

USE OF CEFEPIME FOR THE TREATMENT OF INFECTIONS CAUSED BY EXTENDED SPECTRUM BETA-LACTAMASE-PRODUCING *KLEBSIELLA PNEUMONIAE* AND *ESCHERICHIA COLI*

Dear Sir,

Clinicians treating serious fulminant infections in patients in intensive care (ICU) are obliged to prescribe the most useful locally-available broad-spectrum parental antibiotics. While carbapenem formulations continue to be preferred globally for treatment of extended spectrum β -lactamase (ESBL)-producing bacteria, tigecycline, imipenem-cilastatin, and cefoperazone are alternative drugs used in European countries and the Americas. In several other countries, like India, the choice might be limited to cefepime, meropenem, imipenem and piperacillin-tazobactam. Without retrospective data on the susceptibility profile of circulating organisms, the prescription might be far from ideal. There could be an astounding variation in the recorded performance of antibiotics elsewhere and the local ICU cases. That would be exemplified with cefepime in ESBL-producing *Klebsiella pneumoniae* and *Escherichia coli*.

Cefepime, the fourth generation cephalosporin, has an extended spectrum of activity, enhanced stability to β -lactamase hydrolysis, and superior penetration through the outer membrane of Gram-negative bacteria. Investigations in New York⁽¹⁾ on the efficacy of cefepime to treat infections by ESBL-producing *K. pneumoniae* and *E. coli* on patients in medical ICU or a step-down ICU showed that cefepime was effective in the treatment of these infections. Nevertheless, the situation was different in ICU patients or those with fulminant infection in a tertiary care hospital in an Indian capital metropolis. The in-vitro susceptibility of ESBL-producing *K. pneumoniae* and *E. coli* to cefepime was much lower compared to susceptibility to meropenem and/or piperacillin-tazobactam. That was evident at the Sant Parmanand Hospital, a multi-specialty tertiary care and 140-bed hospital.

ESBL screening has been operational from February 2006 on isolates from patients in the medical, surgical and neonatal ICU and those with fulminant infections. ESBL production was determined according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI) guidelines.⁽²⁾ The disk combination used was of ceftazidime, ceftazidime-clavulanic acid, cefotaxime, cefotaxime-clavulanic acid (Becton Dickinson, Sparks, Maryland). A difference on inhibitory zones of 5 mm or more indicated ESBL production. During the interval from March to October 2006, ESBL-positives identified included 30 patients with *K. pneumoniae* and 12 with *E. coli*. *K. pneumoniae* were drawn from the lungs of 15 patients; the urine of eight patients; the blood of one patient and purulent material of six patients. *E. coli* were isolated from the urine of seven cases; the blood of three cases and the purulent material of two cases. Of the 30 samples of *K. pneumoniae*, 29 were susceptible to meropenem and 25 to piperacillin-tazobactam; and of the 12 samples of *E. coli*, 11 were susceptible to meropenem and another 11 to piperacillin-tazobactam (Table I). Nine samples of *K. pneumoniae* were susceptible to all three antibiotics while a solitary *E. coli* was susceptible to cefepime only (Table II). The performance of cefepime was inferior to meropenem and piperacillin-tazobactam while the latter two profiles were similar. Fisher's exact probability test values were worked out online at the following webpage: <http://faculty.vassar.edu/lowry/fisher.html>.

Table I. Susceptibility profile of ESBL-positive isolates.

Antimicrobial	<i>K. pneumoniae</i> (n = 30) [susceptible/resistant]	<i>E. coli</i> (n = 12) [susceptible/resistant]	Fisher's test of significance between <i>E. coli</i> and <i>K. pneumoniae</i>
Cefepime	12/18	5/7	Not significant
Meropenem	29/1	11/1	Not significant
Piperacillin-tazobactam	25/5	11/1	Not significant

Cefepime susceptibility for *K. pneumoniae* and *E. coli* were poor in comparison with meropenem and piperacillin-tazobactam; Fisher's $p < 0.001$ and $p = 0.0011$, respectively).

Table II. Differential susceptibility profile of ESBL-producers.

Organism	Susceptible to meropenem, piperacillin-tazobactam and cefepime	Susceptible to meropenem, resistant to piperacillin-tazobactam but susceptible to cefepime.	Susceptible to meropenem only	Susceptible to cefepime only
<i>K. pneumoniae</i>	9	1	4	1
<i>E. coli</i>	0	1	0	0

Poor cefepime in-vitro susceptibility in the hospital has been rather surprising. During 2004–2005, 128 ESBL-positive isolates of *K. pneumoniae* from Iranian patients at two teaching hospitals in Iran were uniformly susceptible to meropenem and imipenem. On the contrary, 40% were resistant to cefepime.⁽³⁾ The over-the-counter sale of medicines and counterfeit medicines have been common without any benefits for the patients.⁽⁴⁾ Furthermore, any suboptimal dose and/or duration of therapy would support selection and dissemination of cefepime resistant ESBL-producing *K. pneumoniae* and *E. coli*.

There would be some delay in prescribing antibiotics matching the in-vitro susceptibility for an ICU isolate. Nevertheless, retrospective susceptibility profiles on local ICU isolates should support the rational selection of broader-spectrum antibiotics. This has indeed been the case with us while awaiting in-vitro reports; meropenem or piperacillin-tazobactam would be preferred over cefepime.

Yours sincerely,

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