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# Drug Resistance Pattern of Salmonella Typhi in Patients Suffering from Enteric Fever - Experience from Tertiary Care Hospital of Peshawar.

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## ABSTRACT

**Background:** Enteric fever is one of the most common infections in Southeast Asia. Over the last decade, increasing drug resistance against salmonella has been documented.
**Objectives:** This study aimed to determine the drug resistance pattern of salmonella typhi at a tertiary care hospital in Peshawar.
**Material and Methods:** A cross-sectional observational study was conducted at Rehman Medical Institute, Peshawar over one year, from June 2022 to June 2023. All the patients who had culture-proven typhoid were included in the study. Antibiotic sensitivity was determined against conventional and latest antibiotics used for typhoid fever. Data was analyzed through SPSS24.
**Results:** Out of 284 patients, 60.6% (n=172) were males and the mean age was 24.07±11.65 years. Only 11.3% (n=32) had non-resistant typhoid fever. Extended Spectrum Beta lactamase resistance was noted in 43.3 % (n=123), Extensive drug resistance (XDR) in 37.3% (n=106), and multidrug resistance (MDR) in 8.1% (n=23) of total cases. Salmonella typhi was sensitive to Azithromycin and Meropenem in 100% and 99.6% of cases respectively. Its sensitivity to cotrimoxazole, Chloramphenicol, and Ampicillin was 48.9%, 17.6%, and 7.70% respectively. Only 2.5% of typhoid cases were sensitive to Ciprofloxacin.
**Conclusion:** Drug-resistant typhoid has shown a rising trend. Conventional antibiotic therapy has developed significant resistance. Azithromycin and Meropenem have shown good sensitivity to Salmonella.
**Keywords**: Drug Resistance, Sensitivity, Typhoid

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## INTRODUCTION

Enteric fever, also known as typhoid fever is caused by Salmonella Typhi and ParatyphiA, B, or C gram-negative rod. It is one of the most common infections in lower-middle-income countries, especially in South East Asia.[1] According to estimates from the Global Burden of Disease Study carried out in 2017, 14 million people suffered from typhoid fever of which almost 136000 died.[2] Countries Pakistan, India, and Bangladesh report a high prevalence of typhoid fever cases. Pakistan is on the top list harboring 493.5 per 100,000 typhoid cases in the year 2018.[3]

The emergence of drug-resistant typhoid in Pakistan has made it more prominent. In 2016, 1st case of extensive drug-resistant (XDR) typhoid was notified in Hyderabad, thereafter a sharp rise in drug-resistant typhoid cases was seen not only in Sindh but also in the whole of Pakistan.[3] This new strain has made typhoid fever difficult to treat. The ongoing drug-resistant pattern has decreased the utility of Fluoroquinolones and Third-generation Cephalosporins in the treatment of typhoid fever. They have been the mainstay of treatment even in complicated typhoid fever a decade ago. Ultimately we are stepping towards stronger and broad-spectrum antimicrobials like Carbapenems and Azithromycin.[4]

Antibiotic resistance is a huge problem in the case of Salmonella. Based on antibiotic resistance, WHO has classified enteric fever as non-resistant typhoid (NRT), multidrug-resistant (MDR), and extensively drug-resistant (XDR).[5] In the past, the first line of chosen drugs for typhoid was Ampicillin, Chloramphenicol and Trimethoprim Sulfamethoxazole. MDR Typhi strains are resistant to these drugs. Second-line antibiotic (fluoroquinolones) resistance has also been reported frequently. Ceftriaxone, a third-generation cephalosporin is used to treat typhoid fever when other options are rendered fruitless.[6] If conventional antibiotics are rendered it will lead to the treatment of suspected Typhoid Fever difficult. Currently, the treatment of enteric fever relies primarily on Azithromycin due to its high intracellular concentration and good clinical response. It is the only highly effective oral antibiotic left for the treatment of Enteric fever.[4] The unjudicial use of Azithromycin in respiratory symptoms, especially in the context of Coronavirus infection has posed a serious concern of its resistance shortly.[4] Moreover in typhoid with complications, gastrointestinal

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symptoms, oral bioavailability, and tolerance hinder its effect. We are left with the last possible intravenous antibiotics i.e. Carbapenems.

The present study was planned to see the prevailing pattern of drug resistance in the recently isolated strains of S. Typhi. The study aimed to determine the drug resistance pattern of salmonella and to determine the sensitivity of salmonella to individual antibiotics.

## MATERIAL AND METHODS

This cross-sectional observational study was conducted in Rehman Medical Institute, Peshawar over One year, from 20th June 2022 to 20th June 2023.

The study population was selected by non-probability consecutive sampling technique. The sample size was calculated with an Open Epi sample size calculator by taking the prevalence of drug-resistant Enteric fever as 66 %, keeping a CI of 95%, turning out 284 subjects.[7] Patients who had salmonella-positive cultures were included. Patients who already had taken antibiotics or suffering from any other concurrent infections were excluded.

### Data Collection

The research project was carried out in the RMI Department of Medicine. Ethical approval was taken from RMI-REC under diary number RMI/RMI-REC/Approval/131 on 10th June 2022. Written informed consent was taken from study participants. Patients admitted with Enteric fever were considered for the study. Blood cultures were sent before the administration of antibiotics and those with salmonella typhi-positive cultures were included in the study.

The patient's demographic details were noted. On Admission CBC, CRP and Blood culture were sent to RMI labortaory. Blood was inoculated in 40-45ml brain-heart infusion broth using a BactT automated blood culture machine. It was Incubated at 37 $^{0}$C. The cultured salmonella typhi isolates were checked for drug susceptibility by the Kirby-Bauer disc diffusion method. Mueller-Hinton agar was used for drug susceptibility. The susceptibility of the organism was checked against Meropenem (10 µg), Ampicillin (10 µg), Ceftriaxone (30 µg), Azithromycin (15 µg), Co-trimoxazole (1.25/23.75 µg), Ciprofloxacin (5 µg) and Chloramphenicol (30 µg). The Clinical and Laboratory Standards Institutes (CLSI) guideline[7] were followed to categorize drug-resistant status typhoid fever. All the information was collected on pre-defined pro forma.

The resistant pattern of typhoid was defined as per classification issued by the Medical Microbiology and Infectious Disease Society of Pakistan (MMIDSP) Typhoid fever was categorized into NRT if it is sensitive to conventional antibiotics for typhoid fever including first-line drugs, fluoroquinolones, and third-generation cephalosporins. MDR was defined as strains resistant to first-line drugs, sensitive to third-generation cephalosporins, with or without resistance to second-line drugs. XDR was resistant to all first, second-line, and 3rd generation cephalosporin antibiotics. ESBL typhoid fever is Typhoid fever caused by S. Typhi strains which are resistant to third-generation cephalosporins but sensitive to any one of the first-line drugs like Chloramphenicol, Cotrimoxazole or second-line drugs.

### Data Analysis

After data collection, data was entered into SPSS 24. The results were analyzed, and frequencies and percentages were calculated for every antibiotic's sensitivity/resistance. Typhoid fever was classified as NRT, MDR, XDR, and ESBL strains. The data was presented in the form of tables and charts. The Chi-square test was applied to see the Factors (age, gender, on-admission CRP, TLC, Platelet) associated with resistance. A p-value of <0.05 was taken as statistically significant.

## RESULTS

A total of 284 patients were included in the study in which there were 172 males (60.6%) and 112 females (39.4%) and the average age calculated was 24.07±11.65 years. Our sample comprised the population from all over KPK, the majority were from Peshawar 212(74.6%), and then the remaining from other parts of the district i.e. Kohat 32(11.3%), Malakand 25(8.8%), Mardan 9(3.2%), Bannu 4(1.5%) and D.I Khan 2(0.7%).

We recorded the arrival TLC, CRP, and platelet counts of our patients under study. The mean TLC count on the arrival of the patients was 7.37±3.70 cells/cmm. The mean CRP on arrival was 10.95±10.91 mg/dl and the platelet count was 202.58±110.971 cells/cmm. A total of 24 (8.7%)

patients had leukopenia and 68(24.2%) had thrombocytopenia.

A resistance pattern of Salmonella typhi strains against antibiotics was recorded. Only 32 (11.3%) patients had NRT, rest 88.7% suffered from resistant typhoid. ESBL was the most common resistant pattern making up 123 (43.3 %) cases followed by XDR 106 (37.3%). MDR cases constitute 23 (8.1%) of total cases.

Talking about individual drug sensitivity, salmonella was sensitive to Azithromycin and Meropenem in 284 (100%) and 283 (99.6%) cases respectively. Cotrimoxazole was also effective in almost half of the patients with 139 (48.9%) sensitivity. On the other hand, 3rd generation cephalosporin which has been frequently used in the treatment of enteric fever, only 55(19.4%) of our salmonella strains were sensitive to it. Its sensitivity approaches the oldest drug treatment for typhoid i.e. Chloramphenicol 50 (17.60%). Salmonella was sensitive to ampicillin only in 22 (7.70%) cases. The minimum sensitivity was recorded against 2nd generation anti typhoid drug Ciprofloxacin i.e. 7 (2.50%) (Figure 01).

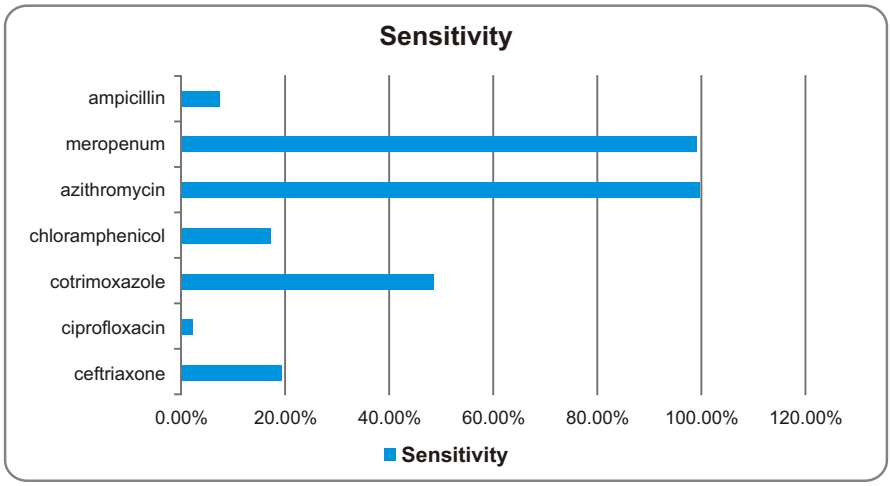



**Figure 01. Drug sensitivity pattern**

We individually studied the different types of enteric fever resistance patterns and the factors associated with them. The association was seen with age, arrival total leukocyte counts, platelet counts, and their CRPs (table 01). Resistant typhoid was recorded more in younger people(P value 0.001. No statistically significant association of resistant species was found with the arrival of TLC, PLT, and CRP.

**Table 01. Factors associated with resistance pattern**

| Factors | NRT | MDR | XDR | ESBL | P-value |
|---|---|---|---|---|---|
| Age (mean±SD) | 30.5±14.37 | 25.91±9.75 | 22.83±11.48 | 23.11±10.93 | 0.001 |
| Arrival TLC | 7.82±4.70 | 6.79±4.96 | 7.73±3.58 | 7.05±3.24 | 0.46 |
| Arrival PLT | 181.87±101.65 | 156.04±102.29 | 206.92±115.94 | 212.79±108.79 | 0.19 |
| Arrival CRP | 8.58±10.73 | 9.94±10.92 | 11.18±9.58 | 11.57±12.04 | 0.27 |

Overall resistant cases were more common in females as compared to males, 95.5% (n=107) females suffered from resistant typhoid as compared to 84.3% (n= 145) males (P value 0.003).

The detail of the wise resistant pattern is narrated in Figure 03.

ESBL typhoid was noted in Peshawar (48.1%), Bannu (50%), Mardan (44.4%), and DI Khan(100%). XDR pattern was observed the most in patients coming from the Malakand(56%)and Kohat( 59.4%) divisions. However, no statistically significant relation in terms of the area was found with a resistant pattern of typhoid. The details can be seen in Figure 02.

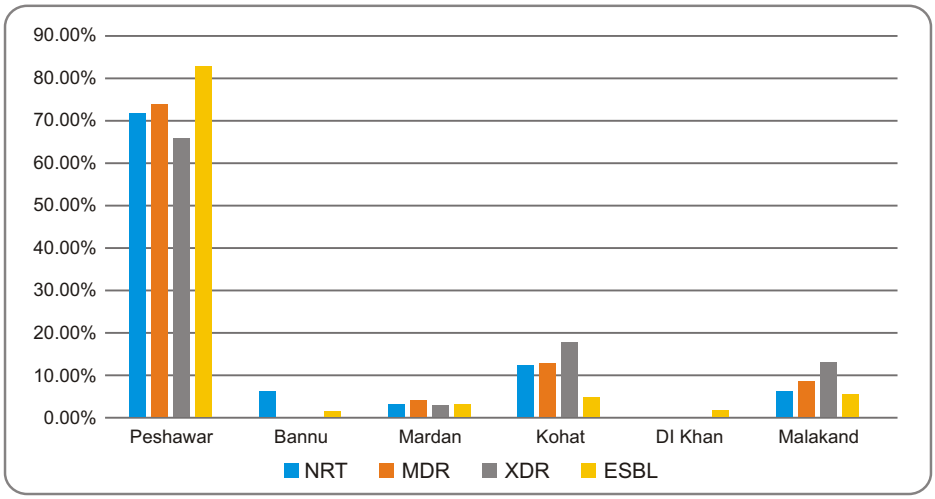



**Figure 02. Area-wise Resistance pattern**

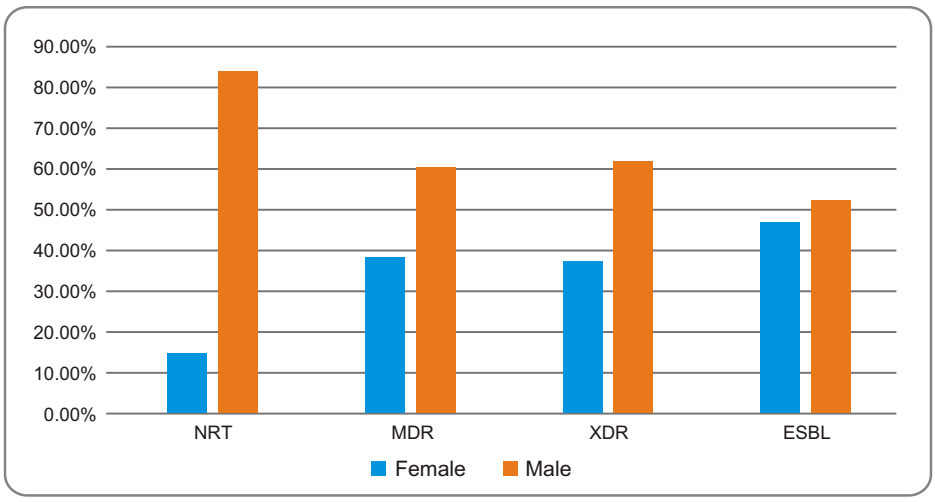



**Figure 03. Gender-wise resistance pattern**

## DISCUSSION

Our study participants were mostly young males which is consistent with the universal trend of typhoid fever due to increased exposure of young males to outside. Most patients were from Peshawar due to easy accessibility to the RMI.

Raised CRP in the presence of normal or low normal TLC was observed in our patients at admission which is consistent with laboratory features of Enteric fever.[8] In our study majority of patients had normal TLC values and only 8.7% exhibited leukopenia. It is consistent with a study carried out in 3 countries that showed 9.2 % of patients having typhoid fever had leukopenia, however in the Pakistani population the trend was more as 13.1 % of patients developed leukopenia in the course of enteric fever.[8] The difference in this regard may be due to the different phases of disease at which TLC was checked.

Thrombocytopenia is reported in up to 10% to 15% of cases of enteric fever. Its etiology is multifactorial and can vary with severity.[8,9] Almost a quarter of our patients (24.2%) had thrombocytopenia. Previous studies have not given such a significant percentage of thrombocytopenia in enteric fever. Aiemjoy et al, described thrombocytopenia in only 8.9%, while 14.5 % of the Pakistani population was reported to have thrombocytopenia in the same study.[8] A study by Malik et al. from Malaysia reported thrombocytopenia in 26% of patients with a diagnosis of enteric fever.[10] The difference in this regard may be due to host demographic features as literature has mentioned young age and male gender are more prone to develop thrombocytopenia.[11] Moreover the early presentation to the hospital and non severe illness may mask the true picture.

There is a sharp rise in resistance against salmonella. NRT cases have declined from 100% in 2009 to 44% in 2019, whereas drug-resistant typhoid cases have sharply increased with 16%of MDR and 40% of XDR.[12]

National Institute of Health (NIH) Islamabad, has reported 14,360 XDR enteric fever cases only in Karachi from 2017 to 2021.[13] A study from Lahore carried out on 57 salmonella-positive cultures described 68.42 % XDR, 12.28% MDR, and Only 17.54 % NRT salmonella.[14] Talking about our province KPK, data from 2015 to 2018 showed that of a total of 598 positive cultures, 62.7% were MDR, 5.01% were XDR and only 33% was NRT.[15]On comparison, our study describes an alarmingly decreasing trend in NRT to 11.3% and increasing trend of XDR i.e. 37.3%. However, the trend of MDR is showing a decline due to emerging ESBL strains and their detection in our data. In our study, ESBL was the most common resistance pattern i.e. 43.3%. The increasing frequency of ESBL strain is also noted by a Nigerian study describing 40.7% ESBL isolates.[16] This discrepancy in the results can be explained based on different regional strains of S. Typhi, different antibiotic trends, and ongoing mutation in salmonella strains. However, the Increasing frequency of ESBL calls for recycling older conventional medicine in the treatment of typhoid.

The rising trend in drug-resistant cases of typhoid fever is a point of concern not only for our part of the world but it is also a threat to international outbreaks. In this study, only 19.4 % of isolates were sensitive to Ceftriaxone, it is far less than a study by Ahmad et al, which showed 38.7% sensitivity to ceftriaxone.[17] A study from Lahore Pakistan described that 95.6% of salmonella were sensitive to ceftriaxone.[18] Studies from Central Asia and Pakistan have demonstrated up to 100% sensitivity to Ceftriaxone.[19,20]

In studies from Nigeria and Nepal 66.6% and 72.2% of patients were sensitive to Ciprofloxacin respectively.[16,21] Umair and Siddiqui from Pakistan described 37.3% sensitivity for Ciprofloxacin.[18] Our study describes a surprisingly higher rate of resistance while only 2.50% were sensitive to Ciprofloxacin, our results are consistent with two studies from India that reported only 3.1% and 2.1% ciprofloxacin sensitivity to salmonella respectively.[16,22]

Chloramphenicol, the use of it has been discontinued for its known serious side effects like bone marrow suppression. Our study has shown significantly less sensitivity to this drug as supported by another study from Pakistan.[17] On the other hand a study from Karachi described 41% sensitivity to this drug. Few national and international studies have shown 95-100% chloramphenicol sensitivity against salmonella.[19,21] This increasing sensitivity may be due to prolonged discontinuation of this drug from clinical practice.

Ampicillin was only sensitive in 7.70% of patients in our study which is far less than other studies conducted at national and international levels. Umair et al, and Shah et al, from Pakistan, reported ampicillin-sensitive salmonella in 57.6% and 54% of cases respectively[18,19] A study from Nepal showed that 100% pediatric population was sensitive to ampicillin and 97.3 % in the Indian study.[21,22]

Cotrimoxazole was surprisingly sensitive to almost half of the strains in our study. It is contrary to two other studies from Pakistan and Nigeria reporting 29% and 7% sensitivity for the said drug.[11,18] On the other hand Balaji et al documented 96.4% sensitivity towards this drug.[22] This increasing sensitivity trend towards conventional drug therapy is bringing us towards their use. However their in vivo efficacy and use in complicated diseases is still questionable.

Nowadays, Azithromycin is the mainstay of oral antibiotic treatment for typhoid, our study showed 100% sensitivity but a study by Ahmad et al described 1 case resistant to azithromycin.[17] Meropenem, a broad-spectrum antibiotic, is being used nowadays as the only choice for complicated typhoid fever, but unfortunately, we have documented 1 case resistant to even Carbapenem. It has not been mentioned in the literature before.[17] The emerging resistance against Azithromycin and Meropenem will lead us to the era of pan-resistant typhoid fever. However, the susceptibility of organisms towards older 1st generation drugs may be a hope in the future.

The diversity of results speaks for the regional strain resistance, growing resistant pattern, and unjudicial prescription of specific antibiotics in certain areas. Furthermore, certain host-related factors like age, gender, and previous exposure to

antibiotic therapy may play a role in this discrepancy. The laboratory methods used to check antibiotic susceptibility, lack of surveillance of antibiotic prescription, and availability of over-the-counter antibiotics are a few important determinants of antibiotic resistance patterns in certain regions.

### Limitations

It is a single Centre study so the results cannot be generalized. We haven't focused on clinical features and serial changes in laboratory parameters in. Furthermore, we used the disk diffusion method or Azithromycin sensitivity in place of the ideal E strip method

## CONCLUSION

Drug-resistant typhoid seems to be quite common. Quinolones and cephalosporins which were considered to be the main pillars of therapy, have been knocked out due to resistance. Higher sensitivity than some other studies reviewed, to Cotrimoxazole is noted in our study. Currently, Azithromycin and Meropenem are showing promising results for the treatment of drug-resistant typhoid fever.

### Recommendations

Proper sanitation, safe water supply, and mass vaccination are the only solutions to cope with the increasing burden of disease. Furthermore, the unjudicial use of antibiotics should be prohibited to control ongoing drug resistance. Further research is needed to explore newer antibiotics for ongoing drug-resistant salmonella strains.

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### Ethical Consideration

This study was approved by the ethical board of Rehman Medical Institute, Peshawar, Pakistan.

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### Conflicts of interest

Authors declare no conflicts of interest.

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**DATA SHARING STATEMENT:** The data that support the findings of this study are available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions.

**AUTHOR'S CONTRIBUTION**
The following authors full fill authorship criteria as per ICMJE guidelines;

**Qayyum W, Yousafzai ZA:** Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
**Afridi M, Khan MF:** Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.
**Kundi RA:** Analysis and interpretation of data, drafting the manuscript, final approval, agreed to be accountable for all the work.
**Iqbal B:** Analysis and interpretation of data, critical revision,final approval, agreed to be accountable for all the work.

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