

Ceftolozane/Tazobactam: “A New Treatment option against Multi-Drug Resistant *Salmonella typhi*”

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Abstract

Objectives: The current study was aimed to investigate the antimicrobial susceptibility of ceftolozane/tazobactam (5th generation cephalosporin) against *S. typhi*.

Design: Preclinical experimental study.

Place and Duration of Study: The study was conducted at Baqai Medical University Karachi from April 2019 to July 2019.

Patients and Methods: Total of 625 blood samples were collected from indoor and out-door patients using non-probability sampling technique. The included samples were cultured in specific media and culture and sensitivity of antibiotics were analyzed through Kirby-Bauer disc diffusion technique on Mueller Hinton agar (Oxoid, England).

Results: 200 samples were identified as positive *S. typhi*. Out of them 125 were recruited as MDR *S. typhi*. Analysis of demographic data showed 52% (n=66) female and 47% (n=59) male patients. The highest sensitivity was recorded against ceftolozane/tazobactam 94% and the highest resistance was recorded against chloramphenicol 92%, followed by ciprofloxacin 87% and ofloxacin 84%.

Conclusion: Ceftolozane/Tazobactam could be an alternative choice in the treatment of MDR *S. typhi* infections.

Keywords: *S. typhi*; Resistant strains; Ceftolozane/Tazobactam

Introduction

Typhoid fever is a major risk to health in underdeveloped countries due to poor sanitation and lack of surveillance programs [1,2]. A systemic review in 2010 reported that the worldwide incidence of enteric fever is nearly 12 million cases and reported mortality is 130,000 annually. The incidence rate in South East Asian countries exceeded 100 cases per 1,00,000 people/year and particularly in Pakistan that is 413 cases/1,00,000 persons in one year [3,4]. If the patients with typhoid fever are not diagnosed earlier and treated promptly they may develop severe complications that may lead them to mortality. Treatment with antibiotics may be life-saving but in the last few decades, the resistance against first and second-line antibiotics is highly increasing which is a growing public health concern nowadays [4].

For the treatment of typhoid fever preferably chloramphenicol was prescribed but in 1970 to early 1980 plasmid-mediated Multidrug Resistance (MDR) was observed against chloramphenicol, ampicillin and co-trimoxazole [5,6]. After the emergence of resistance, second-line Fluoroquinolone (ciprofloxacin and ofloxacin) has become the preferred drug for the treatment of MDR *S. typhi*. Fluoroquinolones are supposed to be superior to cephalosporin, but decreased susceptibility against ciprofloxacin has limited their effectiveness [7,8]. In developing countries third-generation cephalosporin (ceftriaxone) and macrolide (azithromycin) were also recommended for the treatment of invasive pathogen but due to irrational and prejudice prescription of antibiotics increased the resistance particularly in Pakistan, India, Bangladesh, Middle East and Africa [9-12].

Experts believe that Pakistan's dreadful sewerage systems coupled with low vaccination rates in endemic areas and

overpopulated cities are the root causes of the spread of MDR *S. typhi*.

Persistent occurrence of antibiotic resistance has steered to treatment failure and became a nightmare for the physicians to treat *S. typhi*, so there is a need to explore a new antibiotic or some other alternative which may show more sensitivity among commonly used antibiotics. The current study was aimed to investigate the antimicrobial susceptibility of ceftolozane/tazobactam (5th generation cephalosporin) against *S. typhi*.

Methods

It was a preclinical experimental study conducted at Baqai Medical University Karachi from April 2019 to July 2019. Blood samples were collected from indoor and outdoor patients using a non-probability sampling technique. Total of 625 suspected cases of either sex was selected for the study. After taking informed consent from patients detailed history was recorded on a proforma. The blood samples were collected and sent to the Microbiology lab on the same day for culture and sensitivity. Samples with positive *S. typhi* culture were included while those with negative reports were excluded from the study. A blood sample was inoculated into 30 ml Brain-Heart Infusion (BHI) broth (Oxoid, England) and was incubated for 5-7 days at 35 ± 2°C. After the growth of organism culture specimens were sub-cultured on blood agar and MacConkey agar plates (Oxoid, England). Colonies with positive biochemical reactions of Salmonellae were confirmed serologically by type-specific antisera (Bio-Rad).

Table 1: Antibiotic disc size on the Kirby-Bauer disc diffusion method.

Antibiotic	Zone of inhibition on Kirby-Bauer disc diffusion test
Ampicillin	10 µg
Azithromycin	15 µg
Ceftriaxone	30 µg
Chloramphenicol	30 µg
Ciprofloxacin	5 µg
Imipenem	10 µg
Meropenem	10 µg
Ofloxacin	5 µg
Ceftolozane/tazobactam	30/10 µg
Ceftazidime	10 µg

In the current study, the Kirby-Bauer disc diffusion technique on Mueller Hinton agar (Oxoid, England) was used to identify the patterns of antimicrobial sensitivity. Aerobic incubation of agar plates was performed at 35 ± 2°C, for 24 hours. The antimicrobial discs utilized in this study are shown in **Table 1**.

Statistical analysis

Data was scrutinized by using SPSS version 21. Numerical variables were mentioned as Mean with standard deviation. Frequencies and percentages were calculated for categorical variables. Chi-square test was applied to analyze the association between sensitivity and resistance of drugs. p-value <0.05% was considered as statistically significant.

Results

Out of 625 blood samples, 200 samples showed positive growth for *Salmonella* however 125 samples were MDR *S. typhi*. Analysis of demographic data showed 52% (n=66) female and 47% (n=59) male patients. Gender distribution and frequency of MDR *S. typhi* in different age groups are expressed in **Table 2**.

Table 2: Gender distribution and frequency of MDR *S. typhi* in different age groups.

Age	MDR <i>S. typhi</i>	<i>S. typhi</i>	p-value
1 month-20 years	45 (36%)	98 (49%)	
21-40 years	36 (28.8%)	56 (28)	
41-60 years	25 (20%)	26 (13)	0.029
61-80 years	16 (12.8%)	15 (7.5)	
80 years and above	3 (2.5%)	5 (2.5%)	
Gender distribution	MDR <i>S. typhi</i>	<i>S. typhi</i>	
Females	66 (52.8%)	112 (56%)	
Male	59 (47.2%)	88 (44%)	0.035
Total	N 125	N 200	

Antibiogram showed the resistance pattern of MDR *S. typhi* against empirical and conventionally used antibiotics. The highest sensitivity was recorded against ceftolozane/tazobactam 94% and highest resistance was recorded against chloramphenicol 92%, followed by ciprofloxacin 87% and ofloxacin 84%. The antimicrobial sensitivity patterns of other antibiotics are shown in **Figure 1**.

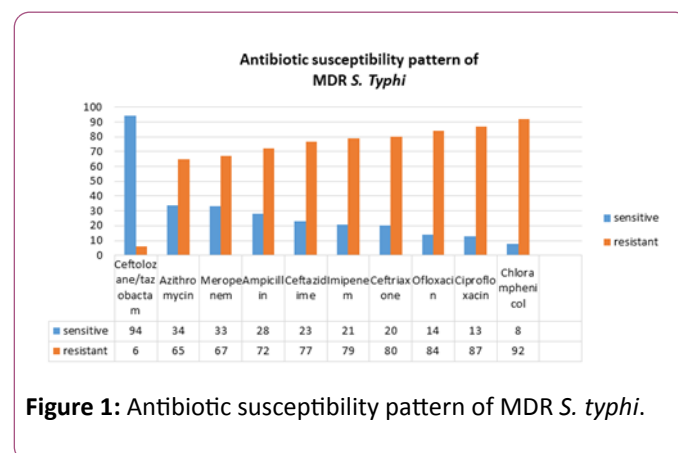


Figure 1: Antibiotic susceptibility pattern of MDR *S. typhi*.

Discussion

After the occurrence of resistance by *S. typhi* against chloramphenicol, resistance to new antimicrobial treatment has emerged persistently which has become a global problem. The decreased sensitivity to ampicillin, fluoroquinolones and chloramphenicol has become a major concern in recent years. Extensive use of antibiotics has now headed to decreased susceptibility of organisms across the globe especially among the Asian population. In our study the prevalence of MDR *S. typhi* was 64.9%; that is parallel to the studies conducted in different regions of Pakistan, India and Nigeria [13-15]. While Mohammad Ishaq et al. [16], has reported 30% prevalence of MDR *S. typhi* in a tertiary care hospital of Karachi. The high prevalence of MDR *S. typhi* in our setup is may be due to inadequate infrastructure of sewerage and environmental sanitation, unhealthy foods are a major cause of the problem.

Due to an increase in resistance against conventional antibiotics (i.e. chloramphenicol, ampicillin and ceftazidime), fluoroquinolones are prescribed frequently which has resulted in decreased fluoroquinolones susceptibility. In our study, the resistance against Fluoroquinolones (Ciprofloxacin and ofloxacin) is found to be 84% and 87% respectively which coincides with the results of further studies that have reported high resistance from the different regions of Pakistan which is a quite alarming situation for the clinicians [17-20]. The resistance against conventional drug chloramphenicol is 92% in our setup while similar results are mentioned in studies from Islamabad and Multan [17,21]. Overuse of third-generation cephalosporin could result in overproduction of ESBL (Extended Spectrum Beta-Lactamase Enzyme) [22], however, the increased emergence of resistance against third-generation cephalosporin is observed in our study. Consequently, ceftriaxone resistant *S. typhi* cases are reported in different parts of the world [22,23]. Due to poor clinical response, azithromycin is not ideal to be used as a single drug in severe typhoid fever. In our study Azithromycin is 65% resistant, less sensitivity was also demonstrated by other studies [24,25].

Ceftolozane/tazobactam demonstrated enhanced activity against MDR *S. typhi* as compared to other β -lactams with limited cross-resistance. Data collected in 2018, by Elaine Chan et al. [26], reported superior activity of ceftolozane/tazobactam toward MDR *Salmonella*. In the near future, this novel drug may be prescribed as an excellent choice in the treatment of MDR *S. typhi*. This will be due to the fact that ceftolozane/tazobactam has low MICs and more specifically it is unaffected by efflux pumps that could affect the other antibiotics [27]. To the best of our knowledge, this is the first study conducted in Pakistan regarding the susceptibility of ceftolozane/tazobactam against *S. typhi*. This study will give a new chapter for physicians to treat this lethal organism.

Conclusion

High prevalence rate and consistent emergence of drug resistance by organisms have led us to treatment failure. In the

era of drug resistance, Ceftolozane/tazobactam could be an alternative choice in the treatment of MDR *S. typhi* infections.

Future Recommendations and Limitation of the Study

The therapeutic use of broad-spectrum antibiotics should be reserved only for severe and life-threatening infections. Continuous investigation of multidrug-resistant organisms and antimicrobial stewardship is needed to have the best treatment options and better antibiotic selectivity.

This study was conducted in only one center of Karachi. It is strongly recommended that the same kind of research must be conducted at a larger scale with the involvement of multiple clinical settings of the country to obtain a more valid antibiotic susceptibility pattern against this virulent organism. This will help in controlling the spread of infections and will also be useful for better management of infectious diseases.

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