

An Overview of Extensively Drug-resistant Salmonella Typhi from a Tertiary Care Hospital in Pakistan

Sirichand¹, Asma Bilal², Kausar Keerio³, Kanwal Shaikh⁴, Muhammad Tariq⁵, Muhammad Aslam Chandio⁶

¹Assistant Professor of Pediatrics, Hamdard University of Medicine and Dentistry Karachi Pakistan.

Email: siritajreja@hotmail.com

²Registrar Pediatrics, Prime Hospital Dubai Garhoud UAE.

Email: drasmabilal111@gmail.com

³Senior Registrar Pediatrics, Liaquat University of Medical and Health Sciences Jamshoro Pakistan.

Email: kausarkeerio@gmail.com

⁴Paeds Emergency Incharge, National Medical Centre Karachi Pakistan.

Email: kanwalsh@hotmail.com

⁵Muhammad Tariq, Consultant Paediatrician, Pakistan Institute of Medical sciences Islamabad Pakistan.

Email: muhammadtariq55494@gmail.com

⁶Assistant Professor of Pediatrics, Department of Pediatric Medicine, Shaheed Mohtarma Benazir Bhutto Medical College Lyari Karachi Pakistan.

Email: dr_chandio79@yahoo.com.

*Correspondence author: Sirichand (siritajreja@hotmail.com)

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Abstract

Objective: The study was aimed to investigate the prevalence of multi drug resistant (MDR) and extended drug resistant (XDR) *S. Typhi* in a tertiary care hospital. **Background:** The MDR and XDR cases of *S. Typhi* causing typhoid fever have been significantly increased in Pakistan, just taking Hyderabad alone out of several cities in Pakistan, more than 800 cases of XDR typhoid were identified in year 2016-17, which labeled the whole region as endemic for typhoid. **Study Design:** A retrospective study. **Place and Duration:** This study was conducted in Hamdard University of Medicine and Dentistry Karachi from September 2022 to September 2023 **Methodology:** We included 21 of patients who tested positive for XDR *Salmonella Typhi* on blood culture test. The isolates were tested for the susceptibility of chloramphenicol, ciprofloxacin, co-trimoxazole, ampicillin, azithromycin and ceftriaxone. The disk diffusion method detected the production of Extended-spectrum beta- lactamases (ESBL). Beside drug resistant, age and genders was recorded. Data was entered and analyzed using SPS version 26.0 **Results:** There were total 479 patients who tested positive with *S. Typhi*. Out of the 479 total cases, 21 cases were identified with blood culture-proven XDR *S. Typhi*. There were 12 (57.14%) males and 9 (42.86%) females. *Salmonellae Typhi* was seen in 479 cases. Amongst these 479 cases, 279 (58.25%) were Multi drug resistant and 21 (4.38%) were extremely drug resistant. **Conclusion:** This study emphasizes the presence of XDR *S. typhi* in the given city. Surveillance studies are essential at all levels to assess risk and control this illness.

Keywords

Extensively Drug-Resistant *Salmonella Typhi*, Drug Resistance, Pakistan, Multidrug Resistant

Salmonella Typhi is gram negative bacteria which causes typhoid fever, nearly affecting a sizable

proportion of 14 million worldwide. Marking its fatality up to 70%, *S. Typhi* resulted in 130000 mortalities in 2017 [1]. It was the first Chloramphenicol used as antibiotic to treat typhoid till the mid of 19th century [2, 3, 4], later co-trimoxazole was introduced by 1970s due to development of resistant to Chloramphenicol. However, research from the 1980s indicated *S. Typhi* strains' resistance to all previously used antibiotics [5]. Trimethoprim-sulfamethoxazole appeared to be the treatment option besides ampicillin since the typhoid developed resistance to chloramphenicol. However, it was not long before resistance to these two medications was observed all throughout the world, with rising mortality rates being associated with resistant strains. This led to the use of fluoroquinolones, such as ciprofloxacin, to treat enteric and typhoid fever [6]. The MDR and XDR cases of *S. Typhi* causing typhoid fever have been significantly increased in Pakistan, just taking Hyderabad alone out of several cities in Pakistan [7], more than 800 cases of XDR typhoid were identified in year 2016-17 which labeled the whole region as endemic for typhoid [8,9]. Only a few years after index case of XDR *S. typhi*, in Karachi in 2016, 17000 cases have been reported in the province [10]. Although many research in Pakistan have historically focused on Sindh, there have been reports of rising cases across the country [11, 12] and elsewhere as a result of provincial and worldwide travel [16].

The present study was aimed to investigate the prevalence of XDR/ MDR *S. Typhi* by reviewing the hospital records over the previous four years at given Hospital. Patients' age and antibiotic sensitivity patterns were also studied to determine the resistance.

Methodology

We included 21 of patients who tested positive for XDR *Salmonella Typhi* on blood culture test. The growth attributes of the organism were studied after 24 hours of incubation of those cases who showed positive gram negative rods on blood culture and MacConkey agar plates. The organism was identified as *S. typhi* and confirmed by *S. typhi* polyvalent antiserum (Bio-Rad, France) serologically.

We used disk diffusion technique to test Antimicrobial susceptibility of the isolates and interpreted the zones of inhibition using the Clinical & Laboratory Standards Institute (CLSI) guidelines [17]. On the isolates were tested for the susceptibility of

chloramphenicol, ciprofloxacin, co-trimoxazole, ampicillin, azithromycin and ceftriaxone. The disk diffusion method detected the production of Extended-spectrum beta-lactamases (ESBL). The phenotypic confirmation of ceftazidime and cefotaxime was performed separately and in combination with clavulanate. Beside formal consent from the patient, the mandatory ethical approval was also obtained from the institutional ethical review board. The data was obtained from hospitals microbiology record. For numerical variables we used mean and standard deviation and frequency & percentages were used to report the categorical variables. Data was entered and analyzed using SPS version 26.0.

Results

In the present study, there were total patients 479 patients who tested positive with *S. Typhi*. Out of the 479 total cases, 21 cases were identified with blood culture-proven XDR *S. Typhi*. There were 12 (57.14%) males and 9 (42.86%) females. Out of the 21 cases 9 (42.86%) were under 10 years of age and only 2 (9.52%) were more than 40 years age, rest of the cases were aged between 10 to 40 years. Before being confirmed as XDR *S. Typhi*, 10 (47.62%) patients were already given with cefixime, while azithromycin and ceftriaxone was given to 7 (33.33%) and 4 (19.05%) cases respectively. (As shown in Table 1)

Table I: Various characteristics of patients presenting with Extensively Drug-Resistant *Salmonella Typhi* (n=21)

Patients Age	n	%
Age (Years)		
Less than 10	9	42.86
10 to 20	5	23.81
21 to 30	3	14.29
31 to 40	2	9.52
More than 40	2	9.52
Gender		
Male	12	57.14
Female	9	42.86
Drugs Used before being identified as XDR		
Cefixime	10	47.62
Azithromycin	7	33.33
Ceftriaxone	4	19.05

In the 4 years record, 744 cases admitted with enteric fever caused by different species of *Salmonellae*, out of those, *Salmonellae Typhi* was seen in 479 cases. Amongst these 479 cases, 279 (58.25%) were Multi drug resistant and 21 (4.38%) were extremely drug resistant. (As shown in Table II)

Table II: *Salmonella Typhi* isolates on blood culture-proven (2020 to 2023 - n = 479)

Year	Cumulative Isolates		Multi-drug Resistant		XDR	
	n	%	n	%	n	%

2020	114	23.80	63	13.15	5	1.04
2021	122	25.47	88	18.37	2	0.42
2022	109	22.76	72	15.03	3	0.63
2023	134	27.97	56	11.69	11	2.30
Total	479	100.00	279	58.25	21	4.38

Discussion

Following the detection of the XDR *S. typhi* in Hyderabad, local monitoring was undertaken, resulting in the identification of hundreds of cases in Sindh [18]. A few instances were found through international monitoring [19]. However, outside from Sindh, there is a scarcity of evidence on instances across Pakistan. Our exhaustive review of local literature yielded relatively few XDR *S. typhi* cases. In 2012, a study reported the first instance of *S. typhi* generating extended-spectrum β -lactamase [20]. The second incidence was reported from Rawalpindi in 2016 [21].

In the present study, there were total patients 479 patients who tested positive with *S. Typhi*. Out of the 479 total cases, 21 cases were identified with XDR *S. Typhi*. A 2017 investigation in Islamabad found that 64 *S. typhi* and five *S. Paratyphi* isolates were MDR [22].

In our study, before being confirmed as XDR *S. Typhi*, 10 (47.62%) patients were already given with cefixime, while azithromycin and ceftriaxone was given to 7 (33.33%) and 4 (19.05%) cases respectively. Another retrospective multicenter investigation on identifying antibiotic resistance patterns in blood culture-proven typhoid patients found a significant prevalence of fluoroquinolone-resistant and MDR *S. typhi* strains [23].

In the present study more than 1/3rd of our patients were children, which is in line with the findings of other reported in Pakistan [1-2, 7]. In our study proportion of males seemed to be higher than females. Rendered gender inequity emphasized exploring XDR *S. typhi* further. Unclean edibles and water, insufficient cleanness measures, and the use of sewage water are all significant causes of spread of typhoid [24]. Reportedly, the establishment and spread of XDR *S. typhi* to Sindh's deteriorating sewage and water infrastructure, poor vaccination rates, inappropriate antibiotic usage, and overcrowded city residences [25]. In the present study we evaluated last 4 years record, there were 744 cases admitted with enteric fever caused by different species of Salmonellae, out of those, Salmonellae Typhi was seen

in 479 cases. Amongst these 479 cases, 279 (58.25%) were Multi drug resistant and 21 (4.38%) were extremely drug resistant.

Antibiotic overuse in farm animals contributes to the emergence of antibiotic-resistant genes in foodborne pathogens [22- 27].

The significant upsurge in cases of XDR *S. typhi* necessitates that prompt prevention steps be implemented. The government must take thorough efforts to provide safe water for drinking, to provide for effective and to enforce food safety standards for food and beverage businesses. Its dire need of the hour to evaluate the frequency of chronic Salmonella carriers, who may be a key source of typhoid transmission.

Conclusions

This study emphasizes the presence of XDR *S. typhi* in the given city. Investigative and survey studies are essential at all levels to assess risk and control this illness. Our findings also highlight the need of preventative measures, judicious use of antibiotics, and immunization at the national level in mitigating this threat.

Conflict

None

Funding

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Ethical Approval

It was taken before study.

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