COMMUNICATION TO THE EDITOR

Antimicrobial activity of cefepime–tazobactam combination tested against clinical isolates of Enterobacteriaceae

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Gram-negative pathogens such as members of Enterobacteriaceae are established nosocomial pathogens.¹ These bacteria have acquired several resistance mechanisms to evade the lethal effect of antibiotics. Extended spectrum β -lactamases (ESBLs) production is one of the most vital mechanisms of resistance against β -lactam antibiotics.² In India, the ESBL-producing strains are highly prevalent, making majority of the available antibiotics ineffective. Consequently, we are left with very few treatment options, including β -lactam and β -lactamase inhibitor (BL–BLI) combinations, carbapenems and colistin. BL–BLI combinations inhibit the β -lactamase enzyme and thus have activity against ESBLs but their role in severe infections caused by ESBLs is not reliable.² In addition to that, resistance to carbapenems and colistin has also been observed to be mounting up recently leading to a world without antibiotics.^{3,4}

All this has compelled the researchers to find newer agents and to generate newer combinations with already available antibiotics. Cefepime, the fourth-generation cephalosporin, has an extended spectrum of activity against Gram-negative pathogens. It is stable against both AmpC and OXA, but lacks activity against ESBLs,⁵ while tazobactam is active against ESBLs.⁶ Thus, a novel combination of cefepime–tazobactam (CPT) is expected to increase susceptibility of Enterobacteriaceae, by effectively covering all the three major mechanisms of resistance (ESBL, AmpC and OXA). The present study was carried out in an 1800 bedded tertiary care super-speciality teaching hospital in North India to assess the *in vitro* activity of CPT and to compare it with various other routinely used antibiotics. This study is a part

of the ongoing ‘ASCENT’ study, which is a study of *in vitro* sensitivity of cefepime–tazobactam and other antimicrobial agents against enterobacteriaceae isolated from hospitalized patients of a tertiary care hospital in India. A total of 500 consecutive, non-duplicate isolates of *Escherichia coli* (167), *Klebsiella pneumoniae* (250), *Enterobacter aerogenes* (48), *Proteus mirabilis* (25) and *Citrobacter* spp. (10) isolated from various clinical specimens, blood (408), pus (74), body fluids (08), respiratory (07) and cerebrospinal fluid (03) between August 2012 and March 2013, were included in the study. These isolates were identified by standard conventional methods and antibiotic susceptibility testing was performed by Kirby Bauer disk diffusion method as per Clinical and Laboratory Standards Institute (CLSI), 2013.⁷ Owing to the lack of CLSI interpretive criteria for cefoperazone–sulbactam (CSL) and CPT, we have used the zone interpretative criteria for cefoperazone and cefepime, respectively. *E. coli* ATCC 25923 was used as the control. The strains were tested for ESBL production according to CLSI guidelines, 2013 and for AmpC– β -lactamase production by EDTA disc test.^{7,8}

The prevalence of ESBL-producing strains in India is very high. ESBL rate in our study

was also found to be 60%, which is comparable to the other studies. The prevalence of ESBLs in India has now reached epidemic proportions, ranging from 62 to 100% in *E. coli* and *Klebsiella* spp. isolated from various clinical samples as was observed from 10 Indian medical centers as part of SENTRY study (a global ongoing surveillance for monitoring antimicrobial resistance).⁹ In our study, as shown in Table 1, carbapenems were found to be the most effective drugs (imipenem more effective than meropenem) for all the isolates. In routine, these agents are considered to be the last resort to combat infections by multi-drug-resistant bacteria, especially in intensive care units and high-risk wards. In contrast, the third-generation cephalosporins (ceftazidime and cefotaxime) were found to be the least effective for all the isolates. CPT was only next to carbapenems with high susceptibility against *E. coli*, *E. aerogenes* and *P. mirabilis*. However, it was not found to be much effective against *K. pneumoniae* with only 36% isolates being susceptible to it. This drug combination also gave better results for all the isolates when compared to either cefepime or piperacillin–tazobactam (PTZ) used alone. Among the BL–BLI combinations (PTZ, CSL and CPT) tested, CPT displayed

Table 1 Comparison of the susceptibility of CPT to various other antibiotics (in percentage)

Organism (no. of isolates)	IPM	MER	FEP	CAZ	CTX	PTZ	CSL	CPT
<i>Escherichia coli</i> (167)	94	53	22	13	12	58	63	75
<i>Klebsiella pneumoniae</i> (250)	86	54	19	12	13	35	33	36
<i>Enterobacter aerogenes</i> (48)	98	67	29	21	21	46	50	58
<i>Proteus mirabilis</i> (25)	100	70	56	40	52	80	70	88

Abbreviations: CAZ, ceftazidime; CPT, cefepime–tazobactam; CSL, cefoperazone–sulbactam; CTX, cefotaxime; FEP, cefepime; IPM, imipenem; MER, meropenem; PTZ, piperacillin–tazobactam.

better susceptibility for the study isolates. Similar results were observed by Sood¹⁰ also, whereby, among six BL–BLI combinations tested against Enterobacteriaceae, CPT was found to be the best combination with sensitivity of 90.6%, followed by CSL (84.9%) and PTZ (54%). *In vitro* susceptibility results of our study suggest that CPT can act as a carbapenem saving antibiotic as repeated exposure to carbapenem has its own cost in terms of emergence of other multi-resistant organisms.¹¹

As only limited number of studies are available for this agent, extensive studies are required to establish breakpoint levels for susceptible and resistant categories and to further verify the activity of this novel antibiotic combination.

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