

## Original Research Article

# Cefepime/tazobactam as a new treatment option for multidrug resistant gram negative bacilli

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### ABSTRACT

**Background:** Every time an antibiotic is used, whether appropriately or not, the probability of the development and spread of antibiotic resistant bacteria is increased. Thus, multidrug resistant bacteria particularly ESBL (Extended spectrum  $\beta$ -lactamase), Amp C and carbapenemases producing gram negative bacilli have emerged as a major health problem all over the world. Considering new treatment options as a carbapenems sparing and resistance prevention modality, this study was aimed to know the in vitro susceptibility pattern of Cefepime/Tazobactam (CPM/TZ) in comparison to other  $\beta$ -Lactam/  $\beta$ -Lactamase inhibitors (BL/BLI) and carbapenems against GNB.

**Methods:** A prospective study was conducted on all clinical samples received for a period of about 1 year. Identification and susceptibility of all isolates was done by Vitek 2 Compact system. Susceptibility of CPM/ TZ was done by disc diffusion method on the basis of CLSI guidelines. Both fermenters (*E. coli* and *Klebsiella pneumoniae*) and non-fermenters (*Acinetobacter baumannii* and *Pseudomonas aeruginosa*) were included in the study.

**Results:** Out of 550 GNB isolates the most common was *E. coli* (61.8%), *Acinetobacter baumannii* (16%), *Klebsiella pneumoniae* (14.9%) and *Pseudomonas aeruginosa* (7.3%). Cefepime/tazobactam had a much higher susceptibility of 68% compared to cefepime (28%). Among the BL/BLI combinations tested cefepime/tazobactam (68%) showed the maximum percentage of susceptibility followed by cefoperazone/sulbactam (61.5%) and piperacillin/tazobactam (57.6%). Amongst all GNB isolates cefepime/tazobactam (68%) sensitivity was very much comparable to imipenem (71.8%) and meropenem (69.6%).

**Conclusions:** CPM/TZ exhibited the best in vitro activity in comparison to the other BL/BLI. This new combination of cefepime/tazobactam appears to be a promising alternative therapeutic option to carbapenems. Clinical studies are needed to confirm this in vitro study result.

**Keywords:** Cefepime/Tazobactam, Carbapenems,  $\beta$ -Lactam/ $\beta$ -Lactamase inhibitors

### INTRODUCTION

The bacterial disease burden in India is among the highest in the world, consequently increasing steadily antibiotic use in recent years. Every time an antibiotic is used, whether appropriately or not, the probability of the

development and spread of antibiotic resistant bacteria is increased. Thus, multidrug resistant bacteria have emerged as a major health problem all over the world.

There is a clear need for new antibiotics to address the emerging resistant microorganisms.<sup>1</sup>

Multidrug resistance is seen among gram negative bacilli (GNB) in the Indian setting. Resistance to the cephalosporins is shown by ESBL (Extended spectrum  $\beta$ -lactamase) and Amp C producers leading to rampant use of carbapenems. Excessive use of carbapenems has resulted in emergence of newer and dangerous bugs like NDM1 and MBL producers. The need of the hour is to reduce use of carbapenems.<sup>2</sup> Cefepime/tazobactam is a new promising combination already licensed by the drug controller general of India (DCGI) and increasingly used in Indian hospitals. Combination of a fourth-generation cephalosporin with a  $\beta$  lactamase inhibitor has the theoretical advantage of additional activity against Amp C and possibly OXA enzymes over a third-generation cephalosporin-BLI combination.<sup>3</sup> No significant clinical data is available on this drug and limited number of in vitro studies is published till now. The aim of this study was to analyze the antibiotic sensitivity pattern of gram-negative bacteria to carbapenems and BL-BLI combinations.

## METHODS

A prospective study was conducted on all clinical samples (urine, pus, sputum, blood, body fluids, endotracheal aspirate etc.) received over a period of about 6 months (February 2016 to July 2016) in the Department of Microbiology at Regency Hospital, Kanpur, Uttar Pradesh, India. The samples were both from out-patients and in-patients (Wards and ICUs- medical, surgical, NICU and PICU). Thus including 550 non repetitive, aerobic, gram negative pathogens both from community acquired and hospital acquired infections.

All samples other than blood were collected in sterile wide mouthed universal container and blood was collected with sterile technique in BacT/Alert blood culture bottles.<sup>4</sup> Positive blood culture bottles and all other samples were processed by standard microbiological procedures using media like MacConkey agar, blood agar, chocolate agar and CLED for isolation of pure colonies.<sup>5,6</sup> Identification of the gram negative isolates thus obtained was done using GNID cards in Vitek 2 Compact system.

Antibiotic susceptibility testing was done by Kirby Bauer disc diffusion method according to CLSI guidelines on Muller Hinton agar for isolated *E. coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. The following antibiotics were tested cefepime (30  $\mu$ g), cefepime/tazobactam (30/10- $\mu$ g), piperacillin/tazobactam (100/10 $\mu$ g), cefoperazone/sulbactam (75/30  $\mu$ g), imipenem (10  $\mu$ g), ertapenem (10  $\mu$ g), and meropenem (10  $\mu$ g). The interpretation of zone size as susceptible, susceptible dose dependant, intermediate or resistant was done using CLSI guidelines 2016. Since, cefoperazone/sulbactam and cefepime/tazobactam interpretative criteria was not available, cefoperazone and cefepime zone size as per

CLSI 2016 was used to interpret these two drug combinations.<sup>7</sup>

A zone size of  $\geq 25$  for *Enterobacteriaceae* and  $\geq 18$  for *Acinetobacter baumannii* and *Pseudomonas aeruginosa* was considered as susceptible for cefepime-tazobactam (30/10 $\mu$ g). Quality control of all discs were done as per CLSI 2016 approved disk diffusion QC ranges against *S. aureus* ATCC 25923, *E. coli* ATCC 25922, *K. pneumoniae* ATCC 700603, and *P. aeruginosa* ATCC 27853.<sup>7</sup>

## Inclusion criteria

Non-repetitive, consecutively isolated *E. coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.

## Exclusion criteria

All gram-positive bacteria and gram-negative bacilli other than *E. coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Repeated isolates from the same patients were excluded.

## RESULTS

This study includes 550-gram negative bacilli isolated from all types of clinical samples. These gram-negative bacterial isolates were obtained from the patients who presented to the Outpatient Departments-OPDs (59.5%) or were admitted to the Intensive Care Units-ICUs (32.2%) and wards (25.2%) of Regency Hospital, Kanpur, Uttar Pradesh, India.

Urine specimens accounted for a majority (62.9%) of the clinical specimens which yielded gram negative bacteria, followed by respiratory samples (19.6%), pus (13.5%) and blood specimens (5%).

The most common bacterial isolate was *E. coli* (61.8%) followed by *Acinetobacter baumannii* (16%), *Klebsiella pneumoniae* (14.9%) and *Pseudomonas aeruginosa* (7.3%) (Table 1).

In comparison to cefepime, which was susceptible in 28% of the GNB, cefepime tazobactam had a much higher susceptibility of 68%. Among the BL/BLI combinations tested piperacillin/tazobactam was susceptible to 57.6% of the isolates followed by cefoperazone/sulbactam being 65.1% susceptible and cefepime/tazobactam (68%) showing the maximum percentage of susceptibility.

To consider cefepime/tazobactam as a carbapenem sparing drug its sensitivity was very much comparable to imipenem (71.8%) and meropenem (69.6%). The sensitivity of CPM/TZ was 77.7% for fermenters and ertapenem was sensitive in 83.5% (Table 2).

Amongst BL/BLI susceptibility to piperacillin/tazobactam was 68%, 23.4%, cefoperazone/sulbactam was 72.5%, 40.6% and CPM/TZ was 77.7%, 35.9% respectively for fermenter and non-fermenter GNB.

Comparatively equivalent percentage of sensitive isolates was seen for CPM/TZ and carbapenems with imipenem showing a sensitivity of 82.5%, 36.7% and meropenem showing a sensitivity of 82.9%, 25.8% respectively for fermenters and non-fermenters (Table 3).

**Table 1: Percentage distribution of gram-negative bacterial isolates.**

Organism	Total isolates (N=550)	%
<i>E. coli</i>	340	61.8%
<i>Klebsiella pneumoniae</i>	82	14.9%
<i>Acintobacter baumannii</i>	88	16%
<i>Pseudomonas aeruginosa</i>	40	7.3%

**Table 2: Antibiotic susceptibility patterns of gram-negative bacterial isolates.**

Organism	Antibiotics						
	Cefepime	Cefepime/Tazobactam	Piperacillin/Tazobactam	Cefoperazone/Sulbactam	Imipenem	Ertapenem	Meropenem
<i>E. coli</i>	124 (36.5%)	293 (86.2%)	257 (75.6%)	273 (80.3 %)	308 (90.6%)	307 (90.3%)	310 (91.2%)
<i>Klebsiella pneumoniae</i>	15 (18.3%)	35 (42.7%)	30 (36.6%)	33 (40.2%)	40 (48.8%)	45 (54.9%)	40 (48.8%)
<i>Acintobacter baumannii</i>	4 (4.5%)	12 (13.6%)	13 (14.8%)	18 (20.5%)	11 (12.5%)	-	10 (11.4%)
<i>Pseudomonas aeruginosa</i>	11 (27.5%)	34 (85%)	17 (42.5%)	34 (85%)	36 (90%)	-	23 (57.5%)
Total	154 (28%)	374 (68%)	317 (57.6%)	358 (65.1%)	395 (71.8%)	352 (83.5%)	383 (69.6%)

**Table 3: Antibiotic susceptibility pattern of fermenters and non-fermenters.**

Organism	Antibiotics						
	Cefepime	Cefepime/Tazobactam	Piperacillin/Tazobactam	Cefoperazone/Sulbactam	Imipenem	Ertapenem	Meropenem
Fermenters	32.9%	77.2%	68%	72.5%	82.5%	83.5%	82.9%
Non-fermenters	3.6%	35.9%	23.4%	40.6%	36.7%	-	25.8%

## DISCUSSION

The global concerns regarding the increased resistance of Gram-negative bacteria to antibiotics is increasing. This concern is further strengthened by the near empty newer antibiotic pipeline. Accordingly, there is an increased interest in the newer combination drug Cefepime Tazobactam. Cefepime is a semi-synthetic, broad-spectrum cephalosporin which is classified within the fourth-generation class. Cefepime has an excellent activity against a wide range of Gram +ve and Gram -ve organisms. It has a better activity against the gram-negative bacteria that produce the extended spectrum  $\beta$ -lactamases than the other commercially available oxyiminocephalosporins. Its 3' side chain provides some stability against the Amp C  $\beta$ -lactamases. Tazobactam is the most promising inhibitor, which unlike Sulbactam and clavulanic acid, has its own antibacterial activity.

Tazobactam provides inhibitory action against a wide range of beta lactamases that includes group I cephalosporinases, group 2br TEM beta lactamases and group 3 metallo-beta lactamases. The resulting combination, cefepime-tazobactam, henceforth is predicted to be active against ESBL, Amp C and possibly OXA enzymes producers.<sup>8,9</sup>

Very few previous Indian studies have evaluated and compared the in-vitro activity of the following three  $\beta$ -lactam and  $\beta$ -lactamase inhibitor combinations piperacillin-tazobactam, cefoperazone sulbactam and cefepime tazobactam. In the present study, cefepime tazobactam has better susceptibility than the other two BL/BLI combination tested, same was reported by Sood S et al, and Abdul K et al.<sup>9,10</sup>

Further, it has also been demonstrated in this study that in comparison to cefepime the cefepime-tazobactam combination exhibited good activity against *E. coli*, *Klebsiella pneumoniae*, *Acintobacter baumannii* as well as *Pseudomonas aeruginosa*. The increased susceptibility percentage of cefepime in combination formulation with tazobactam was also shown by Sood S et al, and Susan M et al.<sup>9,11</sup>

The current data reveals an interesting picture of a very comparable susceptibility of *Enterobacteriaceae* (fermenters) to CPM/TZ (77.2%) and carbapenems (82.5% to 83.5%). In non-fermenters, CPM/TZ (35.9%) susceptibility is, in fact, better than that of meropenem (25.8%) and comparable to imipenem (36.7%). Similarly, it has been documented in other Indian studies that cefepime/tazobactam performed equally well or better

than the carbapenems against fermenters and non-fermenters.<sup>3,12</sup>

The emergence of an alarming resistance to the carbapenems in the gram-negative bacteria in Kanpur, Uttar Pradesh, India has been highlighted in a study by Prakash S et al.<sup>13</sup> Thus, emerging requirement for alternatives. Cefepime-tazobactam can be used for treatment of *Enterobacteriaceae* and non-fermenters. This will help to reduce the usage of carbapenems and prevent development of carbapenem resistance. This combination has shown good in-vivo response in many patients who were treated. Further detailed clinical evaluation of this combination is required.

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