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FREQUENCY OF MULTI-DRUG RESISTANT (MDR) AND EXTENDED DRUG RESISTANT (XDR) *SALMONELLA TYPHI* IN PATIENTS PRESENTING WITH CULTURE PROVEN ENTERIC FEVER AT TERTIARY CARE HOSPITAL

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ABSTRACT

Objectives: To determine frequency of multi-drug and extended drug resistance *Salmonella typhi* in patients presenting with culture proven enteric fever and its distribution based on age, gender and duration of typhoid fever.
Study Design: Prospective descriptive study.
Place and Duration of Study: Department of Medicine, Pakistan Institute of Medical Sciences, Islamabad from 01/10/2024 to 31/03/2025.
Methodology: A total of 202 culture proven cases of enteric fever were included. Baseline characteristics including age, gender and duration of fever were documented. In all these patients, subcultures will be sent to determine antibiotic sensitivity pattern of the *Salmonella* strains. Based on results of culture and sensitivity, multi-drug resistant and extended drug-resistant strains were identified.
Results: In present study, there were 78 (78.00%) males and 22 (22.00%) females. Mean duration of enteric fever was 5.31 ± 1.94 days. Frequency of multi-drug and extended drug-resistant strains of *Salmonella typhi* was 37 (18.32%) and 88 (43.56%), respectively.
Conclusion: Frequency of multi-drug and extensively drug-resistant strains of *Salmonella typhi* is quite high in target population of present study.

INTRODUCTION

Salmonella typhi is a flagellated, gram-negative, rod-shaped organism that manifests clinically as enteric fever which is a major public health issue particularly in poor countries imposing a significant monetary burden on the health system.[1] This organism is transmitted from one person to the other by faeco-oral route. In Pakistan, it has been found that the prevalence of this infectious disease is quite high and is reported at around 22%. [2] Comparatively, incidence of enteric fever in India has been reported to be equally high and is reported that in every 100,000 people per years, 703.7 are affected by this disease. [3] Antibiotics are the primary therapeutic option to effectively manage enteric fever and prevent its potential complications. [4]

When it comes to the susceptibility of *Salmonella typhi* to various antibiotics, a major problem that is encountered by the physicians these days is the growing resistance to commonly prescribed antibiotics used for its eradication. [5] This persistent increase in the antibiotic resistance has resulted in contraction of the choice of antibiotics physicians can use against *Salmonella* and only a few antibiotics are left behind for this purpose including azithromycin, carbapenems and tigecycline. [6] Both Meropenem and Azithromycin have been reported to provide excellent clinical response against both the multi-drug resistant (MDR) as well as extended drug resistant (XDR) strains of the *Salmonella typhi*. [7-9]. Despite availability of these drugs, there is always a possibility of alteration in the antibiotic susceptibility and resistance pattern since it is highly dependent of the local antibiotic prescription trends. [10] Therefore, it is highly important to continuously monitoring the frequency of both the MDR and XDR strains of S. typhi in the community so that any change in the trend and its burden can be determined as early as possible to effectively mitigate its impact on the patients and the healthcare systems. For this purpose, present study was conducted with the aim to determine burden of multi-drug and extended drug resistance *Salmonella typhi* in patients presenting with culture proven enteric fever and its distribution based on age, gender and duration of typhoid fever. Results from present study may help not only to document the burden of these highly dangerous microbial strains in local community but will also help raising awareness among physicians to modify and improve their antibiotic prescription practices.

Methodology

This prospective descriptive study was conducted at Department of Medicine, Pakistan Institute of Medical Sciences, Islamabad from 01/10/2024 to 31/03/2025. Sample population was selected using non-probability consecutive sampling method. Data of 202 patients was collected by research team on a predesigned proforma approved by the institutional ethical committee (F-5-2/2024 (ERRC)/PIMS, approval granted on 01/10/2024) Male and female patients aged between 20-70 years who had blood culture proven enteric fever were included in the study. Patients with history of malaria, dengue, malignancy, chemotherapy, stroke, chronic renal failure, chronic obstructive pulmonary disease, asthma, congestive heart failure and myocardial infarction, and pregnant patients proven by dating scan were excluded from the study. A written consent which was signed by the patients prior to inclusion. Once selected, baseline characteristics including age, gender, and duration of typhoid fever were documented. After incubating at 37°C for 18-24 hours, all blood cultures that tested positive were sub-cultured on “blood” and “MacConkey agars”. Gram staining, colony shape, and culture characteristics were used for preliminary isolate identification. “VITEK 2 system”, “gram-negative (GN) cards” were also used for biochemical bacterial confirmation. An agglutinating antiserum developed according to the “Kauffmann and White system” was used to identify the serotypes of *Salmonella*. [11] To summarize, 20µL of antiserum was combined with the *Salmonella* colony and placed to a glass slide. A noticeable

agglutination was regarded a positive reaction after 5-10 seconds, however uniform milky turbidity was considered a negative reaction, termed as the "Kauffmann-White scheme". Various antibiotics were tested to establish the "minimum inhibitory concentration (MIC)" in µg/mL including "ampicillin", "cotrimoxazole", "chloramphenicol", "ceftriaxone" and "ciprofloxacin" using "antibiotic susceptibility testing (AST)" cards by "VITEK 2 compact system (BioMerieux, France)". As the available "VITEK 2 compact system" lacked the sensitivity panel for Gram-negative bacteria, azithromycin, from (Oxoid UK), it had to be tested manually using the "Kirby-Bauer disc diffusion method". The zones' sizes were interpreted using "Clinical and Laboratory Standards Institute (CLSI)" 2018 guidelines. Based on these results MDR (resistant to sulfamethoxazole-trimethoprim, ampicillin and chloramphenicol) and XDR (resistant to sulfamethoxazole-trimethoprim, ampicillin, chloramphenicol plus ciprofloxacin and ceftriaxone) strains were identified. Appropriate drug therapy based on culture and sensitivity report was provided to all the patients. "Data was analyzed on SPSS Version 22. Data normality was checked by using Shapiro-Wilk test. It was found that age and duration of typhoid fever were normally distributed and were presented as mean ± standard deviation (SD). Frequencies and percentages for the qualitative variables like gender, residence status, MDR and XDR were calculated. Effect modifiers were controlled through stratification of age, gender and duration of typhoid fever to see the effect of these on the outcome variable. Post stratification chi square test or Fischer test were applied and p-value of ≤ 0.05 was considered statistically significant".

Results

A total of 202 patients were included in this study. Mean age of patients was 34.93 ± 9.53 years. There were 78 (78.00%) males and 22 (22.00%) females. Mean duration of enteric fever was 5.31 ± 1.94 days. Antibiotic susceptibility pattern for trimethoprim-sulfamethoxazole (co-trimoxazole), chloramphenicol, ampicillin, ciprofloxacin and ceftriaxone is tabulated below in Table-I:

Table-I: Antibiotic susceptibility pattern of *Salmonella* (n = 202)

Antibiotic	Sensitive	Intermediate	Resistant
Co-trimoxazole	46 (22.77%)	0 (0.00%)	156 (77.23%)
Chloramphenicol	74 (36.63%)	0 (0.00%)	128 (63.37%)
Ampicillin	66 (32.67%)	0 (0.00%)	136 (67.33%)
Ciprofloxacin	8 (3.96%)	65 (32.18%)	129 (63.86%)
Ceftriaxone	114 (56.44%)	0 (0.00%)	88 (43.56%)

Frequency of MDR and XDR "*Salmonella typhi*" was 37 (18.32%) and 88 (43.56%), respectively. Stratification of frequency of *Salmonella* strains identified as MDR and XDR by age, gender and duration of enteric fever is given below in Table-II:

Table-II: Stratification of frequency of *Salmonella* strains identified as MDR and XDR by age, gender and duration of enteric fever (n = 202)

Age stratification				
***Salmonella* strain**	**20-45 years (n = 164)**	**46-70 years (n = 38)**	**X^2**	**p-value**
MDR	29 (17.68%)	8 (21.05%)	0.872	0.647
XDR	74 (45.12%)	14 (36.84%)		
Gender stratification				
***Salmonella* strain**	**Male (n = 137)**	**Female (n = 65)**	**X^2**	**p-value**
MDR	30 (21.90%)	7 (10.77%)	6.513	0.039
XDR	52 (37.96%)	36 (55.38%)		

Duration of enteric fever stratification				
***Salmonella* strain**	**≥ 4 days (n = 45)**	**< 4 days (n = 157)**	**X^2**	**p-value**
MDR	6 (13.33%)	31 (19.75%)	1.501	0.591
XDR	20 (44.44%)	68 (43.31%)		

Discussion

One of the major healthcare concerns of present decade is the persistently increasing resistance to a wide variety of antibiotics. [12] Enteric fever, commonly named as "typhoid" in Pakistani population is caused by "*Salmonella typhi*" which has been labelled by the World Health Organization as "priority pathogen" owing to its growing resistance against majority of antibiotics. [13, 14] Enteric fever is amongst the commonest infectious disease encountered at healthcare settings on day to day basis. [15] This high prevalence often results in a wrong presumption of considering every fever as "enteric fever" resulting in injudicious use of antibiotics which is the primary cause of antibiotic resistance. [16, 17] Present study was thus conducted with the aim to determine the frequency of "multi-drug resistant (MDR)" and "extended drug resistant (XDR)" *Salmonella typhi* in patients presenting with "culture proven enteric fever". Upon analysis of the gender distribution of the patients with enteric fever, which is an infectious disease, it was observed that the majority of patients who had enteric fever were males. This trend was similar to the trend observed in a study conducted by Njoya et al. [18] who also found men to be much more affected by this infectious disease as compared to women. This can be explained by higher chances of transmission of organism to men due to their outdoorsy nature and habit of dining out much more frequently as compared to females. [19] Upon assessment of fever duration it was observed that average duration was five days. This is explainable by the fact that most patients seek medical help if their fever lasts longer than a few days. Frequency of MDR and XDR "*Salmonella typhi*" in present study was 18.32% and 43.56%, respectively. Compared to this, Zakir et al. [9] conducted a stud with the similar aim and found the frequency of MDR and XDR cases was 24.5% and 46.1%, respectively, in sufferers of typhoid fever. In another study conducted by Baig et al. [20] frequency of these strains was reported at 21.9% and 56.8%, respectively, which is relatively higher as compared to present study. In one study, it was observed that although the frequency of MDR cases was 44.6%, which was higher as compared to present study, the frequency of XDR cases was merely 0.7%. [21] Compared to Pakistani statistics, a study conducted in India reported that amongst all the strains of *Salmonella typhi* assessed, the frequency of MDR strains was merely 2%. [22] Current study demonstrates the alarming situation of rising resistance to antibiotics in "*Salmonella typhi*" with a considerable frequency of both the MDR and XDR strains. This necessitates a national initiative to educate the general public as well as physicians to strictly avoid the unnecessary utilization of antibiotics for all cases of fever. In addition, this also makes it essential to educate the physicians to completely avoid the use of antibiotics that are used to eradicate MDR and XDR strains of "*Salmonella typhi*". Limitations of present study included limited sample size and lack of assessment of the treatment outcomes in cases.

Conclusion

Frequency of multi-drug and extensively drug-resistant strains of *Salmonella typhi* is quite high in target population of present study.

Conflict of interest

None

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