

# The Clinical Course of Typhoid Fever And Resistance Pattern of Salmonella Typhi In Patients Admitted To A Tertiary Care Hospital In Pakistan

Jamal Azfar Khan, Muhammad Irfan Khattak, Fazila Sikandar, Muhammad Luqman Satti\*, Kashif Razzaq, Nadia Aziz Ather

Department of Medicine, Pakistan Navy Ship Shifa Hospital Bahria University Medical & Dental College Karachi Pakistan, \*Department of Pathology, Pakistan Navy Ship Shifa Hospital Bahria University Medical & Dental College Karachi Pakistan

## ABSTRACT

**Objective:** To investigate and document the clinical course of typhoid fever and the sensitivity pattern of Salmonella typhi to antibiotics among patients admitted to Pakistan Naval Ship Shifa Hospital.

**Study Design:** Cross-sectional study.

**Place and Duration of Study:** Pakistan Naval Ship Shifa Hospital, from Jul to Dec 2021.

**Methodology:** The patients admitted with typhoid fever to the hospital during the study period were included using consecutive sampling. After getting informed consent, the patients' demographic characteristics, course of the disease, blood culture sensitivity, the treatment administered, the complications that emerged, and the length of their hospital stay were noted.

**Results:** There were 77 patients with culture-proven typhoid fever admitted during the study period. The mean age was 18.6±11.84 years (range 1-55 years). The most frequent presenting complaints were fever, abdominal pain, and vomiting. Additional symptoms included a rash, bodily aches, and weariness. Out of the 77 patients, 76(99%) were extensively drug-resistant (sensitive to Meropenem and Azithromycin only). The complications noted were hepatitis, myocarditis, ascites, pleural effusion, and shock. The mean length of stay in the hospital was 16.56±3.87 days. The typical time gap between commencing culture-specific antibiotics and fever defervescence was 4.03±2.84 days.

**Conclusion:** Almost all (99%) patients admitted with typhoid fever in PNS Shifa are extensively drug-resistant and require a relatively longer hospital stay for management.

**Keywords:** Azithromycin; Drug resistance, Meropenem; Pakistan; Salmonella typhi; Typhoid fever

**How to Cite This Article:** Khan JA, Khattak MI, Sikandar F, Satti ML, Razzaq K, Ather NA. The Clinical Course of Typhoid Fever And Resistance Pattern of Salmonella Typhi In Patients Admitted To A Tertiary Care Hospital In Pakistan. Pak Armed Forces Med J 2024; 74(2): 464-468.

DOI: <https://doi.org/10.51253/pafmj.v74i2.8498>

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

## INTRODUCTION

Typhoid is an infectious disease prevalent in South Asia, including Pakistan.<sup>1</sup> It is spread by a bacterium called Salmonella typhi via contaminated food or water.<sup>2</sup> The disease causes excessive pressure on health resources and causes considerable morbidity and mortality. Typhoid was treated with antibiotics like Ampicillin, Co-trimoxazole and chloramphenicol till the 1970s.<sup>3</sup> Then resistance appeared to these first-line drugs. The disease caused by the resistant strains was called Multi-Drug Resistant (MDR) typhoid, and Fluoroquinolones became the drugs of choice for treating it.<sup>4</sup> However, the Fluoroquinolone-resistant S. typhi appeared, so 3rd generation Cephalosporins were used to treat this disease.<sup>5,6</sup> Recently, in Pakistan, there has emerged an "Extensively Drug-Resistant" (XDR) typhoid caused by S. typhi strains, which are resistant to the first-line antibiotics, fluoroquinolones, as well as 3rd generation cephalosporins.<sup>7,8</sup> The

emergence of XDR typhoid is attributed to injudicious use of antibiotics.

The XDR typhoid epidemic was first reported in Hyderabad, Pakistan. Then, it was reported from Karachi, a metropolitan city and the largest in Pakistan. Karachi is a neighbouring city of Hyderabad. Currently, the highest number of XDR typhoid cases are registered in Karachi. We carried out this study in a tertiary care hospital in Karachi to share our experience of managing Typhoid fever patients in a city where XDR typhoid is routinely reported now.

## METHODOLOGY

The cross-sectional study was conducted at Pakistan Naval Ship (PNS) Shifa Hospital Karachi from July to December 2021, after PNS Shifa Ethical Committee approval (letter number ERC/2021/MED/72). Sample size calculation was difficult because reporting confirmed typhoid cases in Pakistan is "woefully poor and haphazard".<sup>9</sup> The issue is significantly worse with XDR, as there is little accessible data. The instances have been reported exclusively in Pakistan, with a preference for Karachi.

**Correspondence:** Dr Jamal Azfar Khan, Department of Medicine, Pakistan Navy Ship Shifa BUM&DC Karachi Pakistan

Received: 08 Apr 2022, revision received: 05 Aug 2022; accepted: 09 Aug 2022

Only case reports are available from the rest of the world. According to a study, the illness was widespread in Sindh and had a documented frequency of less than 1% in Pakistan.<sup>10</sup>

**Inclusion criteria:** All patients admitted to PNS Shifa Hospital with blood culture-proven typhoid fever were included.

**Exclusion Criteria:** The patients whose clinical diagnosis was enteric fever but could not be confirmed by blood culture, the patients who had culture-proven typhoid fever but got themselves discharged before completion of treatment were excluded.

All patients admitted to PNS Shifa Hospital during the study period with typhoid fever were enrolled in the study (consecutive sampling). The patients who develop fever usually present in the Primary Care Clinic, Medical Outpatient Clinics, or Hospital Emergency Department. They are evaluated, relevant investigations are ordered, and empirical treatment is given. If the fever does not settle or there is some alarming clinical feature or investigation result, the patient is admitted to the hospital. All patients admitted to PNS Shifa Hospital during the study period were informed about the research study, and their consent was obtained to include them in the project. All the patients consented to participate in the study. The participants' medical record was accessed. Their demographic data, history of their illness, and clinical findings were noted. They were followed until the blood culture report was received. The patients whose blood culture isolated *Salmonella typhi*, thus confirming Typhoid fever, were included in the study, while the rest were excluded. These patients were followed throughout their hospital stay to document their treatment, the complications they developed, their time for defervescence, and their duration of stay. Time for defervescence was defined as the number of days from the start of appropriate antibiotics to becoming afebrile for 24 hours or more. Typhoid fever was treated empirically with third-generation Cephalosporin. Later, if necessary, the treatment was changed in accordance with the culture sensitivity report.

The data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 21.00 and MS Excel 2016. Frequency and percentages were calculated for categorical variables and mean and standard deviations were determined for continuous variables.

## RESULTS

Our study involved 77 participants. The mean age of the patients was  $18.6 \pm 11.84$  years. However, the age ranged from 1 to 55 years (Table-I).

**Table-I: Demographic Characteristics of Patients admitted with Typhoid Fever (n=77)**

Characteristics	n (%)
<b>Gender</b>	
Male	58(75.3)
Female	19 24.7)
<b>Age (years)</b>	
1-10	25(32.47)
11-20	14(18.18)
21-30	29(37.66)
31-40	5(6.49)
41-50	3(3.9)
51-60	1(1.3)

The primary symptom of study population was fever. Sixty patients (76 %) developed a fever of 102F (38.9C) or higher, while the rest had a lower-grade fever. The other frequently encountered symptoms were stomach discomfort and vomiting. More than 80% of patients had at least one of these three symptoms. The other symptoms were skin rash, body pains, and fatigue, although their overall contribution to the presentation of typhoid fever symptoms was less than 20%.

The mean hospital stay was  $16.56 \pm 3.87$  days. The minimum hospital stay was ten days, while the longest stay was 35 days. The average length of stay in the hospital for female patients was  $17.89 \pm 5.05$  days, while it was  $16.12 \pm 3.34$  days for male patients.

The antibiotic sensitivity patterns revealed that 76(98.7%) isolates were XDR, susceptible only to Meropenem and Azithromycin. Only one case (1.3%) was infected by MDR *Salmonella typhi*, sensitive to Ceftriaxone (Table-II).

**Table-II: Sensitivity pattern of *Salmonella typhi* (n=77)**

Organism	Sensitivity	n (%)
<i>Salmonella typhi</i>	Meropenem, Azithromycin	76 (98.7)
<i>Salmonella typhi</i>	Meropenem, Azithromycin, Ceftriaxone	1 (1.3)
<i>Salmonella typhi</i>	Pan-resistant	0 (0)

Various complications were also encountered in these patients with varying frequencies. The one patient who had multi-drug-resistant typhoid did not develop any complications.

One patient developed myocarditis and remained admitted for 35 days. The various complications and their frequencies are given in Table-III. The mean

interval between initiating antibiotics and fever defervescence was  $10.84 \pm 3.2$  days. If only culture sensitivity-appropriate antibiotics administration is considered, the mean time for fever defervescence was  $4.03 \pm 2.84$  days. The mean hospital stay was  $16.56 \pm 3.87$  days (range 10-35 days).

**Table-III: Complications of Typhoid Fever in Patients treated at PNS Shifa Hospital (n=77)**

Complications	n (%)
Hepatitis	5 (6.49)
Myocarditis	1 (1.3)
Ascites	1 (1.3)
Pleural effusion	1 (1.3)
Shock	1 (1.3)

## DISCUSSION

The first city where an outbreak of XDR typhoid occurred in the world was Hyderabad, Pakistan. Fatima *et al.* conducted a study in which they reviewed the medical records of typhoid cases in 5 hospitals in Hyderabad.<sup>11</sup> They found 66% of typhoid cases to be XDR. As per Akram *et al.*, the disease burden of XDR typhoid has been 64.4% (5274 out of 8188 typhoid cases) from 2016 to 2018 in Sindh, which Hyderabad and Karachi are part of.<sup>12</sup> There was a study carried out in our setup in 2019 in which the drug resistance of Salmonella typhi isolates was documented.<sup>13</sup> The researchers found out that 48% of the isolates were XDR. However, we have recorded the frequency of XDR typhoid to be 99% in our patients in 2021. XDR typhoid is also being reported in other parts of the country. Jalal *et al.* conducted a study in Lahore that analyzed the sensitivity pattern of S. typhi.<sup>14</sup> They also observed an alarming rise in XDR typhoid cases, being 13 out of 29 in 2018 and 58 out of 69 in the first four months of 2019. This is an alarming situation. Our research demonstrates the illness burden and rising issue of XDR in developing countries such as Pakistan. Karachi is especially hard hit in Pakistan. The unplanned exponential population growth in Karachi and its crumbling infrastructure might be responsible for the alarming rise of XDR typhoid in this city. Our study findings not only verify the earlier published research about XDR typhoid but also emphasize the necessity for novel approaches since resistance is ubiquitous and rising exponentially.

The time taken for defervescence in XDR typhoid was also documented in our research. After receiving the bacterial culture sensitivity report, it was four days after starting the appropriate antibiotics. This documented time for defervescence was the same as

the time documented in the study conducted in 2019 by Hussain *et al.* in the same hospital.<sup>13</sup> In another study, Qureshi *et al.* reported that the average time to defervescence was around seven days.<sup>15</sup> Hence, it can be assumed that varied strains of Salmonella typhi may show varied responses to antibiotics.

XDR typhoid is susceptible to Azithromycin and Carbapenems (Meropenem).<sup>16</sup> There are other antibiotic choices, but their experience treating typhoid fever is limited.<sup>17</sup> Recently, Azithromycin has been used extensively to treat COVID-19 patients. This may result in the development of bacteria resistant to Azithromycin. There are already reports of Azithromycin resistance in typhoid strains. If widespread resistance to Azithromycin ensues, the only treatment options left will be injectable. This will create a very difficult situation in countries where typhoid is endemic, as all typhoid patients will have to be treated indoors.<sup>18</sup>

The combination of Meropenem and Azithromycin has emerged as the most important weapon against XDR typhoid fever. The time to defervescence in administering the combination of Meropenem and Azithromycin has been shown earlier to be shorter than that of Azithromycin alone.<sup>15</sup> They only mentioned hepatobiliary complications and only made a passing reference to systemic complications. They stated that 20% of patients with non-resistant typhoid, 29% with MDR, and 18% with XDR typhoid developed acute hepatitis. We carried out our research to include all the complications. In our study population, 71 out of 77 patients had no complications. The remaining 6(7.79%) patients developed complications, including hepatitis, pleural effusion, ascites, myocarditis and shock. However, we did not encounter even a single case with encephalopathy. Myocarditis was a serious complication, and we had to treat that patient for five weeks. The other patients with complications did not have a longer than usual stay in the hospital.

Our study was one of the few in South Asia that connected cultural sensitivity patterns and the clinical course of the disease. Most of the past writings needed this element. We also researched complications of XDR typhoid, which many yet-to-be authors had to explore. Another aspect of our study was that we included all ages in our investigation. Previous literature was mostly limited to adults-only or pediatric-only populations.<sup>19</sup> Based on solid clinical evidence, this data is anticipated to result in a

complete knowledge of disease behaviour and more effective management methods.

We could have created another group of classical enteric fever patients and compared the two cohorts for clinical parameters and sequelae. However, we did not do this as we had only one patient who did not have XDR typhoid. This study can be a launching point for further comparative studies. Long-term follow-up could have offered more important clinical information, but it was out of the scope of our investigation. Our data corroborated prior research on typhoid in general and XDR in specific. Additionally, it raised awareness of changes in the clinical spectrum of disease, including an increased rate of complications, which were not previously recorded.

### CONCLUSION

XDR Typhoid has been spreading at an alarming rate. We must implement antimicrobial stewardship nationwide to curb excessive antibiotic usage and halt the spread of pan-resistant Salmonella typhi. Second, vaccination campaigns and emergency improvements to the country's sanitary conditions may help to contain the spread of this highly resistant bacterium in the population.

**Conflict of Interest:** None.

### Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

JAK & MIK: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

FS & MLS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

KR & NAA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

### REFERENCES

- Qamar FN, Azmatullah A, Kazi AM, Khan E, Zaidi AK. A three-year review of antimicrobial resistance of Salmonella enterica serovars Typhi and Paratyphi A in Pakistan. *J Infect Dev Ctries* 2014; 8(8): 981-986. <https://doi.org/10.3855/jidc.3817>
- WHO. Typhoid; 2018 [Internet]. Available at: <https://www.who.int/news-room/fact-sheets/detail/typhoid> [Accessed on September 6, 2021]
- Saeed M, Rasool MH, Rasheed F, Saqalein M, Nisar MA, Imran AA, et al. Extended-spectrum beta-lactamases producing extensively drug-resistant Salmonella Typhi in Punjab, Pakistan. *J Infect Dev Ctries* 2020; 14(2): 169-176. <https://doi.org/10.3855/jidc.12049>
- Munir T, Lodhi M, Ansari JK, Andleeb S, Ahmed M. Extended spectrum beta lactamase producing cephalosporin resistant Salmonella Typhi, reported from Rawalpindi, Pakistan. *J Pak Med Assoc* 2016; 66(8): 1035-1036.
- Cuyppers WL, Jacobs J, Wong V, Klemm EJ, Deborggraeve S, Van Puyvelde S. Fluoroquinolone resistance in Salmonella: insights by whole-genome sequencing. *Microb Genom* 2018 ; 4(7): e000195. <https://doi.org/10.1099/mgen.0.000195>
- Britto CD, Wong VK, Dougan G, Pollard AJ. A systematic review of antimicrobial resistance in Salmonella enterica serovar Typhi, the etiological agent of typhoid. *PLoS Negl Trop Dis* 2018; 12(10): e0006779. <https://doi.org/10.1371/journal.pntd.0006779>
- Khan EA. XDR Typhoid: The Problem And Its Solution. *J Ayub Med Coll Abbottabad* 2019; 31(2): 139-140.
- Klemm EJ, Shakoor S, Page AJ, Qamar FN, Judge K, Saeed DK, et al. Emergence of an Extensively Drug-Resistant Salmonella enterica Serovar Typhi Clone Harboring a Promiscuous Plasmid Encoding Resistance to Fluoroquinolones and Third-Generation Cephalosporins. *mBio* 2018 ; 9(1): e00105-118. <https://doi.org/10.1128/mBio.00105-18>
- Haqqi A, Khurram M, Din MSU, Aftab MN, Ali M, Ahmed H, et al. COVID-19 and Salmonella Typhi co-epidemics in Pakistan: A real problem. *J Med Virol* 2021; 93(1): 184-186. <https://doi.org/10.1002/jmv.26293>
- Butt MH, Saleem A, Javed SO, Ullah I, Rehman MU, Islam N, et al. Rising XDR-Typhoid Fever Cases in Pakistan: Are We Heading Back to the Pre-antibiotic Era? *Front Public Health* 2021; 9: 794868. <https://doi.org/10.3389/fpubh.2021.794868>
- Fatima M, Kumar S, Hussain M, Memon NM, Vighio A, Syed MA, et al. Morbidity and Mortality Associated with Typhoid Fever Among Hospitalized Patients in Hyderabad District, Pakistan, 2017-2018: Retrospective Record Review. *JMIR Public Health Surveill* 2021; 7(5): e27268. <https://doi.org/10.2196/27268>
- Akram J, Khan AS, Khan HA, Gilani SA, Akram SJ, Ahmad FJ, et al. Extensively Drug-Resistant (XDR) Typhoid: Evolution, Prevention, and Its Management. *Biomed Res Int* 2020;2020:6432580. <https://doi.org/10.1155/2020/6432580>
- Hussain A, Satti L, Hanif F, Zehra NM, Nadeem S, Bangash TM, et al. Typhoidal Salmonella strains in Pakistan: an impending threat of extensively drug-resistant Salmonella Typhi. *Eur J Clin Microbiol Infect Dis* 2019; 38(11): 2145-2149. <https://doi.org/10.1007/s10096-019-03658-0>
- Jalal K, Khan K, Hassam M, Abbas MN, Uddin R, Khusro A, et al. Identification of a Novel Therapeutic Target against XDR Salmonella Typhi H58 Using Genomics Driven Approach Followed Up by Natural Products Virtual Screening. *Microorganisms* 2021 ; 9(12): 2512. <https://doi.org/10.3390/microorganisms9122512>
- Qureshi S, Naveed AB, Yousafzai MT, Ahmad K, Ansari S, Lohana H, et al. Response of extensively drug resistant Salmonella Typhi to treatment with meropenem and azithromycin, in Pakistan. *PLoS Negl Trop Dis* 2020; 14(10): e0008682. <https://doi.org/10.1371/journal.pntd.0008682>
- Basnyat B, Qamar FN, Rupali P, Ahmed T, Parry CM. Enteric fever. *BMJ* 2021; 372: n437. <https://doi.org/10.1136/bmj.n437>
- Parry CM, Ribeiro I, Walia K, Rupali P, Baker S, Basnyat B. Multidrug resistant enteric fever in South Asia: unmet medical needs and opportunities. *BMJ* 2019; 364: k5322. <https://doi.org/10.1136/bmj.k5322>

## Resistance Pattern of Salmonella Typhi

18. Mansoor H, Ahmed K, Fida S, Uzair M, Asghar A, Iqbal J. Gastrointestinal and Hepatobiliary Complications of Extensively Drug-Resistant Typhoid at a Tertiary Care Hospital in Pakistan. *Cureus* 2020; 12(10): e11055. <https://doi.org/10.7759/cureus.11055>
  19. Iqbal J, Dehraj IF, Carey ME, Dyson ZA, Garrett D, Seidman JC, et al. A Race against Time: Reduced Azithromycin Susceptibility in *Salmonella enterica* Serovar Typhi in Pakistan. *mSphere* 2020 ; 5(4): e00215-220. <https://doi.org/10.1128/mSphere.00215-20>
-