ORIGINAL ARTICLE

Current trends of antimicrobial susceptibility of typhoidal salmonellae in adult population in a federal tertiary care hospital - Islamabad

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ABSTRACT

Background: *Salmonella typhi* and *Salmonella paratyphi A, B,* and *C* are the primary causes of typhoid fever, which affects about 21 million people yearly and poses a serious health risk. Pakistan's population is especially susceptible because of the disease's high frequency. The increasing prevalence is made worse by *Salmonella typhi* types that are resistant to antibiotics, which emphasizes the need for thorough investigation and action. The purpose of this study was to evaluate the patterns of antibiotic susceptibility among typhoid patients.

Material and Methods: This cross-sectional study was conducted in Islamabad from June 2021 to December 2022. Patients with healthy positive blood cultures, both male and female, were enrolled in the study. Susceptibility testing was performed on 110 samples of *Salmonella typhi* and 40 isolates of *Salmonella paratyphi* against seven antibiotics. Information was gathered in a tertiary hospital in Islamabad, Pakistan.

Results: It is concerning to note that 47% of *Salmonella typhi* isolates showed extensive drug resistance (XDR), and 25% showed multidrug resistance (MDR). Interestingly, no MDR or XDR was seen in any of the isolates of *Salmonella paratyphi*.

Conclusion: Urgent action is required to combat the growing threat of typhoid fever caused by antibiotic resistance. The study emphasizes the need to use antibiotics wisely and effectively. The results highlight the necessity of close monitoring and a diversified strategy to tackle the growing threat of drug-resistant *Salmonella typhi*.

Keywords: Typhoid fever, *Salmonella typhi*, *Salmonella paratyphi*, Antibiotic resistance, Multidrug resistance, Azithromycin sensitivity, Healthcare challenges

BACKGROUND

Salmonella enterica subspecies enterica serovar typhi and serovar paratyphi A,B,C are the causative agents for enteric fever which is also known as typhoid fever. Typhoid affects about 21 million people each year, with Pakistan's citizens being the most vulnerable among Asian nations where the disease is still common.[1] According to 2018 estimates, 9 million cases of typhoid fever are reported each year, resulting in approximately 110 000 deaths. Pakistan has the highest estimated incidence rate of typhoid fever in South Asia (493.5 per 100,000 people per year).[2] Globally the incidence of paratyphoid fever was approximately 3.8 million cases in 2019, which makes up 29.2% of the total incidence of enteric fever.[3] *S.typhi* and *S.paratyphi A* causes clinically similar syndromes (fever, headache, nausea, malaise, anorexia, and myalgias but they have different epidemiology, geographical distributions, and different tendencies to develop resistance to antimicrobials.[4] Currently, the rise of Salmonella resistance has limited the effectiveness of many antibiotics. Globally, *Salmonella typhi* from Asia and Africa are increasingly being found to have multidrug resistance (MDR).[2] In nations with high illness burdens, like Pakistan, the rise of MDR has severely constrained therapeutic options.[5] Salmonella enterica serovar Typhi strains that are extensively drug-resistant (XDR) have lately emerged as a result of decades of indiscriminate antibiotic use. Therefore,

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typhoid fever outbreaks that are highly drug-resistant have been reported in Pakistan[1].

The advent of *S.typhi* strains resistant to drugs indicated for treatment has led to an increase in the incidence rates of typhoid fever. The Centers for Disease Control and Prevention (CDC) considers antibiotic-resistant *S.typhi* to be a severe danger that necessitates ongoing surveillance and prevention to limit the spread of resistant strains. Historically, first-line antibiotics for typhoid treatment included chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole.

Multidrug resistant (MDR) *S.typhi* appeared in the late 1980s, classified as strains resistant to these first-line antibiotics. This resulted in fluoroquinolones (like ciprofloxacin) being used as the first-line medication. However, the use of third-generation cephalosporins (such as ceftriaxone) as a suggested first-line treatment has been advocated in the case of treatment failure due to rising fluoroquinolone nonsusceptibility. *S. typhi* bacteria are labeled as XDR *S. typhi* when they exhibit resistance to fluoroquinolones, chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, and third-generation cephalosporins.[6] In November 2016, a large outbreak of ceftriaxone-resistant typhoid fever started in Hyderabad, a city of southern Pakistan. The associated organism was a H58 *S.typhi* exhibiting resistance to five classes of antimicrobials (chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, fluoroquinolones, and third-generation cephalosporins) and was consequently labeled as extensively drug-resistant (XDR) *S.typhi.*

MATERIAL AND METHODS

This cross-sectional study was conducted in a tertiary care hospital in Islamabad, Pakistan from June 2021 to December 2022. Sample technique was consecutive non-probability. Demographic detail of patients were collected on predefined Performa. Prior to the conduction of the study ethical approval was obtained from ethical review committee PIMS vide reference number F.3-1/2023 (ERRB)/Chairman dated 4th July 2023.

Only the samples which tested positive for *Salmonella typhi* and *paratyphi* were included in the study age group where all those were excluded which failed to give a positive result. Bacterial culture was performed using an automated blood culture system (VersaTREK) Signal-positive samples were plated on MacConkey agar, Blood agar that had 5% sheep blood added to it, and chocolate agar (Oxoid,). The API20E biochemical test (bioMérieux,) and Salmonella serology (Oxoid, Hampshire, United Kingdom) were carried out concurrently for the identification of salmonella enterica. The Kirby Bauer disk diffusion technique was applied for sensitivity testing of Ampicillin, Azithromycin, Ciprofloxicin 5µg, Cortimoxazle 25µg, Imepenem 10µg, Meropenem 10µg, Chloramphenicol 30µg, Ceftriaxone 30µg, (Oxoid). The results were interpreted according to the Clinical Laboratory Standard Institute criteria (CLSI 2022)[7]. The frequency and percentages were calculated for qualitative variable like gender. The percentage of various isolate against different antibiotic were calculated. Means and standard deviation were calculated for qualitative variable such as age and different wards. P value of < 0.05 were taken significant. The data were analyzed using SPSS 28.

RESULTS

The sensitivity pattern of 110 *S.typhi* and 40 *S.paratyphi* isolates was studied against recommended antibiotics, the sensitivity of *Salmonella typhi* isolates was 50% for ampicillin, 53% for co-trimoxazole, 75% for chloramphenicol, ciprofloxacin showed an intermediate sensitivity of about 42%, ceftriaxone being 53% sensitive whereas azithromycin and meropenem showed a sensitivity of 95% and 100% respectively. *S.paratyphi* was 67% sensitive to ampicillin, 98% sensitive to co-trimoxazole, 98% sensitive to chloramphenicol, 69% sensitive to ciprofloxacin, and 100% sensitive to ceftriaxone, azithromycin, and meropenum (Table-I).

Among *S.typhi* isolates, 25% were multidrug-resistant (MDR) whereas 47% were found to be extensively drug-resistant (XDR). Individual resistance to 1st line antibiotics was noted in *S.paratyphi* isolates but no MDR or XDR isolates were found (Table-II). The number of positive samples and their proportion for each patient age group are shown in the (Table-III) The age group of 12 to 20 years old has the highest positive rate (39%) followed by the 21 to 40-year-old group (30%), the 41 to 60-year-old group (21%), and the patients aged 61 and over (10%). This indicates a decreasing trend in positivity with increasing age.

Table-I: Sensitivity Pattern of *Salmonella typhi* and *Salmonella paratyphi.*

Antibiotics	Antibiotics *Salmonella typhi* (n=110)	*Salmonella paratyphi*(n=40)
	Sensitivity %	Sensitivity %
Ampicillin	50%	67%
Co-trimoxazole	53%	98%
Chloramphenicol	75%	98%
Ciprofloxacin	I [42%] S[9.5%]	69%
Ceftriaxone	53%	100%
Azithromycin	95.47%	100%
Meropenem	100%	100%

Table-II: MDR & XDR numbers (%) of *Salmonella typhi* and *Salmonella paratyphi.*

	Salmonella typhi n=110 (%)	*Salmonella paratyphi* n=40 (%)
MDR	n = 28 (25%)	n= 0 (0%)
XDR	n = 52 (47%)	n= 0 (0%)

Table-III: Positive samples and their proportion for each patient's age.

Patient Age Group (yrs)	No of Positive Sample %age
12-20	59 (39%)
21-40	44 (30%)
41-60	32 (21%)
61 >	15 (10%)

DISCUSSION

Salmonella typhi and *Salmonella paratyphi* are foodborne and waterborne pathogens that cause enteric fever and have emerged as a major cause of morbidity and mortality worldwide.[8] Disease burden of typhoid fever is highest in Asia. In Bangladesh, children aged 2-4 years had the greatest crude typhoid incidence (217 [195-239] per 100 000 person-years, whereas children younger than 2 years had the highest incidence in Pakistan. The emergence of drug resistance has led to an evolution in the pattern of prescription in the management of enteric fever.[9] Inappropriate usage of antibiotics has led to the development of multidrug-resistant strains and more recently, extensively drug-resistant (XDR) strains of *Salmonella typhi*.[10] In 2017-2018 largest outbreak of ceftriaxone resistant *Salmonella typhi* was reported in Pakistan.

In our study, 25% percent of the *S.typhi* isolates showed resistance to Chloramphenicol, Cotrimoxazole and Amoxicillin hence falling in the MDR category. According to local statistics, a retrospective study conducted in Karachi and Hyderabad reported a high percentage of MDR strains that were sensitive to cephalosporins. Another more recent study conducted in Jamshoro found that paediatric cases of *S.typhi* had significantly smaller percentages of MDR strains associated with lower rates of ceftriaxone and cefixime sensitivity with greater rates of first-line anti-biotic sensitivity.[11] A study conducted in 2016 in India reported that *S.typhi* and *S.paratyphi* isolated in equal frequency. Both species reported high sensitivity to third-generation cephalosporins, cotrimoxazole, ampicillin and chloramphenicol. However, the most significant levels of resistance were observed against nalidixic acid and ciprofloxacin.

Multi-drug resistance against first- line antibiotics was significantly low which is consistent with the results of our study as ciprofloxacin showed only an intermediate sensitivity of 42% for *S.typhi* and a sensitivity of 69% for *S.paratyphi* isolates whereas, the sensitivity of these isolates to 1st line antibiotics has significantly improved when compared to previous studies.[12]

A research review including data from five endemic Asian nations, China, India, Indonesia, Pakistan, and Vietnam, showed a 7–65% incidence of MDR salmonella isolates. It also reported Ciprofloxacin and ceftriaxone as some of the best treatment options available. However, a study conducted in Kenya reported a high frequency of MDR organisms as well as reduced susceptibility to ciprofloxacin. The isolates displayed high sensitivity to ceftriaxone.[13] In our study MDR (25%) may be because these drugs were not commonly used these days for typhoid in our country.

Forty-seven percent of *S.typhi* isolates showed resistance to 3rd gen cephlosporins (ceftriaxone) and were placed in the category XDR typhi. These isolates were sensitive to carbapenems like imipenem and meropenem. When compared to the findings of a recent study conducted in Karachi, where 8.7% of the total

S.typhi cases were categorised as XDR,[14] our investigation in Islamabad identified a substantially larger incidence of XDR typhi cases. A retrospective study conducted a few years back in PIMS reported the detection of 0.7% XDR *S.typhi* isolates 8. Another study in Islamabad found that XDR *S.typhi* cases contributed 5.01% of total *S.typhi* isolates during a span of four years (2015-2018).[6]

Over the past years about 30% and 50% of XDR *S.typhi* cases were reported in 2018 and 2019 respectively in the province of Punjab.[15] The reason of this increase in XDR is mostly because mismanaged patients report to the tertiary care hospitals. Over the past years Lahore reported an alarmingly high number of XDR *S.typhi,* they were almost 48.25% in a study conducted in 2021 [16]. A study from Karachi indicated over 53% XDR *S.typhi* isolates in 2020, and azithromycin and imipenem were found to be susceptible to all of these *S.typhi* isolates.[17] The first XDR outbreak was reported in Sindh but today cephalosporin-resistant strains of *S.typhi* have also been found in India, Bangladesh, Iraq and the Philippines.[18] In our study XDR is 47%, because we conducted research on adults while most of the studies includes children in their studies.

Thirty-three percent (33%) of *S.paratyphi* isolates were resistant to ampicillin, 10% of isolates were resistant to co-trimoxazole and chloramphenicol respectively but no such isolate was found which could be classified as multi-drug resistant (MDR) or extensively drug resistant (XDR). *S.paratyphi* cases, on a whole, considerably displayed very low incidence of resistance against first-line antibiotic than *S.typhi* cases. These findings were similar to studies conducted in Islamabad as well as southern Pakistan. The sensitivity patterns displayed sensitivity to cephalosporins and imipenems but resistance to nalidixic acid and ciprofloxacin 8, 10, 11. In our study, *S.paratyphi* isolates were 100% sensitive to ceftriaxone, azithromycin and meropenem and out of the total 40 *S.paratyphi* isolates tested, none proved to be falling in the category MDR hence indicating that the incidence of resistance collectively against all 1st line antibiotics in *S.paratyphi* isolates is not detected.

In a study conducted in Karachi the percentage of multidrug-resistant (MDR) isolates in *S.paratyphi* were reported to be about 34% (18 isolates) out of a total of 292 typhoidal Salmonella isolates which were cultured.[19] In England, a significant increase in cases of *S.paratyphi A* was noted from 2018 to 2019, the genomic analysis of these isolated revealed ciprofloxacin-resistant clones from India and Pakistan to be the most commonly imported strains. However, in the same study, *S.paratyphi B* case numbers remained relatively stable and the isolates have remained susceptible to antibiotics since 2015[20] but this could change soon and a time may come when MDR and XDR strains of *S.paratyphi* start emerging in developed countries as well.

Azithromycin showed a sensitivity of about 95.47% for *Salmonella typhi* isolates in our study. Previously *S. typhi* was 99.9% susceptible to azithromycin, with a mean MIC of 4.98 g/mL.[21] It is evident that azithromycin susceptibility is decreasing, which clinicians are using as a last resort for the treatment of XDR typhoid fever, along with carbapenems. The MICs of *Salmonella typhi* isolates ranged from 2 to 16ug/mL and were all sensitive to Azithromycin according to CLSI criteria, but when compared to MICs of pre-covid isolates, the MICs of isolates were still relatively higher. A research conducted at Agha Khan University Hospital identified *Salmonella typhi* isolates with a point mutation in the acrB gene and it is proposed that the said mutation is responsible for Azithromycin resistance in those isolates. Similarly, Bangladesh reported 12 Azithromycin-resistant *S. typhi* strains and these strains too showed acrB gene mutation [22]. Furthermore, India has reported 7 *S. typhi* organisms resistant to Azithromycin 1 with the R717Q mutation in the acrB gene.[23]

A recently conducted study showed that 6.6% of *Salmonella typhi* isolates were resistant to Azithromycin by the disk diffusion method but a relatively lower resistance was reported when the Broth microdilution (BMD) method was used.[24] According to our research, typhoid fever is more prevalent in Pakistan among young adult and teenagers. According to a 2018 study, individuals over the age of 18 had a higher incidence of *Salmonella typhi*, but children ages 5 to 18 had a higher prevalence of *Salmonella paratyphi*. Therefore, the BMD method should used in the future to confirm or rule out azithromycin resistance reported by the disk diffusion method. With typhoid fever treatment options dwindling, typhoid presents itself as a grave concern that requires immediate attention before it becomes a global health concern. Judicial use of antibiotics along

with the introduction of Typhoid conjugate vaccine (TCV) is the need of the hour.

LIMITATION

MIC and E-strip tests were not performed due to limited resources and funds available in our tertiary care center.

CONCLUSION

There has been a significant regional increase in the incidence of XDR *Salmonella typhi*, which is alarming. When compared to previous studies, azithromycin sensitivity has decreased, which can be attributed to its extensive use during COVID pandemic. As a result, antibiotic stewardship is essential, and carbapenems like meropenum should not be used injudiciously to prevent the development of resistance against them.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Muhammad Moaaz Ali: Study concept, questionnaire design, data analysis, data interpretation, manuscript writing, final approval, accountable for every aspect of this research work

Umme Farwa: Main conception of the work, study design, interpretation of data, revised it critically final approval, accountable for every aspect of this research work

Samia Wazir: Study concept, questionnaire design, data analysis, data interpretation, manuscript writing, final approval, accountable for every aspect of this research work

Fatima Kaleem: Main conception of the work, study design, interpretation of data, revise it critically, final approval, accountable for every aspect of this research work

Mariam Tariq: Data analysis final approval, accountable for every aspect of this research work

Shahid Ahmad Abbasi: Overall supervision, final approval, accountable for every aspect of this research work

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