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Cefepime/Tazobactam – A Newer and Better β-Lactam/β-Lactamase Inhibitor Combination to Spare Carbapenem Drugs

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A B S T R A C T

Gram negative pathogens acts as a significant etiological agent in causing both hospital and community acquired infections for the past few decades. Various resistance mechanisms, especially β-lactamases triggered extensive use of β-lactams. Carbapenems stands as the last resort to save many life threatening diseases. To prevent extensive Carbapenemases dissemination, this study was aimed to know the in vitro susceptibility pattern of Cefepime/tazobactam with carbapenems and other BL/BLI combinations. Between January and December 2015, with 947 non-repetitive Gram negative isolates from various respiratory samples (sputum, broncho-alveolar lavage, pleural fluid, endotracheal aspirates and throat swabs) this prospective study was done in a tertiary care hospital, Puducherry. Isolates were identified and antibiotic susceptibility testing was done with Cefepime/tazobactam and its results were compared with carbapenems and other BL/BLI combinations. Out of 947 isolates, *E. coli* (44%) was the predominant isolate identified, followed by *Klebsiella spp.* (27%) and others. The sensitivity pattern of all our Gram negative isolates towards Cefepime/tazobactam ranged from 59% to 100%. Towards carbapenems it ranged between 68%-100% and for other BL/BLI combinations 47%-100% susceptibility was observed. To overcome this emerged β-lactamase enzymes in hospital and community settings, appropriate and adequate antibiotic practices is needed. As there are very few new antibiotics in the pipe-line, antibiotic restriction policy will definitely reserve the high-end antibiotics for the future. We conclude that Cefepime/tazobactam will be a challenging combination almost equal to carbapenems and far better than other BL/BLI combinations in the practice.

Introduction

Gram negative pathogens, especially *Enterobacteriaceae* and non-fermenters like *Pseudomonas spp.*, *Acinetobacter spp.*, are more prone to initiate Hospital Associated Infections (HAIs) as well as community acquired infections. By rapidly acquiring, β-lactamase enzyme production these pathogens rendered most of the available antibiotics ineffective (Smita, 2013; Perez *et al.*, 2009). As a result, it creates therapeutic failure or increases the morbidity among the patients. Though there are adequate antimicrobial agents available to act against various microbial pathogens, it is becoming more challenging to tackle microbes and to save the patients' lives now-in recent few years. The

increasing prevalence of ESBL's and AmpC producing Gram negative bacterial pathogens, initiated a very wide range of carbapenem usage in various health care setups, especially in intensive care areas for life threatening infections (Chaudhuri *et al.,* 2011, Ramanpreet *et al.,* 2014, National treatment guidelines 2016).

Following these carbapenem increased usage as an empirical agent predominantly in critical care areas (Abdul 2010, Hawser *et al.,* 2009). Carbapenemase producers emerged, which now become a global challenging healthcare issue as the therapeutic option is too narrowed down to Colistin and Polymyxins. In order to overcome this critical antimicrobial resistance scenario, clinicians are narrowed down only to few options like, carbapenem sparing and restriction policy and also to explore or adopt an alternative treatment strategy with β-lactam/β-lactamase inhibitor combinations (Jauregui *et al.,*1990; Karaman *et al.,* 2015; Bodey *et al.,*1996).Considering this therapeutic challenges, this study was aimed to compare the in-vitro antimicrobial effect of carbapenems, piperacillin/tazobactum and cefaprazone/sulbactam with Cefepime/ tazobactam – a new β-lactam/β-lactamase inhibitor combination.

Materials and Methods

During 2015 from January to December, a prospective observational study was done in a tertiary care hospital at Puducherry to study the *in vitro* effectiveness of Cefepime/tazobactam (CPT) (30/10µg Hi Media, Mumbai) against various bacterial isolates and to compare its susceptibility with other β-lactam/β-lactamase inhibitor combination like piperacillin/tazobactam (PTZ), cefaprazone/sulbactam (CFS) and carbapenems [imipenem (IMP) and meropenem (MRP)]. A total of 947 non-repetitive, consecutive aerobic Gram negative bacterial pathogens from various respiratory clinical samples (sputum, broncho-alveolar lavage [BAL], pleural fluid, endotracheal aspirates and throat swab) were included in this study. Isolates were identified with a battery of standard biochemical tests and antibiotic susceptibility testing was done by Kirby Bauer disc diffusion method according to standard guidelines (Collee *et al.,* 1996). Since cefoperazone/sulbactam and Cefepime/tazobactam interpretative criteria was not available, cefoperazone and cefepime zone size as per CLSI 2010 was used to interpret these two drug combinations (CLSI 2010).ESBL and AmpC beta lactamase production for all these isolates were done by phenotypic confirmatory method and AmpC disc method. Repeated isolates from the same patients were excluded. ATCC control *strains, E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were used as controls.

Results and Discussion

Of this 947 Gram negative clinical isolates, the majority were isolated from endotracheal aspirates (42%) followed by sputum (25%), broncho-alveolar lavage (16%), pleural fluid (15%) and throat swabs (2%). Out of all these samples, *E. coli* were the predominant bacterial isolate (44%) followed by *Klebsiella spp.* (27%), *Acinetobacter spp*. (11%), *Pseudomonas aeruginosa* (8%), *Citrobacter spp.* (6%) and *Enterobacter spp*. (3%).

Among 44% *E. coli* isolates, the sensitivity pattern towards CPT was 83%, IMP-96%, MRP– 93%, PTZ-79% and CFS-82%. Followed by this, *Klebsiella spp.* (27%) showed susceptibility of 82% on CPT, IMP-92%, MRP-89%, PTZ-54%, and CFS-75%. *Acinetobacter spp.* (11%) showed 59%, 68%, 74%, 45% and 57% sensitivity towards CPT, IMP, MRP, PTZ and CFS respectively.

Pseudomonas aeruginosa showed highest susceptibility of 90%, 89%, 86% on CPT, IMP and MRP followed by 76%, 75% on PTZ and CFS. *Citrobacter spp*. showed highest percentage of 92%, 89% susceptibility towards meropenem and imipenem, followed by 76%, 68% and 47% towards CFS, CPT, PTZ. *Enterobacter spp*. showed 100%, 100%, 76%, 75% and 63% sensitivity towards CPT, CFS, MRP, IMP and PTZ. Proteus spp. showed 100%, 97%, 91%, 90% and 90% susceptibility towards MRP, IMP, CPT, PTZ and CFS (Table 1).

Resistance percentage of all the Gram negative isolates were 18% towards CPT and 34%, 23%, 10% and 11% against PTZ, CFS,IMP, MRP respectively (Table 2).

Among these 947 Gram negative bacillary isolates, 37% were ESBL producers and 13% were AmpC producers. None of the CPT resistant (16%) and intermediate (2%) isolates was either ESBL or AmpC producers. But CPT sensitive and corresponding IMP/MRP resistant or intermediate isolates were only ESBL or AmpC producers. Cefepime a semi-synthetic broad spectrum bactericidal, 4th generation cephalosporin antibiotic now available in combination with tazobactam. Tazobactam sodium, a triazolylmethyl penicillanic acid sulphone which is a potent inhibitor of various beta lactamases in particular to plasmid mediated enzymes (Indian Pharmacopeia 2014). It commonly cause resistance to penicillins and cephalosporins including third – generation cephalosporins (British Pharmacopeia 2014, Thomson *et al.,* 2005, Anuradha *et al.,* 2007). Cefepime acts as an effective bactericidal agent against Gram-negative and Gram-positive pathogens and it was known to be stable against both AmpC and OXA but lacks activity against ESBLs (Livermore *et al.,* 1989, Livermore *et al.,* 2008, Erdal 2002). This novel combination of cefepime and tazobactam (30/10µg) results in significant synergistic effect that expands the spectrum of activity of cefepime against many beta-lactamase producing bacterial strains (Ghafur *et al.,* 2012, Livermore *et al.,* 2008, Biswas *et al.,* 2013).

Table.1 List of antibiotics and their in-vitro sensitivity pattern

Isolates	**Cefepime/ tazobactam**	**Imipenem**	**Meropenem**	**Piperacillin/ tazobactum**	**Cefaprazone /sulbactam**
E. coli (414)	83%	96%	93%	79%	82%
Klebsiella spp. (253)	82%	92%	89%	54%	75%
Acinetobacter spp. (100)	59%	68%	74%	45%	57%
Pseudomonas aeruginosa (80)	90%	89%	86%	75%	76%
Citrobacter spp. (54)	68%	89%	92%	47%	76%
Enterobacter spp.(24)	100%	75%	76%	63%	100%
Proteus mirabilis(22)	91%	97%	100%	90%	90%

Table.2 Distribution of Resistance pattern

Antimicrobial agents	Resistant (%)	Intermediate (%)	Sensitive (%)
CPT	16%	2%	82%
PTZ	23%	11%	66%
CFS	18%	5%	77%
IMP	7%	3%	90%
MRP	9%	2%	89%

By augmenting and protecting cefepime, this cefepime tazobactam (30/10µg) combination was found to be very effective against many ESBL producing Gram negative organism (Ghafur*et al.,* 2012, Livermore *et al.,* 2008). The indications for this novel combination wasto treat uncomplicated and complicated Urinary tract infection (UTI), Skin and soft tissue infections, complicated intra-abdominal infections and severe lower respiratory tract infections (Perez *et al.,* 2009). Patient who was found to develop hypersensitivity reaction to this combination and other cephalosporins, this drug can be contraindicated. As there is lack of studies in favor of this combination in case of pregnancy and lactation, it cannot be commented.

Due to recent extensive use of carbapenems, against various life threatening infections in critical areas, Metalloβ-lactamase producers (MBL) had emerged already which created a substantial threat to all the stake holders. High prevalence of ESBLs among hospital and community acquired infections acted as the trigger to induce Carbapenemase production (Biswas *et al.,* 2013). As an alternative to carbapenems, many BL-BLI combinations were experienced to be near equally effective drugs (Jauregui *et al.,* 1990, Karaman *et al.,* 2015, Bodey *et al.,* 1996, Anuradha *et al.,* 2007, Erdal 2002). This cefepime a 4th generation cephalosporin with clavulanate, a highly effective inhibitor of ESBL enzymes was tested for its in vitro effectiveness with our respiratory clinical isolates to support carbapenems sparing/leaving policy, in order to prevent the emerged Carbapenemase resistance (Livermore *et al.,* 2008, Goel *et al.,* 2011).

All our isolates showed very significant percentage of sensitivity towards the new β-lactam/β-lactamase inhibitor combination (Cefepime/tazobactum) equally to carbapenems (imipenem and meropenem). In correlation with our results, Biswas *et al.,* (2013) with a total of 269 Gram negative isolates, reported 52% ESBL production and also documented that all their isolates were found to be most sensitive to IMP, MRP followed by CPT, CFS and PTZ. Similarly, Panchatcharam *et al.,* (2012) also reported very significant susceptibility pattern by *E.coli* (91.4%), *Klebsiella spp*. (76.7%), *Pseudomonas aeruginosa* (85.7%), *Acinetobacter spp*. (50%), 83.8% towards CPT and emphasized that CPT is a promising option in the management of infections due to enterobacteriaceae.

Mudshingkar *et al.,* (2014) reported 62% ESBL production and with their Gram negative isolates they showed only 65.4% sensitivity towards cefepime/tazobactam followed by 53.7% towards imipenem, 33.5% piperacillin/tazobactam and 29.7% Cefoperazone/sulbactam. In contrarily we documented only 37% ESBLs and in addition we also recorded 13% AmpC production from our isolates. All our Gram negative isolates showed 82% sensitivity towards CPT which was very close to our carbapenem susceptibility rate. We also documented a very significant percentage of 66% and 77%

susceptibility towards other BL/BLI combinations (piperacillin/tazobactum and Cefoperazone/sulbactam).

Smita Sood (2013) in his in-vitro comparative evaluation study with six β-lactam/β-lactamase inhibitor combinations documented that CPT was found to be 90.64% susceptible followed by CFS 84.89%, PTZ 53.95% and by other combinations by Gram negative bacilli. This was very much similar to our results. With respect to NFGNB, only 49% sensitivity got reported, but very close to them59% susceptibility was noticed with our *Acinetobacter spp.* In contrast to our findings, Anuradha *et al.,* (2007) reported piperacillin/tazobactum as the most effective combination against Gram negative bacilli and also *Acinetobacter spp*. Very fortunately all our *Pseudomonas aeruginosa* isolates showed 90% susceptibility towards CPT, which was very much variance with others. Many other studies also concluded that piperciin/tazobactum as most sensitive combination when compared to Cefepime-tazobactum (Mohanty *et al.,* 2005; Chitnis *et al.,* 2003; Gupta *et al.,* 2006). All our ESBL and AmpC producers were found to be 100% sensitive to CPT when compared to carbapenems and other β-lactam/β-lactamase inhibitor combinations, which were very much correlating with other reports (Smita 2013). Even though we experienced, this cefepime/tazobactam combination as almost equally a better warrior against Gram negative pathogens, the limitation could be, lack of in-vivo effectiveness, patient tolerance, dosage and also wide coverage of all clinical infections, not only respiratory tract infections.

With very rapid spread and distribution of β-lactamases, almost all the available antimicrobial agents became highly ineffective. As this already created pressure in opting therapeutic option against various life-threatening conditions, new combination like cefepime/tazobactammay spare the other high-end antibiotics like carbapenems, colistin and polymyxin B. We finally conclude that, all our Gram negative isolates were found to be highly susceptible to this new β-lactam/β-lactamase inhibitors combination when compared to other two combinations. And also we found that cefepime/tazobactam was equally effective similar to imipenem and meropenem. Thus to circumvent this plasmid-mediated β-lactam resistance, cefepime/tazobactam will be an effective combination.

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