

## Enteric susceptibility profile: Finding hope amidst despair

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### Abstract

**Objective:** To assess the overall antimicrobial susceptibility profile of enteric fever patients in a tertiary care setting.

**Method:** The retrospective study was conducted at Pakistan Institute of Medical Sciences, Islamabad, Pakistan, and comprised data from January 2019 to April 2023 of patients aged >12 years who were admitted with febrile illness and had a blood culture positive for salmonella typhi. Demographic data as well the antimicrobial susceptibility profile parameters, like multidrug resistance, extensive drug resistance and extended spectrum beta lactamase status, were recorded. Data was analysed using SPSS 25.

**Results:** Of the 734 cases, 522(71.1%) were males and 212(28.9%) were females. There were 88(11.98%) patients with multidrug resistance, 178(24.25%) with extensive drug resistance, and 50(6.81%) were positive for extended spectrum beta lactamase. There were 452(62.6%) patients sensitive to first-line drugs, 509(69.5%) to second-line drugs, and 722(99.2%) to third-line drugs.

**Conclusion:** Drug resistance in enteric fever patients was found to be alarming.

**Keywords:** Typhoid fever, Salmonella typhi, Multidrug resistance, Extensive drug resistance, Beta-lactamases.

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### Introduction

Enteric fever, also known as typhoid fever, is a systemic illness caused by the bacterium salmonella enterica serovar typhi (*S. Typhi*). This bacterial infection is typically spread through the consumption of contaminated food or water, or through direct contact with an infected individual.<sup>1</sup>

Symptoms of enteric fever can include fever, headache, malaise, abdominal pain and constipation or diarrhoea. Diagnosis is typically made through blood or stool cultures, although serological tests may have a limited role. Treatment involves antibiotics, and supportive care may be necessary to manage complications.<sup>2</sup> Complications of enteric fever include gall bladder carrier state, intestinal perforation and intestinal obstruction.<sup>3</sup> The gall bladder carrier state may prolong the duration of illness, requiring antimicrobial therapy for an extended period.<sup>4</sup> Furthermore, it is postulated that the gallbladder carrier state may lead to gall bladder carcinoma.<sup>5-7</sup>

Enteric fever remains a significant global health challenge and as per the World Health Organisation (WHO), approximately 9 million cases are reported and more than 110,000 of them die annually.<sup>8</sup> Moreover, the emergence of multidrug resistant (MDR) strains has complicated

treatment options.<sup>9</sup> Over 10,000 lab-confirmed typhoid cases were reported in Karachi from 2017 to 2020. Out of these, 68% cases were recorded as having extensive drug resistance (XDR) typhoid.<sup>10</sup> Resistance to first-line antibiotics, such as ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole, has become widespread, and fluoroquinolone resistance has also emerged in Pakistan. Resistance to the last resort oral antibiotic azithromycin has been reported particularly after injudicious use during the coronavirus disease-2019 (COVID-19) pandemic.<sup>11</sup> In addition, cases of self-medication and antibiotic abuse may also have contributed to drug resistance.<sup>12</sup>

Establishing local drug sensitivity patterns at regional level is the cornerstone of optimal management of any infectious agent. The current study was planned to assess the overall antimicrobial susceptibility profile of enteric fever patients in a tertiary care setting.

### Materials and Methods

The descriptive, cross-sectional, retrospective study was conducted at Pakistan Institute of Medical Sciences, a tertiary hospital in Islamabad, Pakistan, and comprised data from January 2019 to April 2023. After approval from the institutional ethics review committee, the sample size was calculated using the WHO calculator with anticipated population proportion 44.6%,<sup>13</sup> absolute precision 0.5 and confidence interval 95%. The sample was raised using non-probability consecutive sampling technique, and data of all the patients who met the inclusion criteria was included. Patients aged >12 years who were admitted with febrile

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illness and had a blood culture positive for *S. Typhi* were included. Patients having blood culture reports with missing drug susceptibility profile were excluded.

The 2022 Medical Microbiology and Infectious Disease Society of Pakistan (MMIDSP) guidelines for typhoid fever were employed to classify patients as non-resistant (NR), MDR, XDR, ESBL-positive cases. NR was defined as typhoid fever caused by strains that were sensitive to first-line drugs and third-generation cephalosporins with or without resistance to second-line drugs. MDR was defined as typhoid fever caused by strains that were resistant to first-line drugs and sensitive to third-generation cephalosporins with or without resistance to second-line drugs. XDR was defined as typhoid fever caused by strains that were resistant to all the recommended antibiotics for typhoid fever. ESBL-positivity was defined as typhoid fever caused by strains that were resistant to third-generation cephalosporins, but were sensitive to chloramphenicol, cotrimoxazole or fluoroquinolones.<sup>14</sup>

Data was analysed using SPSS 25. Continuous variables were expressed as mean±standard deviation. Categorical variables were expressed as frequencies and percentages.

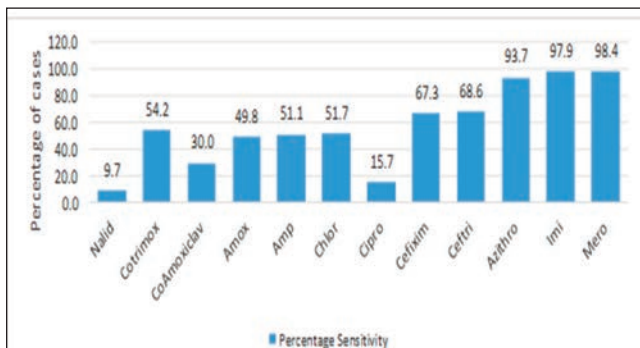
**Results**

Of the 734 cases, 522(71.1%) were males and 212(28.9%) were females. The Mean age of the participants was 38.98±14.352 years. The least drug sensitivity was for nalidixic acid 30(9.7%), while the highest sensitivity was for meropenem 377(98.4%) (Figure 1).

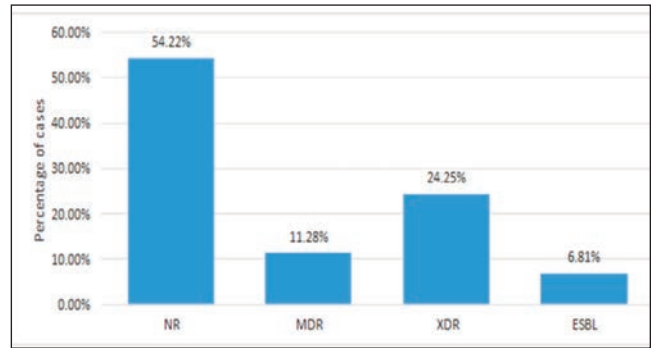
There were 398 NR cases, while 88(11.98%) were MDR, 178(24.25%) were XDR and 50(6.81%) were ESBL-positive (Figure 2).

There were 452(62.6%) patients sensitive to first-line drugs, 509(69.5%) to second-line drugs, and 722(99.2%) to third-line drugs (Figure 3).

Overall sensitivity profile of cases resistant to third-line drugs was also noted (Table).

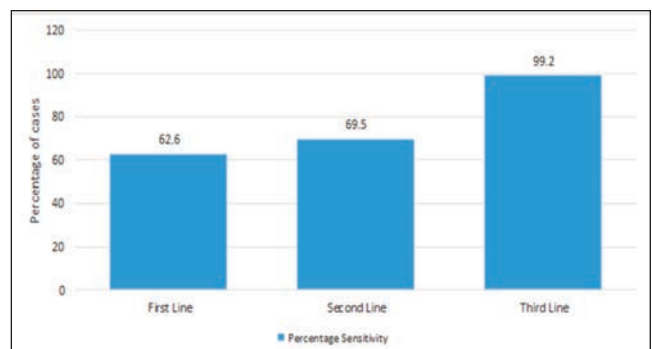


**Figure-1:** Bar graph of patients sensitive to individual antimicrobial drugs.



**Figure-2:** Bar graph of patients in each enteric resistance category.

NR: Non-resistant typhoid, XDR: Extensively drug resistant typhoid, ESBL: Extended spectrum beta lactamase-producing typhoid.



**Figure-3:** Bar graph of patients in each enteric resistance category.

NR: Non-resistant typhoid, XDR: Extensively drug resistant typhoid, ESBL: Extended spectrum beta lactamase-producing typhoid.

**Table:** Sensitivity profile of meropenem, imipenem and azithromycin.

Drugs	Meropenem Resistant n (%)	Imipenem Resistant n (%)	Azithromycin Resistant n (%)
Amoxicillin	0 (0)	3 (42.9)	11 (37.9)
Ampicillin	0 (0)	0 (0)	1 (14.3)
Co trimoxazole	1 (50)	2 (40)	15 (50)
Chloramphenicol	3 (60)	3 (60)	20 (54.1)
Ciprofloxacin	1 (16.7)	2 (28.6)	11 (26.8)
Cefixime	1 (20)	3 (50)	22 (56.4)
Ceftriaxone	2 (40)	4 (57.1)	29 (70.7)
Azithromycin	4 (80)	3 (60)	-
Meropenem	-	-	25 (92.6)
Imipenem	-	-	15 (93.8)

**Discussion**

Enteric fever is one of the highly prevalent diseases in underdeveloped and developing countries, like Pakistan, with a significant rise in cases of XDR typhoid fever whose first outbreak was reported in 2016.<sup>15</sup> The disease burden in Pakistan is growing with every passing day owing to the emergence of resistance to third-line drugs, leading to a very limited options of antibiotics available to treat such cases. However, limited data is available to evaluate the antibiotic susceptibility pattern in enteric fever in Pakistani

population.

The current cross-sectional study, conducted at one of the largest tertiary care facilities in the region, revealed a total of 316 resistant strains of *S. Typhi*, with 88 cases being MDR, 178 XDR and 50 ESBL-positive.

Till 1990, the first-line drugs for enteric fever included chloramphenicol, amoxicillin and trimethoprim-sulfamethoxazole. However, the emergence of MDR strain led to the introduction of fluoroquinolones for enteric fever. A systematic review of studies published between 1990 and 2018 noted increasing frequency of cases resistant to fluoroquinolones in South Asia and Africa.<sup>16</sup> The current findings were quite similar, showing an overall poor sensitivity of the cases to fluoroquinolones, with only 15.7% being sensitive to ciprofloxacin. A 2019 study in Nepal did not report even a single case sensitive to ciprofloxacin via disc diffusion test, while two cases were found to be susceptible according to minimum inhibitory concentration (MIC) breakpoint.<sup>17</sup> This further stresses the predominantly reduced sensitivity of ciprofloxacin.

As compared to ciprofloxacin, the conventional first-line drugs were found to be a more effective treatment option in enteric fever as 54.2% of the cases studied were sensitive to cotrimoxazole, 51.7% to chloramphenicol, while 51.1% and 49.8% responded to ampicillin and amoxicillin, respectively. A 100% sensitivity pattern to chloramphenicol, amoxicillin and cotrimoxazole was reported in two similar studies done in Nepal.<sup>17,18</sup> Thus, we can presume that switching over to fluoroquinolones and third-generation cephalosporins from the first-line agents due to the emergence of MDR strains in late 1990s may have led to the re-establishment of the sensitivity of *S. Typhi* strains to these drugs.

On the whole, the current study found the sensitivity of first-line drugs to be comparable to those of second-line drugs (62.6% vs 69.5%). Amongst these drugs, the sensitivity pattern of amoxicillin, a preferred oral agent, was not much different from that of ampicillin, usually given via the intravenous (IV) route, with the latter being superior by just 1.3%. This was similar to the results of cefixime, an orally administered drug, with 67.3% of the cases being sensitive compared to 68.3% sensitive to IV-administered ceftriaxone. It can be suggested that first-line agents or third-generation cephalosporins should be used in cases resistant to ciprofloxacin, so that azithromycin and other third-line agents can be reserved for non-responsive cases only. Third-generation cephalosporins, including ceftriaxone and cefixime, represent a preferred empirical therapy in South Asia which may be the leading factor behind the emergence of antimicrobial resistance.<sup>19</sup> This is

supported by the unresponsive cases reported in India and Pakistan.<sup>20-23</sup> Such widespread use of these drugs has led to the emerging resistant strains together with the emanation of ESBL-producing strain of this gram-negative bug. Out of the 734 patients in the current study, 50 were infected with an ESBL-positive strain.

An outbreak of XDR typhoid fever in Pakistan in 2016 left the healthcare system with very limited options other than azithromycin and IV carbapenems.<sup>24,25</sup> The current study also highlighted the sensitivity of meropenem being the maximum with 98.4% of the patients sensitive to the drug, followed by that of imipenem and azithromycin, with 97.9% and 93.7% of the susceptible cases, respectively. However, due to widespread use of these antibiotics, especially in the COVID-19 era, the slowly but surely increasing trend of its pattern of resistance needs to be worked upon because such a scenario may leave us with no options to treat enteric fever successfully. Probing into the details of cases resistant to third-line drugs, it can be inferred that patients resistant to azithromycin responded well to carbapenems, but the response to ceftriaxone was also sufficiently good, with 70.7% of the cases being sensitive to it. On the other hand, azithromycin had reasonable sensitivity profile in patients resistant to carbapenem. Moreover, chloramphenicol gave adequate results amongst most of the first- and second-line agents in patients resistant to third-line drugs.

The current study has limitations as it was conducted at a single centre. The findings may not represent the community at large as patients with fever tend to present in community clinics first and those who recover with initial antimicrobials do not present to a tertiary care setup. As such, the resistance profile in the current study might have been exaggerated.

## Conclusion

MDR and XDR enteric fever cases were high, while carbapenem and azithromycin resistance was alarming. Quinolones seemed to have reached a worse profile than even older first-line drugs. Emerging improvement in first-line drugs susceptibility might be a ray of hope for future as indicated by ESBL-positive cases. Focussing on antimicrobial stewardship is a must to stop the loss of last-resort options in the management of enteric fever.

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**Conflict of Interest:** None.

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### Author Contribution:

**AS:** Protocol designing, statistical analysis, data interpretation, writing and review.

**HST:** Protocol designing, data acquisition, entry and writing.

**FS:** Literature review and writing.

**SS:** Protocol designing and review