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Clinical Spectrum, Outcomes, and Quality of Life Implications of Extensively Drug-Resistant Salmonella Typhi

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Author`s Contribution

[1,5]Substantial contributions to the conception or design of the work; or the acquisition, Drafting the work or revising it critically for important intellectual content [2]Supervision [3,4]Active participation in active methodology,[2]analysis, or interpretation of data for the work

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ABSTRACT

Objective: To evaluate the clinical spectrum, management strategies, treatment outcomes, and long-term recovery, including health-related quality of life, in patients with extensively drug-resistant (XDR) Salmonella Typhi infection.

Methodology: A cross-sectional study was conducted at Shifa International Hospital, Islamabad from March 2025 to February 2026. Both male and female patients aged 14 years and above, with blood culture–confirmed XDR Salmonella Typhi, infection were included. Clinical outcomes included need for admission, length of stay among admitted patients, intensive care unit (ICU) admission, development of complications during hospitalization, discharge status, and in-hospital mortality. Analyses were performed using SPSS. Continuous variables Age, and days of hospitalization were summarized as median and IQR as they were not normally distributed.

Results: Seventy-five patients were included; median age was 25 years (25-30). Fever was present in 97.3% of patients. 60% required hospitalization and 9.3% required intensive care stay. Median days of hospitalization were 5 days. Complications included bicytopenia (18%), pancytopenia (4%), gastrointestinal bleeding (6.7%), anemia (10%), septic encephalopathy (6.7%) and septic shock (2.7%). No in-hospital deaths were recorded.42.7% received antibiotic monotherapy, while 53.3% received combination therapy; 60.0% of patients required hospitalization, while 7 (9.3%) required intensive care admission. 52 % of patients had no symptoms of chronic fatigue syndrome on follow-up.

Conclusions: XDR Salmonella Typhi infection was associated with substantial healthcare utilization and clinical complications, however no in-hospital deaths occurred. Most patients required treatment with carbapenem-based regimens. On follow-up 52% of patients reported no symptoms suggestive of chronic fatigue syndrome, suggesting generally favorable long-term recovery and health-related quality of life among survivors.

Keywords: Typhoid fever; XDR Salmonella Typhi; Antimicrobial resistance; Carbapenems; Azithromycin; Hospitalization; Quality of life; Pakistan.

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Introduction

Enteric fever is a multisystemic illness which is caused by gram negative bacterium Salmonella enterica.[1] Enteric fever is posing increasing burden on health care resources and has considerable morbidity and mortality rates. Initially typhoid fever was treated with ampicillin, chloramphenicol and co-trimoxazole, however with the emergence of multi-drug resistant (MDR) strains of Salmonella, fluroquinolones became the treatment of choice. Recently emergent, "Extensively Drug-Resistant" (XDR) Salmonella strains are resistant to the first-line antibiotics, including fluoroquinolones, as well as 3rd generation cephalosporins. Gradual increase in cases of XDR strains of Salmonella enterica is posing threat to health care system, by leaving very limited antibiotic options for treatment. [2]

Enteric fever can present with insidious onset of variable symptoms including the following, fever, generalized weakness, anorexia, headache, malaise, or abdominal symptoms. Patients can develop significant complications in case of delayed or inappropriate treatment**.** A recent

study showed that among patients with Salmonella XDR, 23.66% presented with malaise, 10.84% with body aches and 26.53% with diarrhea. It also showed that almost all patients had fever as a presenting symptom. [3] Another study showed that the mean duration of fever was 19.04±8.39 days in typhoid patients.[4] The common complications which develop with typhoid fever, include the following, anemia, gastrointestinal bleeding, intestinal perforation, bone marrow suppression, encephalopathy, disseminated intravascular coagulation, and shock.[5] With widespread antimicrobial resistance, inappropriate antibiotic therapy leads to longer clinical course with higher rate of complications.[6] A global meta-analysis done in 2020 showed that among 10,335 cases of confirmed typhoid fever,26.3% had complications .[7]

The incidence of extensively drug-resistant salmonella has considerably increased over the past decade. A recent study showed that blood cultures of patients admitted with enteric fever, 50.5 % isolated Salmonella XDR, 46.6 % isolated Salmonella MDR and only 2.9 % isolated drug sensitive strains of Salmonella. The same study also demonstrated that the predominant S. typhi strain rapidly changed from MDR to XDR over the course of a year, with 78.4% of MDR patients registered in 2017 compared to 38.6% in 2018, and XDR cases increased from 16.4% in 2017 to 59.1% in 2018.The same study also showed that 65.52 % of total patients, with different strains of salmonella infection, received monotherapy; while 62.8% of patients with Salmonella XDR received combination therapy. Mean duration of hospital stay in these patients with Salmonella XDR was 8 days. Mortality rate was documented as zero percent in this study.[3]

Disease burden is not fully captured by mortality alone. Prolonged febrile illness, hospitalization, and complications may delay return to usual activities and adversely affect health-related quality of life (HRQoL). Large enteric fever surveillance initiatives have incorporated follow-up assessments to evaluate post-illness outcomes and recovery trajectories.[8] Furthermore, the need to better quantify the long-term health and socioeconomic consequences of enteric fever has been emphasized by global health partners.[9] However, clinical studies of XDR typhoid in Pakistan have rarely evaluated HRQoL directly, and evidence regarding persistent impairment in HRQoL following successful treatment remains limited.

Most existing studies have focused on antimicrobial resistance patterns and treatment practices, while comprehensive data regarding clinical presentation, complications, treatment outcomes, and post-treatment quality of life remain scarce. This study aimed to describe the clinical spectrum, antimicrobial treatment patterns, and clinical outcomes of patients with blood culture–confirmed XDR Salmonella Typhi infection at a tertiary care hospital in Islamabad, Pakistan. We also aimed to follow up on quality of life of patients after completion of treatment. The findings may contribute to improved clinical management, epidemiological surveillance, and strategies aimed at reducing the morbidity associated with XDR typhoid fever.

Methodology

We conducted a cross-sectional study at Shifa International Hospital, Islamabad, Pakistan. The study included patient presenting to hospital between March 2025 and February 2026. The study was approved by the Institutional Review Board of Shifa International Hospital (IRB #504-25), on 29.12.2025, and it was conducted in accordance with the Declaration of Helsinki.

Patients aged 14 years and above were included in the study, if they had blood culture–confirmed Salmonella Typhi infection, meeting the definition of extensively drug-resistant (XDR) based on the susceptibility pattern reported by the microbiology laboratory. The sample size for this study was calculated using WHO calculator, based on statistical tests, anticipated population was 26.3%, (see reference number 7 in the introduction), Confidence interval was set at 95% and absolute precision was set at 10%.

Patients, aged 14 years and above, diagnosed during the study period in inpatient, outpatient, and day-care settings were included. Patients aged less than 14 years and blood cultures confirming antibiotic sensitive or multi-drug-resistant salmonella typhi were excluded from the study. For blood culture, approximately 18–20 mL of blood was collected aseptically into aerobic and anaerobic culture bottles and processed in the microbiology laboratory. Standard laboratory methods were performed to identify organisms on blood culture. Antibiotic susceptibility testing was performed using disc diffusion, and interpretation was done using Clinical and Laboratory Standards Institute (CLSI) guidance.

Electronic medical records were reviewed for demographics (age, gender), presenting symptoms,

laboratory parameters which included complete blood count antimicrobial regimens, and clinical outcomes.

Long Term Health-related quality of life and post-treatment symptom burden were assessed using the DePaul Symptom Questionnaire–Brief (DSQ-Brief), a validated four-item instrument that evaluates fatigue, post-exertional exhaustion, unrefreshing sleep, and memory difficulties through separate frequency and severity rating.[10] Patients were interviewed on telephone after treatment completion, and were screened for presence of any symptoms of myalgic encephamyelitis/chronic fatigue syndrome using the frequency and severity rating scale present in the DSQ-Brief Questionnaire. Please find the questionnaire attached in the appendix.

Clinical outcomes included need for admission, length of stay among admitted patients, intensive care unit (ICU) admission, development of complications during hospitalization, discharge status, and in-hospital mortality. Complications of interest included anemia, thrombocytopenia, bicytopenia, pancytopenia/, gastrointestinal bleeding, intestinal perforation (including need for surgery), septic encephalopathy, and septic shock.

Analyses were performed using Statistical Package for the Social Sciences, version 29. Continuous variables Age, and days of hospitalization were summarized as median and IQR as they were not normally distributed. Categorical variables were summarized using frequencies and percentages.

Results

A total of 75 patients with established diagnosis of Salmonella XDR typhoid fever were included in the study, 54 (72 %) patients were males. (Figure I). Median age of patients at presentation was 25 years (20-35).

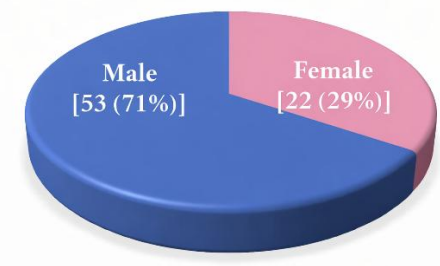


Figure I. Gender Distribution. (n=75)

45 out of 75 patients (60%) required hospitalization, while remaining patients were treated in outpatient (OPD) or emergency departments. Almost all patients had fever as the presenting symptoms, 97.3%, along with other signs and symptoms. Other commonly presented symptoms included 33.3% diarrhea, 30.9% vomiting, 30.7% abdominal pain, 16% cough, 13.3% headache, 12% generalized weakness, 9.3 % decreased appetite and 2.7% constipation. 5 out of 75 (6.7%) patients were drowsy on presentation. (Table I)

Table I: Commonly reported symptoms in enrolled patients. (n=75)

Presenting Symptoms	Percentages
Fever	73 (97.3%)
Abdominal Pain	23 (30.7%)
Diarrhea	25 (33.3%)
Constipation	2 (2.7%)
Vomiting	23 (30.7%)
Decreased Appetite	7 (9.3%)
Cough	12 (16%)
Drowsiness	5 (6.7%)
Headache	10 (13.3%)
Generalized weakness	9 (12%)

Complications included bicytopenia (24%), pancytopenia (5.3%), thrombocytopenia (8%), gastrointestinal bleeding (6.7%), anemia (13.3%), septic encephalopathy (6.6%), and septic shock (2.6%). No in-hospital deaths were recorded. (Table: II) Lab workup also showed that 53.3% of patients had deranged liver enzymes, transaminitis. Radiology workup revealed that among patients presenting with XDR Salmonella Typhi infection 14.6 % has hepatosplenomegaly, 17.3% had hepatomegaly and 5.3 % had hepatomegaly.

Table II: Commonly reported hematological derangements and complications in enrolled patients. (n=75)

Hematological Derangements /Complications	N(%)
Pancytopenia	4 (5.3%)
Bicytopenia	18 (24%)
Thrombocytopenia	6 (8%)
Anemia	10 (13.3%)
Intestinal Perforation	1 (1.3%)
Gastrointestinal Bleeding	5 (6.7%)
Hepatosplenomegaly	11 (14.7%)
Splenomegaly	4 (5.3)
Hepatomegaly	13 (17.3)
CNS manifestations (Encephalopathy)	5 (6.7%)
Shock	2 (2.6%)

Among 75 patients with XDR *Salmonella Typhi* infection, 32 (42.7%) received antibiotic monotherapy, while 40 (53.3%) received combination therapy; 3 (4.0%) patients were lost to follow-up and did not receive treatment. Meropenem was the most frequently prescribed single agent (21.3%), followed by

azithromycin (8.0%) and ertapenem (4.0%). The most common combination regimen was meropenem plus azithromycin (42.7%), followed by ertapenem plus azithromycin (6.7%). Detailed treatment regimens are presented in Table III.

Overall, 45 (60.0%) patients required hospitalization, while 7 (9.3%) required intensive care admission. The median duration of hospitalization was 5 days (IQR: 3–6 days) (Figure II). No mortality was observed during the study period.

Follow-up assessment using the DePaul Symptom Questionnaire–Brief demonstrated that 39 (52.0%) patients reported no symptoms suggestive of persistent fatigue-related impairment. Residual symptoms were uncommon and generally mild, with fatigue, exertional fatigue, unrefreshing sleep, and memory difficulties reported by a small proportion of patients.

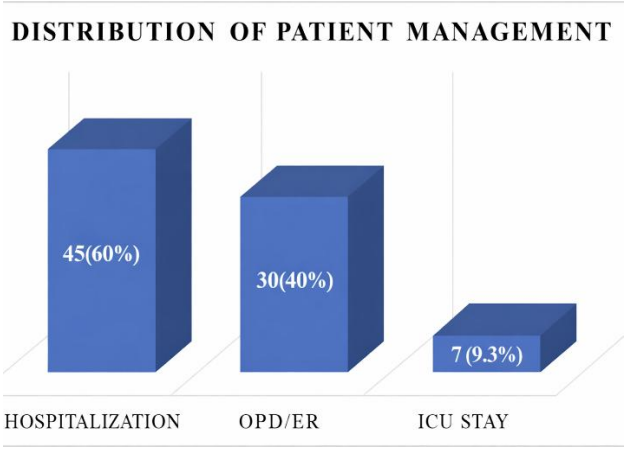


Figure II. Known Outcome of Enrolled Patients. (n=75)

Table: III: Characteristics of enrolled patients. (n = 75)

Category	Characteristics	%
(CLINICAL SPECTRUM) Demographics	Age Median [IQR]	25 (20-35)
	Male	53 (71%)
	Female	22 (29%)
Treatment as per Antibiotic sensitivity	Single Drug	32 (42.7%)
	Dual Drug	40 (53.3%)
	No Treatment due to loss to follow up	3 (4%)
(CLINICAL OUTCOME)	Hospitalization	45(60%)
	OPD/ER	30(40%)
	Discharged after intensive care	7 (9.3%)
	Death	0
	Hospitalization Median [IQR]	5 (3-6)

Discussion

This study evaluated the clinical presentation, antibiotic treatment patterns, clinical outcomes, and post-treatment HRQoL among patients with confirmed XDR Salmonella Typhi infection. The principal findings were a high rate of hospitalization (57.3%), measurable ICU utilization (9.3%), extensive use of carbapenem-based therapy, absence of in-hospital mortality despite clinically significant complications, and generally favourable post-treatment HRQoL.

The high hospitalization rate observed in our study reflects the substantial morbidity associated with XDR typhoid. Similar findings have been reported in recent Pakistani studies, where patients frequently required inpatient care because of prolonged fever, gastrointestinal manifestations, and complications requiring close monitoring.[11,12] Longley et al. likewise demonstrated that severe illness and hospitalization remain common among enteric fever patients across South Asia.[8]

The antibiotic treatment patterns observed in our study are consistent with the current resistance profile of Salmonella Typhi in Pakistan. Resistance to first-line agents, fluoroquinolones, and third-generation cephalosporins has substantially narrowed therapeutic options.[13,14] Consequently, carbapenems and azithromycin have become the cornerstone of treatment for severe XDR disease, and most of our patients received carbapenem-based regimens, often combined with azithromycin, an approach consistent with that reported in a study carried out in Karachi and Hyderabad.[15] Although carbapenems and azithromycin remain effective, emerging resistance threatens the sustainability of this strategy, as reduced azithromycin susceptibility and recent reports of carbapenem-resistant Salmonella Typhi underscore the importance of antimicrobial stewardship and continued surveillance.[16,17,18.]

These findings also carry implications for antimicrobial stewardship. The current dependence on carbapenems for severe XDR typhoid is a major concern, since these agents are otherwise reserved for treatment of multidrug-resistant Gram-negative infections.[19] Therefore routine use of in an endemic setting can increase the risk of carbapenem-resistant Enterobacterales at both patient and institutional levels. Carbapenem resistance in Salmonella Typhi has already been documented in Pakistan A case report has identified sequential isolates of Salmonella typhi acquiring blaNDM-5, resulting in carbapenem resistance and clinical treatment failure that ultimately required last-resort therapy.[18] This indicates that Typhi can acquire carbapenemase genes under sufficient selection pressure. These data support culture-confirmed

diagnosis when feasible, standardized susceptibility testing, and structured intravenous-to-oral step-down pathways when oral options remain active.

Fever was the predominant presenting symptom in our study, consistent with previous reports indicating that fever occurs in nearly all patients presenting with enteric fever.[20] Gastrointestinal symptoms including diarrhea, vomiting, and abdominal pain were also frequently observed, and likely contributed to the need for inpatient management and parenteral therapy. Despite the severity of illness in many patients, no deaths occurred in our study, consistent with contemporary Pakistani studies reporting very low mortality among patients receiving timely diagnosis and effective antimicrobial therapy.[11,12,15] Nevertheless, clinically important complications were observed — cytopenias, anemia, encephalopathy, ICU admission, and surgical intervention for perforation — consistent with the systematic review by Marchello et al., which reported complications in approximately one-quarter of patients with confirmed typhoid fever worldwide.[7]

An important strength of our study is the assessment of post-treatment HRQoL using the DSQ-Brief, a validated screening tool for chronic fatigue syndrome/myalgic encephalomyelitis (ME/CFS).[10] We found that 56.2% of patients had normal HRQoL after treatment, 4.1% reported mild symptoms consistent with chronic fatigue syndrome, and 2.7% had symptoms consistent with severe ME/CFS. Existing typhoid literature has largely focused on acute clinical outcomes, mortality, relapse, and economic burden, while the long-term impact of illness on fatigue and quality of life remains poorly characterized; consequently, data specifically addressing post-treatment HRQoL among patients recovering from XDR Salmonella Typhi are scarce, making direct comparison difficult. The closest available comparison is the Surveillance for Enteric Fever in Asia Project (SEAP), where structured six-week follow-up interviews assessing relapse and morbidity found that most patients with access to appropriate care recovered without severe clinical outcomes[8]; summaries of this follow-up similarly showed that only a minority reported ongoing symptoms or sought additional care, suggesting most patients resume recovery within weeks.[21] Our findings are broadly consistent with this pattern. Prospective Pakistani studies incorporating validated HRQoL tools, time-to-return-to-activity endpoints, and longer follow-up (3–12 months) are needed to determine whether long-term HRQoL is generally preserved and to identify subgroups at risk of prolonged impairment.

Strengths of this study include microbiological confirmation of XDR infection and systematic capture of in-hospital complications and ICU utilization. Limitations include single-centre design, modest sample size, cross-sectional methodology, and absence of standardized severity scoring. Future studies should use the longer-form DSQ instrument to better characterize functional recovery after treatment.

Conclusion

XDR *Salmonella Typhi* infection was associated with substantial healthcare utilization and clinical complications, however no in-hospital deaths occurred. Most patients required treatment with carbapenem-based regimens. On follow-up 52% of patients reported no symptoms suggestive of chronic fatigue syndrome, suggesting generally favorable long-term recovery and health-related quality of life among survivors.

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