

CEPHALOSPORIN RESISTANCE IN TYPHOID AND PARATYPHOID INFECTIONS - AN ALARMING SITUATION

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ABSTRACT

Objective: To determine the frequency of resistance to third generation cephalosporins in use i.e ceftriaxone and cefixime in patients with typhoid and para typhoid infections.

Material and Methods: This longitudinal observational study was conducted at Khan Research Laboratories Hospital, Islamabad from June 2019 to Nov 2019. All patients presenting with fever having positive blood culture for salmonella typhi or paratyphi A were included. Patient's febrile period, duration of hospital stay and days of antibiotics given were also recorded. Age, gender, Salmonella serovar and sensitivity to 11 antimicrobial drugs were taken into account. The tested antimicrobial drugs were ampicillin, trimethoprim/sulphamethoxazole, chloramphenicol, nalidixic acid, ciprofloxacin, ofloxacin, levofloxacin, ceftriaxone, cefixime, imipenem and azithromycin. Data was analyzed using statistical package for social sciences version 22 (SPSS 22).

Results: Out of 125 patients 80 (64.0%) were males while 45 (36.0%) were females. 110 (88%) patients had salmonella typhi on blood culture while 15 (12%) had salmonella paratyphi A. 35 (28%) isolates were resistant to ceftriaxone and cefixime. All isolates were sensitive to imipenem and azithromycin. Majority of patients (68%) stayed in hospital for 8 to 10 days.

Conclusion: Cephalosporin resistance in enteric fever is rising. An earlier blood culture result is mandatory to prevent complications in all resistant cases.

Keywords: Typhoid, Salmonella, Ceftriaxone, drug resistance, Pakistan, azithromycin.

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INTRODUCTION

Typhoid fever is a systemic infection caused by *Salmonella typhi* and *Salmonella paratyphi A*. It is a major public health concern in developing nations. Globally, 14.3 million cases of typhoid and paratyphoid fevers occurred in 2017 with estimated 135.9 thousand deaths from typhoid and paratyphoid fever globally in 2017.¹

South Asia has the highest cases of typhoid fever. Among the 16 countries in Asia where typhoid is prevalent, inhabitants of the Punjab and Sindh provinces of Pakistan were at the highest risk of developing typhoid.²

With the development of multi-drug resistance (resistance to ampicillin, chloramphenicol, co-trimoxazole) in *Salmonella enterica* serovar Typhi and Paratyphi A, Fluoroquinolones were the drug of choice. Subsequently fluoroquinolone resistance was noted in nearly 90% of S

Typhi and S Paratyphi isolates.³ The treatment of ciprofloxacin-resistant typhoid infection is now limited to third- and fourth-generation cephalosporins, azithromycin, tigecycline and penems.⁴

Third generation cephalosporin such as ceftriaxone, cefotaxime and cefoperazone have been used successfully to treat typhoid fever, with courses as short as 3 days showing similar efficacy to usual 10 to 14 days regimens. Excellent response rates have been reported when administered for 5 to 7 days.^{5,6}

Although ceftriaxone remains the most effective drug for typhoidal *Salmonella* isolates, with susceptibility of almost 100% over the past 15 years, ceftriaxone resistance was observed for the first time in 2011.⁷ Ceftriaxone resistance has remained rare, with <1% of strains resistant during 2009–2014 in Pakistan.⁸ Since 2016, outbreaks of extensively drug resistant S Typhi strains that are resistant to ceftriaxone and cefixime have been reported in parts of Pakistan.⁸

The Extensive drug resistant *Salmonella Typhi* (XDR Typhi) strain is only susceptible to azithromycin and carbapenems. Azithromycin should be used to treat patients with suspected uncomplicated typhoid fever who have traveled to or from Pakistan. Patients with suspected

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severe or complicated typhoid fever (which includes encephalopathy , intestinal perforation , peritonitis , intestinal hemorrhage or bacteremia with sepsis or shock) and who have travelled to or from Pakistan might need to be treated with carbapenem.⁹

Azithromycin, is still active against extensively drug-resistant typhoid; however, further genetic mutation could make typhoid untreatable in some areas.¹⁰

Azithromycin reduces the clinical failure rate and duration of hospital stay in comparison to fluoroquinolones and relapse rate in comparison to ceftriaxone, when used in the treatment of typhoid fever in populations with multidrug resistant typhoid fever.¹¹

Without further understanding of the mechanism of drug resistance and development of strategies to control for resistance, treatment of typhoid and paratyphoid infections are likely to become the real future challenge.

The rationale of this study was to highlight the emerging resistance to cephalosporin which till now was the standard to treat typhoid and paratyphoid infections in Pakistan.

MATERIAL AND METHODS

This longitudinal observational study was conducted at Khan Research Laboratories Hospital, Islamabad from June 2019 to Dec 2019. All patients presenting with fever having positive blood culture for salmonella typhi and paratyphi A were included. Patient's febrile period , duration of hospital stay and days of antibiotics given were also recorded. Age, gender ,Salmonella serovar and sensitivity to 11 antimicrobial drugs were taken into account. The tested antimicrobial drugs were ampicillin, trimethoprim/sulphamethoxazole, chloramphenicol, nalidixic acid, ciprofloxacin, ofloxacin, levofloxacin , ceftriaxone ,cefixime, imipenem and azithromycin. Data was analyzed using statistical package for social sciences version 22 (SPSS 22).

RESULTS

Out of 125 patients 80 (64.0%) were males while 45 (36.0%) were females. This is shown in table 1. Table 2 shows pattern of bacterial growth. Table 3 shows emerging resistance to third generation cephalosporins . All isolated pathogens were sensitive to imipenem and azithromycin. Table 4 shows hospital stay of patients

Table 1: Gender distribution

Gender	No of Patients & % ages
Male	80 (64.0)
Female	45 (36.0)
Total	125 (100.0)

Table 2: Patteren of bacterial growth

Salmonella serovar	Frequency & % ages
Salmonella typhi	110 (88.0)
Salmonella Paratyphi A	15 (12.0)
Total	125 (100.0)

Table 3: Cephalosporin resistant

Antibiotics	Frequency & % ages
Ceftriaxone, cefixime sensitive.	90 (72.0)
Ceftriaxone, cefixime resistant.	35 (28.0)
Total	125 (100.0)

Table 4: Hospital stay of patients

Hospital stay	No. of patients with %ages
Upto 7 days	%25.6) 32)
8 to 10 days	%68.0) 85)
11 to 14 days	%6.4) 08)

DISCUSSION

Extensively drug resistant (XDR) typhoid fever is emerging in Pakistan, raising the fear of antibiotic failure globally. The cause of drug resistance can be attributed to misuse of antibiotics which are available over the counter and their unchecked use without proper prescription. In our study salmonella typhi was positive in 88.0% patients and paratyphi 12.0%. No other strains were identified. These results were comparable with other studies. S. typhi vs. S. paratyphi A (57.8% vs. 41.6%)¹², (77.3% vs. 22.4%)¹³ and (83.8% vs 16.2%).¹⁴ In this study 28% patients were resistant to ceftriaxone and cefixime. All were sensitive to imipenem and azithromycin.

In a study from Agha Khan University including 101 cases , all cultured isolates were resistant to ampicillin, chloramphenicol, cotrimoxazole, ciprofloxacin, and exhibited ceftriaxone MICs of >64 µg/mL but remained sensitive to azithromycin, imipenem, and meropenem.¹⁵

In another study from India ceftriaxone resistance was present in 12.1%.¹⁶ In a 10-month period between 2016 and 2017, health authorities in Pakistan detected more than 800 cases of extensively drug-resistant typhoid in the city of Hyderabad alone.^{17,18} The Pakistan Health Authorities documented the outbreak of XDR typhoid fever cases from 2016 to 2018 in the province of Sindh, citing 5,274 cases of XDR typhoid of a total of 8,188 typhoid fever cases.¹⁹ A study conducted among children with enteric fever revealed 28% resistance to ceftriaxone.²⁰

LIMITATIONS

Main limitation of this study is that it is a single center study.

CONCLUSION

Cephalosporin resistance in enteric fever is rising. An earlier blood culture result is mandatory to prevent complications in all resistant case.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

Ali A: Concept, Design, Analysis, interpretation of data.

Naeem F: Literature Review, Bibliography.

Syed RI: Data Collocation.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.