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Original Article

Association of Demographic and Clinical Determinants with Antibiotic Resistance Patterns in Salmonella enterica Serovar Typhi: A Cross-Sectional Study

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Abstract

Background: Salmonella enterica serovar Typhi remains a major cause of enteric fever in low- and middle-income countries, particularly Pakistan, where antimicrobial resistance (AMR) is rapidly escalating. The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains has significantly compromised treatment efficacy, necessitating continuous surveillance of resistance patterns and associated risk factors.

Objective: To determine the antibiotic resistance patterns of Salmonella enterica serovar Typhi and evaluate their association with demographic and clinical characteristics among patients in a tertiary care setting.

Methodology: This cross-sectional study was conducted at a tertiary care hospital in Karachi from January to June 2021. A total of 200 blood culture-confirmed Salmonella enterica serovar Typhi isolates were analyzed. Antimicrobial susceptibility testing was performed using the Kirby–Bauer disc diffusion method on Mueller–Hinton agar following CLSI M100 2023 guidelines. MDR and XDR classifications were defined according to established criteria.

Results: Among 200 patients, the majority were aged 10–19 years (34%) and 55.5% were males. Prior antibiotic use was reported in 37.5% of cases, while 34% required hospitalization. High resistance rates were observed for ampicillin (64%), co-trimoxazole (63.5%), and chloramphenicol (61.5%), with notable resistance to ciprofloxacin (53%). Younger age (<20 years), urban residence ($p = 0.027$), prior antibiotic use ($p = 0.009$), and comorbidities ($p = 0.032$) were significantly associated with resistance, whereas gender and hospitalization were not.

Conclusion: Antibiotic resistance in Salmonella enterica serovar Typhi is significantly influenced by demographic and clinical factors, particularly younger age, urban residence, prior antimicrobial exposure, and comorbid conditions. Strengthening antimicrobial stewardship, expanding Typhoid Conjugate Vaccine (TCV) coverage, and implementing targeted public health interventions are essential to mitigate resistance in high-risk populations.

Keywords: Antimicrobial resistance, Pakistan, Salmonella enterica serovar Typhi, Typhoid fever, multidrug resistance.

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Introduction

Salmonella enterica serovar Typhi, the causative agent of typhoid fever, is transmitted through the fecal–oral route and remains a major public health concern in developing countries due to poor sanitation, unsafe drinking water, and irrational antibiotic use [1-3]. Globally, an estimated 11–17.8 million cases of typhoid fever occur annually, with a significant burden in South Asia, particularly in Pakistan [4]. Historically, first-line antimicrobial therapies included ampicillin, chloramphenicol, and co-trimoxazole; however, their effectiveness has been severely compromised due to the emergence of resistant strains [5].

Antimicrobial resistance (AMR) in Salmonella enterica serovar Typhi has evolved into a critical global health challenge, especially in low- and middle-income countries. Multidrug-resistant (MDR) strains, defined as resistance to ampicillin, chloramphenicol, and co-trimoxazole, first emerged in the late 20th century and rapidly spread across endemic regions [6-8]. More recently, the emergence of extensively drug-resistant (XDR) strains, which are resistant to fluoroquinolones and third-generation cephalosporins, has further limited therapeutic options, leaving only a few effective agents such as azithromycin and carbapenems [9,10]. This alarming trend has led to prolonged illness, increased risk of complications, higher healthcare costs, and increased mortality.

Pakistan has reported one of the largest outbreaks of XDR typhoid fever worldwide, particularly in densely populated urban areas such as Karachi and Hyderabad. Since 2016, thousands of cases have been documented, emphasizing the urgent need for continuous surveillance of antimicrobial resistance patterns [11,12]. Contributing factors include overcrowding, inadequate sanitation infrastructure, and widespread over-the-counter availability of antibiotics, all of which facilitate the transmission of resistant strains and exert selective pressure on bacterial populations.

In addition to microbiological determinants, patient-related factors such as age, residential status, prior antibiotic exposure, and comorbid conditions may significantly influence the distribution and transmission of resistant infections. Previous studies have shown that younger individuals, urban residents, and those with prior antibiotic exposure are more likely to develop resistant Salmonella infections [8]. Understanding these associations is crucial for identifying high-risk populations and designing targeted preventive strategies, including vaccination programs, improved hygiene practices, and rational antibiotic use policies [13].

Several studies have identified prior antibiotic use, urban residence, younger age, and comorbidities as important contributors to antimicrobial resistance, primarily due to increased selective pressure and repeated healthcare exposure [14]. Despite the growing burden of AMR, there is limited local evidence in Pakistan linking demographic and clinical characteristics with antibiotic resistance patterns at the institutional level [15]. Such data are essential to guide empirical treatment decisions, strengthen antimicrobial stewardship programs, and inform public health interventions, including the implementation and expansion of Typhoid Conjugate Vaccine (TCV) strategies [16].

Therefore, this study aims to evaluate the antibiotic resistance patterns of culture-confirmed Salmonella enterica serovar Typhi isolates and to determine their association with demographic and clinical factors in a tertiary care hospital setting, thereby contributing to improved clinical management and evidence-based public health strategies.

Methodology

Study Design

This study was designed as a cross-sectional analytical study conducted to evaluate the association between demographic and clinical factors with antibiotic resistance patterns in Salmonella enterica serovar Typhi. The cross-sectional design allowed simultaneous assessment of exposure variables (demographic and clinical characteristics) and outcomes (antibiotic resistance profiles) within a defined time frame, thereby facilitating identification of statistically significant associations without implying causality.

Ethics

Ethical approval for the study was obtained from the Institutional Review Board of Ziauddin University (ERC No. 0611118ZIMIC). Written informed consent was obtained from all adult participants prior to enrollment. For pediatric participants, consent was obtained from parents or legal guardians along with age-appropriate assent. All procedures adhered to the ethical principles outlined in the Declaration of Helsinki [17]. Confidentiality and anonymity were strictly maintained by de-identifying patient data prior to analysis.

Setting

The study was conducted at the microbiology laboratory of Ziauddin Hospital, Karachi, Pakistan, a tertiary care facility that caters to a diverse urban and peri-urban population.

Data collection was carried out over a six-month period from January to June 2021, ensuring adequate representation of seasonal disease variation.

Participants

Participants included patients presenting with acute febrile illness and abdominal symptoms, who were subsequently confirmed to have Salmonella enterica serovar Typhi infection through blood culture. Inclusion criteria comprised all individuals with culture-confirmed Salmonella Typhi isolates, regardless of age or gender. Exclusion criteria included patients with negative blood cultures, non-typhoidal Salmonella infections, contaminated samples, incomplete clinical records, or prior concurrent bacterial infections. Enrollment was strictly based on culture confirmation, and Widal test results alone were not considered for inclusion.

Variables

The primary outcome variable was antibiotic resistance, defined as non-susceptibility (intermediate or resistant) to at least one tested antimicrobial agent. Independent variables included demographic factors (age, gender, residence, socioeconomic status) and clinical characteristics (duration of illness, prior antibiotic use, hospitalization, and comorbidities). Resistance categories such as multidrug-resistant (MDR) and extensively drug-resistant (XDR) were defined according to CLSI standards and established literature criteria [4].

Data Sources / Measurement

Blood samples were processed using standard microbiological techniques. Positive blood cultures were subcultured on Blood Agar Plate (BAP), MacConkey Agar (MAC), and Xylose Lysine Deoxycholate (XLD) agar using commercially available media. Incubation was performed at 37°C for up to 7 days. Identification of isolates was based on Gram staining, colony morphology, and biochemical tests including Triple Sugar Iron (TSI), Simmons Citrate, Urease, Indole, Motility, and Oxidase tests. Motility was assessed using MIU medium.

Serological confirmation was performed using O and H antisera, while ambiguous cases were verified using the VITEK 2 automated system. Antimicrobial susceptibility testing (AST) was conducted using the Kirby–Bauer disc diffusion method on Mueller–Hinton Agar in accordance with CLSI M100 2023 guidelines [18]. The antibiotics tested included ampicillin, chloramphenicol, co-trimoxazole, ciprofloxacin, ceftriaxone, azithromycin, meropenem, and piperacillin–tazobactam.

Quality control was ensured using standard reference strains including E. coli ATCC 25922, S. Typhimurium ATCC 14028, S. Typhi ATCC 6539, S. aureus ATCC 25923, and E. faecalis ATCC 29212. Routine quality checks, reagent validation, and disc potency verification were performed to ensure accuracy and reproducibility.

Bias

Efforts were made to minimize potential sources of bias. Selection bias was reduced by including all eligible culture-confirmed cases within the study period. However, as the study was hospital-based, there remains a possibility of selection bias, limiting generalizability to community settings. Information bias was minimized through standardized laboratory protocols; however, recall bias may have affected self-reported variables such as prior antibiotic use. Laboratory misclassification bias was reduced through adherence to CLSI guidelines and use of quality control strains.

Study Size

A total of 200 blood culture-confirmed isolates of Salmonella enterica serovar Typhi were included in the final analysis. The sample size was based on the number of eligible cases presenting during the study period, ensuring adequate power to detect statistically significant associations between variables.

Quantitative Variables

Quantitative variables such as age were expressed as mean ± standard deviation, while categorical variables such as gender, residence, and clinical characteristics were summarized using frequencies and percentages. Antibiotic resistance outcomes were categorized as sensitive, intermediate, or resistant based on CLSI-defined breakpoints.

Statistical Methods

Data were entered and analyzed using SPSS version 26. Descriptive statistics were computed for all variables. The association between demographic/clinical factors and antibiotic resistance was evaluated using the Chi-square test. A p-value of <0.05 was considered statistically significant. All analyses were conducted using a two-tailed approach to ensure robustness of findings.

Results

Participants

A total of 200 blood culture-confirmed isolates of Salmonella enterica serovar Typhi were included in the final analysis. All enrolled participants met the predefined

inclusion criteria, and no cases were excluded after confirmation. The study population represented a diverse age range and both genders, with a predominance of cases from urban settings. The participant flow and final sample characteristics are summarized in Table 1.

Descriptive Data

The demographic distribution of participants revealed that the largest proportion (34%) belonged to the 10–19 years age group, followed by 20–39 years (29.5%), indicating a higher burden of disease among younger individuals. Patients aged below 10 years accounted for 17.5%, while those aged ≥40 years comprised 19% of the cohort. Males constituted 55.5% of the study population, whereas females accounted for 44.5%. A majority of participants (66%) were residents of urban areas, reflecting the higher disease burden in densely populated settings. Socioeconomic analysis showed that nearly half of the participants (48.5%) belonged to the low-income group, followed by middle-income (41.5%) and high-income groups (10%) (Table 1).

Clinical characteristics demonstrated that 48% of patients presented with symptoms lasting 7–14 days, while 24% had symptoms for less than 7 days and 28% for more than 14 days. A history of prior antibiotic use was reported in 37.5% of cases, highlighting substantial exposure to antimicrobials before diagnosis. Approximately one-third of patients (34%) required hospitalization, and comorbid conditions were present in 19.5% of participants. These findings are detailed in Table 2, which summarizes the clinical profile of the study population.

Outcome Data

The antimicrobial susceptibility profile of Salmonella enterica serovar Typhi isolates demonstrated high resistance rates to traditional first-line antibiotics, including ampicillin (64%), co-trimoxazole (63.5%), and chloramphenicol (61.5%). Resistance to ciprofloxacin was also notable at 53%, indicating reduced efficacy of fluoroquinolones. In contrast, relatively higher susceptibility was observed for ceftriaxone (72%) and azithromycin (76%), although emerging resistance was evident. Carbapenems (meropenem) and piperacillin–tazobactam showed excellent susceptibility (>90%), suggesting their continued effectiveness as treatment options. These antibiotic susceptibility patterns are comprehensively presented in Table 3.

138 isolates (69%) were resistant to at least one antibiotic, based on the operational definition of resistance. The distribution of sensitive, intermediate, and resistant isolates for each antibiotic is detailed in Table 3.

Main Results

Statistical analysis revealed significant associations between antibiotic resistance and several demographic and clinical factors. Younger age (<20 years) was significantly associated with higher resistance rates ($p = 0.041$), indicating increased vulnerability among children and adolescents. Similarly, urban residence showed a significant relationship with resistance ($p = 0.027$), reflecting the impact of population density and antibiotic misuse in urban settings.

A history of prior antibiotic use demonstrated a strong association with resistance ($p = 0.009$), emphasizing the role of inappropriate or excessive antimicrobial exposure in the development of resistant strains. Additionally, the presence of comorbidities was significantly associated with resistance ($p = 0.032$), suggesting that patients with underlying health conditions may be at higher risk.

In contrast, gender ($p = 0.083$) and hospitalization status ($p = 0.112$) were not significantly associated with antibiotic resistance. These findings are summarized in Table 4, which presents the relationship between patient characteristics and resistance patterns.

Table 1. Demographics of Patients with Culture-Confirmed Salmonella enterica serovar Typhi (N = 200)

Variable	Category	(n)	(%)
Age Group (years)	<10	35	17.5
	10–19	68	34.0
	20–39	59	29.5
	≥40	38	19.0
Gender	Male	111	55.5
	Female	89	44.5
Residence	Urban	132	66.0
	Rural	68	34.0
Socioeconomic Status	Low	97	48.5
	Middle	83	41.5
	High	20	10.0

Table 2. Clinical Characteristics of Patients with Culture-Confirmed Salmonella enterica serovar Typhi (N = 200)

Variable	Category	(n)	(%)
Disease Duration	<7 days	48	24.0
	7–14 days	96	48.0
	>14 days	56	28.0
Prior Antibiotic Use	Yes	75	37.5
	No	125	62.5
Hospitalization	Yes	68	34.0
	No	132	66.0
Comorbidities	Present	39	19.5
	Absent	161	80.5

Table 3. Antibiotic Susceptibility Profile of Salmonella enterica serovar Typhi Isolates (N = 200)

Antibiotic	S n (%)	I n (%)	R n (%)
Ampicillin	54 (27.0)	18 (9.0)	128 (64.0)
Chloramphenicol	67 (33.5)	10 (5.0)	123 (61.5)
Co-trimoxazole	59 (29.5)	14 (7.0)	127 (63.5)
Ciprofloxacin	73 (36.5)	21 (10.5)	106 (53.0)
Ceftriaxone	144 (72.0)	11 (5.5)	45 (22.5)
Azithromycin	152 (76.0)	9 (4.5)	39 (19.5)
Meropenem	189 (94.5)	4 (2.0)	7 (3.5)
Piperacillin–Tazobactam	182 (91.0)	5 (2.5)	13 (6.5)

S = Sensitive, I = Intermediate, R = Resistant.
All results obtained using CLSI 2023 breakpoints.
MDR = resistance to ampicillin, chloramphenicol, and co-trimoxazole.
MDR plus resistance to fluoroquinolones and third-generation cephalosporins.

Table 4. Association of Patient Characteristics with Antibiotic Resistance (N = 200)

Factor	Resistant n (%)	Sensitive n (%)	p-value
Age <20 years	75 (72.1)	29 (27.9)	0.041*
Gender (Male)	76 (68.4)	35 (31.6)	0.083
Urban Residence	93 (70.5)	39 (29.5)	0.027*
Prior Antibiotic Use	59 (78.3)	16 (21.7)	0.009*
Hospitalization	45 (66.2)	23 (33.8)	0.112
Comorbidities Present	33 (75.0)	11 (25.0)	0.032*

Chi-square test applied; $p < 0.05$ considered statistically significant.
"Resistant isolate" = resistance to ≥1 antibiotic.
"Resistance was defined as non-susceptibility (I or R) to at least one tested antibiotic.

Discussion

The present study demonstrates that antibiotic resistance in Salmonella enterica serovar Typhi is not uniformly distributed but is significantly influenced by specific demographic and clinical factors. A markedly higher prevalence of resistance was observed among younger individuals, urban residents, patients with prior antibiotic exposure, and those with comorbid conditions.[18] These findings are consistent with previous studies conducted in Pakistan and other endemic regions, where children and adolescents frequently experience repeated infections and are often exposed to empirical antibiotic therapy without microbiological confirmation, thereby increasing selective pressure for resistant strains [19].

The significant association between urban residence and antibiotic resistance observed in this study aligns with earlier reports from major metropolitan areas such as Karachi, where high population density, inadequate sanitation, and easy access to over-the-counter antibiotics contribute to the rapid dissemination of resistant strains, particularly XDR Salmonella Typhi [20]. Urban environments may also facilitate faster transmission cycles and clustering of resistant infections, further exacerbating the burden of antimicrobial resistance.

Prior antibiotic use emerged as one of the strongest predictors of resistance in this study, reinforcing the well-established role of inappropriate or incomplete antimicrobial therapy in driving the emergence of MDR and XDR strains. This finding underscores the urgent need for improved antimicrobial stewardship programs, rational prescription practices, and strengthened regulatory control over antibiotic distribution. It also highlights the importance of promoting diagnostic stewardship to minimize unnecessary antibiotic exposure and ensure targeted therapy.

The association between comorbidities and antibiotic resistance, although less extensively studied in the context of typhoid fever, may reflect increased healthcare utilization and repeated exposure to antimicrobial agents among patients with chronic illnesses. Such individuals may serve as reservoirs for resistant organisms, thereby contributing to the persistence and spread of resistant strains within the community.

The resistance patterns observed in this study are comparable with national and regional trends, showing high resistance rates to traditional first-line antibiotics and substantial resistance to fluoroquinolones [21]. While susceptibility to ceftriaxone, azithromycin, and carbapenems remains relatively preserved, emerging resistance to these agents has been reported, raising concerns about the potential exhaustion of effective therapeutic options [22]. These findings highlight the necessity for continuous surveillance of antimicrobial susceptibility patterns to inform empirical treatment guidelines and prevent treatment failures.

Importantly, the associations identified in this study should not be interpreted as causal relationships due to the cross-sectional study design. Instead, they should be considered indicators of high-risk populations that may benefit from targeted interventions. From a public health perspective, these findings have significant implications for typhoid control strategies in Pakistan. The introduction and expansion of Typhoid Conjugate Vaccine (TCV) programs have shown promising results in reducing the incidence of XDR typhoid, particularly among children—the group most affected by resistant infections. Evidence from Sindh province indicates substantial reductions in disease burden following TCV implementation, supporting its inclusion in routine immunization schedules [23].

Therefore, a comprehensive approach integrating vaccination, antimicrobial stewardship, improved sanitation, and public awareness campaigns is essential to effectively control the spread of resistant Salmonella enterica serovar Typhi and reduce the overall burden of typhoid fever.

Limitations

This study has several limitations that should be considered when interpreting the findings. First, it was conducted at a single tertiary care center using a hospital-based sample, which may limit the generalizability of results to other regions or community settings with different epidemiological profiles. Second, antimicrobial susceptibility testing was performed using the Kirby–Bauer disc diffusion method without minimum inhibitory concentration (MIC) determination, which may reduce precision for certain antibiotics such as azithromycin, ceftriaxone, and carbapenems where MIC values provide more detailed clinical insight.

Third, the study did not include molecular or genotypic characterization of isolates, thereby limiting the ability to identify specific resistance genes, plasmid-mediated mechanisms, or circulating MDR/XDR lineages. Fourth, potential information bias may have occurred, particularly for variables such as prior antibiotic use, which relied on patient self-reporting and may be subject to recall inaccuracies.

Additionally, environmental and seasonal factors such as temperature, rainfall, water quality, and sanitation conditions—which are known to influence typhoid transmission—were not assessed. Socioeconomic variables were broadly categorized and did not capture important contextual factors such as education level, hygiene practices, and informal antibiotic access, which may play a critical role in resistance dynamics.

Finally, due to the cross-sectional nature of the study, causal relationships between risk factors and antibiotic resistance cannot be established, and residual confounding from unmeasured variables may persist. Future multicenter, longitudinal studies incorporating molecular epidemiology and environmental determinants are recommended to provide a more comprehensive understanding of resistance patterns.

Conclusion

Antibiotic resistance in Salmonella enterica serovar Typhi is highly prevalent and is significantly associated with younger age, urban residence, prior antibiotic exposure, and the presence of comorbidities. These findings highlight the urgent need for targeted interventions aimed at high-risk populations.

Strengthening antimicrobial stewardship programs, enforcing rational antibiotic prescribing practices, and improving regulatory control over antibiotic use are critical to curbing the emergence and spread of resistant strains. In parallel, expanding the coverage of Typhoid Conjugate Vaccine (TCV), particularly among children and urban populations, can play a pivotal role in reducing disease burden and limiting transmission of resistant organisms.

Authors' Contributions:

All authors meet the ICMJE criteria for authorship.

Author 1: Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 2: Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 3: Analysis and interpretation of data, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 4: Analysis and interpretation of data, critical revision, final approval, agreed to be accountable for all the work.
Author 5: Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 6: Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.

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