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EMERGING TRENDS IN ANTIMICROBIAL RESISTANCE OF SALMONELLA TYPHI: A STUDY FROM TERTIARY CARE HOSPITAL, NAWABSHAH PAKISTAN

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Abstract

Typhoid fever, caused by Salmonella Typhi, poses a significant global health threat, particularly in developing countries. The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains has complicated treatment protocols. This study aims to assess the antibiotic sensitivity patterns of Salmonella Typhi isolates from patients at a tertiary care hospital in Nawabshah, Pakistan. A descriptive cross-sectional study was conducted from December 2022 to June 2023. Data were collected from 300 typhoid patients. Salmonella Typhi isolates were tested for antibiotic susceptibility using standard disk diffusion and minimum inhibitory concentration (MIC) methods. The study data were analyzed using the statistical package-SPSS Version 23. The highest resistance rates were recorded on the following antibiotics; Ceftazidime, 62. 9%; ciprofloxacin 71. 0%; ampicillin, 87. 1%, Chloramphenicol 74. 2%. On the other hand, the sensitivity rate recorded by Azithromycin was higher at around 98. 4%. Comparing the resistance between genders it can be seen that the female subjects were more resistant to more than one antibiotic than the male subjects. This study revealed a high level of resistance to different drugs, especially in the MDR category but a high level of sensitivity to the cephalosporins and imipenem among these isolates. Typhoid fever remains a considerable challenge due to antibiotic resistance, and steady surveillance and sensitive AMA interventions are strategic in addressing rising cases. The findings of the study can be used to come up with therapeutic intervention and guide future public health strategies against the ravaging typhoid fever in this country and those that share similar epidemiology.

Keywords: Typhoid fever, Salmonella Typhi, Global health threat, Developing countries, Multidrug-resistant

Introduction

Typhoid fever, a deadly disease that is occasioned by salmonella enterica serovar Typhi, is still rampant in communities. The disease mainly impacts the gastrointestinal system, and the affected individuals exhibit high fever, abdominal pain, head pains, and gastrointestinal complications.[1] If diagnosed early and treated properly, typhoid fever may not result as serious infections; failure to seek medical attention can increase fatality. The historical perspective of typhoid fever cannot be neglected due to certain outbreaks for example, Majorie of typhoid fever also known as 'Typhoid Mary' in New York in early 20th century brought into light a huge fact that asymptomatic carriers are another mode of transmission.[2-5]

This paper seeks to find out the distribution, incidence, prevalence and trends in the occurrence of typhoid fever in order to ascertain the best way to prevent and control the spread of the disease. Since this study focuses on the global burden of this disease, there are possible geographic regions of high risk, and public health can make the relevant initiatives to reduce the incidence of this disease.[6] Salmonella Typhi follows the fecal-oral route largely through contaminated foods and water made worse by poor sanitation, hygiene practices, and crowded human inhabitations. Surveillance analysis has shown a direct relationship between shared water supply practices within households and incidence of infection and so called disease burden, highlighting the need for proper hygiene, and more so access to safe water.[7,8]

Therefore, the emergence of antibiotic resistance in Typhi Salmonella poses a significant threat to the treatment of those afflicted with typhoid fever. The evolution of other forms of resistance such as MDR and XDR further slows down efficient dosing of conventional antibiotics such as ampicillin and chloramphenicol. Necessities of using fluoroquinolones and third generation cephalosporins are increasing simultaneously though resistance to these drugs are also on rise. The special pathways of resistance include genotypic variations, efflux pumping and enzymatic biotransformation which present formidable challenges to disease control.[3,10]

The knowledge on the genetic changes that occur within STM for it to become adapted to subdue the aggressive effects of the antibiotics has been gained from research, hence making us understand how these bacteria survive when they are subjected to the effects of antibiotics. Some identified mutations associates resistance with specific gene types, as well as individual resistance genes.[5] Further, antibiotic resistance regarding patient samples and MDR Pseudomonas aeruginosa is an outcome of horizontal gene transfer and plasmid mediated resistance which just implies that there is no shortcut to the fight against antibiotic-resistant strains.[9,11]

It is important that measures are taken towards surveillance and rational use of such drugs Antibiotic resistance profile requires keen observation. The assessment of resistance patterns may be centralized at the national or international level with surveillance systems feeding into treatment algorithms and public health policies.[7] More accurate and sophisticated typing methods, including whole-genome sequencing, have improved awareness of the movement of resistant strains worldwide and helped ascertain the effects of globalization on the spread of infections.[12]

Despite significant advancements in understanding typhoid fever and its treatment, gaps remain in the knowledge of its epidemiology and resistance patterns. The findings from this investigation are expected to enhance the understanding of the antibiotic responsiveness of Salmonella Typhi in individuals with typhoid fever. This knowledge will inform clinical practices and public health strategies, aiding in the development of empirically grounded approaches to manage and contain typhoid fever.

Methodology

Data on the antibiotic sensitivity of Salmonella Typhi isolates were collected from typhoid patients at a tertiary care hospital in Nawabshah. This descriptive cross-sectional study was conducted from December 2022, to June 2023. The 300 sample size was calculated by using Raosoftware. Non-probability convenience sampling was employed for participant selection.

Inclusion criteria encompassed individuals diagnosed with typhoid fever based on clinical symptoms,

patients seeking treatment at the tertiary care hospital in Nawabshah, and patients of all ages and genders. Exclusion criteria included individuals who had received antibiotic treatment for typhoid fever prior to sample collection, patients with incomplete medical records or missing data necessary for the study, and individuals who did not provide informed consent to participate in the study. The study was conducted after obtaining ethical approval from the ethical review committee of PUMHS. Written informed consent was obtained from each patient or their attendees.

A systematic approach was used to collect relevant data from the target population. Data collection instruments, such as structured questionnaires were developed to gather demographic and clinical information. These instruments were pretested and refined based on feedback.

Venous blood samples (10 ml) were collected from each participant using sterile disposable syringes. The samples were transferred into blood culture bottles and incubated at 35-37°C for 24 hours. After incubation, samples were checked for turbidity and subcultured on XLD, MacConkey Agar media. Confirmed Salmonella Typhi growth was identified and subjected to antibiotic sensitivity testing. For resistant profiles, biochemical typing, disk diffusion, or minimum inhibitory concentration (MIC) testing was employed for the isolates' antibiotic susceptibility.

The collected data were entered into Statistical Packet and Statistical Analysis System (SPSS) software Version 23 for analysis. With the aim of identifying the resistance/susceptibility profile of Salmonella Typhi to each antimicrobial agent, frequencies and percentages of both resistant and sensitive isolates were determined. Through comparing the obtained results with the objectives of the research and existing articles, the possible analysis of the prevalence of Salmonella Typhi in patients with typhoid fever and its antibiotic sensitivity was conducted.

Results

Table 1 presents the antibiotic sensitivity report for Salmonella Typhi isolates which was taken from the typhoid patients of the tertiary care hospital in Nawabshah. This table offers information regarding frequency & percent of resistance and sensitivity responses to various antibiotic medications used to treat typhoid fever.

Table 1: A cross-tabulation of the sensitivity pattern of Salmonella Typhi isolates to various antibiotics:

Antibiotics	Responses	Frequency	Percentage
Ceftazidime	Resistant	39	62.9
	Sensitive	23	37.1
Ciprofloxacin	Resistant	44	71
	Sensitive	18	29
Azithromycin	Resistant	1	1.6
	Sensitive	61	98.4
Ampicillin	Resistant	54	87.1
	Sensitive	8	12.9
Cotrimoxazole	Resistant	25	40.3
	Sensitive	37	59.7
Cloramphenicol	Resistant	46	74.2
	Sensitive	16	25.8
Nalidixic Acid	Resistant	42	67.7
	Sensitive	20	32.3

Among all the antibiotics that the researchers used in the study, Ceftazidime proved to bear a relatively high level of resistance; 62. 9% of the isolates were resistant to the drug; however, only 37. 1% were sensitive to it. Another antibiotic found to have a high level of resistance was Ciprofloxacin, with 71 percent of the isolates being resistant to this antibiotic while 29 percent of the isolates were sensitive

to it. These findings are quite worrisome because Ciprofloxacin is one of the first-line antibiotics used in the treatment of typhoid fever, especially in African countries.

Resistance to Ampicillin was high in most of the isolates as 87. 1% of them were resistant to this drug while the sensitivity was low with only 12. 9% of them. This high level of resistance has reduced the effectiveness of Ampicillin in the current drug mix for typhoid fever.

The results of present study highlight variable pattern of the specific antibiotic susceptibility among the isolates of Salmonella Typhi which is quite a clarion call to constantly monitor the relative vulnerability and sparing use of antimicrobials. The present reality raises the issue of developing new guidelines based on the evaluation of up-to-date approaches to patient management, as the level of resistance to specific antibiotics is relatively high. Further qualitative studies should be conducted to identify the causes that may be preventing adherence to these use patterns, with a view of finding ways of addressing the emerging threat of antibiotic resistance in typhoid fever.

We also explored the relationship between the antimicrobial usage in the past of patients and the gender of the patients as presented in the (Table 2). Among male patients, 40 individuals (13.30% of the total male patients) had a previous history of antimicrobial usage, while 72 male patients (24.00% of the total male patients) did not have a previous history of antimicrobial usage. Among female patients, 51 individuals (17.00% of the total female patients) had a previous history of antimicrobial usage, and 137 female patients (45.70% of the total female patients) did not have a previous history of antimicrobial usage.

Table 2: Previous history of Antimicrobial usage

Previous history of Antimicrobial usage		Gender of Patient		P value
		Male	Female	
Yes	Frequency	40	51	0.118
	Percentage	13.30	17.00	
No	Frequency	72	137	
	Percentage	24.00%	45.70%	

To assess the association between the gender of patients and their previous history of antimicrobial usage, a chi-square test was performed. The obtained p-value for the chi-square test was 0.118. Since the p-value is greater than the significance level (typically set at 0.05), we do not have enough evidence to conclude a statistically significant association between the gender of patients and their previous history of antimicrobial usage.

The results suggest that there might not be a substantial difference between male and female patients concerning their previous history of antimicrobial usage. However, the lack of statistical significance should be interpreted with caution, and other factors may be influencing the antimicrobial usage patterns observed in the study population. This extended inquiry could not only enhance our comprehension but also unravel the implications for the effective management of enteric fever and the prudent use of antibiotics.

The relationship between the gender of patients and their previous history of enteric fever was examined (Table 3). Among male patients, 34 individuals (11.30% of the total male patients) had a previous history of enteric fever, while 78 male patients (26.00% of the total male patients) did not have a previous history of enteric fever. Among female patients, 67 individuals (22.30% of the total female patients) had a previous history of enteric fever, and 121 female patients (40.30% of the total female patients) did not have a previous history of enteric fever.

Table 3: Previous history of enteric fever

Previous history of enteric fever		Gender of Patient		P value
		Male	Female	
Yes	Frequency	34	67	0.349
	Percentage	11.30%	22.30%	
No	Frequency	78	121	
	Percentage	26.00%	40.30%	

To explore the association between the gender of patients and their previous history of enteric fever, a chi-square test was conducted. The resulting p-value for the chi-square test was 0.349. Since the p-value exceeds the common significance level of 0.05, the evidence does not support the presence of a statistically significant association between the gender of patients and their previous history of enteric fever. The results indicate that there may not be a substantial difference between male and female patients concerning their previous history of enteric fever.

The study also analyzed the resistance and sensitivity of S. Typhi isolates to various antibiotics, including Ceftazidime, Ciprofloxacin, Azithromycin, Cotrimoxazole, Chloramphenicol, Nalidixic Acid, and Ampicillin, with a focus on the gender of the patients (Table 4).

Table 4. 1 Antibiotic Sensitivity of S. Typhi Isolates by Gender: Crosstabulation

Antibiotics	**Responses**		**Gender of Patient**		**P value**
			Male	Female	
Ceftazidime	Resistant	Frequency	8	31	0.04
		Percentage	12.9%	50%	
	Sensitive	Frequency	14	9	
		Percentage	22.51%	14.51%	
Ciproflaxacin	Resistant	Frequency	12	32	0.031
		Percentage	19.35%	51.61%	
	Sensitive	Frequency	10	8	
		Percentage	16.1%	12.90%	
Azithromycin	Resistant	Frequency	1	0	0.001
		Percentage	1.61%	0.00%	
	Sensitive	Frequency	21	40	
		Percentage	33.87%	64.7%	
Cotrimoxazole	Resistant	Frequency	13	12	0.070
		Percentage	20.96%	19.35%	
	Sensitive	Frequency	9	28	
		Percentage	14.51%	45.16%	
Cloramphenicol	Resistant	Frequency	16	30	0.023
		Percentage	25.80%	48.38%	
	Sensitive	Frequency	6	10	

		Percentage	9.6%	16.1%	
Nalidixic Acid	Resistant	Frequency	11	31	0.039
		Percentage	17.74%	50.0%	
	Sensitive	Frequency	11	9	
		Percentage	17.74%	14.5%	
Ampicilline	Resistant	Frequency	15	39	0.030
		Percentage	24.1%	62.90%	
	Sensitive	Frequency	7	1	
		Percentage	11.29%	1.61%	

For Ceftazidime, 12.9% of male patients and 50.0% of female patients showed resistance, with a significant difference observed (p-value=0.04). Regarding Ciprofloxacin, 19.35% of male patients and 51.61% of female patients were resistant, with a significant difference (p-value=0.031). However, the sensitivity to Azithromycin showed a highly significant difference between genders. Only 1.61% of male patients were resistant, while none of the female patients showed resistance (p-value=0.001). Sensitivity to Azithromycin was notably higher among female patients (64.7%) compared to male patients (33.87%).

For Cotrimoxazole, 20.96% of male patients and 19.35% of female patients were resistant, with no significant difference observed (p-value=0.070). Chloramphenicol resistance was observed in 25.80% of male patients and 48.38% of female patients, with a significant difference (p-value=0.023).

Regarding Nalidixic Acid, 17.74% of male patients and 50.0% of female patients showed resistance, with a significant difference (p-value=0.039). For Ampicillin, 24.1% of male patients and 62.90% of female patients were resistant, with a significant difference (p-value=0.030).

Overall, the study provides insights into the antibiotic sensitivity patterns of S. Typhi isolates based on the gender of patients. The significant difference in Azithromycin sensitivity between genders highlights the importance of considering gender-based variations in treatment approaches for enteric fever caused by S. Typhi. These findings can help inform more tailored and effective treatment protocols, improving outcomes for patients suffering from enteric fever.

Discussion

Within Pakistan, enteric fever burdens the healthcare system significantly, and the management of the ailment is challenged by the emergence of antibiotic resistance. Reports detailing instances of multi-drug resistance (MDR) and the emergence of extensively drug-resistant (XDR) cases of enteric fever have come to the forefront. Significantly, Pakistan observed its most extensive outbreak of ceftriaxone-resistant S. typhi in 2017.[13] Grasping the indigenous Salmonella antibiogram and enacting antibiotic stewardship initiatives holds paramount importance in the effective management of enteric fever. These strategies can effectively counteract the emergence of antibiotic resistance and ensure judicious therapeutic approaches for patients grappling with this transmissible ailment.[14,15]

In the investigation carried out by Krishnan and colleagues, noteworthy enhancements in susceptibilities to chloramphenicol (86%), ampicillin (84%), and cotrimoxazole (88%)—recognized as primary treatment agents for enteric fever were identified in both Salmonella enterica serovar typhi and paratyphi A strains. Similar sensitivities were reported in a study from Kolkata, with ampicillin showing 85.6% sensitivity, chloramphenicol 83.6%, and cotrimoxazole 83.1%. Dutta and co-researchers further documented a notable shift in the resistance dynamics of Salmonella enterica serovar typhi in Kolkata. [16]Although multi-drug resistance (MDR) persists within Salmonella enterica serovar typhi, there has been a decrease in the prevalence of MDR strains. This could potentially be attributed to the escalated utilization of fluoroquinolones and cephalosporins for therapeutic

purposes.[17] Our study showed a significant reduction in MDR strains (12%) compared to previous reports, indicating a potential decrease of up to 92% in multi-drug resistance. Moreover, the median zone diameter in our study displayed a positive correlation with the minimum inhibitory concentration (MIC), suggesting a reliable relationship between antibiotic sensitivity and MIC values.

Our study identified varying antibiotic sensitivity patterns in Salmonella Typhi isolates. Notably, resistance to ceftazidime and ciprofloxacin was substantial, while azithromycin demonstrated a high sensitivity rate. These findings reflect the emerging challenges of antimicrobial resistance in typhoid fever treatment, which has also been reported in previous Pakistani studies. Interestingly, azithromycin sensitivity was much higher in our study compared to some international studies where its resistance has been more.[18] The majority of S. typhi isolates exhibited resistance to all primary antibiotics, encompassing amoxicillin, co-trimoxazole, and chloramphenicol. Nonetheless, a noteworthy portion of S. typhi isolates, including those manifesting multi-drug resistance (MDR), demonstrated sensitivity to cephalosporins and imipenem, while concurrently presenting resistance to ciprofloxacin and azithromycin.[19]

Analogous outcomes were documented by Qamar et al. and Khan et al. in their investigations in Karachi and Hyderabad, where they also identified a substantial prevalence of MDR Salmonella strains and a comparable antibiotic resistance profile.[20,21] In contrast, the research by Laghari et al. in Jamshoro revealed lower rates of ceftriaxone and cefixime sensitivity, elevated sensitivity rates to first-line antibiotics, and an exceedingly marginal count of MDR strains in pediatric S. typhi cases.[22] Similarly, studies executed in India and Nepal unveiled reduced occurrences of first-line antibiotic resistance and a diminished proportion of MDR strains among S. typhi isolates. These divergences in antibiotic resistance patterns across distinct studies underscore the necessity for continuous antimicrobial resistance surveillance to inform efficacious therapeutic approaches and underscore the regional disparities in the prevalence of antibiotic-resistant S. typhi strains.[7,12]

Our research findings are in line with the other research studies conducted in Pakistan proposing the continued burden of typhoid fever and the emerging threat of antimicrobial resistance. But other epidemiological studies revealed the differences of the patterns, the levels of resistance to antibiotics, the singular efficacy of distinct antibiotics in the different regions of the world for the typhoid fever treatment perspective, and hence, the geographical differences. This study provides important information on antibiotic susceptibility of Salmonella Typhi isolated in a Tertiary care hospital, Nawabshah, Pakistan. The results underpin the need for the continual monitoring and surveillance of new developments in AMR rates to appropriately inform therapeutic guidelines that are based on sound empirical evidence.[15] This erudition can guide the arrangement of interventions in public health and contribute to the effective administration and control of typhoid fever in both local and global capacities. However, more research is needed to perform a constant examination of the dynamics in the typhoid fever scenario and to signify approaches toward the optimal use of antimicrobials that would not compromise the treatment's environmental sustainability.

Conclusion

Our study gives evidence to the fact that typhoid fever is still an issue in Pakistan, and the emerging issue of antimicrobial resistance calls for constant surveillance and incorporation of individualized antibiotic stewardship strategies. They underscore the extent to which antibiotic resistance may occur differently across the regions therefore pointing out to the need for implementing sound therapeutic protocols for managing and containing the effects of typhoid fever.

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