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ASSESSING THE ANTIMICROBIAL SUSCEPTIBILITY PATTERN AND FREQUENCY OF EXTENSIVELY DRUG RESISTANT TYPHOID IN TERTIARY CARE HOSPITALS

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Abstract:

Background:

The emergence of XDR typhoid has been a problem since the early days of antibiotics, and it is particularly prevalent in countries like Pakistan. There is a need to investigate the frequency and antimicrobial susceptibility pattern of XDR typhoid in tertiary care hospitals to inform public health policies and guide clinical management.

Methods:

A cross-sectional descriptive study was conducted to collect 244 samples for culture on broth agar. The disc diffusion method was used for further identification, and antimicrobial susceptibility testing was performed on MHA plates to identify XDR typhoid.

Results:

Out of 244 samples, 203 (83.20%) were identified as Salmonella typhi, while 41 (16.80%) were identified as Salmonella paratyphi A. Among the Salmonella species, 126 (51.64%) were extensively drug resistant, while 118 (48.36%) were non-extensively drug resistant and sensitive to most antibiotics. Ciprofloxacin showed the most resistance (98.77%), and imipenem showed the least resistance (1.64%).

Conclusion:

The XDR typhoid (51%) was mainly due to the misuse or overuse of antibiotics. This study provides valuable insights into the frequency and antimicrobial susceptibility pattern of XDR typhoid in a tertiary care hospital, which can inform public health policies and clinical management strategies.

Key Words: Extensively drug resistant, salmonella typhi, salmonella para typhi, ampicillin ciprofloxacin azithromycin

Introduction:

Typhoid fever, derived from the Greek word "typhus" meaning "smoky," has a rich historical background dating back to the observations of Pierre Louis, a French Pathologist, who noted lesions in the abdominal lymph nodes of a patient who succumbed to gastric fever in 1829 (1). This infectious disease poses a serious public health threat, especially in underdeveloped nations, and is caused by a specific strain of Salmonella known as Salmonella typhi (S. typhi) (2). Salmonella typhi, a gram-negative, rod-shaped, mobile facultative anaerobe, is the culprit behind typhoid fever. Its polysaccharide capsule enhances its pathogenicity by shielding it from phagocytosis (3).

In cases of multidrug-resistant S. typhi infections, third-generation cephalosporins like ceftriaxone, cefotaxime, and cefoperazone are considered effective treatment options (4). However, there have been recent reports of rare instances and outbreaks of S. typhi strains resistant to cephalosporins. Upon ingestion, Salmonella Typhi bacteria proliferate and disseminate throughout the bloodstream (5).

Noteworthy instances of S. typhi generating extended-spectrum lactamase were reported by the Social Security Hospital in Lahore, Punjab, in 2012 (6) and subsequently in Rawalpindi in 2016 (7). Furthermore, the World Health Organization (WHO) documented two cases of extensively drug-resistant (XDR) S. typhi linked to international travelers who had visited Lahore and Islamabad (8).

The current gold standard for diagnosing typhoid fever involves isolating S. Typhi from blood samples (9). While culturing bone marrow bacteria yields more accurate results, this method is invasive and not suitable for routine use.

Treatment options for typhoid fever typically include ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole as first-line choices (10). Fluoroquinolones were previously used as second-line agents in the region, but the rise in fluoroquinolone resistance has been notable. Presently, third-generation cephalosporins are preferred for treating typhoid fever, especially in cases where other treatments are ineffective (5).

In 2015, 17 million cases of typhoid and paratyphoid fever were reported globally, with the highest burden and incidence observed in South Asia, Southeast Asia, and sub-Saharan Africa. Untreated cases of these fevers were estimated to contribute to 178,000 deaths worldwide in 2015 (8, 11). Recent data indicates that annually, 21 million individuals contract typhoid, with 161,000 fatalities. Among the 16 Asian nations where typhoid is prevalent, residents of Punjab and Sindh provinces in Pakistan face the highest risk of infection (12). In 2019, Sindh reported over nine million cases of typhoid fever, resulting in approximately 110,000 deaths. Children are particularly vulnerable, and the disease thrives in areas lacking clean water and basic sanitation (13).

While the disease has been less widespread in KPK compared to Sindh, under-reporting of cases may contribute to this trend. Notably, eight individuals from KPK were affected, with no prior reports of XDR S. typhi cases from this region (14). Typhoid fever, caused by Salmonella typhi, remains a severe public health concern, especially in underdeveloped regions. The emergence of extensively drug-resistant (XDR) typhoid poses a significant global health challenge due to its resistance to most antibiotics. Understanding the frequency and susceptibility pattern of XDR typhoid is essential for devising effective treatment strategies and combating further drug resistance. Hence, the aim of this study is to determine the frequency and antimicrobial susceptibility pattern of extensively drug-resistant Salmonella typhi in a tertiary care hospital in Peshawar, Pakistan.

Material and Method:

A cross-sectional descriptive study was conducted at the pathology laboratory of Rehman Medical Institute, Hayatabad Peshawar, over a period of three months. The study included patients diagnosed with typhoid caused by Salmonella typhi. Patients

with false positive results or those with typhoid secondary infections were excluded from the study. The sample size of 244 was determined using WHO software, with a population size of 3000, a margin of error of 5%, and a confidence level of 95%. Convenient sampling technique was employed for sample selection. Ethical approval was obtained from the head of the GSC department and the research ethical committee of RMI.

SAMPLE COLLECTION:

After ethical committee approval blood samples was collected and was received in microbiology department of clinical laboratory of tertiary care hospital Peshawar and further processed. The blood samples were kept in BactAlert machine for detection of bacteria. After 24 hours the samples were observed and positive samples were isolate. The positive samples were then transferred to culture plate which contained Macconkey and blood agar for identification of bacteria. The antimicrobial susceptibility testing were done through the disc diffusion technique. For this, we took inoculum of bacteria from the culture plates and made a dilution based on MC Frland standard. From that solution, we took a swab stick and made a lawn on Muller Hinton Agar plates. After lawning on MHA plates, the antibiotic discs were placed on it.

Antimicrobial Susceptibility Testing:

The antimicrobial susceptibility testing were done through the disc diffusion technique. For this, we took inoculum of bacteria from the culture plates and made a dilution based on MC Frland standard. From that solution, we took a swab stick and made a lawn on Muller Hinton Agar plates. After lawning on MHA plates, the antibiotic discs were placed on it.

Incubation:

The MHA plates were incubated at 37*C 24/48 hrs. For determination antimicrobial susceptibility.

Examination:

After Incubation the MHA plates was examined for zone of inhibition, the zone surrounded the antibiotic disc was measured and we determined the antimicrobial susceptibility profile of *salmonella typhi* isolates.

Identification of XDR:

After identification of *salmonella typhi*, and determination of its antibiotic susceptibility we identified the extensively drug resistant *salmonella typhi* by examining the susceptibility to different antibiotics.

For data analysis we use SPSS (statistical package for the social sciences) and data was entered into the MS Excel spread sheet.

Results:

Typhoid fever is an infection that is caused by different strains of *salmonella*. In this study we find out the frequency of extensively drug resistant typhoid among tertiary care hospitals in Peshawar. A total of 244 *salmonella* isolates were collected from tertiary care hospitals in Peshawar. Out of total 244 samples 203(83.20%) were identified as *Salmonella typhi*, while 41(16.80%) were identified as *Salmonella para typhi A* (Table 1).

Table 1 Frequency of Salmonella Typhi and salmonella para typhi A

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Salmonella Typhi	203	83.2	83.2	83.2
	Salmonella para typhi A	41	16.8	16.8	100.0
	Total	244	100.0	100.0	

In the study we find out that, out of 244 *salmonella* species 126(51.64%) of the species were extensively drug resistant, while 118(48.36%) were non extensively drug resistant, and sensitive to most of the antibiotics Figure 1.

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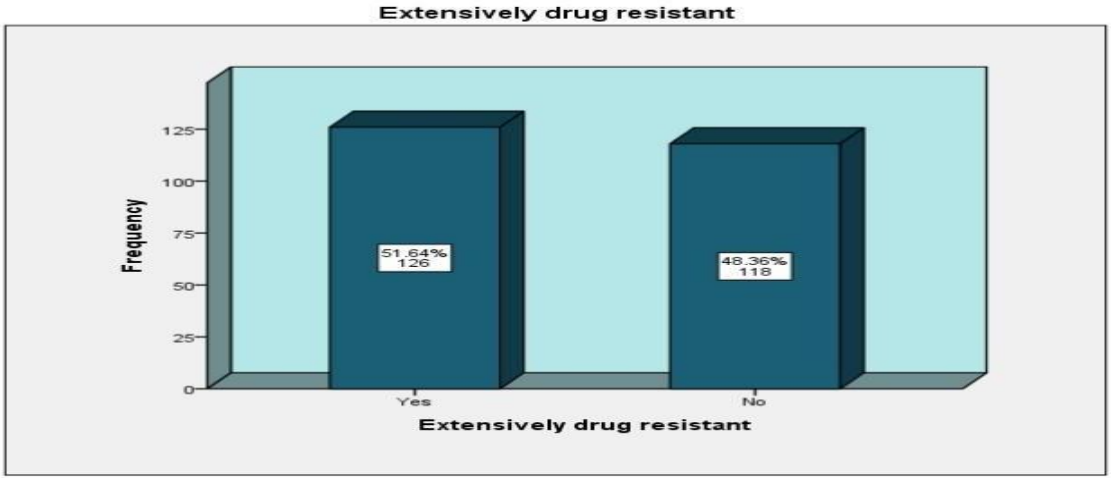

Figure 1 Frequency of Extensively drug resistant salmonella typhi

Out of 244 *salmonella* species 142 (58.2%) shows resistant against Ampicillin while 97 (39.75%) were found sensitive to Ampicillin .

Table 2 Frequency of Ampicillin resistance among Salmonella isolates.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Sensitive	102	41.8	41.8	41.8
	Resistant	142	58.2	58.2	100.0
	Total	244	100.0	100.0	

Out of 244 salmonella species 147 (60.25%) shows resistant against chloramphenicol while 97 (39.75%) were found sensitive to chloramphenicol.

Table 3 Frequency of Chloramphenicol resistance.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Sensitive	97	39.8	39.8	39.8
	Resistant	147	60.2	60.2	100.0
	Total	244	100.0	100.0	

Out of 244 *salmonella* species 147 (60.25%) show resistant against co trimaxzole while 97 (39.75%) were found senstive to co-trimaxzole

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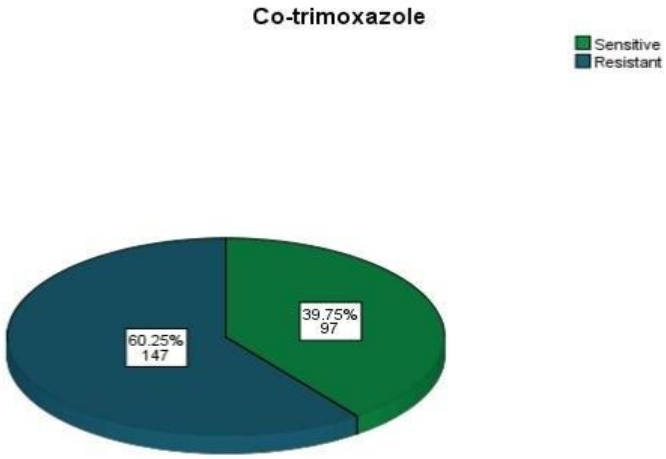

Figure 2 Frequency of Co-trimoxazole resistance.

Out of 244 *salmonella* species 241 (98.77%) show resistant against to ciprofloxacin while 3 (1.23%) were found sensitive to ciprofloxacin.

Table 4 Frequency of Ciprofloxacin resistance.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Sensitive	3	1.2	1.2	1.2
	Resistant	241	98.8	98.8	100.0
	Total	244	100.0	100.0	

Among all 244 *salmonella* species 126(51.64%) show resistant against ceftriaxone, However, 118(48.36%) of isolates were found sensitive to ceftriaxone.

Table 5 Frequency of Ceftriaxone resistance.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Sensitive	118	48.4	48.4	48.4
	Resistant	126	51.6	51.6	100.0
	Total	244	100.0	100.0	

Out of total 244 *salmonella* species 4 (1.6%) show resistant against imipenem whereas 240 (98.4%) of isolates were found sensitive to imipenem.

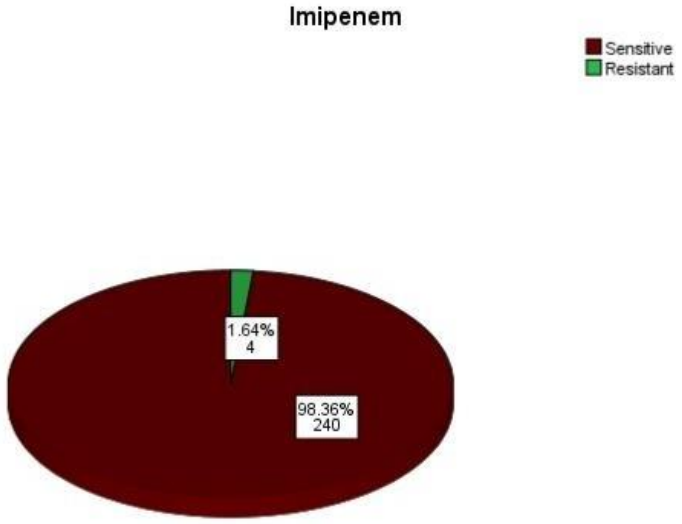

Figure 3 Frequency of Imipenem resistance**.**

Among 244 *salmonella* species 4 (1.6%) were found resistant against meropenem, whereas 240 (98%) of the isolates were found sensitive to meropenem.

Table 6 Frequency of Meropenem resistance.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Sensitive	240	98.4	98.4	98.4
	Resistant	4	1.6	1.6	100.0
	Total	244	100.0	100.0	

Discussion:

In our results out of total 244 samples 203(83.20%) were identified as *Salmonella* typhi , while 41(16.80%) were identified as *Salmonella* para typhi A which is also reported by Asma ejaz and et.al that *salmonella* typhi which was (83.87%) were higher than *salmonella para typhi* A which was (16.12%) (15).

In the study we find out that, out of 244 *salmonella* species 126(51.64%) of the species were extensively drug resistant, while 118(48.36%) were non extensively drug

resistant which is also reported by the study of shaifa nasir and et.al that (46.8%) were extensively resistant to drugs while (54.2%) were non-resistant (16).

Our study showed that Out of 244 *salmonella* species 141 (57.8%) shows resistance against Ampicillin while 102 (41.8%) were found sensitive to ampicillin which is supported by the results of research done by Fatima et.al also reported in their study that higher percentages(49%) of *salmonella* showed resistance to Ampicillin while lower percentages were sensistive (17).

The results of our study showed that Out of 244 *salmonella* species 147 (60.25%) shows resistant against chloramphenicol while 97 (39.75%) were found sensitive to chloramphenicol A study conducted by Fatima et al also find out that higher percentages(50&85%) of *salmonella* species were resistance to chloramphenicol and lower percentages were sensitive to the particular drug (17).

It was found out from our study that Out of 244 *salmonella* species 147 (60.25%) show resistant against co trimaxzole while 97 (39.75%) were found senstive to co-trimaxzole which is also reported by Fatima et al whose results showed higher percentages(47 &84%) of *salmonella* resistance while lower percentages sensitive to co-trimaxzole (17).

Our results showed that Out of 244 *salmonella* species 241 (98.77%) show resistant against to ciprofloxacin while 3 (1.23%) were found sensitive to ciprofloxacin which is supported by Fatima et al also reported in their study which showed that (59%) were resistant to ciprofloxacin while (41%) were sensitive (17).

It was found out that Among all 244 *salmonella* species 126(51.64%) show resistant against ceftriaxone, However, 118(48.36%) of isolates were found sensitive to ceftriaxone results by research of Fatima et al also showed where higher percentages showed resistance while lower percentages were resistant to the particular drug (17).

Results from our study showed that Out of total 244 *salmonella* species 4 (1.6%) show resistant against imipenem whereas 240 (98.4%) of isolates were found sensitive to imipenem which is similar to the result of study conducted by Liaquat National Hospital and medical university in karachi whose results showed 3% resistance while 97% sensitivity (18).

It was found out from our results that Among 244 *salmonella* species 4 (1.6%) were found resistant against meropenem, whereas 240 (98%) of the isolates were found sensitive to meropenem which is also reported by ressearch done by Liaquat national

hospital and medical university in karachi where 9% species showed resistance while 91% were sensitive to the particular drug (18).

Conclusion:

We concluded that there is a high prevalence of extensively drug resistant among *Salmonella* in typhoid patients. The result showed 51.64% of extensively drug resistant *Salmonella* isolates which shows a wide spread of XDR typhoid among our community. It was also concluded that the resistance pattern shows a very high resistance against ciprofloxacin among all *Salmonella* species, whereas, a very rare resistance was found against carbapenem antibiotics (imipenem and meropenem). Now a day's ciprofloxacin is one of the most common antibiotics which is used as a self-medication, due to misused of such kind of antibiotics a very high resistance is spreading against ciprofloxacin among *Salmonella* species. And also self-medication is one of the most important reason for resistance against antibiotics and patients should follow a physician prescription while taking medication, so that we can control the resistance pattern among such type of antibiotics, further self-medication must be prohibited.

This study recommends that the use of self-medication should be prohibited, while a proper prescription must be followed when taking antibiotics. The study also recommends Molecular and genetic methods for further identification and characterization of the gene responsible for resistant pattern.

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