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Antimicrobial sensitivity patterns of enteric fever in Pakistan: a comparison of years 2009 and 2019

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Abstract

Background: Pakistan is one of the endemic regions for typhoid fever and paratyphoid fever. This study aimed to identify the evolving antimicrobial sensitivity patterns of *Salmonella* species causing enteric fever and its implications on the clinical prescribing of antimicrobials.

Methods: This was a retrospective descriptive study conducted at a university hospital. Antimicrobial resistance was defined in terms of non-resistant, multidrug resistant (MDR) and extended drug resistant (XDR) as per WHO guidance. Data were collected from the years 2009 and 2019. Chi squared was applied to test for statistical significance ($p < 0.05$).

Results: A total of 200 patients (100 from 2009 and 100 from 2019) were included in the study. Non-resistant enteric fever cases reduced from 100% in 2009 to 44% in 2019, whereas the MDR and XDR enteric fever cases increased to 16% and 40%, respectively ($p < 0.05$). Cross tabulation carried out for individual drugs showed an independent rise in the sensitivities of individual first-line antimicrobials.

Conclusion: Antimicrobial resistant enteric fever has become a big challenge for Pakistan. The choice of antibiotic prescription has narrowed down to broader spectrum antimicrobials making it difficult to treat, leading to increased morbidity and mortality.

Keywords: antimicrobial resistance, enteric fever, extended drug-resistant enteric fever, MDR, multidrug-resistant enteric fever, XDR

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Introduction

Enteric fever is a gastrointestinal infection with systemic manifestations caused by *Salmonella typhi* and *Salmonella paratyphi*. The mode of transmission remains the orofecal route, while humans are the only reservoir of this infection. The illness caused by *S. typhi* predominantly manifests within 14 days of infection, in the form of fever and abdominal complaints, including nausea, vomiting, diarrhoea and constipation. However, with the passage of time various atypical manifestations of *Salmonella* infection have appeared, especially as a fever of unknown origin. Despite being a potentially treatable condition, enteric fever still carries a high mortality rate in developing countries. According to the most recent estimates, between 11 and 21 million cases, and 128,000–161,000 typhoid-related deaths occur annually worldwide.[1,2]

The clinical course of illness can be altered by effective and appropriate antimicrobial therapy. Delay in initiating antibiotics predispose to longer course of disease with various complications, including acute abdomen, sepsis and even death. Mortality rate goes as high as 30% in untreated or inappropriately treated cases. However, when treated effectively, the fever subsides in 5 days on average and mortality rate also declines to less than 1%.[3]

Antimicrobial resistance (AMR) has been the biggest challenge of our times. It has the potential to affect people at almost every stage of life. Every year, more than 35,000 deaths occur in USA owing to antimicrobial resistant drug infection.[4] *Salmonella* species have shown a variable trend worldwide, with high incidence in regions endemic for typhoid. However, even for endemic regions there have been differences in the temporal distribution of drug resistance, as seen for trends of multidrug-resistant (MDR) and extended drug-resistant (XDR) enteric fever in Asia and Africa.[5,6]

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Table 1 Classification of antimicrobials for treatment of enteric fever

Classification	Antimicrobial
First-line antimicrobials	TMP-SMX, ampicillin, chloramphenicol
Second-line antimicrobials	Fluoroquinolones (ciprofloxacin)

SEAP (Surveillance for Enteric Fever in Asia Project) has reported 90% fluoroquinolone resistance in *S. typhi* in Pakistan, and universal resistance to ciprofloxacin in *Salmonella* isolates in India.[7,8] This is an alarming situation, which has seen an increased trend towards carbapenems as a potential treatment of *Salmonella* infection.[9,10] The purpose of this study was to asertain the changes in drug sensitivity patterns of *S. typhi* and *S. paratyphi* over two time periods of 2009 and 2019 in terms of non-resistant, MDR and XDR enteric fever at a University Hospital in Lahore, Pakistan.

Methods

This retrospective descriptive study was conducted at University of Lahore Teaching Hospital, in the Department of Medicine, in collaboration with the Department of Microbiology. The study was approved by ethical review board of The University Hospital (ERC 01/20/01). A total of 200 patients were included. Of these, 100 patients' data were used retrospectively from the year 2009, and 100 patients were included from the year 2019 using non-probability consecutive sampling. The antimicrobials used for the treatment of enteric fever have been categorised as first- and second-line antimicrobials (Table 1). In addition, third-generation cephalosporins (ceftriaxone) have been recommended for enteric fever treatment. Enteric fever has been defined as fever lasting for at least 5 days or more with *S. typhi* and *S. paratyphi* isolates on blood cultures. Furthermore, on the basis of various sensitivity patterns, enteric fever has been classified into three types: non-resistant, MDR and XDR enteric fever. The details are shown in Figure 1.

The study included the patients above the age of 15 years who had at least 5 days of fever and had tested positive for *S. typhi* and *S. paratyphi* on blood cultures. The patients who had been treated as suspected typhoid fever/enteric fever with negative blood culture results and the patients with febrile illness who had growth of other organisms at culture studies were excluded from the study. Data were collected from the Department of Microbiology and correlated with the medical records for the clinical presentation and management plans. All the information was entered in the structured questionnaire. Data were analysed in the SPSS version 21.0. Frequency and percentages were calculated for gender, sensitivity, and resistance patterns. Cross tabulation was carried out for sensitivity and resistance patterns of individual drugs for the years 2009 and 2019. Chi squared test has been used to assess for statistical significance ($p < 0.05$).

Table 2 Tests for statistical significance

Test	Value	p-value
Pearson Chi-Squared	77.778[a]	0.000
Likelihood ratio	99.995	0.000
Linear-by-linear regression	70.851	0.000
Number of valid cases	200	–

[a]0 cells (0.0%) have expected count less than 5. The minimum expected count is 8.00

Results

The mean age of the patients was 37 ± 12.23 years. Of them, 53% (n = 106) were males and 47% (n= 94) were females. Antibiotic resistance patterns were studied in both the groups of patients. In the year 2009, typhoid fever was 100% sensitive to all the first-line drugs (chloramphenicol, ampicillin, TMP-SMX). There were no MDR and XDR enteric fever cases in 2009. This pattern changed over 10 years. In 2019, non-resistant enteric fever cases have shown a downward trend to 44% compared with 100% in 2009, whereas MDR and XDR enteric fever cases increased to 16% and 40%, respectively. (Figure 2). The difference between the antimicrobial sensitivity patterns in both the years was statistically significant ($p < 0.05$; Table 2).

Cross tabulation was carried out for both the sensitivity and resistance patterns in the years 2009 and 2019. The sensitivity to first-line drugs including chloramphenicol was 19%, which increased to 41% in 2019. Similar trends have been observed for ampicillin (20% in 2009 to 34% in 2019)

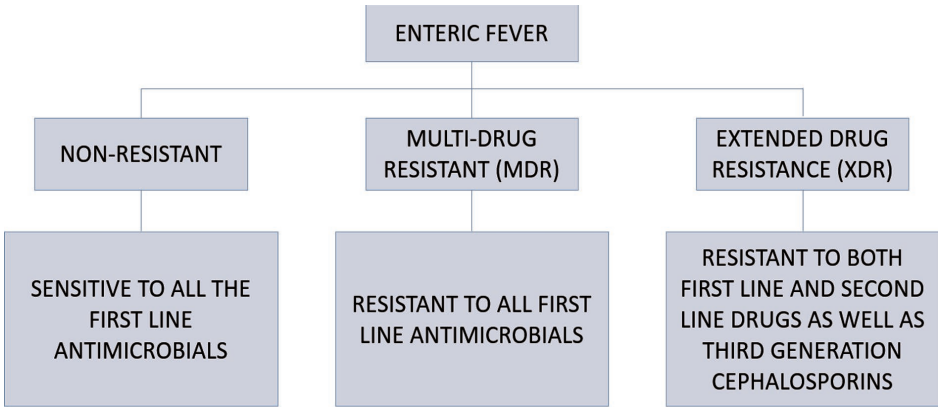

Figure 1 Classification of enteric fever

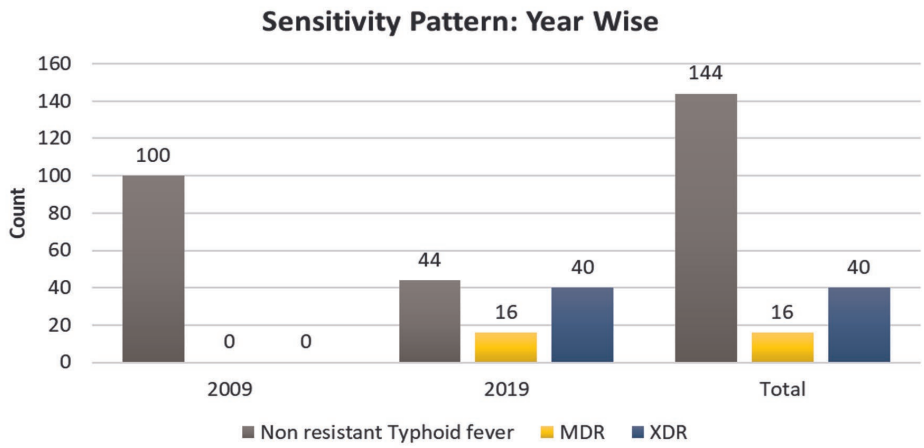

Figure 2 Percentages of antimicrobial resistant typhoid cases: temporal distribution. MDR: multidrug-resistant; XDR: extended drug-resistant

and TMP-SMX (10% in 2009 to 37% in 2019). Third-generation cephalosporins and second-line agents (i.e. fluoroquinolones) showed an inverse trend in sensitivities, which reduced to 36.8% for ciprofloxacin and 25% for ceftriaxone in 2019. Broad spectrum antimicrobial (Meropenem) has shown a 1% decline in sensitivity pattern when compared in both the years (100% sensitivity and 99% sensitivity in 2009 and 2019, respectively).

Figure 3 shows the resistance patterns of individual antimicrobials over time.

Discussion

The pattern of prescription of *Salmonella* has evolved significantly over the passage of time. Historically, in 1948, chloramphenicol emerged as a drug of first choice for typhoid fever. However, the indiscriminate use of antibiotics led to emergence of resistant strains of *S. typhi* in as early as the 1950s in the UK.[11,12] Ever since, cases of resistance to chloramphenicol increased until 1972, when chloramphenicol resistance became an area of major concern, especially in Mexico, India, Korea and Vietnam. Later, in the 1980s cases of MDR typhoid fever were documented in Southeast Asia.[13] The trend of antibiotic prescription then shifted to second-line agents including fluoroquinolones and second- and third-generation cephalosporins. However, as early as in 1992, resistance to fluoroquinolones was reported in UK. Nevertheless, ciprofloxacin and parenteral ceftriaxone have been used for a significant time with promising results.[14]

In recent years, concerns in antibiotic resistance were seen when an XDR typhoid fever case was reported from Hyderabad, Pakistan, in November 2016. Over a period from 1 November 2016 to 9 December 2018, 5274 cases of XDR typhoid have been documented by provincial disease surveillance and response unit in Sindh, Pakistan. Worldwide six travel-associated XDR typhoid cases have been reported, including one from the UK and five from United States. The injudicious use of antibiotics and ease of availability of antibiotics over the counter has led to development of the current grave situation of typhoid fever in Pakistan.[15] This has been reflected in our study where over a period of 10 years, 44% of the strains have developed extended resistance of all the first- and second-line drugs. This is an alarming situation as in this scenario, azithromycin remains the only suitable oral alternative. However, due to its extended use in a variety of clinical conditions, the trend has shifted towards prescribing carbapenems in the treatment of typhoid fever, which is not a cost-effective option, and can have a huge impact on the struggling economies of developing countries.[10]

However, the other end of the spectrum that points towards possible renaissance of sensitivity to first-line antityphoid drugs. A cross-sectional study conducted in Kathmandu at a tertiary care hospital, showed the emergence of sensitivity of *S. typhi* to first-line antimicrobials for typhoid fever. Of the 83 *Salmonella* species, 98% were sensitive to chloramphenicol and co-trimoxazole, whereas 97.6% were sensitive to ampicillin.[16] Our study also testifies this trend. We have observed a decline in the resistance of chloramphenicol and TMP-SMX by 12.4% and 17.1%, respectively. This trend warrants the need of further

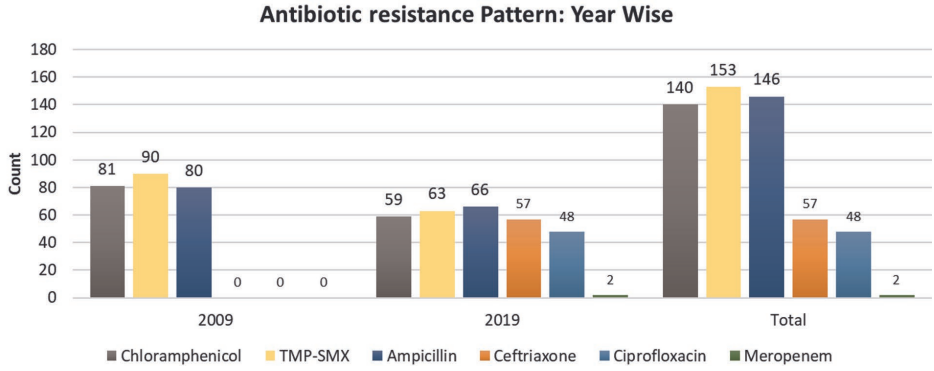

Figure 3 Resistance of individual antimicrobials: temporal distribution

prospective studies to establish the effectiveness of first-line antimicrobial sensitivities as it can turn the prescription pattern once again to the first-line drugs that would be a cost-effective and clinically effective alternative.

In conclusion, our study confirms that the emergence of a drug resistance in enteric fever is a big challenge for endemic regions. This needs prompt and effective measures to prevent the evolution of resistant strains. Effective measures are warranted to control injudicious antimicrobial prescription and to stop over the counter availability of antimicrobials. The extended drug-resistant strains isolated from Pakistan require serious and organised measures at present to prevent morbidity and mortality from a potentially treatable *Salmonella* infection.

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