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Comparison of *in vitro* Activities of Ceftazidime-Tazobactam, Piperacillin-Tazobactam, and Cefoperazone-Sulbactam and the Implication on Therapy in a Tertiary Care Teaching Hospital

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A B S T R A C T

Resistance in pathogenic bacteria against antibiotics is a challenge for our clinicians for the management of various infections. The emergence of antibiotic resistance has caused great concern among health professionals and the prevalence of multidrug-resistant organisms has been increasing. Over-ambitious use of broad spectrum antibiotics is playing an important role in the increased incidence of infections due to MDR bacteria. Multiple drug resistance (MDR) mediated through R plasmids among Gram-negative bacteria has become a major nosocomial problem worldwide. Broad-spectrum β-lactams, such as imipenem, cefdinir, cefepime and cefpirome, and β-lactamase inhibitor combinations, such as piperacillin/tazobactam, cefoperazone/sulbactam and ticarcillin/clavulanate have been introduced in the market to overcome this resistance. Aim: To compare the antibiotic sensitivity of piperacillin/tazobactam, ceftazidime/tazobactam and cefoperazone/ sulbactam for gram negative isolates in our institute from various samples received in the hospital. This study was aimed at identifying the possible etiologic agents and determining their antibiotic sensitivity pattern, thereby allowing formulation of a reasonable initial empirical therapy regimen. OBJECTIVE: To choose the optimal antibiotic as the treatment for our patients who are developing infections. Overall, the sensitivity to ceftazidime/tazobactum was much higher compared to cefoperazone/sulbactum, piperacillin/tazobactum. The sensitivity was observed in medical wards for CAZ/TAZ (81.3%), CFS/SUL (49%), PIP/TAZ (47.4%), whereas in surgical wards the sensitivity observed was CAZ/TAZ (66%), CFS/SUL (32%), PIP/TAZ (27%) respectively. The sensitivity to Enterobacteriaceae group was CAZ/TAZ (69.3%), CFS/SUL (67%), PIP/TAZ (59%). The sensitivity to non-fermenters were CAZ/TAZ (31%),CFS/SUL (33%), PIP/TAZ (41%). Among non-fermenters, the sensitivity to PIP /TAZ (41%) was much better than CAZ/TAZ. Beta lactam inhibition combinations are used more in surgical patients than medical patients and the sensitivity to these combination drugs decreases with increased usage which clearly shows multidrug resistant pattern of organism. This can be prevented by following antibiotic policy and hand hygiene practice to avoid multidrug resistant organisms.

Keywords

Ceftazidime-Tazobactam, Piperacillin-Tazobactam and Cefoperazone-Sulbactam

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Introduction

Anti microbial resistance constitutes one of the major threats which are related to the pathogenic microorganisms. In any community or nosocomial setting, widespread antibiotic usage influences the prevalence and distribution of antibiotic resistance in

common pathogens.[1] Gram-negative pathogens such as *Enterobacteriaceae* (especially those which produce the extended-spectrum β-lactamases), *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* have acquired an important role in the nosocomial infections, which is of particular concern, because of the associated broad spectrum of the antibiotic resistance. The emergence of antibiotic resistance has caused great concern among health professionals due to increased prevalence of multidrug-resistant organisms. Multidrug-resistant organisms (MDROs) are labelled as such because of their in vitro resistance to more than one antimicrobial agent.[2] Treatment of infectious diseases have become more challenging with each passing year. It is estimated that 80% of all hospital deaths are directly or indirectly related to HAIs. HAI are most commonly associated with lower respiratory tract infections, urinary tract infections, pneumonia, wound infections, bloodstream infections, surgical site infection (SSI) and sepsis which are primarily caused by a range of gram-negative organisms particularly E. coli, *Acinetobacter* spp, *Klebsiella* spp., *Pseudomonas* spp., Enterobacter spp. In any community or nosocomial setting, widespread antibiotic usage influences the prevalence and distribution of antibiotic resistance in common pathogen. Multiple drug resistance (MDR) mediated through R plasmids among Gram-negative bacteria has become a major nosocomial problem worldwide.[3] Due to multiple drug resistance to β-lactams, aminoglycosides and quinolones, antimicrobial treatment of nosocomial infections caused by these bacteria is compromised [4]. Among the β-lactams, third generation cephalosporins, such as ceftazidime, cefotaxime, and ceftriaxone are routinely used in our clinical setting, and resistance to these drugs, due to β-lactamase production is frequently observed. [5]Broad-spectrum β-lactams, such as imipenem, cefdinir, cefepime and cefpirome, and β-lactamase inhibitor combinations, such as piperacillin/tazobactam, cefoperazone/ sulbactam and ticarcillin/clavulanate, have been introduced in the market to overcome this resistance. With the development of new antimicrobial agents, bacteria too are developing resistance against these newer agents. We measured the degree of in vitro activity of these new β-lactam drugs against clinical isolates belonging to the family Enterobacteriaceae, *Pseudomonas* spp. and *Acinetobacter* species, which were resistant to routinely used third generation cephalosporins, such as ceftazidime, cefotaxime and ceftriaxone. The present study was done to compare the in vitro activity of combination of beta lactamase inhibitor combination on the inpatients samples in a tertiary care teaching hospital.

Materials and Methods

This study was done in our institute from Jan 2019 to June 2019. The study was a prospective study and the samples were collected from all the inpatients of the hospital. All the age group of the patients were included in the study. We did not include out patients in our study. Ethical clearance was obtained from the Institute before starting the study. Out of 1154 isolates 100 samples which were multidrug resistant were taken for the further study. Various clinical samples included sputum, pus, urine, blood and other body fluids (CSF, pleural fluid, BAL etc.) that were received at the Microbiology department. The samples were processed, and the strains were identified and characterized by the following tests. Gram stain, oxidase test, catalase test, motility by both hanging drop and semi-solid agar methods, Hugh & Leifson O/F test, citrate utilization, urease production, nitrate reduction, indole production, phenylpyruvic acid production, pigment production, lysine &

ornithine decarboxylation, arginine dihydrolase test, and oxidation of 1% glucose, lactose, sucrose and mannitol. The antibiotic sensitivity was determined by means of the Kirby Baeur disc diffusion method, according to CLSI (Clinical Laboratory Standard Institute) guide lines 2019.[6] The strains that were resistant to ceftazidime, cefotaxime, ceftriaxone were tested for our further study. Extended Spectrum BetaLactamase (ESBL) production was confirmed by CLSI recommendations using cephalosporin-clavulanate combination discs. A difference of >5 mm between the zone diameter of either of the cephalosporin discs and their respective cephalosporin-clavulanate discs was taken to be the phenotypic confirmation of ESBL production. We used betalactam inhibitor combination of tazobactam, sulbactam for our study. The combinations that were added in our study were ceftazidime, ceftazidime/tazobactam, piperacillin, piperacillin/tazobactam, cefoperazone, cefoperazone /sulbactam. All the above-mentioned antimicrobial discs were obtained from Hi-media.[7]

Statistical Methods

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, Assumptions: 1.Dependentvariables should be normally distributed, 2.Samples drawn from the population should be random, Cases of the samples should be independent

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. Fisher Exact test used when cell samples are very small.

Results and Discussion

Out of 1154 samples that were processed, the samples that were resistant to ceftazidime, cefotaxime and ceftriaxone were taken for study. Totally 100 multidrug resistant samples were taken for study. The samples that we received included 33 male patients and 67 female patients [Table -1]. The samples included urine 65, sputum 12, pus 20 and tissue 3 [Table 2]. We received 59 samples from various medical wards and 41 samples from different surgical wards. The organisms isolated were *Acinetobacter* spp. 10, *Citrobacter* spp 3, *E. coli* 49, *Klebsiella* spp 21. *Pseudomonas* spp.15, *Proteus mirabilis* 2 from various samples.

Table.1 Sample type distribution of patients studied

Sample	No. of patients	%
Pus	20	20.0
Sputum	12	12.0
Tissue	3	3.0
Urine	65	65.0
Total	100	100.0

After isolating the multidrug resistant isolates, we compared the antibiotics susceptibility pattern with regards to CAZ/CAZ/TAZ, CFS, CFS/SUL, PIP, PIP/TAZ. Overall the sensitivity of the organisms to the drugs CAZ/CEF/TAZ was high in both medical and surgical wards. Sensitivity being high for CEF/TAZ- 48 (81/.3%), CFS/SUL- 29(49%) and for PIP/TAZ -28 (47.4%) from various medical wards where as in case of surgical wards the sensitivity for CAZ/TAZ -27 (66%), CFS/SUL - 13 (32%), PIP/TAZ - 11(27%) respectively. The resistant to all the three drug combinations were high in surgical

wards compared to medical ward samples because combination drugs are used mostly in surgical wards following surgeries. When we compared the sensitivity to pattern to organisms we found in case of Enterobacteriaceae, the sensitivity pattern to CAZ/TAZ -52 (69.3%), CFS/SUL- 28 (67%), PIP/TAZ -23 (59%) whereas in case of non-fermenters, the sensitivity pattern to CAZ/TAZ- 23 (31%), CFS/SUL- 14 (33%), PIP/TAZ - 16 (41%) respectively.

Table.2 Organism distribution of patients studied

Organism	No. of patients	%
Acinetobacter sp	10	10.0
Citrobacter sp	3	3.0
E.coli	49	49.0
Klebsiella sp	21	21.0
Proteus mirabilis	2	2.0
Pseudomonas sp	15	15.0
Total	100	100.0

The present study has demonstrated CAZ/TAZ as the most effective beta lactam inhibitor combination antibiotic with respect to combination antibiotic. Owing to the changing resistance patterns and increased prevalence of β lactamase producing strains, relevant pathogens may not be susceptible and therapy with a single antibiotic may promote antimicrobial resistance. Anuradha *et al.,* [8] have reported PIP/TAZ as the most active combination of the agent against Enterobacter, *Pseudomonas* spp but they found Ticarcillin/Clavulinic acid to be highly effective against *Acinetobacter* spp. And *Sternotrophomonas maltophilia*. In our study we found PIP/TAZ was effective against non fermenters than CAZ/TAZ. A study from Chandigarh says both CFS/SUL and PIP/TAZ as effective as combination against gram negative isolates. [9]IN as tudy on gram negative bacteria which were isolated form medical oncology patients, the activity of CFS/SUL were compared to that of PIP/TAZ. They found that CFS/SUL was found to efficient than PIP/TAZ.[10] Studies in India have shown PIP/TAZ to be better than CFS/SUL especially against *Pseudomonas* sp, *Klebsiella* sp, and *E. coli*.[11,12]Tazobactam is the most promising inhibitor which unlike sulbactam and clavulanic acid has its own antibacterial activity. Sulbactam containing combinations have not demonstrated strong selective pressures for ESBL producing Enterobacteriaceae. In contrast to clavulanate, sulbactam does not induce class I (Amp C) chromosomal beta-lactamases in Enterobacteriaceae.[13] In Gupta *et al.,* study Only 5.3% of the strains were resistant against cefoperazone/sulbactam. Various studies have shown that sulbactam increases the activity of cefoperazone against Enterobacteriaceae and nonfermenters.[14] [Table 6]. We found CAZ/TAZ had better sensitivity than CFS/SUL. In our study we found CAZ/TAZ combination was sensitive to most of the organisms in the wards. There was not much of a difference with respect to CFS/SUL and PIP/TAZ/. The variation in the susceptibility rates of β lactam/ β lactamase inhibitor combination in different studies could be due to the difference in the hospital organism and also PIP/TAZ [Table 7] is the most commonly used drug in surgical wards. This could have resulted in a selection pressure for the development of resistance to the drug. The emergence of resistance in microbes can be prevented by implication of strict guidelines for antibiotic prescribing and appropriate infection control measures.

It is concluded that the present study was important from a practical point of view. The clinical and therapeutic implication of antibiotic resistance implies that strict guidelines for antibiotic prescribing and appropriate infection measures are required to prevent MDS strains.

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