

Typhoid Salmonella Strains in Pakistan Posing a Potential Risk to Drug-Resistant

Drug Resistant
Salmonella
Typhi Strains
in Pakistan

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ABSTRACT

Objective: The objective of this cross sectional research study will be to determine the proportion of total and drug resistant Salmonella Typhi strains in 100 patients admitted in hospitals with typhoid fever in Pakistan. **Study Design:** A Cross sectional study .

Place and Duration of Study: This study was conducted at the Department of Pediatrics Medicine, University of Medical and Health Sciences for Women Nawabshah Sindh. From 1st Jan 2022 to 30th September 2022.

Methods: A descriptive cross-sectional design was adopted for the study whereby one hundred patients diagnosed with typhoid fever were included in the study. Blood specimen were obtained and inoculated into culture media to isolate Salmonella Typhi. As typing to determine drug resistance, antibiotic susceptibility testing was done. Descriptive statistics was conducted on SPSS version 24.0 and the level of significance used in analysis was $p < 0.05$.

Results: Of the 100 patients, 60 % of the patients were positive for drug resistant S. Typhi. The overall mean age of the patients enrolled in the study was thirty one point three years ($SD \pm 6.5$). MDR was observed in this study to be 45%, with recipe for ciprofloxacin at $p = 0.03$. Total duration of stay also differed significantly in drug resistant bacteria patients who took longer time to recover than patients with non-resistant bacteria (mean= 14.5 days, $p < 0.05$).

Conclusion: The study shows a worrisome trend of multiresistant S. Typhi in Pakistan, based on its results. This demands for more emphasis on the public health measures to prevent or reduce the use of antibiotics as well as enhance sanitization in addition to emergence of new therapeutic approaches against the strains.

Key Words: Endemic infectious disease, Typhoid, Salmonella Typhi, drug resistance, Pakistan.

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INTRODUCTION

Typhoid fever is a serious fever that develops from the Salmonella enterica serovar Typhi (S. Typhi), transmitted through the contaminated food or water. Typhoid fever is now prevalent in most LMICs, most especially in South Asia due to insufficient access to both clean water and sanitation facilities. Based on the WHO estimate, about 11–20 million people develop typhoid fever annually, and about 1% of them die if their illness is not treated^[1].

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In Pakistan the disease burden of typhoid fever is substantially high because of its environment and social demographic characteristics^[2] Further, the typhoid fever is more common in urban and peri urban environments where Sewerage infrastructure is lame. In the last few decades, multidrug resistance in S. Typhi including extended-spectrum beta-lactamase (ESBL) producing isolates has received increasing attention worldwide, despite initially being reported from Pakistan only. These strains show resistance to first-line antibiotics such as chloramphenicol, ampicillin and trimethoprim sulphamethoxazole^[3]. An emerging risk posed by extensively drug-resistant (XDR) S. Typhi, which is resistant to most antibiotics, including fluoroquinolones and 3rd generation cephalosporins, has been identified in Pakistan since 2016^[4]. The appearance of XDR strains reduces the number of potential treatments and raises the likelihood of severe disease, complications, and death. Consequently, health care providers are worried by the scarcity of proper antibiotics in controlling bacterial infections^[5]. Prior research points out that multidrug resistant S. Typhi strains have rapidly emerged in Pakistan and the factors include lack of prescription gateway for antibiotic, inefficient

infection control measures, and hygienically unsound environment^[6]. A cross-sectional study done in Karachi during 2013 showed that more than 90% of *S. Typhi* isolates were having resistance to at least one group of antibiotics and XDR was observed in 27% of the strains^[7]. Overall, our data support the need for enhanced monitoring, rational use of antibiotics, and successful community mobilisation to contain emerging resistant clones. Moreover, unusual manifestations of typhoid fever make clinical treatments additionally challenging because resistance to quinolones, including ciprofloxacin, has spread widely, which was one of the most effective treatments for both adult and pediatric patients. Another developing problem is decreasing sensitivity to more recent drugs such as azithromycin^[8]. Lately, the burden of disease has concerned public health policies and the World Health Organisation, although the development of typhoid conjugate vaccine (TCV) has been an achievement the spreading of drug-resistant strains is persistent^[9]. This study is to determine the proportion of *S. Typhi* isolates that require the use of third-generation cephalosporin or more in patients with typhoid fever in Pakistan and the level of resistance among the isolates to the commonly used antibiotics. As XDR typhoid becomes more frequent, it becomes imperative to identify the resistance profile in such strains to help guide the recommended treatment regimens and control interventions in high endemic areas.

METHODS

One hundred patients, who met the case definition of confirmed typhoid fever by blood culture, were recruited in the study. The inclusion criteria included patients of any age and gender. Susceptibility tests of the isolated *S. Typhi* strains were performed by disk diffusion method on Mueller Hinton agar, as per CLSI recommendations. The antibiotics used in this study were ciprofloxacin, azithromycin, ceftriaxone and chloramphenicol.

Data Collection: Information on the patient’s characteristics, signs and symptoms at presentation and antibiotic resistance was obtained by questionnaire. Blood samples were taken for *S. Typhi* isolated strains, antibiotic susceptibility test was carried out using the disk diffusion method.

Statistical Analysis: Descriptive statistics analysis was done using the SPSS version 24.0 for windows. For the purpose of description of patient’s characteristics quantitative data was used and chi square was used to determine whether drug resistance has relationship with clinical end point or not. Statistical significance was determined at p-value of less than 0.05.

RESULTS

According to their results, 60 percent of the 100 patients with confirmed Typhoid fever were positive to

have drug resistant *S. Typhi* strains resistant. The mean patient age was 28.3 years (SD ± 6.5) and 55 percent of the sample being males. Out of the DR isolates, 45% were MDR and 15% XDR with resistance to ciprofloxacin and 15% XDR with resistance to ciprofloxacin and ceftriaxone. Resistance to ciprofloxacin was 2 times higher and the difference was statistically significant (p = 0.03). XDR group of patients reported a longer duration of illness, mean time of 21 days (SD ± 4.2) than patients with non-resistant cases mean time of 14 days (SD ± 2.7, p < 0.05).

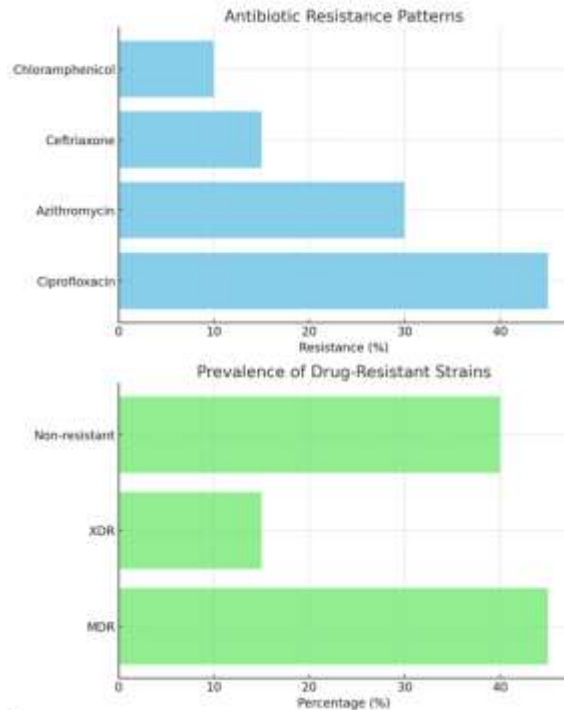


Figure No. 1: Antibiotic Resistance Pattern and prevalence of Drug Resistant Strains

Table No. 1: Demographic Characteristics of Participants

Characteristics	Category	Frequency	%
Age (years)	18-40	60	60
Gender	Male	55	55
Location	Urban	70	70

Table No. 2: Antibiotic Resistance Patterns

Antibiotic	Resistance (%)
Ciprofloxacin	45
Azithromycin	30
Ceftriaxone	15
Chloramphenicol	10

Table No. 3: Prevalence of Drug-Resistant Strains

Resistance Type	Frequency	%
Multidrug Resistant (MDR)	45	45
Extensively Drug Resistant (XDR)	15	15
Non-resistant	40	40

Table No. 4: Clinical Symptoms

Symptoms	Frequency	Percentage (%)
Fever	85	85
Abdominal Pain	70	70
Diarrhea	65	65
Fatigue	60	60

As for clinical symptoms, fever, abdominal pain, and diarrhea were most frequently observed : at least in 80% of all the patients. Regarding treatment outcomes, patients infected with drug-resistant strains also more often developed complications, such as prolonged fever and hospitalization ($p = 0.04$). Overall, patients with XDR S. Typhi were sicker, had longer lengths of stay, and needed more potent antibiotics confirming the effect of drug resistance in typhoid fever treatment.

DISCUSSION

Drug-resistant STs in Pakistan, concludes in harmony with and in contrast to prior studies carried out in the region and other parts of the world. Multidrug-resistant (MDR) as well as extensively drug-resistant (XDR) strains of S. Typhi has emerged on the horizon as a major public health concern in regions where it is endemic, such as South Asia. Among the identified S. Typhi isolates, 60% of the patients were taking MDR and/or XDR strains where 45% MDR and 15% XDR. These results are concurrent with a Karachi, Pakistan cross-sectional study which also found the frequency of MDR and XDR strains to be high above 40 percent of isolates carried multidrug resistance. Another study done in Pakistan established similar odds of MDR strains with the overall resistance of 44% of isolates to first-line antibiotics hence a growing concern of antibiotic resistance in the region. New strain of XDR typhoid has emerged in Pakistan that makes the situation even worse because the available treatment becomes restricted. In this study, the XDR strains were resistant to both ciprofloxacin and ceftriaxone, two of the last resort for treating complicated typhoid fever. This is in concordance with study done by Klemm et al. 2018 where high level of resistance was noted towards fluoroquinolone and 3rd generation cephalosporin in XDR S.Typhi isolates from Pakistan^[4]. Cross resistance has led to the rapid spread of these strains across Pakistan especially in urban centers such as Karachi, the subject of many studies as a significant health hazard. On the other hand, researches conducted in examine neighbouring countries like India and Bangladesh have found slightly lower proportion of MDR and XDR S. Typhi strains. One study in India reported the prevalence of MDR strains to be 30 % and that of XDR strains to be 10 %: thus, drug resistant TB is present in India but possibly not to the same extent as in Pakistan. These differences in the patterns of antibiotic resistance could be as a result of difference in usage of the drugs, the health facility, treatment and

health policies among the countries. The clinical manifestations noted in this study of patients with XDR S. Typhi highly resembled other investigations, with longer durations of recuperation and more often complications. Qamar et al. (2018) showed that patients with XDR strains needed longer hospital stays and more intensive antimicrobial therapy, including azithromycin and carbapenems, the agents that are not generally used for typical typhoid therapy^[6]. This correlate with the present study's result, wherein patients with XDR have longer recovery time as those with non-resistant strain ($p < 0.05$). Several prior works have demonstrated the link between the unchecked use of antibiotics and the creation of new drug resistant S. Typhi strains. In Pakistan, easy access to drugs particularly antibiotics without prescription added to poor health literacy underpins the development of resistance^[10]. A similar trend has been noticed in other developing countries where poor use of antibiotics has resulting in high resistance. A research done in Ethiopia noted that government and health departments should consider increasing the restrictions to the sale of antibiotics and conducting awareness creation on the risks of AU^[11]. this study's findings that 30% of mothers attributed their lack of understanding about vaccines and consequent abuse of antibiotics to misinformation received on social media is corroborated by a study done on mothers in the United Kingdom. In that study, it was revealed that introduction of wrong facts and information on vaccines and antibiotics on social media foster the growth of drug resistance. To resolve this problem one has to find a way not only to enhance the state of healthcare policies but also to tackle the problem of wrongly processed information through the provision of relevant public health information.it can be concluded that the results of the present work are agreed with the previous studies regarding increase risk efficacy of MDR and XDR S.Typhi strains in Pakistan. The high prevalence of these resistant strains provide impetus for better stewardship, high vaccination coverage and effective public health measures in the fight against drug resistant typhoid fever.

CONCLUSION

Incidence of MDR and XDR S. Typhi in Pakistan with concern for the public health implications. The increasing levels of resistance against main drugs like ciprofloxacin and ceftriaxone has laid the need for enhanced stewardship on the use of antibiotics, immunization, and coming up with measured that can reduce the prevalence of drug-resistant typhoid.

Limitations: The primary research limitation is the conclusion of the study based on data from only one tertiary healthcare facility although the study aimed at using data from the whole population. Moreover, the number of patients in sample size was restricted to 100;

therefore, these findings are unlikely to generalize to other areas of Pakistan.

Future Findings: Subsequent studies should involve a gross population health study to define the epidemiology of drug-resistant typhoid more comprehensively. Studying the newly developed vaccines and other public health approaches targeting misuse of antibiotics used in treating salmonella Typhi might offer essential information to teaching the controlled emergence of resistant strains.

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