

EXTENSIVELY DRUG RESISTANT (XDR) *SALMONELLA TYPHI* RED FLAG FOR CLINICIANS AT KARACHI

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ABSTRACT

Background: *Salmonella typhi* cause enteric fever which is a grave community health problem with increasing antibiotic resistance. *Salmonella typhi* is responsible for 10.9 million morbidities and 116800 mortalities worldwide with the greatest burden falling on third world countries. It is common among children with incidence rate of typhoid fever 573.2 per 100,000 in aged 2-5years and 451.7 cases per 100,000 children per year among 2-15years old in Pakistan. Early detection of *Salmonella typhi* and selection of appropriate antibiotics are important to mitigate the morbidity and fatality rate related to these kinds of infections. We have conducted this study to assess the extensively drug resistance in isolates of *Salmonella typhi* in Karachi, Pakistan.

Material and Methods: This cross-sectional study was done at private set up, Karachi from 2019-2021. This study was ethically approved from hospital management. Data related to phenotypic detection of antimicrobial susceptibility was obtained from LIMS (Laboratory Information Management System). According to record both in-door and out-door patients were included in the study. The collected data was scrutinized by using descriptive statistics performed with SPSS version 24. Chi-square was used to test for statistical significance ($P \leq 0.05$).

Results: Total 10564 samples were extracted from data, out of which 4582 samples were found positive for growth of different microorganisms. *Salmonella typhi* were positive in 1500 cases and only 412 samples were exhibiting XDR *Salmonella typhi*. Maximum cases of XDR *Salmonella typhi* were detected in age group 5-10 years with 38.8%. There were 61% male and 39% female.

Conclusion: Our study explains that cases of enteric fever as a result of *Salmonella typhi* are swarming in all cities of Pakistan and particularly at Karachi. XDR is not restricted to Karachi but it is the tip of the iceberg. There is an urgent need to detect these cases timely and start appropriate treatment to overcome complications.

Keywords: *Salmonella typhi*, XDR, Antimicrobial susceptibility, Ceftriaxone, Azithromycin.

BACKGROUND

Salmonella typhi isolates exhibit extensively drug-resistance is alarming situation in the city of Karachi. *S. typhi* bacteria are known as extensively drug resistant (XDR) *S. typhi* when they confer resistance to ampicillin, chloramphenicol, cephtriaxone, fluoroquinolones, trimethoprim sulfamethoxazole.¹

Typhoid (enteric fever) is global issue and 14.3 million patients of typhoid were documented in 2017,

followed by 135.9 thousand deaths with a considerable pressure(69.6%) in South Asia.² Typhoid fever is endemic in third world countries of South Asia, like Pakistan, as a result of poor hygiene, lack of clean drinking water and well established sewerage system.³ This is critical illness presented with severe complications especially in children, with rate of 451.7 cases per one lakh children aged 2-15 years.⁴ In Pakistan pure and safe water can be provided only 20% of the population and the left over are compelled to utilize impure and dirty water.⁵ However, in the 1980s, extensive spread of IncH1 plasmids in *Salmonella* led to immediate resistance to all these antibiotics, known as multidrug-resistant (MDR) *Salmonella*. Firstly, the ceftriaxone resistant isolates of *Salmonella* was reported as endemic in Hyderabad in the year of 2016.⁶ According to the report of World Health Organization (WHO), the Provincial Disease Surveillance and Response Unit (PDSRU), 5274 XDR *S. typhi* cases were present in 14 districts of Sindh from 2016 to

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2018. These revealed 4% cases from different districts of Sindh, 76% cases from Karachi city, and 27% cases from Hyderabad district.⁷ Seven patients were diagnosed with XDR *Salmonella typhi* in UK, USA and Canada, all had a visit to Pakistan.^{8, 9} The Government of Pakistan and disease controlling institutions have tried to control the situation but still marked rise in detected cases of XDR of *Salmonella typhi* from 2017 to 2021.¹⁰

Frequency of extensively resistant cases of enteric fever is high but still limited data regarding this infection is available. This study was designed to detect these blood culture-proven XDR *S. typhi* cases along with their age overview and therapy options. It also showed the resistance pattern of *S. typhi*, suggesting the contribution burden made by XDR *S. typhi* isolates, at private hospital of Karachi. We can determine the frequency of XDR *Salmonella* cases. Situational alertness of the XDR *Salmonella typhi* will facilitate physicians to choose appropriate antibiotics in order to overcome the dissemination of resistant pathogen. Furthermore, the study is likely emphasizing the seriousness of this waterborne/food borne communicable disease and motivate community toward preventive actions like personal hygiene, proper sewerage system, clean water supply, and also vaccination campaigns by government.

This study will raise and detect the XDR typhoid cases for future outlook of antibiotic stewardship and maintenance of surveillance program. This study will facilitate to overcome resistant cases before it is no longer manageable and leads back to pre-antibiotic era.

MATERIAL AND METHODS

This cross-sectional study was conducted at private set up, Karachi from 2019-2021. This study was ethically approved from hospital management. Data related to phenotypic detection of antimicrobial susceptibility was obtained from LIMS (Laboratory Information Management System). According to record both indoor and out-door patients were included in the study. Non-probability convenient data collection technique was used. Typhoid patients with blood culture confirmation for *S. Typhi* and resistance to the five classes of antibiotics (ampicillin, chloramphenicol,

trimethoprim-sulfamethoxazole, fluoroquinolone, and 3rd generation cephalosporin (ceftriaxone or cefixime) were eligible to be included in this study.

Those patients who were on antibiotics for last two weeks were excluded from study. Patients with incomplete medical records especially missing information on antimicrobial treatment, duration of treatment, and treatment failure were excluded from the study.

After processing of blood samples in BACTEC automated blood culture system, gram staining was done in order to differentiate gram positive from gram negative. Biochemical identification was done by API 20E (Biomérieux) in order to interpret species of *Salmonella typhi*. Serological tests were done in order to differentiate species. Lawning was done on Muller Hinton agar plated with antibiotic discs and antimicrobial susceptibility was performed by using the Kirby-Bauer disk diffusion method. Ampicillin 30µg (oxid), ceftriaxone 30 µg (oxid), ciprofloxacin 5 µg (oxid), trimethoprim sulphamethoxazole 30 µg (oxid) and chloramphenicol (30µg) were used and antibiotic susceptibility interpretation was checked by the Clinical and Laboratory Standards Institute (CLSI) M100 criteria.¹¹ The data collected was analyzed using descriptive statistics performed with Statistical Package for the social sciences (SPSS) version 24:00. Chi-square was used to compare with p-value, which is considered statistically significant as ($P \leq 0.05$).

RESULTS

Out of 10564 samples of patients were extracted from data, 4582 samples were found positive for growth of different microorganisms. *Salmonella typhi* were positive for 1500 cases and only 412 samples were exhibiting XDR *Salmonella typhi* from June 2019 to June 2021 at Karachi.

Maximum cases of XDR *Salmonella typhi* were detected in age group 5-10 years with 38.8%. There were 61% male and 39% female. Women have strong immune system and show powerful immune response to all antigens than males.¹²

Table-1: Age distribution with XDR *Salmonella typhi* (n=412).

| Age | Frequency | Percent (%) |
|--------------|------------|--------------|
| ≤ 5years | 60 | 14.6 |
| 5-10 years | 160 | 38.8 |
| 11-20years | 100 | 24.3 |
| 21-40years | 92 | 22.3 |
| Total | 412 | 100.0 |

Table-2: *Chi-square test was applied for significance at p-value ≤0.05AMP (Ampicilline), SXT (trimethoprim sulphamethoxazole), C (Chloramphenicol), CRO (ceftriaxone), CIP (ciprofloxacin), (MEM) meropenem, IMP (Imipenem), AZI (Azithromycin)

| | | Age | | | | P-value |
|-----|------------|--------------------|-----------------------|-----------------------|----------------------|---------|
| | | ≤ 5years (n=60) | 5-10 years (n=160) | 11-20years (n=100) | 21-40years (n=92) | |
| AMP | Sensitive | 0 0.0% | 0 0.0% | 0 0% | 0 0 | 0.000 |
| | Resistant | 60 100.0% | 160 100.0% | 100 100% | 92 92% | |
| SXT | Sensitive | 0 0.0% | 0 0% | 0 0% | 0 0% | 0.000 |
| | Resistant | 60 100.0% | 160 100.0% | 100 100% | 92 92% | |
| C | Sensitive | 0 0.0% | 0 0% | 0 100.0% | 0 0% | 0.000 |
| | Resistant | 60 100.0% | 160 100% | 100 100% | 100 100% | |
| CRO | Sensitive | 0 0.0% | 0 0% | 0 0% | 0 0% | 0.000 |
| | Resistant | 60 100.0% | 160 100% | 100 100.0% | 100 100% | |
| CIP | Sensitive | 0 0.0% | 0 0.0% | 0 0.0% | 0 0% | 0.000 |
| | Resistant | 60 100.0% | 160 100.0% | 100 100.0% | 92 92% | |
| MEM | Sensitive | 138 | 137 | 137 | 100% | 0.00 |
| | Resistant | 0 | 0 | 0 | 0 | |
| AZI | Sensitive | 117 | 200 | 95 | 100% | 0.00% |
| | Resistance | 0 | 0 | 0 | 0 | |
| IMP | Sensitive | 112 | 25 | 265 | 100% | 0.000 |
| | Resistance | 0 | 0 | 0 | 0 | |

Table-3: Frequency of XDR *Salmonella typhi*.

| Total number of <i>Salmonella typhi</i> | MDR | Percentage (%) | XDR | Percentage (%) |
|---|-----|----------------|-----|----------------|
| 1500 | 500 | 33.33 | 412 | 27.46 |

DISCUSSION

We report phenotypically detected XDR *Salmonella typhi*. *Salmonella typhi* strain exhibits resistance towards penicillin, cloramphenicol, cephalosporin, ciprofloxacin and co-trimethoprim.

Typhoid fever is alarming threat in Karachi, Pakistan, with the maximum rate in children less than 15 years, which is in accordance to preceding studies from India and Bangladesh.^{13,14} Situation was aggravated during pandemic of COVID-19, with highest rate in children is similar to our study.¹⁵ Local surveillance

program was activated after detection of the XDR *S. typhi* from Hyderabad, and multiple cases were reported in the province of Sindh.¹⁶ Antibiotic susceptibility pattern was detected in this study, similar situation is faced by our neighbor country like India.¹⁷ From other parts of Pakistan, similar alarming condition of antibiotic resistance in isolates of *Salmonella typhi* was reported.¹⁸ Similar cases of XDR *Salmonella typhi* were detected in study conducted at Aga Khan university.¹⁹ Decades of

rampant and inappropriate use of antibiotics has obsessed the emergence extensively drug-resistant (XDR) *Salmonella typhi* (*S. Typhi*) strains in Beijing.²⁰ Our study is also supported by another study conducted in India and reported XDR *Salmonella typhi*.²¹ One study was conducted at Peshawar which showed a case of extensively resistant *Salmonella typhi* with multiple abscesses in spleen.²² Both azithromycin and meropenem are last hope to save lives of patients, another study conducted in Pakistan in association with our results.²³ Azithromycin resistance was also reported by Bangladesh at molecular level.²⁴ Even people travelled from Pakistan to other countries like United Kingdom and United States, were diagnosed as XDR typhoid and responsive only to two drugs as meropenem and azithromycin.²⁵ Azithromycin is now considered as the only oral antibiotic option. The potential emergence of azithromycin resistance is superfluous threat; if attained by the XDR strain of *S. Typhi*. Even patients will be killed with typhoid because it may become practically terminal. We as a nation facing XDR *Salmonella* are in red zone because India suffered from spontaneous emergence of azithromycin resistance.²⁶ On other hand, meropenem exhibits poor response as monotherapy, showed red flag for all physicians and patients.²⁷ We have to face some limitations like patients already started antibiotics before the antibiotic susceptibility test. These people have started either self-medication at home or prescribed by general physicians. This is facilitating the dissemination of antibiotic resistance encoding genes.

Our research showed XDR *Salmonella typhi* susceptibility and resistance pattern, for guidance of physician and establishment of antibiotic stewardship. This also emphasizes the use of TCV vaccine both for children and adults.

CONCLUSION

It is concluded that our country is in red zone in case of XDR *Salmonella typhi*. We need to catch our flaws and established epidemiological data as well as awareness of vaccine.

CONFLICT OF INTEREST

None

AUTHOR CONTRIBUTION:

Shaista Bakhat: Original idea, Literature search, Manuscript write up, final layout

Saman Nadeem: Data collection, Data entry

Ashfaq Hussain: Data entry

Saba Sarwar: Data collection

Beenish Hussain: Coordination

Faisal Faheem: Statistical analysis

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