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ORIGINAL ARTICLE

TREND ANALYSIS OF RESISTANCE TO FIRST-LINE ANTIBIOTICS IN SALMONELLA BLOOD ISOLATES

Imran Khan[1], Mehwash Iftikhar[2], Nazeer Shah[3], Sheraz Jamal Khan[4]

[1]Assistant Professor, Hayatabad medical complex, Khyber Girls 'Medical College, Peshawar
[2]Assistant Professor, Hayatabad medical complex, Khyber Girls 'Medical College, Peshawar
[3]AssociateProfessor, Hayatabad medical complex, Khyber Girls 'Medical College, Peshawar
[4]Professor and Dean, Hayatabad medical complex, Khyber Girls 'Medical College, Peshawar

Correspondence:
Mehwash Iftikhar
Email:Mahwish.iftikhar86@yahoo.com

Abstract

Background: Salmonella Typhi causes significant morbidity and mortality worldwide, particularly in low- and middle-income countries (LMICs), where resistance to first-line antibiotics, including multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains, challenges treatment. This study evaluated resistance trends in Salmonella blood isolates from a regional cohort.

Objective: To assess the prevalence and patterns of antibiotic resistance among Salmonella Typhi blood isolates to first-line antibiotics in a tertiary care hospital in Peshawar, Pakistan, and identify trends in MDR and XDR strains to inform local treatment protocols and antimicrobial stewardship.

Material and Methods: This retrospective cross-sectional study analyzed 626 Salmonella blood isolates collected from January 2022 to December 2023 at Hayatabad Medical Complex, Peshawar, after getting ethical approval vide No.222, dated13.12.2023 Antibiotic susceptibility was tested using CLSI guidelines, targeting ampicillin, ciprofloxacin, trimethoprim-sulfamethoxazole (TMP-SMX), and third-generation cephalosporins. Data were analyzed using SPSS Version 26.

Results: Resistance rates were 70% for ampicillin, 65% for TMP-SMX, 30% for ciprofloxacin, and 20% for third-generation cephalosporin's, with a significant increase in ceftriaxone resistance from 15.2% in 2022 to 24.8% in 2023 (p=0.002). MDR and XDR strains accounted for 37.9% and 8.5% of isolates, respectively, necessitating updated treatment strategies.

Conclusion: The rising resistance to first-line antibiotics, especially in MDR and XDR Salmonella strains, requires urgent attention. Enhanced surveillance, vaccination, improved sanitation, and antibiotic stewardship are critical to address this growing threat.

Keywords: Salmonella, MDR, XDR, Blood culture, Antibiotic resistance.
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Introduction:

Salmonella Typhi is a gram-negative bacterium that causes typhoid fever, a significant enteric illness that predominantly affects low- and middle-income countries (LMICs). Globally, typhoid fever is a major public health issue, with an estimated 9 to 16 million cases and over 100,000 deaths annually.[1] Both Salmonella Typhi and Paratyphi are responsible for this illness, with transmission primarily occurring through contaminated food and water.[2] Although high-income countries (HICs) have seen a decline in typhoid incidence due to widespread vaccination, improved water quality, and better sanitation, endemic regions, particularly South Asia (including Pakistan, India, Bangladesh, and Afghanistan), continue to experience a high disease burden.[3]

Treatment for typhoid fever has evolved significantly over the past century. Chloramphenicol, introduced in the 1940s, was the first effective treatment, but resistance emerged as early as the 1970s.[4] Subsequently, first-line antibiotics such as ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX) were used, but resistance to these treatments also became widespread by the 1980s, contributing to the rise of multidrug-resistant (MDR) Salmonella strains.[5] Fluoroquinolone, such as ciprofloxacin, became the mainstay of treatment in the 1990s, but resistance to

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these agents followed shortly thereafter.[6]

The emergence of MDR and extensively drug-resistant (XDR) Salmonella strains, particularly in South Asia, presents a serious treatment challenge. MDR strains, resistant to ampicillin, TMP-SMX, and Chloramphenicol, were first reported in the 1980s and now constitute a large portion of infections in countries like Pakistan and India.[7] The rise of XDR Salmonella, resistant to first-line antibiotics and third-generation cephalosporins, has further complicated treatment protocols. Pakistan experienced a significant XDR typhoid outbreak in 2016, which quickly spread nationwide.[8]

The financial burden of treating MDR and XDR infections, especially in LMICs, is immense, as these cases often require prolonged hospital stays, costly second-line treatments, and intensive care, greatly inflating healthcare costs.[9] Globally, antimicrobial resistance (AMR) is recognized as a critical threat to public health, with Salmonella resistance a key concern. The World Health Organization (WHO) has emphasized the need for a global strategy to combat AMR through enhanced surveillance, new drug development, and a strengthened healthcare infrastructure.[10] Continued research, improved sanitation, vaccination programs, and the rational use of antibiotics are vital steps toward addressing this issue.[11]

Material and Method:

Study Design, Place & Duration: This retrospective cross-sectional study analyzed antibiotic sensitivity data from 626 Salmonella species isolated from blood cultures collected between January 2022 and December 2023 at Hayatabad Medical Complex, a tertiary care hospital in Peshawar, Pakistan. Routine susceptibility testing followed Clinical Laboratory Standards Institute (CLSI) guidelines, testing ampicillin, ciprofloxacin, trimethoprim-sulfamethoxazole (TMP-SMX), third-generation cephalosporins, and carbapenems.

Data Collection: Data on patient demographics (age, gender) and antibiotic susceptibility results were extracted from laboratory records. Statistical analysis was performed using SPSS Version 26, focusing on resistance trends to first-line antibiotics.

Results:

Study on Salmonella Blood Isolates:

The study included 626 Salmonella blood isolates. A majority (75.1%) of the patients were males, with the most affected age group being 16-28 years (59.7%). The demographic characteristics are summarized in Table 1.

Table 1: Demographic Characteristics of Patients

Mean age (years)	17.8 ± 6.3	-	95% CI: 17.3-18.3
0-5 Years	82	13.1	F = 27.4, p<0.001*
6-15 Years	170	27.2	
16-28 Years	374	59.7	

Statistically significant at p<0.05

The chi-square test confirmed a significant gender disparity among infected patients ($\chi^2 = 158.3$, p<0.001). Analysis of variance (ANOVA) revealed significant differences in infection rates across age groups (F = 27.4, p<0.001), with post-hoc Tukey's test confirming significantly higher rates in the 16-28 years group compared to both younger cohorts (p<0.001 for both comparisons).

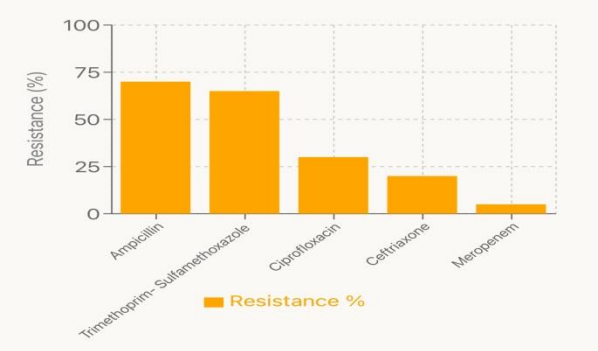
Table 2: Resistance Patterns in Salmonella Blood Isolates

Antibiotic	Number of Resistant Isolates (n=626)	Resistance (%)	95% Confidence Interval	p-value
Ampicillin	438	70.0	66.3-73.5	<0.001*
TMP-SMX	407	65.0	61.2-68.7	<0.001*
Ciprofloxacin	188	30.0	26.5-33.8	<0.001*
Ceftriaxone	125	20.0	16.9-23.3	<0.001*
Meropenem	31	5.0	3.4-7.0	<0.001*

Statistically significant at p<0.05

Multidrug resistance (MDR), defined as resistance to ≥3 antibiotic classes, was observed in 37.9% (237/626) of isolates (95% CI: 34.1-41.8%). Extensively drug-resistant (XDR) isolates, resistant to all first-line antibiotics including ceftriaxone, constituted 8.5% (53/626) of the sample (95% CI: 6.4-10.9%). Binary logistic regression analysis revealed that younger age (OR: 1.8, 95% CI: 1.3-2.5, p=0.002) and male gender (OR: 1.5, 95% CI: 1.1-2.2, p=0.03) were significant predictors of MDR infections.

Temporal analysis comparing the first and second



years of the study period showed a significant increase in ceftriaxone resistance from 15.2% to 24.8% ($\chi^2 = 9.37$, p=0.002), suggesting a concerning upward trend in resistance to this important reserve antibiotic.

A visual representation of the resistance rates to key antibiotics is shown graphically:

Graph: Antibiotic Resistance Patterns in Salmonella Blood Isolates.

Discussion:

This study highlights the growing problem of antimicrobial resistance (AMR) in Salmonella blood isolates, particularly with the rise of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. This is particularly alarming in regions like South Asia, where antibiotic misuse is prevalent and healthcare infrastructure struggles to keep pace with the increasing resistance trends. Our data shows significant resistance to key first-line antibiotics, with ampicillin resistance at 70%, TMP-SMX at 65%, and ciprofloxacin at 30%. These findings are consistent with trends observed globally and regionally. For example, a study in India noted that resistance to fluoroquinolone, such as ciprofloxacin, has been steadily increasing due to over prescription and widespread use in outpatient settings.3,4 Similarly, a 2018 study in Pakistan reported resistance rates of over 60% for ampicillin and TMP-SMX in Salmonella Typhi, reflecting our findings.[5]

MDR Salmonella strains have been reported in several regions, especially South Asia and Sub-Saharan Africa.6-8 In our study, we observed significant multidrug resistance, complicating treatment protocols and limiting effective oral treatment options. Studies from both Pakistan and India have highlighted the impact of MDR strains on treatment outcomes.[9,10]

Even more concerning is the rise of XDR Salmonella strains, which are resistant to almost all available oral antibiotics, including third-generation cephalosporins and fluoroquinolone. Pakistan has been at the epicenter of XDR typhoid outbreaks, with the first major outbreak reported in Sindh in 2016.[11] The strain responsible for this outbreak was resistant to ampicillin, TMP-SMX, ciprofloxacin, and even third-generation cephalosporins, making treatment extremely difficult.[12]

The rising cost of living, tagged with the cost of treating MDR and XDR infections, particularly in LMICs, speaks volumes about the need for improved antibiotic stewardship and public health interventions. Effective vaccination programs, better sanitation, and responsible use of antibiotics are essential to stopping the spread of resistant Salmonella strains.[13]

The results of this study highlight the concerning increase in resistance to first-line antibiotics used for treating Salmonella infections, such as ampicillin, trimethoprim-sulfamethoxazole (TMP-SMX), and ciprofloxacin. With resistance rates for these drugs reaching as high as 70% for ampicillin and 65% for TMP-SMX, treatment of Salmonella infections with these agents has become increasingly ineffective. Additionally, the rising resistance to third-generation cephalosporins, such as ceftriaxone, further limits the treatment options available for managing Salmonella infections.

Given these resistance patterns, carbapenems have emerged as a key class of antibiotics for treating multidrug-resistant (MDR) and extensively drug-resistant (XDR) Salmonella strains. Carbapenems, including drugs such as meropenem, have consistently demonstrated high efficacy against Salmonella strains that exhibit resistance to other antibiotics. In this study, resistance to meropenem was observed in 5% of isolates, indicating that carbapenems remain highly effective against Salmonella infections that are resistant to first-line drugs.

This shift in treatment approach is particularly crucial in regions where MDR and XDR Salmonella strains have become prevalent, such as South Asia.[14-22] The emergence of XDR Salmonella strains, particularly in Pakistan, has made carbapenems one of the few remaining viable options for treating these infections.[16,17] Although the use of carbapenems is generally reserved for severe or resistant infections due to their broad-spectrum activity and cost, the growing resistance to first-line antibiotics has necessitated their use in an increasing number of cases.

It is important to remember that relying too much on carbapenems can be risky. Overusing them could lead to resistance, making it harder to treat Salmonella and other infections. That's why it is crucial to use carbapenems carefully, with strict guidelines, to keep them effective for as long as we can. The community surveillance, sanitation, vaccination programs, laboratory cover in remote areas and facilities of culture and sensitivity pattern would be added advantages to curb the menace of this common infection.[22-25]

Limitations: This study has several limitations. Its retrospective, single-center design at Hayatabad Medical Complex may introduce selection bias and limit generalizability to other regions of Pakistan. The lack of molecular typing prevents confirmation of resistance mechanisms. Additionally, the absence of data on patient outcomes or treatment efficacy restricts the ability to assess clinical impact. Future studies should include multicenter data and molecular analyses to address these gaps.

Conclusion:

This study demonstrates the alarming rise of antibiotic resistance in Salmonella, with high resistance rates to ampicillin (70%) and TMP-SMX (65%). MDR strains (37.9%) and increasing ceftriaxone resistance (from 15.2% to 24.8%) highlight the urgent need for updated treatment guidelines and enhanced antibiotic stewardship. Young adults (16-28 years) were most affected (59.7%), with males comprising 75.1% of

cases. These findings emphasize the importance of surveillance, vaccination programs, and improved sanitation to combat resistance and reduce typhoid fever burden.

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