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

Kalaivani Ramakrishnan1*, Sameera M. Jahagirdar2, M. Ravishankar2 and Seetha Kunigal1

1Department of Microbiology, 2Department of Anesthesiology, Mahatma Gandhi Medical College and Research Institute, SBV University, Pondicherry-607403, India

*Corresponding author

ABSTRACT

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.

Keywords
Cefepime/tazobactam, CPT, BL/BLI, ESBLs, Cefepime.

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/MPR 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 triazolymethyl 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/ tazobactam | Cefaprazone /sublactam |
|-------------------------|----------------------|----------|-----------|--------------------------|------------------------|
| *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%                    |
By augmenting and protecting cefepime, this cefepime tazobactam (30/10µg) combination was found to be very effective against many ESBL producing Gram negative organism (Ghafuret et al., 2012, Livermore et al., 2008). The indications for this novel combination was to 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/tazobactam 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 them 59% susceptibility was noticed with our Acinetobacter spp. In contrast to our findings, Anuradha et al., (2007) reported piperacillin/tazobactam 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 pipericiin/tazobactam as most sensitive combination when compared to Cefepime-tazobactam (Mohanty et al., 2005; Chitinis 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/tazobactam may 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.

**Acknowledgement**

We thank our SBV University for their supports and motivations.

**References**

Abdul Ghafur K. An obituary- On the death of antibiotis. J Assoc Physicians India. 2010; 58: 143-144.

Anuradha V, Sailaja VV, Umabala P, Sateesh T, Lakshmmi V. Sensitivity pattern of Gram negative bacilli to these β-lactam/β-lactamase inhibitor combinations using the automated API system. Ind J Med Microbiol. 2007; 25(3): 203-08.

Biswa S, Kelkar R. P081: Cefepime-tazobactam: a new antibiotic against ESBL producing enterobacteriacea in cancer patients. 2nd International conference on prevention and infection control, Geneva, Switzerland. Antimicrobial resistance and infection control. 2013; 2: 81.

Bodey G, Abi-Said D, Rolston K, Raad I, Whimbey E. Imipenem or cefoperazone-sulbactam combined with vancomycin for therapy of presumed or proven infection in neutropenic cancer patients. Eur J clin Microbiol infect Dis. 1996; 15: 625-634.
British Pharmacopeia, (British Pharmacopeia Commission, expert Advisory groups, panels of experts and working parties. 2014; 438-440.

Chaudhuri BN, Rodrigues C, Balaji V, et al., Incidence of ESBLL producers amongst Gram-negative bacilli isolated from intra-abdominal infections across India. SMART study. J Assoc Physicians India. 2011; 59:1-6.

Chitnis SV, Chitnis V, Sharma N, Chitnis DS. Current status of drug resistance among Gram-negative bacilli isolated from admitted cases in a tertiary care centre. J Assoc Phy Ind. 2003; 51: 28-32.

Clinical Laboratory Standards Institute. Twentieth informational supplement. CLSI document M100-S20.Wayne PA:CLSI:2010. Performance Standards for Antimicrobial Susceptibility Testing.

Collee JG, Miles RS, Wan B. Tests for the identification of bacteria. Mackie and McCartney Practical Medical Microbiology, 14th ed. Churchill Livingstone;1996:131–150.

Erdal AH. Use of beta-lactam/beta-lactamase inhibitor combinations to treat community acquired respiratory tract infections. Infect Dis Clin Ppract.2002; 11:20-26.

Ghafur A, Nagvekar V, Thilakavathy S, Chandra, Gopalakrishnan and Vidyalakshmi PR. “Save Antibiotics, Save lives”: an Indian success story of infection control through persuasive diplomacy. Antimicrobial Resistance and Infection Control.2012: 1:29

Goel N, Wattal C, Oberoi JK, Raveendran R, Datta S, Prasad KJ. Trend analysis of antimicrobial consumption and development of resistance in non-fermenters in a tertiary care hospital in Delhi, India. JA. 2011; 66: 1625-30.

Gupta V, Datta P, Agnihotri N, Chander J. Comparative in vitro activities of seven new β-lactams, alone and in combination with β-lactamase inhibitors, against clinical isolates resistant to third generation cephalosporins. Braz J of infect Dis. 2006; 10(1): 22-25.

Hawser SP, Bouchilllon SK, Hoban DJ, Badal RE, Hsueh Po Ren, Paterson DL. Emergence of High Levels of extended spectrum spectrum β lactamase producing gram negative bacilli in the Asia pacific regions on Chemoth: Data from the study for Monitoring Antimicrobial Resistance Trends (SMART) Program. Antimicrob Agents and Chemother. 2009; 53: 3280-3284.

Indian Pharmacopeia, (The Indian pharmacopeia commission, Indian pharmacopeia laboratory government of India, Ministry of Health & Family welfare, Sector 23, Raj nagar, Ghaziabad-201002, 2014; 1302-1305.

Jauregui LE, Appelbaum PC, Fabian TC, Hagcreage G, Strausbaugh L, Martin LF. A randomized clinical study of cefoperazone and sulbactam versus gentamicin and clindamycin in the treatment of intra-abdominal infections. J Antimicrob Chemother. 1990; 25: 423-433.

Karaman S, Vural S, Yidirmak Y, Emecen M, Erdem E, Kebudi R. comparison of piperacillin tazobactam and cefoperazone sulbactam monotherapy in treatment of febrile neutropenia. Pediatr Blood cancer. 2015; 58: 579-583.

Livermore DM, Akova M, Wu PJ, Yang YJ. Clavulanate &Betalactamase induction. J Antimicrob Chemother. 1989; 24(B): 23–33.

Livermore DM, Hope R, Mushtaq S, and Warner M. Orthodox and unorthodox clavulanate combinations against extended-spectrum β-lactamase producers. ClinMicrobiol Infect. 2008; 14(1): 189–193.
Livermore DM, Hope R, Mushtaq S, and Warner M. Orthodox and unorthodox clavulanate combinations against extended-spectrum β-lactamase producers. Clin Microbiol Infect. 2008; 14(1): 189–193.

Mohanty S, Singhal R, Sood S, Dhawan B. Comparative in vitro activity of beta-lactam/beta-lactamase inhibitor combinations against Gram negative bacteria. Indian J Med Res. 2005; 122: 425–428.

National treatment guidelines for antimicrobial use in Infectious Diseases. National center for disease control. Directorate General of Health services, Ministry of Family Welfare, Government of India, Treatment of multidrug resistant bacterial pathogens. version 1.0. 2016; chapter 3: 42.

Panchatcharam SN, Ramasubramanian V, Gopalakrishnan R, Ghafur A, Thirunarayan M. Cefepime-tazobactam: A promising therapeutic option. Abstract No:50.011, 15th ICID, Bangkok, Thailand. International Journal of infectious diseases. 2012; June 13-16: e470.

Perez Llarena FJ, Bou G. Beta-lactamase inhibitors: The story so far. Curr Med Chem.2009; 16(28): 3740-65.

Ramanpreet Kaur, Vikas Gautam, Lipika Singhal and Pallab Ray. Antimicrobial activity of cefepime–tazobactam combination tested against clinical isolates of Enterobacteriaceae. The Journal of Antibiotics. 2014; 67: 603-604.

Smita Sood. Comparative Evaluation of the in-vitro Activity of Six β-lactam/β-lactamase Inhibitor Combinations against Gram Negative Bacilli. J Clin Diagn Res. 2013; 7(2): 224–228.

Swati S. Mudshingkar, Ashwini K. Dedwal, Meghna S. Palewar, Vaishali B. Dohe, Anju S. Kagal, Renu S. Bhardwaj. Cefepime/tazobactam-a promising BL-BLI combination against multidrug resistant Gram negative bacteria. International J. of Healthcare and Biomedical Research. 2014; 2(3): 127-128.

Thomson JM, Bonomo RA. The threat of antibiotic resistance in Gram-negative pathogenic bacteria: β-actams in peril! CurrOpin Microbiol. 2005; 8(5): 518-24.

How to cite this article:
Kalaivani Ramakrishnan, Sameera M. Jahagirdar, M. Ravishankar and Seetha Kunigal. 2017. Cefepime/Tazobactam – A Newer and Better β-Lactam/β-Lactamase Inhibitor Combination to Spare Carbapenem Drugs. Int.J.Curr.Microbiol.App.Sci. 6(10): 1379-1385.
doi: https://doi.org/10.20546/ijcmas.2017.610.163