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Original Article

Clinical Spectrum, Laboratory Profile, and Antimicrobial Resistance in Pediatric Enteric Fever: A Cross-Sectional Study from Lahore, Pakistan

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ABSTRACT

Objective: To assess the clinical presentation, laboratory abnormalities, and antimicrobial response patterns among children diagnosed with enteric fever.

Methodology: This cross-sectional analytical study was conducted at the Department of Pediatrics, Ittefaq Hospital (Trust), Lahore from January to June 2025. Ethical approval was obtained from the Institutional Review Committee. Informed written consent was sought from parents/guardians of study participants. A sample size of 131 was calculated and children suspected of enteric fever were enrolled using non-probability consecutive sampling technique. Demographic and clinical data was documented. Blood samples were obtained aseptically before antimicrobial therapy and processed for *Salmonella typhi* identification and antimicrobial susceptibility. Data was analyzed using Statistical Package for the Social Sciences (SPSS) version 26.0.

Results: The median age of 131 children was 7.0 years [inter-quartile range (IQR) 3.0-9.0]. Blood culture was positive for *Salmonella typhi* in 75(57.3%) cases including 42(32.1%) multidrug-resistant (MDR) and 33(25.2%) extensively drug-resistant (XDR) strains. Abdominal pain (p=0.004) and constipation (p=0.010) were more frequent in XDR cases. Leukopenia occurred only in XDR cases (p=0.009), and raised C-reactive protein (CRP) was more common in MDR (85.7%) and XDR (90.9%) samples compared to no growth samples (p <0.001).

Conclusion: *Salmonella typhi* was identified in over half of the cases with a high proportion of MDR and XDR strains. Abdominal pain, constipation, and leukopenia were significantly more common among XDR patients compared to MDR patients. C-reactive protein was significantly elevated in both MDR and XDR cases, while erythrocyte sedimentation rate (ESR) showed no association. Multidrug-resistant strains showed sensitivity to ceftriaxone and XDR strains to azithromycin & carbapenems.

Keywords: *Enteric fever. Salmonella typhi. Blood culture. Antimicrobial Resistance.*

INTRODUCTION

Enteric fever is mainly caused by *Salmonella enterica*, *serotypes typhi*, and *paratyphi*, and considered a major public health issue especially among developing countries.[1] Last few decades have seen major improvements in sanitation and overall healthcare access, but still enteric fever causes considerable morbidity and mortality.[2] The Global Burden of Disease study reported 9.3 million cases of enteric fever and approximately 107,000 deaths in 2021, with 40% of fatalities occurring in children under five. The highest burden was observed in endemic regions, particularly South Asia.[3]

The most common symptoms in enteric fever include prolonged fever, abdominal pain, headache, and gastrointestinal disturbances. Atypical presentations like intestinal perforation, hemorrhage, and encephalopathy are somewhat uncommon but can still occur among severe cases. The emergence and spread of multidrug-resistant and extensively drug-resistant *Salmonella typhi* strains have compromised the effectiveness of commonly used antibiotics like chloramphenicol, ampicillin, and trimethoprim sulfamethoxazole.[4]

Recent local data documented a high prevalence of MDR and XDR *Salmonella typhi* in Pakistan, which leaves very few treatment options like azithromycin and carbapenems. The evolving resistance patterns pose significant challenges for treating physicians, increasing the risk of complications, treatment failure, and prolonged disease spans.[5] The local literature exhibits that only one oral antibiotic, azithromycin, is predominantly left as a treatment option in XDR enteric fever.[6]

Enteric fever continues to pose a significant public health burden in children, particularly in resource limited settings where sanitation and access to safe drinking water remain suboptimal. The clinical presentation in children is often diverse and may overlap with other febrile illnesses, while laboratory abnormalities are not always specific, leading to diagnostic uncertainty.[4] Evolving antimicrobial resistance has also reduced the effectiveness of commonly used antibiotics, complicating empirical management. Given these concerns, it is important to generate updated local data on the clinical profile,

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laboratory derangements, and antimicrobial response patterns of pediatric enteric fever to inform evidence based diagnosis and treatment strategies. This study aimed to determine the clinical characteristics, laboratory abnormalities, and antimicrobial responses in children diagnosed with enteric fever.

METHODOLOGY

This cross-sectional analytical study was conducted at the Department of Pediatrics, Ittefaq Hospital (Trust), Lahore from January to June 2025. Ethical approval was obtained from the Institutional Review Committee (Letter No. IHT/Admin/30, 23-12-2023). Informed written consent was sought from parents/guardians of study participants. A sample size of 131 was calculated using a 95% confidence level and a 7% margin of error, based on an anticipated 79% prevalence of XDR *Salmonella typhi* strains.[7] Inclusion criteria were children aged 1 to 14 years, who were suspected to have enteric fever based on criteria of fever for more than 5 days, without any identifiable focus or with gastrointestinal symptoms like vomiting, abdominal pain, or loose stools. Children with a clear alternate diagnosis, ongoing antibiotic therapy before hospital presentation were excluded. Non-probability consecutive sampling technique was adopted.

Upon admission, detailed demographic, and clinical data including gender, age, and associated symptoms were documented on a preformed proforma. Laboratory investigations were conducted as per hospital protocol through the institutional laboratory, and parameters like leukocyte count, ESR, and CRP were evaluated. Blood samples were collected under strict aseptic conditions prior to the initiation of antimicrobial therapy and processed using the BACTEC automated blood culture system. Culture and sensitivity testing were performed to identify the presence of *Salmonella typhi*, and to determine antimicrobial susceptibility patterns. Positive cultures were sub-cultured on blood agar and MacConkey agar. *Salmonella typhi* was identified by colony morphology, gram staining, standard biochemical tests, and confirmed serologically using specific *Salmonella* O and H antisera. Antimicrobial susceptibility testing was performed by the Kirby-Bauer disc diffusion method on Mueller-Hinton agar. Zone diameters were interpreted according to clinical and laboratory standards. The outcomes were categorized as no growth, MDR, and XDR *Salmonella typhi*. Multidrug-resistant *Salmonella typhi* was defined as resistance to first line agents like ampicillin, chloramphenicol, and co-trimoxazole, while XDR *Salmonella typhi* was defined as resistance to first-line agents, fluoroquinolones, and third-generation cephalosporins.[4] Leukocyte count was categorized as normal (4,000-11,000 cells/mm^3), leukocytosis (>11,000 cells/mm^3, and leukopenia (<4,000 cells/mm^3). C-reactive protein was considered normal if ≤6mg/L and raised if >6mg/L.[8] Erythrocyte sedimentation rate was considered normal if ≤10 mm/hr and raised if >10 mm/hr.[9]

STATISTICAL ANALYSIS

The data was entered and analyzed using Statistical Package for Social Sciences (SPSS) version 26.0. Categorical variables were presented as frequencies & percentages, while continuous variables were summarized as median and inter-quartile range (IQR). The comparison of demographic, clinical, and laboratory characteristics was done across outcome categories of blood culture findings (no growth, MDR, and XDR *Salmonella typhi*). The Chi-square test or Fisher's exact test was applied, taking $p < 0.05$ as statistically significant.

RESULTS

Among a total of 131 children, 67(51.1%) were females and 64(48.9%) were males. The median age was 7.00 years (IQR: 3.0-9.0). Vomiting, anorexia, abdominal pain, and loose stools were reported in 63(48.1%), 55(42.0%), 52(39.7%), and 32(24.4%) children, respectively. The median leukocyte count, ESR, and CRP levels were 9.10(6.40-11.81), 28.00(22.00-46.00), and 23.00(9.80-58.00), respectively. Leukocyte count was normal in 92(70.2%) children, while 36(27.5%) had leukocytosis, and 3(2.3%) had leukopenia. Raised ESR was observed in 123(93.9%) children and raised C-reactive protein in 97(74.0%) children.

Blood culture was positive for *Salmonella typhi* in 75(57.3%) cases, of which 42(32.1%) were MDR and 33(25.2%) were XDR strains. No growth was observed in 56(42.7%) cases. There were no significant differences in gender, age groups, or ESR status among the no growth, MDR, and XDR groups ($p > 0.05$). Abdominal pain was significantly more common in XDR cases (63.6%) compared to MDR and no growth cases ($p=0.004$), while constipation was observed only in XDR patients ($p=0.010$). Leukocyte count status showed a significant difference among groups ($p=0.009$), with leukopenia seen only in XDR cases. Raised CRP was significantly more frequent in MDR and XDR cases compared to no growth cases ($p < 0.001$) (Table 1).

When demographic, clinical, and laboratory characteristics were compared between MDR and

XDR groups only, no significant differences in gender, age, leukocyte count, ESR, or CRP levels were recorded (p >0.05). However, abdominal pain (p=0.002) and constipation (p=0.04) were significantly more common in XDR *Salmonella typhi* infections compared to MDR cases. Antimicrobial sensitivity pattern among children with enteric fever is shown in Table 2.

DISCUSSION

In this study, the culture positivity rate for *Salmonella typhi* was 57.3%, slightly higher than the 50% reported by Nusrat et al.[10] The high proportions of MDR (32.1%) and XDR (25.2%) *Salmonella typhi* strains observed in the current study are consistent with the alarming rise in resistant typhoid reported by Zakir et al, where majority of culture positive cases were XDR (46.1%) followed by MDR (24.5%) strains.[11]Another study found that 55.2% of isolates were XDR and 34.7% were MDR.[12] A study conducted in Pakistan demonstrated a similar trend, with 50.7% of children with typhoid having MDR, 47% having XDR, and only 2.3% exhibiting non-resistant infection.[13] Another study documented high rates of resistant *Salmonella typhi*, with 50.5% XDR, 46.6% MDR, and only 2.9% drug sensitive strains, and observed a notable shift from MDR to XDR, along with a decline in drug sensitive cases over one year period.[14]

The resistance patterns in our study with MDR strains remaining largely sensitive to ceftriaxone and XDR strains responsive only to azithromycin or meropenem, align with the findings of Herekar et al., who reported the use of cephalosporins for MDR infections and azithromycin or meropenem, alone or in combination, for XDR cases.[14]

Table 1: Comparison of Clinical and Laboratory Characteristics according to Blood Culture Results in Children with Suspected Enteric Fever

Characteristics			Blood Culture Results				p-value
			No Growth (n=56)	MDR *Salmonella typhi* (n=42)	XDR *Salmonella typhi* (n=33)	Total	
			Frequency & Percentage				
Presenting Complaints	Vomiting	Yes	24(42.9%)	18(42.9%)	21(63.6%)	63(48.1%)	0.118
		No	32(57.1%)	24(57.1%)	12(36.4%)	68(51.9%)	
	Anorexia	Yes	22(39.3%)	21(50.0%)	12(36.4%)	55(42.0%)	0.427
		No	34(60.7%)	21(50.0%)	21(63.6%)	76(58.0%)	
	Abdominal Pain	Yes	19(33.9%)	12(28.6%)	21(63.6%)	52(39.7%)	0.003*
		No	37(66.1%)	30(71.4%)	12(36.4%)	79(60.3%)	
	Loose Stools	Yes	17(30.4%)	6(14.3%)	9(27.3%)	32(24.4%)	0.169
		No	39(69.6%)	36(85.7%)	24(72.7%)	99(75.6%)	
	Constipation	Yes	0(0%)	0(0%)	3(9.1%)	3(2.3%)	0.010*
		No	56(100%)	42(100%)	30(90.9%)	128(97.7%)	
Leukocyte Count Status (cells/mm^3)	Normal		35(62.5%)	33(78.6%)	24(72.7%)	92(70.2%)	0.009*
	Leukocytosis		21(37.5%)	9(21.4%)	6(18.2%)	36(27.5%)	
	Leukopenia		0(0%)	0(0%)	3(9.1%)	3(2.3%)	
ESR (mm/hr)	Normal		2(3.6%)	3(7.1%)	3(9.1%)	8(6.1%)	0.544
	Raised		54(96.4%)	39(92.9%)	30(90.9%)	123(93.9%)	
CRP (mg/L)	Normal		25(44.6%)	6(14.3%)	3(9.1%)	34(26.0%)	<0.001*
	Raised		31(55.4%)	36(85.7%)	30(90.9%)	97(74.0%)	

**Significant p-value*

Table 2: Distribution of Antimicrobial Sensitivity Pattern among Children with Enteric Fever

Salmonella Isolates	Antimicrobial Agent	Sensitivity Frequency (Percentage)
MDR *Salmonella typhi* (n=42)	Ciprofloxacin	3(7.1%)
	Ceftriaxone	39(92.9%)
XDR *Salmonella typhi* (n=33)	Azithromycin	33(100%)
	Meropenem	33(100%)
	Ertapenem	33(100%)
	Piperacillin/Tazobactam	28(84.8%)

Both MDR and XDR strains were found to be sensitive to meropenem and azithromycin in another study.[15] Irfan et al. reported that *Salmonella typhi*, including XDR strains, remained fully susceptible to meropenem and azithromycin, while tigecycline and fosfomycin were identified as alternative treatment options.[16] The universal sensitivity of XDR strains to azithromycin and meropenem underscores their role as last resort agents, highlighting the clinical importance of reserving these antibiotics for confirmed resistant infections to prevent further escalation of resistance.[13] Although 84.8% of XDR *Salmonella typhi* isolates in our series were sensitive to piperacillin/tazobactam, this observation should be interpreted cautiously. In vitro activity against XDR *Salmonella typhi* has been described for piperacillin/tazobactam, but clinical experience is limited, and current treatment discussions more consistently support azithromycin and carbapenems as the principal options for XDR typhoid.

Among 131 children of this study, 51.1% were females and 48.9% were males, with a median age of 7.00 years (IQR: 3.0-9.0). No significant differences in age or gender distribution were observed among the no growth, MDR, and XDR groups in our study ($p > 0.05$). The median age of 7 years, and nearly equal gender distribution reflect the typical vulnerability of the pediatric age group to enteric fever, slightly different from observations made by Shahid et al. who documented median age of 5 years (IQR: 2.0-8.0), with 58% males and 43% females.[13] Herekar et al. reported that children aged 5-6 years were most commonly affected by *Salmonella typhi* infection with no significant differences in age or gender distribution between MDR and XDR strains.[14] Similarly, Irfan et al. observed a mean age of 4.2 years among children under 10 with 59.3% males and 40.7% females, and found no significant differences in age ($p=0.566$) or gender ($p=0.103$) distribution between XDR and non-XDR strains.[16] This demographic pattern supports the notion that school age children remain a key target population for preventive interventions, including vaccination and hygiene education.

The predominance of fever as a universal presenting symptom aligned with previous reports, where fever was consistently reported in all culture positive cases followed by vomiting and anorexia.[13] A study highlighted that the majority of XDR patients had prolonged fever (more than 7 days) at the time of presentation as compared to non-XDR patients ($p < 0.01$). Similar to our results, vomiting, anorexia and loose stools showed no significant differences among XDR and non-XDR groups ($p > 0.05$).[7] Clinical symptomatology in our study showed that abdominal pain was significantly more frequent in children with XDR *Salmonella typhi* (63.6%) compared to MDR (28.6%) and culture negative cases ($p=0.004$). This finding is consistent with others who also identified abdominal pain as a common and prominent symptom in enteric fever patients.[17] Rahim et al. suggested that abdominal pain in XDR typhoid may result from ileocolic inflammation, ulceration, or mesenteric lymphadenitis, which typically resolves with appropriate antibiotics. They also noted that severe or atypical gastrointestinal symptoms could indicate resistant infections, highlighting the need for prompt culture and sensitivity testing.[18] These clinical distinctions reinforce the value of symptom based risk stratification in resource limited settings where immediate culture results may not be available.

Leukocyte count patterns in our study revealed that normal counts predominated across all culture samples, but leukocytosis was notably higher in culture negative patients. Leukopenia was observed only in the XDR patients ($p=0.009$). These findings were consistent with findings from Nusrat et al., where normal counts were reported in the majority (74.5%) of enteric fever children. Leukopenia and other haematological abnormalities, such as anaemia and thrombocytopenia were linked to severe or complicated typhoid infections.[10] Another retrospective study reported normal leukocyte count in 70% cases of suspected enteric fever.[8] In this study, raised ESR was observed in over 90% of patients irrespective of culture status ($p=0.544$), while raised CRP was significantly ($p < 0.001$) more frequent in MDR and XDR infections compared to culture negative cases. Ravi Teja et al. also highlighted the potential utility of elevated acute phase reactants in the inflammatory assessment of enteric fever.[19] However, these laboratory parameters alone are insufficient to differentiate MDR from XDR infections, emphasizing the necessity for microbiological confirmation.

CONCLUSION

Blood culture identified *Salmonella typhi* in more than half of the cases, with a substantial proportion demonstrating MDR and XDR patterns. Multidrug-resistant isolates retained high sensitivity to ceftriaxone, whereas XDR isolates remained uniformly sensitive to azithromycin and carbapenems. Abdominal pain, constipation, and leukopenia were significantly more common among XDR patients compared to MDR patients. Raised CRP levels were significantly observed in both

MDR and XDR cases compared to culture negative cases, while ESR levels showed no such association.

LIMITATIONS & RECOMMENDATIONS

The single-centered setting of this study may limit generalizability to other regions with differing epidemiologic profiles. The cross-sectional design precludes assessment of temporal changes or causality between clinical features and resistance patterns. Lack of molecular characterization of resistance genes limits mechanistic insights into antimicrobial resistance. Future studies should consider multicentre designs with longitudinal follow-up to better capture resistance dynamics and clinical outcomes. Incorporation of molecular diagnostics could enhance detection sensitivity and elucidate resistance mechanisms, guiding more precise treatment and containment strategies. The study also did not evaluate vaccination status or detailed socioeconomic factors, which may influence disease susceptibility and clinical course. Future research incorporating these variables could clarify their roles in disease epidemiology and inform public health interventions. Additionally, the absence of standardized severity scoring may have limited the assessment of clinical correlations with resistance.

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Authors' Contributions:

Authors approved the draft and are accountable in ensuring that questions related to accuracy or integrity of the work are duly investigated and resolved.

S.H: Conception and design, proofreading, critical revisions, approved for publication.
M.U.R: Data collection, drafting, proofreading, critical revisions, approved for publication.
A.S: Data collection, data analysis, proofreading, critical revisions, approved for publication.
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