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Rising Problem of Resistant Gram Negative Pathogens in Tertiary Care Setup and Susceptibility Analysis of Beta Lactams and Beta Lactam + Beta Lactamase Inhibitor Combinations

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A B S T R A C T

Antibiotic resistance has risen perilously in all parts of the world. The lack of appropriate therapeutics to encounter resistant pathogens has enhanced the urge for the development of either new antibiotics or different therapeutic combinations. Hence, this study was aimed to evaluate the antimicrobial efficacy of cefepime plus sulbactam in comparison with cefepime alone and other therapeutics such as third generation cephalosporin (ceftazidime), β-lactam and β-lactamase inhibitor combinations (pipercaillin + tazobactam and cefoperazone + sulbactam) and carbapenem drugs (imepenem and meropenem. The present study was a prospective study conducted over a period of five months (January 2019 – May 2019) in the Department of Microbiology, Grecian Super Speciality Hospital, Mohali (Punjab, India). This study included clinical isolates obtained from clinical specimens collected from outdoor and indoor patients. Antibiotic susceptibility testing was executed in accordance with the recommendations of Clinical Laboratory Standards Institute (CLSI) guidelines. Out of 751 collected specimens, urine specimens contributed 49.67% followed by blood (17.98%), endotracheal secretions (15.98%), sputum (7.06%), pus (4.93%), bronchoalveolar lavage (BAL) (1.73%), wound swab (1.59%), body fluids (0.79%) and CSF (0.27%). *Escherichia coli* were found most prevalent (55.66%) pathogen along with 16.91, 13.72 and 11.32% prevalence of *Pseudomonas aeruginosa*, *Klebsiella penumoniae* and *Acinetobacter baumannii* respectively whereas rest 2.39% presence of other pathogens (*Providencia spp.*, *Proteus spp.*, *M*organella *morganii* and *Citrobacter spp.*) was also observed. The *in-vitro* antibacterial activity revealed that cefepime + sulbactam (82.29%) was 41.81% more active than cefepime alone. Data also depicted 25.17 to 58.06% superiority of cefepime + sulbactam over third generation cephalosporin (ceftazidime) and other BL-BLI combinations (piperacillin + tazobactam and cefoperazone + sulbactam) and also exhibited 2.4% and 17.58% more sensitivity than meropenem and imipenem respectively, hence, found comparable to carbapenem drugs. Susceptibility profile data revealed the equivalence of cefepime + sulbactam with carbapenem drugs and strong superiority over third generation cephalosporin and other BL + BLI combinations against resistant gram negative pathogens. Therefore, the antibiotic resistance breaking efficacy of cefepime plus sulbactam confirms this combination as a carbapenem sparing agent and also as a better choice over other BL-BLI combinations to treat infectious pathogens.

Introduction

Antimicrobial resistance (AMR) is an increasingly recognized concern throughout the globe (Neil, 2014). It has been estimated that by 2050, 10 million lives a year will be at risk due to emergence of the infections raised by AMR pathogens (Neil, 2016). The US Centers for Disease Control and Prevention (CDC) estimates that antibiotic resistance is responsible for more than 2 million infections and 23,000 deaths each year in the United States at a direct cost of $20 billion and additional productivity loss of $35 billion (Neil, 2014; Vasoo *et al.*, 2015). Antibiotics if rendered ineffective, will pose a higher risk of

poor outcomes during surgical procedures, chemotherapies, immunity suppression procedures that may shatter human life (Vasoo *et al.,* 2015). Overuse of antibiotics is considered as the prime reason for hike in antimicrobial resistance. Many countries like BRICS (Brazil, Russia, India, China and South Africa) have accounted for 3/4th of total usage of antibiotic in the world (Yulistiani *et al.,* 2017). Likewise ß lactam antibiotics usage reports for 50 % of global antibiotic consumption (Yulistiani *et al.,* 2017; CDEP 2015). Previously, 66-80% resistance among gram negative bacteria has been observed against third generation cephalosporin drugs and ß lactam- ß lactamase inhibitor (BL-BLI) antibiotics (Datta *et al.,* 2012; Laxminarayan *et al.,* 2013; Vaja *et al.,* 2016; Gashe *et al.,* 2018). Recently, 50-61% resistance was observed among clinical isolates towards third generation cephalosporin (Joshi *et al.,* 2003).

Mechanism behind antimicrobial resistance in these microorganism includes production of extended spectrum ß lactamases (ESBL), changes in membrane permeability, over-expression of efflux pump and production of biofilms etc (Fair and Tor, 2014; Singh and Shukla, 2015; Ruppe *et al.,* 2015; Hamada *et al.,* 2015). Cefepime being fourth generation cephalosporin antibiotic has broad spectrum activity and has high affinity for essential penicillin binding proteins, and is less affected by the non-hydrolytic barrier mechanism of resistance (Shrivastava and Chaudhary, 2009). On the other hand, β-lactamase inhibitor (BLI) such as sulbactam rapidly penetrates bacteria and has high affinity for essential penicillin-binding proteins (Koch, 2000). The use of beta-lactamase inhibitors in combination with β-lactam (BL) antibiotics is currently the most successful strategy to combat a specific resistance mechanism in case of microbial infections (Tehrani and Martin, 2018; Shrivastava and Chaudhary, 2011). Their broad spectrum of activity originates from the ability of respective inhibitors to inactivate a wide range of β-lactamases produced by gram negative, gram positive and anaerobes. Cefepime and sulbactam acts synergistically and has a broad spectrum in vitro activity that in encompasses a wide range of gram positive and gram negative bacteria (Koch 2000; Chaudhary and Payasi, 2014; Chaudhary and Payasi, 2014; CLSI, 2018). Therefore, present study is aimed at microbial efficacy analysis of the combination of cefepime plus sulbactam, in comparison with cefepime alone and other therapeutics such as third generation cephalosporins, other BL-BLI combinations and carbapenem drugs against different clinical isolates.

Materials and Methods

Sample collection

Different clinical specimens such as urine, blood, endotracheal secretions, pus, sputum, BAL, CSF, wound swab and body fluids were collected from indoor and outdoor patients at Grecian Hospital, Mohali (India).

Isolation and identification of microbes

All the samples were collected aseptically in sterile robust leak proof containers in sufficient amount. The samples were transported immediately to microbiology lab for further processing. The samples were inoculated on blood agar and Mac Conkey's agar. The collection and processing of the specimens were done as per Standard Operating Procedures. The growth obtained was identified by the colony characteristics, gram staining and by standard biochemical reactions.

Antibiotic susceptibility testing

The antimicrobial susceptibility testing was done by Kirby Bauer's disk diffusion method

as recommended by the Clinical Laboratory Standards Institute (CLSI) guidelines (CLSI, 2018). Inoculum of 0.5 McFarland standards turbidity was prepared from isolated colony of pathogens selected from 18-24 hour agar plates. Within 15 minutes, a sterile cotton swab was dipped into the inoculum suspension. The swab was rotated several times and pressed firmly against the inside wall of the tube above the fluid level and inoculated on the dried surface of a Mueller-Hinton agar (MHA) plate by streaking the swab over it. For even distribution of inoculum, the swab was streaked two more times at 60° over the agar surface. After 3–5 minutes, antibiotic discs were applied and pressed down to ensure complete contact with agar surface. The discs were distributed evenly to ensure a minimum distance of 24 mm from center to center. The plates are then inverted and incubated for 16-18 hrs aerobically at 37° C within 15 minutes of disc application and zone of inhibition measured in millimetres and the results were interpreted as Sensitive, Intermediate and Resistant.

Results and Discussion

A high-level of resistance has been observed towards cephalosporins and other BL and BL-BLI drugs while cefepime has also been shown to develop resistance particularly because of development of β-lactamase (Fair and Tor, 2014; Singh and Shukla, 2015; Ruppe *et al.,* 2015; Hamada *et al.,* 2015; Koch, 2000).

There are few reports where different combinations of cephalosporins are being used to attain therapeutic significant results (Fair and Tor, 2014; Koch, 2000; Chaudhary and Payasi, 2014). Therefore, present study is taken up to determine the efficacy of combination of cefepime and sulbactam in comparison with cefepime alone and other BL, BLI drugs. A total of 751 clinical isolates [Enterobactericeae = 539 and Non-Enterobacteriaceae = 212], collected from the different clinical specimens were used in this study.

Among Enterobactericeae isolates (n=539), the highest occurrence of pathogens was found in urine samples (60.11%) followed by blood (17.81%), endotracheal secretion (8.35%), pus (5.19%) while rest of the specimens showed <5% prevalence whereas Non-Enterobactericeae (n=212) isolates were more prevalent among endotracheal secretion (35.38%), urine (23.11%), blood (18.40%), sputum (11.32%) while <6% presence was observed among other clinical samples (Table 1).

Table 1 depicts the prevalence percentage of clinical pathogens among different clinical samples. Present results were correlated with Anuradha *et al.,* (2014) and Ravichitra *et al.,* (2014) who also noted similar findings (Fig.1).

On the basis of morphological and biochemical screening eight different pathogens were isolated included *K. pneumoniae, E. coli, A. baumannii, M. morganii, Providencia spp., Citrobacter spp., Proteus spp.* and *P. aeruginosa.* Among all the eight pathogens, *E. coli* (55.66%) was found to be most prevalent in all the clinical samples followed by *P. aeruginosa* (16.91%) and *K. pneumoniae* (13.72%) and *A. baumannii* (11.32%). Many studies have also revealed that gram negative bacteria as a major opportunistic and frequent pathogens and are extremely prevalent in hospital-associated infections which favours recent study (Neil, 2014; Ejaz *et al.,* 2006). Clinical isolates such as *M. morganii, Providencia spp., Citrobacter spp.* and *Proteus spp.* were noticed least (<2% each) prevalent (Figure 1). Incidences of these isolates in clinical specimens corroborates with earlier studies (Patel *et al.,* 2008; Sachdeva, 2016; Goel *et al.,* 2009).

Antibiogram profile of all the pathogens obtained from clinical specimen is presented in Figure 2.

Present data depicted the superiority of cefepime + sulbactam (82.29%) over cefepime alone (40.48%).

Susceptiblity pattren also found cefepime + sulbactam more active than BL drug [ceftazidime (24.23%)], BL-BLI drugs [piperacillin + tazobactam (57.12%) and cefoperazone + sulbactam (52.46%)] and carbapenem drugs [meropenem (79.89%) and imipenem (64.71%)] against clinical isolates.

Table.1 A profile of clinical samples used as a source of the pathogenic isolates

Sr. no.	Specimen	Total isolates (%)	Enterobacteriaceae (%)	Non-Enterobacteriaceae (%)
1	BAL	1.73	0.37	5.19
2	Blood	17.98	17.81	18.40
3	CSF	0.27	0.37	-
4	Body fluids	0.79	0.93	0.47
5	ET secretion	15.98	8.35	35.38
6	Pus	4.93	5.19	4.25
7	Sputum	7.06	5.38	11.32
8	Urine	49.67	60.11	23.11
9	Wound swab	1.59	1.48	1.89
Total (n)	**751**	**751**	**539**	**212**

Fig.1 Prevalence percentage of clinical pathogens among different clinical samples

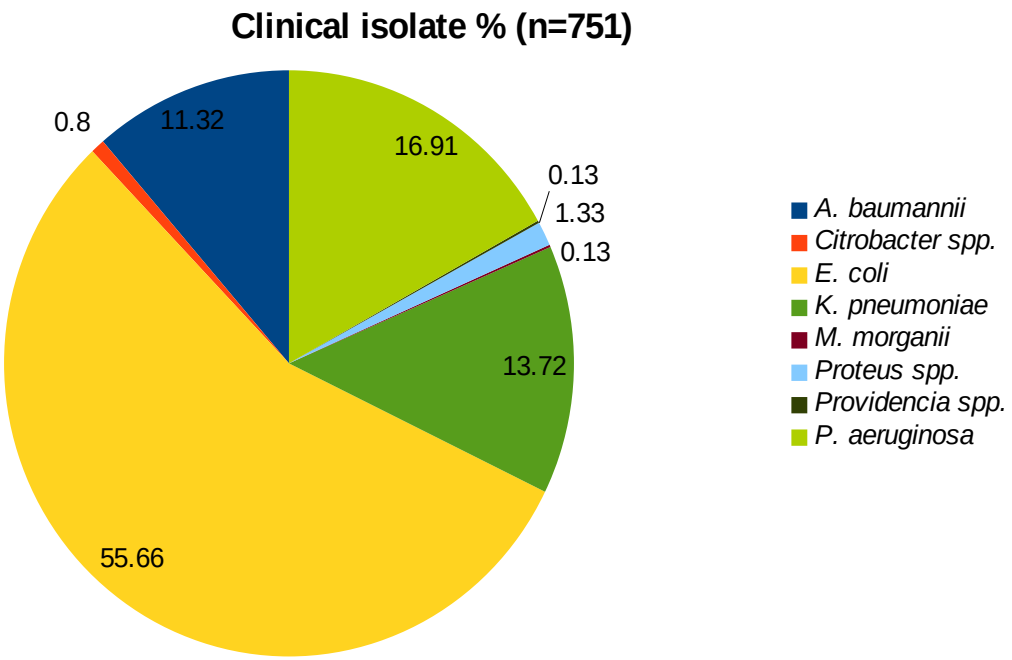


Fig.2 Susceptibility pattern of clinical isolates towards different antibacterial agents

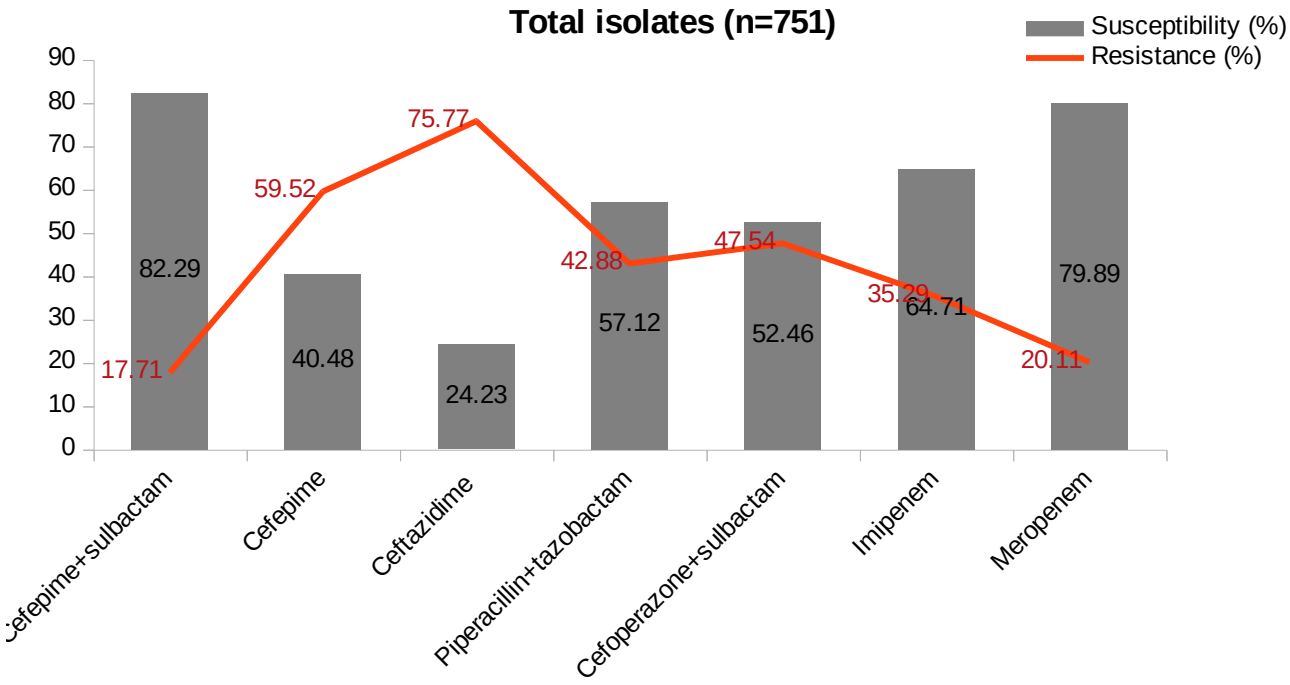
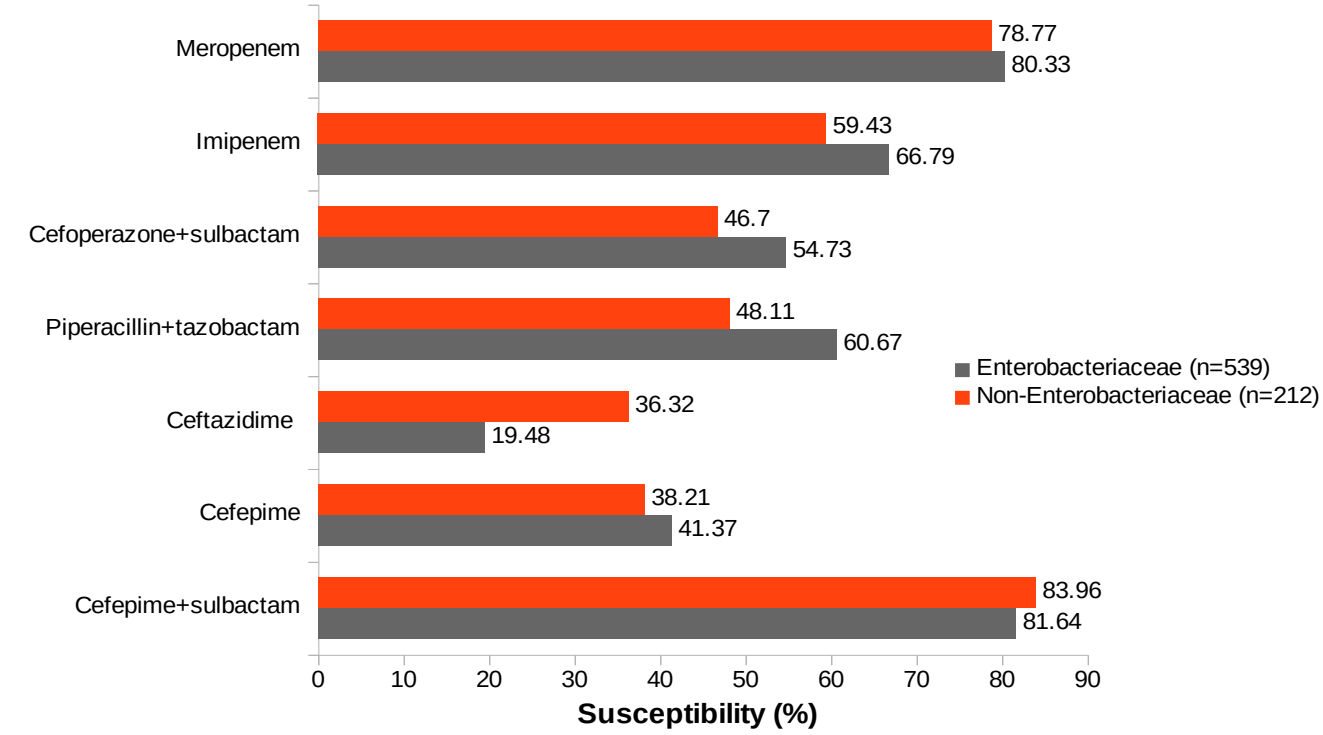


Fig.3 Susceptibility pattern of Enterobacteriaceae and Non-Enterobacteriaceae isolates towards different antibacterial agents



Similar pattern was observed towards Enterobacteriaceae isolates where the activity of cefepime + sulbactam (81.64%) was found comparable to meropenem (80.33%) and higher than rest of the drugs such as cefepime alone (41.37%), ceftazidime (19.48%), piperacillin + tazobactam (60.67%), cefoperazone + sulbactam (54.73%) and imipenem (66.79%) (Figure 3). Likewise, cefepime + sulbactam was the most sensitive drug (85.38%) towards Non-Enterobacteriaceae isolates followed by meropenem (78.77%), imipenem (59.43%), pipercillin + tazobactam (48.11%), cefoperazone + sulbactam (46.70%), cefepime (38.21%), and ceftazidime (36.32%) (Figure 3).

Earlier studies also reported >60% sensitivity of imipenem and meropenem drugs against gram negative isolates which supports present data (Hoban *et al.,* 2010; Ghafur *et al.,* 2012). Likewise, similar results (22-78%) were observed by Ghafur *et al.,* for gram negative pathogens against piperacillin + tazobactam (Hariharan *et al.,* 2015). Earlier reports suggested better activity (>50%) of cefoperazone + sulbactam and cefepime against gram negative isolates (Chaing *et al.,* 2016; Karimzadeh *et al.,* 2017). Hariharan *et al.,* (2015) and Karimzadeh *et al.,* also noticed low activity (20-50%) of ceftazidime against gram negative pathogen (Chaing *et al.,* 2016; Elsolh and Alhajhusain, 2009). Ceftazidime showed more antimicrobial activity against Non-Enterobactericeae than Enterobactericeae isolates which is supported by earlier studies who explained the antipseudomonal activity of this antibiotic, as *Pseudomonas spp*. were prevalent among Non-Enterobactericeae isolates (Elsolh and Alhajhusain, 2009; Rizvi *et al.,* 2015; Bauer *et al.,* 2013). Study also exhibited the higher activity of cefepime + sulbactam over cefepime alone which is supported by earlier report who noted 58-61.6% more sensitivity to cefepime + sulbactam towards gram negative pathogens than cefepime alone (Anuradha *et al.,* 2014). Earlier studies documented third generation cephalosporins, other BL and BL-BLI drugs probably have raised resistance among pathogens by impairment in the permeability of cell wall and production of ESBL genes and biofilm (Fair and Tor, 2014; Singh and Shukla, 2015; Ruppe *et al.,* 2015; Hamada *et al.,* 2015). Previous reports displayed the greater susceptibility (80-100%) of cefepime + sulbactam against various Enterobacteriaceae and Non-Enterobacteriaceae isolates and also noticed the β-lactamase inhibitor, sulbactam, helps the drug to rapidly penetrate bacteria (Koch 2000; Chaudhary and Payasi, 2014; Chaudhary and Payasi, 2015).

Cefepime (fourth generation cephalosporin) has broad range antimicrobial activity than other β-lactam drugs and it has advantage to be less affected by the non-hydrolytic barrier mechanism of resistance in few bacteria (Shrivastava and Chaudhary, 2009). It has been also studied that in the presence of sufficient β-lactamase inhibitor, the β-lactamase enzymes are neutralized and thus the drug used in combination with inhibitor has an opportunity to be more bactericidal and is of therapeutic value in treatment of certain microbial infections, hence, the combination of cefepime and sulbactam is more active than other BL and BL-BLI drugs to combat the resistance developed by clinical isolates (Koch, 2000; Chaudhary and Payasi, 2014).

In the light of above discussions, it is evident that in-vitro efficacy of cefepime + sulbactam in comparison to cefepime alone and other therapeutic drugs such as third generation cephaosporin, BL-BLI drugs and carbapenem drugs was found to be much higher so that it can be placed as better alternative in the treatment of infective diseases caused by multidrug resistant gram negative pathogens.

From the above results, it is evident that cefepime plus sulbactam has enhanced *in-vitro* antibacterial activity when compared to cefepime alone against the clinical isolates. Results also highlighted the superiority (25-30%) of cefepime + sulbactam over other BL-BLI combinations (piperacillin + tazobactam and cefoperazone + sulbactam). One significant finding of this study was that antibiotic resistance breaking efficacy of this combination of cefepime and sulbactam was found comparable to the carbapenem drugs (meropenem and imipenem). Therefore, overall extensive surveillance study suggests that cefepime + sulbactam is a better choice than other BL + BLI drugs to target drug-resistant microorganisms in the clinical settings, and can be considered as empiric choice to spare the overburden of carbapenems.

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