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Original Article

Extensively Drug-Resistant Typhoid Outbreak in Pakistan, Experience at a Tertiary Care Hospital in Lahore; A Tip of An Iceberg

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ABSTRACT

Objective: To provide a laboratory-based surveillance report of typhoid fever cases diagnosed at a tertiary care hospital in Lahore during the ongoing outbreak.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Microbiology, Combined Military Hospital, Lahore Pakistan, from Mar 2018 to Jun 2019.

Methodology: All positive blood culture samples that yielded the growth of *Salmonella Typhi* were included in the study. The samples were dealt with according to standard microbiological procedures. Antimicrobial susceptibility was performed using Clinical and Laboratory Standards Institute (CLSI) guidelines.

Results: During the study period, (377) *Typhoidal Salmonellae* were isolated, of which 327 (86.7%) were *Salmonella Typhi* and 50 (13.3%) were *Paratyphi A*. The percentage of XDR *Salmonella isolates* was 41.9%.

Conclusion: Extensively drug-resistant typhoid fever cases reported in this study represent just the tip of an iceberg. Therefore, nationwide surveillance efforts must be undertaken along with implementing effective preventive measures.

Keywords: Extensively drug-resistant (XDR), *Salmonella typhi*, Outbreak, Typhoid fever.

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INTRODUCTION

Typhoid fever is caused by *Salmonella* enterica subspecies enterica serovar Typhi (*Salmonella Typhi*). It is a systemic febrile illness transmitted by contaminated food and water. According to World Health Organization (WHO), there are 11–21 million cases of typhoid fever and approximately 128,000–161,000 deaths annually, with the majority of the cases from South and South-East Asia and sub-Saharan Africa. The disease, if left untreated, has a fatality rate of 10-30%.[1] Chloramphenicol was the first drug to be used for typhoid fever; the related mortality declined significantly with the discovery and use of this drug for typhoid.[2] However, reports of resistance and therapeutic failure became prevalent in the 1950s. In the subsequent decades, Ampicillin and Trimethoprim-Sulfamethoxazole were widely used. The three drugs, Chloramphenicol, Ampicillin and Trimethoprim-Sulfamethoxazole, were frequently referred to as the first-line anti-typhoidal drugs.[3,4,5]

The emergence of antimicrobial resistance against first and second-line drugs among *Typhoidal Salmonella E* poses a significant clinical and economic challenge.[6-8] The country's poor sanitary conditions, unhygienic cooking utensils and lack of potable water still prevail, thus providing the ideal conditions for sustaining and propagating a typhoid fever epidemic. The WHO has declared an outbreak of XDR *Salmonella Typhi* in Pakistan.[9,10] The situation in Lahore is not so different. Therefore, we are presenting a laboratory-based surveillance report on culture-confirmed cases of typhoid fever.

METHODOLOGY

The study was conducted at the Department of Microbiology of Combined Military Hospital, Lahore Pakistan, from March 2018 to June 2019. This was a laboratory-based surveillance study. Permission was sought from the Institutional Ethical Review Board before the commencement of the study. Blood samples for culture were received from the Outpatient department, Emergency and Medical wards of the hospital.

Inclusion Criteria: Positive blood culture samples that yielded the growth of *Typhoidal Salmonella E* (*S. Typhi* and *S. Paratyphi A*) were included in the study.

Exclusion Criteria: Repeat samples from the same patients were excluded from the study.

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Blood cultures were taken in Brain heart infusion (BHI, Oxoid, Basingstoke UK) broth bottles and incubated at 35±2˚C for seven days. Subcultures were performed on the first, third and sixth day on Sheep blood agar and MacConkey agar (Oxoid, Basingstoke UK). The flat, spreading, non-lactose fermenting colonies were identified based on biochemical reactions using API 20E (Biomerieux, France) and serology with group-specific anti-sera (Bio-Rad). Antimicrobial susceptibility was determined by the modified Kirby–Bauer disc diffusion method on Muller-Hinton agar (Oxoid, UK). Antimicrobial discs used were; Ampicillin (10µg), Ceftriaxone (30µg), Chloramphenicol (30µg), Ciprofloxacin (5µg), Trimethoprim-Sulfamethoxazole (1.25/23.75µg), and Azithromycin (15µg). The Muller Hinton (Oxoid, UK) agar plates were incubated aerobically at 35±2˚C for 18-24 hours. Meropenem susceptibility testing was performed by disk diffusion using 10µg disk and E-strip (Biomerieux, France). The zone diameters were interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines.[10]

Statistical Package for Social Sciences (SPSS) version 21.0 was used for the data analysis. Descriptive statistics were expressed as frequencies & percentages.

RESULTS

A total of 377 positive blood culture samples that yielded the growth of *Typhoidal Salmonellae* (*S. Typhi* and *S. Paratyphi A*) were included in the study The mean age of the patients was 19.6±3.5 years. There were 279 (74.0%) males and 98 (26.0%) females (male: female=2.85:1). During the study period, a total of 377 *Typhoidal Salmonella E* were isolated, out of which 327 (86.7%) were *Salmonella Typhi* and 50 (13.3%) were *Paratyphi A* (Figure-1).

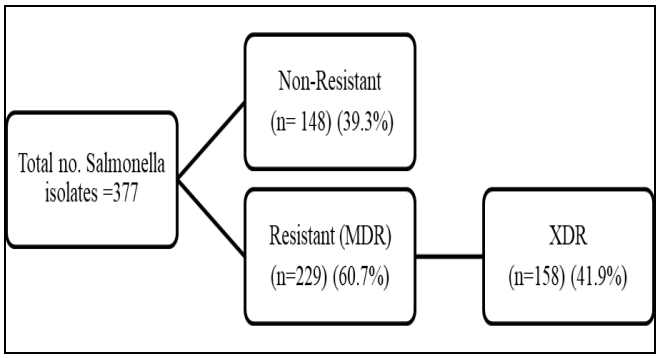

Figure-1: Distribution of MDR and XDR *Typhoidal Salmonellae* Isolates

Timeline of culture positive *Typhoidal Salmonella* cases was shown in Figure-2, while antimicrobial susceptibility pattern was shown in Table.

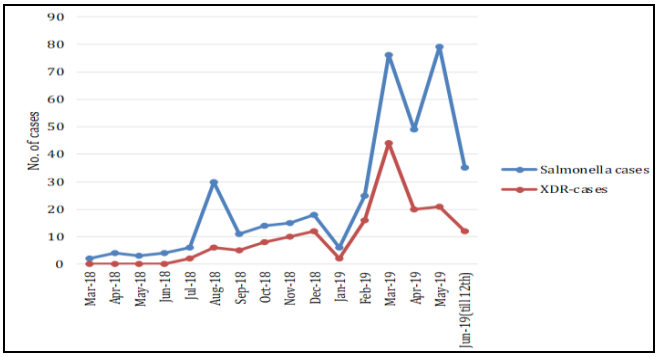

Figure-2: Timeline of Culture Positive Salmonella Cases (March-2018 to June 2019)

Table: Antimicrobial Resistance Pattern of *Typhoidal Salmonellae* (n=377)

Antimicrobial Agents	Resistance %Age
Ampicillin	73.7
Chloramphenicol	68.2
Trimethoprim-Sulfamethoxazole	67.4
Ciprofloxacin	100
Ceftriaxone	41.8
Azithromycin	0
Meropenem	0

DISCUSSION

The first case of XDR- *Salmonella* that was isolated in our laboratory was from the blood culture of a 12-years-old female patient in November 2017. The patient's family had moved from Hyderabad, Sindh. The patient had acquired the infection while in Hyder-abad during the XDR outbreak. This one sporadic case may have been the index case for the outbreak in Lahore. We did not find any XDR cases between November 2017 and March 2018. After which, the XDR cases were more frequently isolated, which prompted active surveillance efforts in our laboratory. According to the National Institute of Health (NIH) report, a total of 6,253 laboratory-confirmed cases of typhoid from different districts of Sindh from January to December 2018 were reported, out of which 3,739 (59.8%) were XDR.[11] In comparison, 339 cases of XDR *Salmonella*e were reported between November 2016 and September 2017.[4] In our setup, 377 cases of culture-positive typhoid were confirmed, out of which 158 (41.9%) were XDR. Another study from Lahore, Pakistan, reported 370 culture-confirmed cases of typhoid from July 2018 to June 2019, out of which 27 were XDR.[12]

Coordinated efforts are required to curtail the menace by adopting preventive measures. The masses need to be educated through public health awareness campaigns.[13-15] The diagnostic laboratories need to be vigilant in reporting cases of XDR typhoid to the

provincial health department.[16,17] Furthermore, the need of the hour is to conserve the available treatment options. Empirical use of Azithromycin and Meropenem should be strongly discouraged. Azithromycin resistance has been reported in Asia.[16,18] With the increasing use of Azithromycin during the current outbreak, it is possible that resistance might spread. Therefore, these drugs should be reserved only for culture-confirmed XDR typhoid cases. Nationwide surveillance must be undertaken at the village, tehsil and district levels to estimate the true disease burden. We have reported the cases from a single laboratory in Lahore, which may be just the tip of the iceberg.

CONCLUSION

Extensively drug-resistant typhoid fever cases reported in this study represent just the tip of an iceberg. Therefore, nationwide surveillance efforts must be undertaken along with implementing effective preventive measures.

Confict of Interest: None.

Author's Contribution

AI:, IAM:, QF:, NS:, AB:, SS: Collecting, analysis of data, drafting of manuscript, approval and review of final version.

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