ORIGINAL ARTICLE

Trend of antimicrobial resistance among *Salmonella typhi* isolated from the pediatric population presenting at a tertiary care hospital in Lahore

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ABSTRACT

Background and Objective: Typhoid fever caused by *Salmonella typhi* (*S. typhi*) is an important cause of morbidity and mortality worldwide. The emergence of resistance against the first and second line of drugs has limited the range of drug choices for its treatment. Therefore, the present study was designed to assess the status of drug resistance in *S. typhi* isolated from the blood samples of pediatric patients reporting at a leading tertiary care hospital in Lahore.

Methods: This descriptive study was conducted at the Pathology Department of Allama Iqbal Medical College, Lahore, Pakistan, over a period of 2 years. A total of 1,306 blood samples were aseptically collected from the pediatric population of Jinnah Hospital, Lahore, Pakistan, after obtaining informed assent from the parents/guardians. The samples were transferred into a Bact/Alert blood culture bottle. After the detection of microbial growth by the Bact/Alert 3-D system, bacterial isolates were identified by standard microbiological procedures. VITEK 2 compact automated identification and antimicrobial susceptibility testing instrument (bioMerieux) was used for the antimicrobial sensitivity testing. Data were entered and analyzed by using Statistical Package for the Social Sciences version 21.0.

Results: A total of 235 out of 1,306 (17.9%) blood culture samples yielded bacterial growth, among which 62.5% (*n* = 147) were *S. typhi*. Among 147 *S. typhi* isolates, 70.6% were multidrug resistant, while 63% were extensively drug resistant (XDR). Maximum resistance against first-line drugs observed was for ampicillin (79.4) and co-trimoxazole (67.2).

Conclusion: The emergence and spread of XDR *S. typhi* with a high level of resistance are quite alarming, leaving limited treatment options for the pediatric population. Moreover, increasing resistance to antibiotics demonstrates the quick waning of the efficacy of available first and second-line drugs in the treatment of typhoid fever.

Keywords: *Salmonella typhi*, multidrug resistant (MDR), extensive-drug resistant (XDR), typhoid fever, antibiotics.

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Introduction

Typhoid fever caused by *Salmonella enterica* serovar *typhi* is a systemic infection resulting in an increased morbidity and mortality rate throughout the world. About 10.9 million new cases and 116,800 typhoid fever-related deaths are reported to be occurring per year globally.[1,2] According to the World Health Organization (WHO), typhoid is a serious public health issue that primarily affects children and young people.[3] The third-highest typhoid rate in the world is reported in Pakistan. In 2020, the prevalence rate of typhoid fever affecting children between the ages of 2 and 5 years was 573.2 per 100,000 population per year in Pakistan.[4] Route of transmission is mainly oral-fecal for enteric fever; therefore, the consumption of fecal-contaminated water and food plays a major role in its spread.[5]

Ampicillin, co-trimoxazole, and chloramphenicol were considered to be the first-line antibiotics for typhoid fever treatment,[6] but during the last few decades, the emergence of multidrug resistance (MDR) in *S. typhi* strains, particularly in developing countries, has been reported in escalation. MDR *S. typhi* strains are generally regarded to be resistant against at least one of the three or more than three categorically differentiated antimicrobials, such as ampicillin, sulfonamides (trimethoprim-sulfamethoxazole), and chloramphenicol, whereas extensively drug-resistant (XDR)

are those which are observed to be resistant to all but one or two antimicrobials, demonstrating resistance against several types of antibiotics, such as chloramphenicol, ampicillin, sulfonamides, fluoroquinolones (ciprofloxacin), and third-generation cephalosporins (ceftazidime, cefuroxime, and ceftriaxone), leaving out few options, such as piperacillin/tazobactam, azithromycin, and carbapenems, as efficient treatment options.[7,8] Acquisition of resistant genes in *S. typhi* strains is mainly caused by transmissible plasmids. The first isolate of MDR *S. typhi* was reported between 1970 and 1980, which exhibited resistance to first-line drugs (ampicillin, co-trimoxazole, and chloramphenicol).[9] Thereafter, ciprofloxacin became the preferred drug for *S. typhi* infections, but resistance developed quickly. The first case of ciprofloxacin resistance was reported in 1991.[10] However, the incidence of MDR-*S. typhi* increased from 34.2% to 48.5% during the period from 2001 to 2006 as reported by the Aga Khan University in Pakistan. During this period, ciprofloxacin resistance also raised from 1.6% to 64.1%.[11]

Third-generation cephalosporins, macrolides, and carbapenems have been used more frequently to treat typhoid fever since the development of MDR *S. typhi* and fluoroquinolone resistance. In Pakistan, the first case of XDR *S. typhi* was reported in Hyderabad in 2016. XDR strain showed resistance against first-line drugs, a fluoroquinolone, and a third-generation cephalosporin.[12,13] Since then, more than 10,365 infections with XDR *S. typhi* have been reported from Pakistan, as per WHO reports.[14] Despite the efforts made by infection control programs to control the disease, there was a gradual increase in documented cases over a 2-year period (2017 to 2018).[14] Therefore, the present study was designed to determine the frequency and current status of drug resistance of *S. typhi* isolated from the blood samples of pediatric patients with septicemia presenting at one of the largest tertiary care hospitals in Lahore, Pakistan.

Methods

The present study was conducted at the Pathology Department of Allama Iqbal Medical College, Lahore, Pakistan, over a period of 2 years, from January 1, 2021 to December 31, 2022. Samples were collected from the college associated with Jinnah Hospital, Lahore. Samples from both genders of pediatric patients, suspected of bacterial sepsis and presenting with fever,[15] within the age group of 0-12 years, were included in the study. Repetitive samples from the same patient were excluded. Also, patients with bleeding disorders, multiple co-morbidities, having any malignancy, or who were already on antibiotic therapy were excluded. A total of 1,306 blood cultures from suspected cases of bacterial sepsis were analyzed. Blood samples (4 ml) were collected in Bact/Alert blood culture bottles from each patient by an experienced staff nurse. The samples were transported to the Microbiology Laboratory. Blood culturing was done through automation in the Bact/Alert 3-D culture system (bioMerieux, Durham, NC).[16] After the detection of microbial growth, Gram staining was performed on the positive samples. Samples were sub-cultured on blood agar (Oxoid Ltd., Basingstoke, UK), chocolate agar (Oxoid Ltd., Basingstoke, UK), and MacConkey agar (Oxoid Ltd., Basingstoke, UK). After sub-culturing, the inoculated culture plates were incubated for 18-24 hours at 37°C aerobically. After overnight incubation, different microbiological procedures were used to identify bacterial isolates.[17] For the identification of Gram-negative bacteria, Analytical Profile Index 20E was used.[18] VITEK 2 compact automated identification and antimicrobial susceptibility testing instruments (bioMerieux) were used for the antimicrobial sensitivity testing.[19] The isolates were labeled "multidrug-resistant" (MDR), which was resistant to first line drugs, and "extensively drug-resistant" (XDR), which showed resistance to more than two classes of antibiotics.[20]

Statistical analysis

Data were entered and analyzed by using Statistical Package for the Social Sciences version 21.0. Sensitivity patterns were presented as frequency and percentages. Cross tabulation was done for gender and age. The chi-square test was used to assess statistical significance with a p-value < 0.05 taken as statistically significant.

Results

Out of 1,306 blood cultures, 235 (17.9%) were positive for bacterial growth. Out of these 235 positive samples, 62.5% yielded *S. enterica* species (72.1% were *S. typhi* while 27.9% were *S. paratyphi* A). The sensitivity pattern of all the isolates (n = 147) indicated 70.6% were MDR while 63% were XDR *S. enterica* isolates (Figure 1).

Antimicrobial susceptibility testing revealed that 79.4%, 74.7%, and 67% of *S. typhi* were resistant to ampicillin, ciprofloxacin, and co-trimoxazole, respectively, while 65.4% isolates were resistant to chloramphenicol. All isolates of *S. paratyphi A* tested for azithromycin were susceptible (Table 1).

Discussion

Enteric fever is a serious public health issue across the world, putting a significant burden on healthcare system, especially in developing countries. In Pakistan, an alarming situation regarding antibiotic resistance has been developed because of the increase in the emergence of MDR and XDR strains.[5] In the present study, 72.1% (n = 106) isolates were of *S. typhi* out of 147 *S. enterica* species. Similar results were reported by Khanal et al.[21] from B. P. Koirala Institute of Health Sciences Hospital, Nepal, in which *S. typhi* was the most

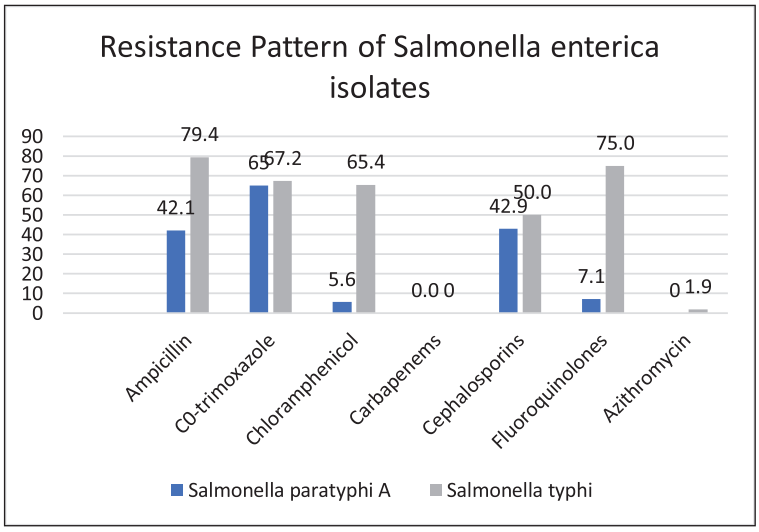

Figure 1. *Resistance pattern of S. enterica serovars against different classes of antimicrobial drugs. Resistance of S. typhi against ampicillin was 79.4%, while 75% and 67.2% of isolates were resistant to fluoroquinolones and co-trimoxazole, respectively. 65% S. paratyphi A isolates were resistant to co-trimoxazole. Carbapenems showed 100% sensitivity against S. typhi and S. paratyphi A.*

Table 1. *Antimicrobial sensitivity pattern of S. typhi among 147 isolates.*

Antibiotics	Sensitive (%)	Resistant (%)
First line drugs		
1. Ampicillin	22 (20.6)	85 (79.4)[a]
2. C0-trimoxazole	35 (32.8)	72 (67.2)
3. Chloramphenicol	37 (34.6)	70 (65.4)
Second line drugs		
1. Ciprofloxacin	27 (25.3)	80 (74.7)
2. Ceftriaxone	54 (46.8)	53 (53.2)
3. Cefipime	62 (58)	45 (42)
Third line drugs[a]		
1. Imipenem	107 (100)	0 (0)
2. Meropenem	107 (100)	0 (0)

[a]Maximum resistance was observed against ampicillin (79.4%), while 100% isolates were sensitive against third line of drugs.

common serotype isolated from the blood samples from the patients with enteric fever. Another study by Zakir et al.[22] from Pakistan in 2021 also reported *S. typhi* as the most common serotype (90%) isolated from patients with enteric fever. In accordance with our study, Fatima et al.[23] and Qamar et al.[24] from Pakistan also reported similar results.

Various studies from all over Pakistan have documented the presence of MDR *S. typhi.*[21-23] MDR *S. typhi* are found to be resistant against first-line antibiotics, which include ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole. In the present study, 70.6% of isolates were found to be MDR. A retrospective study conducted by Klemm et al.,[12] conducted over a period of 9 years, also reported a high burden of MDR and fluoroquinolones-resistant strains. Blood samples were collected from tertiary care hospitals of Karachi and Hyderabad from the Sindh region of Pakistan Similar results were also reported by Park et al.,[25] who showed a rapid increase in MDR *S. typhi* in Ghana, Kenya, and Tanzania, and reported 52% MDR *S. typhi* isolates among the total number of *S. typhi* strains across the samples collected from 11 countries of Sub Saharan Africa. Misuse or uncontrolled use of antimicrobials that are sold over the counter without a prescription or medical supervision may be the root cause of the emergence of MDR strains.

In Pakistan, the majority of MDR strains of *S. typhi* have attained additional resistance to fluoroquinolones and beta-lactams, which marked them as XDR.[12] In the current study, 63% isolates were found to be XDR, which were in accordance with another study conducted in Pakistan which reported 54% XDR strains.[26] Similar to our results, many local and international studies also reported a high prevalence of XDR strains.[25-29] In the current study, 79.4% and 67% of *S. typhi* were resistant to ampicillin and co-trimoxazole, respectively. A study conducted in China documented ascending trends in resistance to ampicillin (91%) and co-trimoxazole (88%) in *S. typhi* isolated from blood samples from patients with enteric fever.[30] The two drugs ceftriaxone and ciprofloxacin are regarded as the main pillars of typhoid treatment, especially in developing countries, but in the present study, high resistance was also observed against these antibiotics. A total of 75% of isolates showed resistance against ciprofloxacin in the current study, which is in accordance with other similar studies published locally and internationally.[12,29,31,32] Similar results were also reported in a study conducted in Taiwan,

Table 2. *Antimicrobial sensitivity pattern of S. typhi with respect to gender (cross tabulation).*

Category	Drugs	Male		Female		*p*-value*
		Sensitive (%)	Resistant (%)	Sensitive (%)	Resistant (%)	
First line drugs	Ampicillin	19.8%	80.2%	21.5%	78.5%	**0.08**
	Co-trimoxazole	36.6%	63.4%	29%	71%	
	Chloramphenicol	35.8%	64.2%	33.4%	66.6%	
Second line drugs	Ciprofloxacin	24.3%	75.7%	26.3%	73.7%	**0.06**
	Ceftriaxone	45.8%	54.2%	47.8%	52.2%	
	Cefipime	54.5%	45.5%	61.5%	38.5%	
Third line drugs	Imipenem	100%	0%	100%	0%	**0.1**
	Meropenem	100%	0%	100%	0%	

*Statistically insignificant results reflect no association between gender and resistance pattern of *S. typhi*.

Table 3. *Antimicrobial sensitivity pattern of S. typhi with respect to age (cross tabulation).*

Category	Drugs	<10 years		>10 years		*p*-value*
		Sensitive (%)	Resistant (%)	Sensitive (%)	Resistant (%)	
First line drugs	Ampicillin	18.8	81.2	22.4	77.6	0.07
	Co-trimoxazole	34.6	65.4	31	69	
	Chloramphenicol	36.8	63.2	32.4	67.6	
Second line drugs	Ciprofloxacin	24.8	75.2	25.9	74.1	0.06
	Ceftriaxone	44.8	55.2	48.8	51.2	
	Cefipime	53.8	46.2	62.2	37.8	
Third line drugs	Imipenem	100	0.0	100	0.0	0.12
	Meropenem	100	0.0	100	0.0	

*Statistically insignificant results depict no association between age and resistance pattern of *S. typhi.*

which showed 69% resistance against ciprofloxacin.[33] Association of the resistance pattern of *S. typhi* with gender and age was found to be statistically insignificant in the present study (Tables 2 and 3), which depicts that gender and age are independent of the antimicrobial resistance pattern in the study population.

Regarding third-line drugs for enteric fever treatment, carbapenems showed 100% sensitivity against *S. enterica* serovars. Azithromycin was also highly sensitive against *S. enterica* isolates. A study conducted by Sjölund-Karlsson et al.[34] also reported 93.6% sensitivity to azithromycin against *S. typhi* isolated from the blood samples of enteric fever patients. Nowadays, azithromycin is the drug of choice for treating uncomplicated enteric fever. The prospect of antibiotic resistance, however, necessitates continuous monitoring of its sensitivity patterns.

While focusing on increasing antimicrobial resistance, actions must be taken to raise health and hygiene awareness among health practitioners as well as for the general population. In developing countries such as Pakistan, where antibiotic stewardship programs are not up to date, this should be a serious concern for organizations working on it. Various practices, including good hand hygiene, improved sanitation, and effective antibiotic policy, can help to control the disease and thereby reduce antimicrobial resistance in the community. To reduce the burden of disease caused by *S. typhi*, effective surveillance, improved diagnostics, more rational antimicrobial usage, and effective mass vaccination will all be crucial.

Conclusion

The emergence and spread of XDR *S. typhi* with a high level of resistance are quite alarming, leaving limited treatment options for the pediatric population in Pakistan. Moreover, increasing resistance to antibiotics demonstrates the quick waning of the efficacy of available first- and second-line drugs in the treatment of typhoid fever. Antibiotic stewardship, continuous surveillance, and vaccination on a mass level should be the priority areas to reduce the spread of this deadly disease.

Limitations of the Study

This was a single-center study; because of the extensive spread of XDR *S. typhi,* a multicenter study should be conducted to determine

a more exploratory and representative picture of the resistance pattern in our region.

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List of Abbreviations

ID/AST	Identification and antimicrobial susceptibility testing
MDR	Multidrug resistant
S. typhi	*Salmonella typhi*
WHO	World Health Organization
XDR	Extensively drug resistant

Conflict of interest

None to declare.

Grant support and financial disclosure

None to disclose.

Ethical approval

The study was approved by the Ethical Review Board of Allama Iqbal Medical College/Jinnah Hospital, Lahore, Pakistan, vide reference no: 47/ERB/2019, dated March 13th, 2019.

Authors' contributions

FR: Concept and design of study, analysis of data, critical intellectual input to the manuscript.
IJ, TT, AY: Drafting the manuscript, acquisition of data.
FA, AA: critical intellectual input to the manuscript.
ALL AUTHORS: Approval of the final version of the manuscript to be published.

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