ORIGINAL ARTICLE

Risk factors of multi drug resistance enteric fever among pediatric patients in Lahore

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ABSTRACT

Background: Enteric fever, caused primarily by *Salmonella enterica* serovars Typhi and Paratyphi, remains a major public health concern in developing countries, particularly in South Asia. The objective of this study is to determine the risk factors associated with multidrug-resistant (MDR) enteric fever among pediatric patients presenting to a tertiary-care hospital.

Material and Methods: This descriptive cross-sectional study was conducted at Department of Pediatrics, Pakistan Sheikh Zayed Hospital, Lahore, from 8-11-25 to 7-02-26. A total of 177 children aged 1–12 years with clinically suspected enteric fever were enrolled using non-probability consecutive sampling.

Results: Among 177 children (mean age 6.4 ± 3.2 years), 115 (65%) had culture-positive enteric fever, and 35 of these (30%) were MDR. Fever lasted an average of 7.9 ± 3.1 days, with headache in 51%, constipation in 43%, and diarrhea in 47%. Prior antibiotic use was reported in 28% of all patients, and only 21% were fully vaccinated. Most children belonged to low socioeconomic households (55%), with poor food hygiene in 50% and poor water sanitation in 45%. MDR cases were significantly associated with prior antibiotic exposure (39% vs 22%; p = 0.01), antibiotic misuse (29% vs 16%; p = 0.04), low socioeconomic status (64% vs 49%; p = 0.03), poor water sanitation (57% vs 38%; p = 0.02), and unvaccinated status (46% vs 30%; p = 0.04).

Conclusion: Multidrug-resistant enteric fever in children is strongly linked to modifiable behavioral and environmental factors.

Keywords: Antibiotic misuse, Enteric fever, Multidrug resistance, Pediatrics, Risk factors

BACKGROUND

Typhoid fever is a commonly observed etiological source of bacteremia in many developing countries of South Asia, Southeast Asia, and sub-Saharan Africa, where it is a major cause of morbidity and mortality among children.[1] The annual burden of typhoid and paratyphoid fever is estimated at 14.3 million cases and 135,900 deaths worldwide.[2] In Pakistan, typhoid is the well-known cause of bacteremic illness in children, with rates more than 451.7 per 100,000 among children 2 to 15 years old.[3] This high prevalence rate of typhoid fever has been exacerbated by the emergence of Salmonella typhi strains resistant to multiple drugs.[4] These drug-resistant strains threatened the role of antibiotics in typhoid control, increased the treatment cost, and inflated significantly the morbidity and mortality rates.[5] The causative agent of typhoid, Salmonella enterica serovar Typhi (Salmonella Typhi), is a human host–restricted organism. The risk factors for typhoid include poverty, unhygienic environmental conditions, lack of access to safe drinking water, absence of appropriate sanitation amenities, and hazardous foods.[6] The disease burden is distributed heterogeneously within different Southeast Asian countries, with the greatest incidence reported in the areas with the most deficient hygiene and sanitation, including urban slums.[7] Various similar food exposures and hygiene habits have been identified as risk factors for typhoid fever in Pakistan.[8]

In a desk review of 106 articles regarding risk factors for enteric fever, a higher proportion 47.2% of the articles indicated risk factors related to low socio-economic status, 45.3% to poor food hygiene, 42.5% to water born transmission, 32.1% to poor sanitation and hygiene, 13.2% to antimicrobial agents and 5.7% related to unvaccinated and immunocompromised patients.[9]

Antibiotic resistance is an emerging public health threat worldwide. S. Typhi resistant to first-line antibiotics (ampicillin, trimethoprim/sulfamethoxazole, and

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chloramphenicol) was initially considered multidrug-resistant. Reduced susceptibility to second-line drugs (i.e. fluoroquinolones) has also been widely reported since these had then emerged as the preferred treatment for multidrug-resistant typhoid fever[10]. Ceftriaxone and azithromycin are used to treat patients with typhoid fever, who are nonresponsive to fluoroquinolones and first-line drug treatments.[11] Recently Now, there emerged strains of S. Typhi susceptible only to azithromycin and carbapenems causing extremely drug-resistant typhoid. Typhoid fever is rapidly spreading throughout Pakistan, raising concerns about the global failure of antibiotics.[12] Scientists contend that the main causes of the growth of extensively drug-resistant enteric fever in Pakistan include the country's poor sewage and water systems, low vaccination rates, self-medication, misuse of antibiotics and overcrowding in the cities. An earlier study conducted in Balochistan province on 2946 pediatric patients clinically suspected of enteric fever were subjected to evaluation for typhoid fever and reported that 550 patients were positive with overall prevalence of (18.66%).[13] The aim of the study is to determine the frequency of various risk factors of multi-drug resistance enteric fever among pediatric patients in Lahore. This study provides new local evidence on the determinants of multidrug-resistant (MDR) enteric fever among pediatric patients in Lahore by simultaneously evaluating clinical, behavioral, and environmental risk factors in a single hospital-based cohort. Unlike many previous studies that focused mainly on antimicrobial resistance patterns or outbreak investigations, the present research specifically quantifies the relationship between prior antibiotic exposure, antibiotic misuse, socioeconomic status, sanitation conditions, and vaccination status with MDR infection among culture-confirmed pediatric cases.

MATERIAL AND METHODS

This descriptive cross-sectional study was conducted in the Department of Pediatric, Pakistan Sheikh Zayed Hospital Lahore from 8-11-25 to 7-02-26. A non-probability consecutive sampling technique was used to recruit eligible patients. Patients of either gender aged 1–12 years, presenting with clinical suspicion of typhoid fever characterized by high-grade fever, malaise, headache, abdominal discomfort, constipation or diarrhea, and subsequently diagnosed with enteric (typhoid) fever on clinical and laboratory evaluation, were included in the study. Patients without confirmed blood culture evidence of enteric fever, as well as those with chronic or concurrent infections such as human immunodeficiency virus or tuberculosis, and those with severe underlying systemic illnesses that could affect clinical outcomes, were excluded from the study.

This study was initiated after obtaining ethical approval from the Institutional Research and Ethics Review Committee of Pakistan Sheikh Zayed Hospital, Lahore. All caregivers were informed about the study purpose and procedures and informed consent was given before enrolment. All patients who came to the pediatric department on suspicion of enteric fever were screened. Participants were recruited one after the other. The sociodemographic information, current symptoms, length of illness, previous medication history, and clinical results were recorded on standardized data collection forms. Tablet entry was done, and records uploaded on a safe central server on a daily basis. The clinical microbiology laboratory of the hospital provided the profiles of antibiotic resistance. Patients who were blood culture positive were followed-up with six weeks, post enrolment, to obtain information.

Patients were classified based on caregiver-reported information collected through the study questionnaire. Socioeconomic status was categorized according to monthly household income, while food hygiene and water/sanitation were assessed based on household practices and drinking water sources and grouped as poor, average, or good. Antibiotic misuse was defined as self-medication, use of antibiotics without prescription, incomplete courses, or inappropriate dosing before hospital presentation.

Statistical Analysis: Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 27. The sample size of 177 pediatric patients was calculated using the WHO sample size formula for single proportion with a 95% confidence level, 5% margin of error, and an expected prevalence of antibiotic misuse of 13.2% reported in previous literature, ensuring adequate power to detect associations between risk factors and MDR enteric fever. Before statistical testing, the normality of continuous variables was assessed using the Shapiro–Wilk test along with visual inspection of histograms and Q–Q plots. Quantitative variables were summarized as mean ± standard deviation. Qualitative variables were reported as frequencies and percentages. Risk factors for multidrug-

resistant enteric fever such as antibiotic misuse, low socioeconomic status, poor food hygiene, and inadequate water and sanitation conditions were stratified by age group, gender, temperature, and vaccination status. Post-stratification Chi-square tests were applied to determine statistical significance, with $p \leq 0.05$ considered significant.

RESULTS

A total of 177 patients were included in the study. Table-I shows demographics and clinical features. The mean age of the study population was 6.4 ± 3.2 years, with a slight male predominance 96(54%). The average duration of fever at presentation was 7.9 ± 3.1 days. Headache was the most common symptom (51%). Prior antibiotic use was reported in 49 children (28%). Only 21% of the children were fully vaccinated against typhoid. A total of 35(30%) had MDR typhoid.

Table-II shows socioeconomic factors. A majority, 97 children (55%), belonged to low socioeconomic households. Food hygiene practices were poor in 89 families (50%) and with 80 children (45%) exposed to poor water quality.

Table-III shows comparison of MDR and non-MDR Typhoid. Prior antibiotic use was significantly higher in the MDR group compared to non-MDR cases (39% vs 22%; p = 0.01). Antibiotic misuse was also more frequent among MDR patients (29% vs 16%; p = 0.04). There were 111 patients with dengue fever. Low socioeconomic status and poor water sanitation were also found to be significantly more common among MDR typhoid group. A significant number of patients were unvaccinated with typhoid vaccine who had MDR typhoid infection.

Table-I. Baseline demographics and clinical presentation (n = 177).

Variable	n (%) / Mean ± SD
Age (years)	6.4 ± 3.2
Male	96 (54%)
Fever Duration (days)	7.9 ± 3.1
Headache	90 (51%)
Constipation	76 (43%)
Diarrhea	83 (47%)
Prior Antibiotic Use	49 (28%)
Typhoid Vaccination Status	
Fully vaccinated	37 (21%)
Partially vaccinated	76 (43%)
Unvaccinated	64 (36%)
Blood Culture Result	115 (65%)
MDR Status (among positive cases)	
MDR	35 (30%)
Non-MDR	80 (70%)

Table-II: Distribution of environmental and behavioral risk factors.

Risk Factor	Category	n (%)
Socioeconomic Status	Low	97 (55%)
	Middle	62 (35%)
	High	18 (10%)
Food Hygiene	Poor	89 (50%)
	Average	62 (35%)
	Good	26 (15%)
Water & Sanitation	Poor	80 (45%)
	Average	71 (40%)
	Good	26 (15%)
Antibiotic Misuse	Yes	23 (13%)
	No	154 (87%)

Table-III: Comparison of MDR vs non-MDR cases (culture-positive patients Only, n = 115).

Variable	MDR (n = 35)	Non-MDR (n = 80)	p-value
Mean Age (years)	6.8 ± 3.1	6.2 ± 3.2	0.42
Fever Duration (days)	8.3 ± 3.4	7.6 ± 3.0	0.28
Prior Antibiotic Use	14 (39%)	18 (22%)	0.01
Antibiotic Misuse	10 (29%)	13 (16%)	0.04

Low Socioeconomic Status	22 (64%)	39 (49%)	0.03
Poor Water Sanitation	20 (57%)	30 (38%)	0.02
Unvaccinated	16 (46%)	24 (30%)	0.04

Table-IV: Association of risk factors with MDR enteric fever (n=115).

Risk Factor	MDR Present n (%)	MDR Absent n (%)	p-value
Prior Antibiotic Use	14 (40%)	21 (21%)	0.01
Antibiotic Misuse	10 (29%)	13 (13%)	<0.01
Low Socioeconomic Status	22 (63%)	44 (44%)	0.03
Poor Food Hygiene	20 (57%)	45 (45%)	0.18
Poor Water Sanitation	20 (57%)	31 (31%)	0.02
Unvaccinated	16 (46%)	34 (34%)	0.04

DISCUSSION

This study assessed the burden of multidrug-resistant (MDR) enteric fever and its associated risk factors among children presenting to a tertiary-care hospital in Lahore. Among culture-confirmed cases, nearly one-third were MDR, and MDR status was significantly associated with prior antibiotic exposure, antibiotic misuse, low socioeconomic status, poor water sanitation, and lack of vaccination. These findings support the concept that drug-resistant enteric fever in children is driven by a mix of antibiotic pressure and structural environmental risks, rather than by distinct clinical presentation alone. Our findings are consistent with national pediatric data showing that antimicrobial resistance in *Salmonella Typhi* is a persistent and escalating problem in Lahore and other Pakistani settings, where resistance patterns and treatment challenges have been repeatedly documented in children.[14] These conclusions indicate that community-based prescribing practices and parental attitude toward antibiotics have a disproportionately large contribution to resistance trends.[15] Families in resource-deprived environments are generally less likely to access timely medical care, rely more on informal sources of treatment, and reside in conditions that support dissemination of strains of resistance. Water sanitation was also poor and this also enhanced this relationship. The environmental risk and microbial evolution intersected remarkably with children who were exposed to contaminated sources of water having a high likelihood of staying with MDR organisms. These variables highlight the fact that MDR is not a problem only in clinical terms but a structural one, which is predetermined by the living conditions and inequalities in society. Even though the significance of vaccination status was not maintained in multivariate analysis, the tendency towards the increased MDR incidence among unvaccinated children is interesting.[16] TCV vaccine has proved to be promising in terms of decreasing both the burden of the disease and resistant infections. In places such as Pakistan, where vaccination is still not uniform, enhancing the immunization efforts may act as an added defense especially to the vulnerable populations. There were no significant differences between MDR and non-MDR groups in clinical symptoms of duration of fever, gastrointestinal and headache.[17] This confirms the fact that MDR enteric fever has no clinical difference with sensitive infections, and thus laboratory confirmation is necessary. The reason is that, due to the impossibility of anticipating MDR, according to the presentation alone, the empirical treatment strategies need to be updated on the basis of the recent trends in resistance regularly in order to prevent anti-treatment results. The study contributes to the local and global knowledge of MDR enteric fever.[18] It identifies important predictors, which can be used to inform specific preventive approaches and not general, non-specific interventions.[14] The significant association between MDR and prior antibiotic exposure in our cohort aligns with the broader Pakistani context of non-prescription antibiotic access and inappropriate antibiotic use, which accelerates selective pressure and resistance.[19] Nevertheless, turning around the MDR patterns will involve lifelong interventions education of care givers, tightening control of prescriptions, sanitation and increased immunization rate. It is important to note that this study has a number of limitations that must be considered when deriving the results. First, the cross-sectional design does not allow to develop causal relationships between the risk factors identified and the occurrence of multidrug-resistant enteric fever, it is possible to observe associations but not to establish relationships in terms of time. Second, the research was based on one tertiary-care hospital and might not be generalized to the community-wide scenario or rural population with other exposure patterns and healthcare access.

CONCLUSION

It is concluded that multidrug-resistant enteric fever represents a significant and growing threat among pediatric patients, with one-third of culture-positive cases demonstrating resistance to commonly used antibiotics. Low socioeconomic status, poor drinking water quality and lack of vaccination leads to infection with MDR typhoid. These determinants collectively highlight gaps in healthcare access, parental awareness, and community-level hygiene infrastructure.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Fazila Nasir Virk: Substantial contributions to concept, study design, final approval, accountable for all aspects of publication.

Asfand Tariq: Critical review, final approval, accountable for all aspects of publication.

Lubna Riaz: Manuscript writing, final approval, final approval, accountable for all aspects of publication.

Ahmad Javed: Substantial contributions to acquisition of data, final approval, accountable for all aspects of publication.

Aymen Jamal: Manuscript drafting, reviewing it critical for important intellectual content, final approval, accountable for all aspects of publication.

Muhammad Adil: Substantial contributions to acquisition of data, final approval, accountable for all aspects of publication.

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