 136 children in Peshawar who had typhoid fever confirmed by blood culture.[13] A serious public health concern is the spread of XDR typhoid fever in children, especially in areas with poor sanitation and restricted access to healthcare.[14, 15] According to Baloch et al., children with typhoid fever had the highest frequency of XDR (83.7%). They found XDR typhoid prevalence rates that were frighteningly high. These findings highlighted the critical need for all-encompassing approaches that address both vaccination campaigns and antibiotic resistance in order to counteract the rising incidence of XDR typhoid in children.[16]

The most prevalent clinical sign of enteric fever, particularly in children, is high grade fever, which makes parents more anxious.[17, 18] The average duration of fever in our study was 6.21 ± 2.22 days. The average temperature was 103.08 ± 0.83 oF. Additionally, we found no

correlation with XDR and a negligible effect of severity of fever or duration on obtaining a full recovery with antibiotics. Additionally, 58.7% of patients experienced a fever for seven to fourteen days prior to admission, according to Memon et al. The majority of them had temperatures above 100 degrees Fahrenheit. This finding is consistent with the retrospective analysis conducted by Parry et al., which found that the median 1ength of fever at the admission time for children with enteric fever was severn days (IQR:5-14 days).[19]

In a cross-sectional investigation, Batool et al., found that approximately 11.3% of blood cultures produced bacterial growth. In all, 23.5% and 54% of S. Typhi were MDR and XDR, respectively, and they were susceptible to carbapenems and azithromycin. S. Typhi showed resistance to ampicillin (78%), co-trimoxazo1e (78%), ciprof1oxacin (59%), ceftriaxone (56%), and chloramphenicol (72%).[20]

The majority of XDR children reacted to azithromycin (53.1%), ceftriaxone with azithromycin (10.2%), meropenem (24.5%), azithromycin with meropenem (2%), and azithromycin with amikacin (2%), according to Ashfaq et al. According to the culture and sensitivity assessment, about 6.1% of patients responded favorably to amikacin when it was first introduced. Despite having a culture sensitivity report indicating resistance to ceftriaxone, about 2% of children demonstrated clinical response to the medication.[21]

According to a study done in Lahore, Pakistan, patients' age and gender have no bearing on their antibiotic resistance in either MDR or XDR typhoid (P value >0.05).[9] Enteric fever caused by resistant bacteria is becoming an increasingly serious problem in developing and resource-constrained countries including Pakistan. Numerous studies have shown that it is prevalent throughout South-East Asia, including Bangladesh, India, Pakistan, and Nepal.[22] In recent years, resistance to first-line antibiotics including amoxicillin, chloramphenicol, and TMP/SMX has grown to be a major problem. Both the over-prescription of medication by incompetent medical experts and the irresponsible use of over-the-counter pharmaceuticals are responsible for the rising number of MDR and XDR typhoid infections.[23]

According to research, 23% of Asian nations have MDR. According to a study, the prevalence of MDR rose from 34.2% to 48.5% between 2001 and 2006.[24] The weekly epidemiological data from the National Institute of Health (NIH) Islamabad states that between January 2017 and June 2021, 14360 cases of XDR enteric fever were reported in Karachi. On the other hand, over the same period, 5,741 cases of XDR were documented throughout the rest of Sindh, with the biggest number of cases (69.5%) occurring in Hyderabad district.[25]

CONCLUSION:

We observed XDR in about half of the population presented with typhoid fever. Thus the risk of XDR is not negligible in children with typhoid fever. Therefore, it is important to prescribe appropriate antibiotics to prevent and reduce the risk of XDR in children. Now in future, we will improve measures to prevent XDR and also improve the diagnostic and management protocols to improve outcomes of antibiotics treatment.

CONFLICT OF INTEREST

None.

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