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Emergence of Extensively Drug-Resistant Typhoid Fever in Pakistan.

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Abstract

Background: Typhoid fever is a significant health concern in Pakistan and Southeast Asia, with Extensively Drug-Resistant (XDR) typhoid fever presenting an escalating public health threat due to increased mortality and morbidity. Recent years have seen two notable XDR typhoid fever epidemics, highlighting the urgent need to investigate this growing problem. This study aims to analyze the prevalence of XDR typhoid fever among patients admitted to our hospital over the past year.

Methodology: This retrospective cohort study analyzed data from patients with culture-confirmed typhoid fever admitted to our hospital between July 2022 and June 2023. Patients were divided into two periods based on their illness onset: the first period (July 2022 to December 2022) and the second period (January 2023 to June 2023).

Results: A total of 341 patients with culture-confirmed typhoid fever were studied, with 72.7% being male and a mean age of 28.38 ± 7.71 years. The average hospital stay was 12.03 ± 2.79 days, and the mean febrile duration was 6.48 ± 2.3 days. Antibiotic resistance was prevalent, with high resistance rates to ciprofloxacin (78.9%), ampicillin (72.7%), and chloramphenicol (72.7%). Resistance rates significantly increased in the second half of the year, correlating with longer hospital stays and prolonged fever durations for resistant cases.

Conclusion: There was a notable increase in the prevalence of XDR typhoid fever within a six-month period. These findings emphasize the need for urgent public health interventions to address the rising threat of XDR typhoid fever.

Keywords

Typhoid Fever, Extensively Drug-Resistant Typhoid Fever, Multi-Drug Resistant Typhoid Fever.

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Introduction

Enteric fever, encompassing typhoid and paratyphoid fevers, is caused by the gram-negative, flagellated bacteria Salmonella typhi and Salmonella paratyphi. This disease represents a significant global public health challenge, particularly in developing countries such as Pakistan, where access to clean water is limited, hand hygiene practices are insufficient, and overcrowding is prevalent. Furthermore, vaccine uptake remains low. As of 2017, the global incidence of typhoid and paratyphoid fever was estimated at 14.3 million cases, resulting in approximately 135.9 thousand deaths, with a disproportionate burden in South Asia[1]. In Pakistan, where only 20% of the population has access to safe drinking water, reliance on contaminated water sources contributes to the increasing prevalence of typhoid fever [2]. The misuse of antibiotics has exacerbated the situation, leading to the emergence of multi-drug resistant (MDR) and extensively drug-resistant (XDR) strains of Salmonella typhi. The first XDR typhoid fever outbreak occurred in Hyderabad in 2016, rapidly spreading to other cities in Sindh province[3]. A study from a tertiary care hospital in Lahore reported high resistance levels, with approximately 56% of Salmonella typhi cultures being XDR[4]. Between 2016 and 2017, Hyderabad alone recorded over 10,000 cases of highly drug-resistant typhoid.

The National Institute of Health (NIH) Islamabad's Weekly Field Epidemiological Report highlights that Karachi reported 14,360 cases of XDR-Typhoid Fever between January 2017 and June 2021, while the remaining districts in Sindh, excluding Karachi, recorded 5,741 confirmed cases during the same period, with Hyderabad District accounting for 69.5% of these cases[5, 6].

A notable outbreak of ampicillin and ceftriaxone-resistant S. typhi isolates in Pakistan was documented on February 8, 2018. Among fifty-eight isolates, 54 were resistant to ciprofloxacin, while 57 were resistant to chloramphenicol. All isolates were susceptible to azithromycin, meropenem, and imipenem[7]. Typhoid fever presents as an acute febrile illness transmitted through the fecal-oral route, with an incubation period of 7 to 14 days. Clinical manifestations range from mild symptoms to severe complications. Blood and bone marrow cultures remain the gold standard for diagnosis.

Historically, chloramphenicol and ampicillin were the first-line treatments for S. typhi infections. However, the emergence of MDR and XDR strains has limited treatment options. The World Health Organization (WHO) defines MDR enteric fever as resistant to first-line drugs but susceptible to third-generation cephalosporins, while XDR strains are resistant to both first and second-line drugs and third-generation cephalosporins[8]. Currently, the treatment options for XDR typhoid fever include meropenem, imipenem, and azithromycin.

In response to the growing threat, Pakistan has introduced two typhoid vaccines. The recent WHO pre-qualification of Typbar-TCV, a novel typhoid conjugate vaccine, has led to its deployment in Sindh, targeting approximately 250,000 children in Hyderabad[9]. Given the rising prevalence of XDR typhoid fever, this study aims to analyze its temporal trends and assess the current public health implications.

Methodology

Study Design

This was a retrospective cohort study conducted to assess data from patients diagnosed with culture-positive typhoid fever. The study focused on patients admitted to the hospital between July 2022 and June 2023. Ethical approval for the study was obtained from the hospital's Ethical Review Board prior to data collection (Reference # F.3-1/2023(ERRB)/chairman; Dated 13th September 2023).

Setting

The study was conducted at a tertiary care hospital where patients with confirmed typhoid fever were admitted for diagnosis and treatment. Data were extracted from the hospital's electronic medical record system.

Participants

The study included all patients with a confirmed diagnosis of culture-positive typhoid fever admitted to the hospital. Patients were selected based on the availability of complete medical records and a positive culture for Salmonella Typhi. Patients with incomplete data or negative culture results were excluded. The analysis divided the patient data based on the time of illness onset: July to December 2022 and January to June 2023.

Data Sources/Measurement

Data were obtained from the hospital's patient management system, with a standardized data collection form used to document key patient information. The data collected for the study included patient demographics such as gender, residence, comorbid conditions, and typhoid vaccination status. Clinical data covered the duration of fever prior to admission, length of hospital stay, and duration of antibiotic therapy. Antibiotic sensitivity data was gathered for multiple antibiotics including ampicillin, amoxicillin, trimethoprim sulfamethoxazole, chloramphenicol, ciprofloxacin, ceftriaxone, meropenem, and azithromycin, assessing resistance and sensitivity patterns. Outcome data included the duration of fever during hospitalization. Additionally, temporal data compared antibiotic resistance patterns between July to December 2022 and January to July 2023.

Bias

Selection bias was minimized by including all patients who met the inclusion criteria over the specified study period. Potential biases due to incomplete medical records were managed by excluding such cases from the study. Despite these measures, the retrospective design carried an inherent risk of recall bias, particularly in terms of missing or incomplete data.

Study Size

The total number of patients was 341. As the study reviewed available records, no specific sample size calculation was necessary.

Statistical Analysis

Statistical analysis was performed using SPSS version 22. Descriptive statistics were used to summarize the data, frequencies and percentages for qualitative variables, and means with standard deviations for quantitative variables. Independent T-tests were employed to compare continuous variables (e.g., length of hospital stay, febrile duration) between the two illness onset periods (July-December 2022 and January-June 2023). For the qualitative variables, including antibiotic sensitivity patterns and treatment outcomes, chi-square tests were used to assess any significant associations between the time periods. A p-value of less than 0.01 was considered statistically significant.

Results

Participants

A total of 341 patients diagnosed with culture-positive typhoid fever were included in this study. The patients were admitted to the hospital between July 2022 and June 2023. Of these, 248 (72.7%) were male, while 93 (27.3%) were female. The age of the patients ranged from 15 to 56 years, with a mean age of 28.38 ± 7.71 years. All patients presented with fever, which was confirmed to be caused by Salmonella Typhi through blood cultures. The study population was divided into two groups based on the time of illness onset: Group 1 (July to December 2022, n = 161) and Group 2 (January to June 2023, n = 180).

Descriptive Data

The average hospital stay for the entire cohort was 12.03 ± 2.79 days, with a range of 4 to 16 days. The mean febrile duration before hospital admission was 6.48 ± 2.3 days, ranging from 2 to 15 days. Comorbid conditions were present in 59 patients (17.3%); 32 patients (9.4%) had diabetes, and 27 (7.9%) had hypertension. Only 13 patients (3.8%) reported having received the typhoid vaccine within the past five years. Geographically, the majority of the patients resided in Islamabad (51.3%), followed by Rawalpindi (13.5%), with the remaining 35.2% coming from other regions.

Outcome Data

Antibiotic resistance was a significant issue in this cohort. The most common resistant antibiotics included ciprofloxacin (78.9%), ampicillin (72.7%), chloramphenicol (72.7%), and trimethoprim-sulfamethoxazole (71%). Resistance to ceftriaxone, a commonly used third-generation cephalosporin, was found in 57.5% of patients. In contrast, resistance to meropenem (4.1%) and azithromycin (4.4%) was relatively low (Table 2).

Main Results

Patients who exhibited antibiotic resistance experienced significantly longer hospital stays and prolonged febrile durations compared to those with antibiotic-sensitive infections.

a) Hospital Stay

Patients resistant to ampicillin, amoxicillin, trimethoprim-sulfamethoxazole, chloramphenicol, ciprofloxacin, and ceftriaxone all had significantly longer hospital stays compared to patients without resistance ($p < 0.01$). For instance, the mean hospital stay for patients with ampicillin resistance was 12.79 ± 2.34 days compared to 9.96 ± 2.81 days for those sensitive to the antibiotic (Table 3). In contrast, resistance to meropenem and azithromycin did not significantly affect the duration of hospital stay ($p = 0.166$ and 0.56, respectively).

b) Fever Duration

Similarly, antibiotic resistance was associated with a longer duration of fever before the resolution of symptoms. Patients with ampicillin resistance had a mean fever duration of 7.03 ± 2.07 days, while those sensitive to ampicillin had a mean fever duration of 4.93 ± 2.21 days ($p < 0.01$). Comparable findings were observed for resistance to amoxicillin, trimethoprim-sulfamethoxazole, chloramphenicol, ciprofloxacin, and ceftriaxone, with all showing significantly longer fever durations in resistant patients ($p < 0.01$) (Table 4).

c) Temporal Distribution of Antibiotic Resistance

Over the course of the study, there was a notable increase in antibiotic resistance during the second half of the study period (January to June 2023) compared to the first half (July to December 2022). For instance, resistance to ciprofloxacin rose from 113 patients in the first half of the year to 156 patients in the second half. Similarly, ampicillin resistance increased from 94 patients in the first half to 154 patients in the latter period (Table 5).

Table 1: Demographics of patients with enteric fever (n=341).

Variables		N(%)
Gender	Male	248(72.7)
	Female	93(27.3)
Residence	Islamabad	175(51.3)
	Rawalpindi	46(13.5)
	Other	120(35.2)
Comorbid Conditions	None	282(82.7)
	Diabetes	32(9.4)
	Hypertension	27(7.9)
Typhoid Vaccination Status	Yes	13(3.8)
	No	328(96.2)

Table 2: Antibiotic resistant pattern during the whole one year.

Antibiotic Resistance	N(%)
Ampicillin	248(72.7)
Amoxicillin	238(69.8)
Trimethoprim Sulfamethoxazole	242(71.0)
Chloramphenicol	248(72.7)
Ciprofloxacin	269(78.9)
Ceftriaxone	196(57.5)
Meropenem	14(4.1)
Azithromycin	15(4.4)

Table 3: Comparison of mean hospital stay (in days) among patients with antibiotic-resistant and antibiotic-sensitive typhoid fever.

Antibiotic	Resistant	Sensitive	P-value
Ampicillin	12.79 ± 2.34	9.96 ± 2.81	<0.01*
Amoxicillin	12.99 ± 2.17	9.83 ± 2.76	<0.01*
Trimethoprim Sulfamethoxazole	12.95 ± 2.20	9.79 ± 2.75	<0.01*
Chloramphenicol	12.91 ± 2.27	9.77 ± 2.66	<0.01*
Ciprofloxacin	12.51 ± 2.52	10.35 ± 2.94	<0.01*
Ceftriaxone	13.55 ± 1.58	9.98 ± 2.76	<0.01*
Meropenem	13.07 ± 2.37	12.02 ± 2.79	0.16
Azithromycin	12.47 ± 2.70	12.04 ± 2.79	0.56

*p<0.05 is considered statistically significant.

Table 4: Comparison of fever duration (in days) among patients with antibiotic-resistant and antibiotic-sensitive typhoid fever.

Antibiotic	Resistant	Sensitive	P-value
Ampicillin	7.03 ± 2.07	4.93 ± 2.21	<0.01*
Amoxicillin	7.21 ± 1.91	4.75 ± 2.22	<0.01*
Trimethoprim Sulfamethoxazole	7.21 ± 1.90	4.68 ± 2.22	<0.01*
Chloramphenicol	7.15 ± 1.96	4.69 ± 2.18	<0.01*
Ciprofloxacin	6.86 ± 2.08	5.06 ± 2.53	<0.01*
Ceftriaxone	7.64 ± 1.44	4.90 ± 2.31	<0.01*
Meropenem	7.36 ± 2.24	6.46 ± 2.30	0.153
Azithromycin	7.07 ± 2.43	5.45 ± 2.29	0.313

*p<0.05 is considered statistically significant.

Table 5: Comparison of antibiotic resistance and sensitivity of bacterial isolates between July to December 2022 and January to July 2023

Antibiotic		July to December 2022	January to July 2023
Ampicillin	R	94	154
	S	63	23
Amoxicillin	R	89	149
	S	68	29
Trimethoprim Sulfamethoxazole	R	95	147
	S	65	31
Chloramphenicol	R	98	150
	S	62	29
Ciprofloxacin	R	113	156
	S	45	23
Ceftriaxone	R	74	122
	S	87	58
Meropenem	R	7	7
	S	150	173
Azithromycin	R	8	7
	S	148	172

R-Resistance; S-Sensitive

Discussion

Our study highlights a concerning rise in extensively drug-resistant (XDR) enteric fever, with 57.5% of patients exhibiting XDR strains over the past year. This prevalence aligns closely with the SEAP surveillance study, which reported a 60% prevalence of XDR enteric fever[10]. Similarly, a tertiary care hospital study in Lahore reported a 46.1% prevalence, reflecting the substantial burden of XDR enteric fever in Pakistan[11]. Notably, our findings reveal a higher incidence in men (72.7%) compared to women (27.3%), which may be attributed to greater male exposure to contaminated environments and a higher tendency for men to seek medical care. These observations are consistent with data from Lahore, where 60.7% of cases were in males[11]. The average patient age of 28.38 years indicates that younger individuals are more susceptible to the disease. The low prevalence of diabetes (9.4%) and hypertension (7.9%) among patients suggests that enteric fever predominantly affects younger, otherwise healthy individuals.

Alarmingly, the prevalence of XDR typhoid fever surged from 46.5% to 67.8% over the last six months, a 21.3% increase. This rise surpasses previous epidemic levels in Sindh and Punjab, where XDR prevalence was reported at approximately 60% and 46.1%, respectively. The initial XDR outbreak in Sindh in 2016 and the subsequent 2019-2020 outbreak in Punjab highlight the progressive escalation in XDR cases[12]. Our hospital data confirms this trend, with XDR cases increasing from 74 out of 159 (46.5%) to 122 out of 180 (67.8%) in six months.

Of particular concern is the identification of 14 cases resistant to Meropenem and 15 to Azithromycin, as these antibiotics are critical for treating XDR typhoid fever. Resistance to second and third-line drugs remains relatively low (3.8% of cases), likely due to Azithromycin's effective intracellular accumulation and extended half-life, which enhances its efficacy against XDR strains[13]. Meropenem's effectiveness, attributed to its stability against Extended-Spectrum Beta-Lactamase (ESBL) and its broad-spectrum activity, is vital for treating severe cases[14, 15].

A CDC Health Advisory reports 71 cases of XDR typhoid fever in the United States, with 87% linked to travel to or from Pakistan within the preceding 30 days. This suggests a potential international spread and underscores the importance of addressing the epidemic in Pakistan[16]. The increased incidence of XDR typhoid fever is closely linked to heightened antibiotic use, poor sanitation, and low vaccination rates. Consumption of unhygienic food and contaminated water remains a primary risk factor, with younger individuals more affected due to their dietary habits.

The extensive use of Azithromycin for COVID-19 treatment in Pakistan raises concerns about potential antimicrobial resistance, which could compromise the effectiveness of treatments for XDR typhoid fever. The ongoing COVID-19 pandemic adds pressure to the healthcare system, complicating the management of XDR typhoid fever[17].

Our current practice involves administering intravenous antibiotics, with Ceftriaxone as the first-line treatment. Patients typically require a 10-day hospitalization with intravenous antibiotics, transitioning to Meropenem if complications arise or if fever persists despite negative blood cultures. XDR typhoid fever is associated with higher complication rates and mortality compared to drug-sensitive strains. A study by Fatima et al. reported a 1.8% mortality rate for XDR cases versus 0.6% for drug-sensitive cases[18]. Complications such as ileal perforation and other severe conditions were noted in XDR patients[19]. Prolonged hospitalizations are common, contributing to increased risks of hospital-acquired infections and a higher financial burden due to the cost of Meropenem compared to Ceftriaxone[20].

Our study has several limitations. Its retrospective nature precludes patient follow-up and future prognosis predictions. We could not ascertain prior antibiotic use or fully assess the financial burden on patients, and the study's geographic focus on Islamabad, with its relatively lower congestion and higher education levels, may not fully represent the broader prevalence of XDR enteric fever.

Conclusion

In conclusion, our study has revealed a strikingly high prevalence of extensively drug-resistant (XDR) typhoid fever among culture-positive patients over the past year, with a particularly alarming surge in the last six months. The emergence of azithromycin resistance in XDR Salmonella typhi a key treatment option, poses a significant concern and highlights the need for vigilant monitoring and prompt action. Given the escalating prevalence and the critical role of azithromycin in empirical treatment, urgent measures are required to address this growing issue, particularly in endemic regions such as Pakistan.

Conflicts of Interest

The authors declare no conflict of interest in any form (financial, technical or otherwise).

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