Cefepime MIC Breakpoint Resettlement in Gram-Negative Bacteria

Cefepime has recently drawn much attention, due mostly to a meta-analysis reported by Yahav et al. (3). They observed higher all-cause mortality for cefepime than for other beta-lactam antibiotics (risk ratio, 1.26; 95% confidence interval [CI], 1.08 to 1.49) and described neurotoxic adverse effects and inadequate in vivo antimicrobial efficacy as plausible reasons for increased mortality.

Bhat et al. (1) observed increased mortality among cefepime-treated patients with bacteremia caused by gram-negative organisms when the MIC was ≥8 µg/ml (54.8%; 17 of 31 died) than when the MIC was <8 µg/ml (24.1%; 35 of 145 died). Based on pharmacodynamic and clinical grounds, they suggested that the current breakpoints (according to which organisms are considered susceptible if the MIC is ≤8 µg/ml by Clinical and Laboratory Standards Institute standards) for cefepime be lowered in countries where cefepime dosages of 1 to 2 g every 12 h is the licensed therapy for serious infections.

However, we suppose that subgroup analysis excluding *Pseudomonas aeruginosa* and *Acinetobacter* spp. should reveal consistent results with statistical evidence to generalize their contention for other gram-negative organisms, because the MICs for *P. aeruginosa* and *Acinetobacter* spp. have been revealed to be much higher than those for other gram-negative organisms. Bhat et al. presented details on 204 bloodstream isolates from individual patients (the clinical outcomes for only 176 patients were analyzed because 21 patients were discharged within 28 days and 7 patients had two episodes of bacteremia), and *P. aeruginosa* and *Acinetobacter* spp. accounted for 79.4% (27 of 34) of the isolates for which the MICs were ≥8 µg/ml while they constituted only 15.9% (27 of 170) of those for which the MICs were <8 µg/ml. We could not identify the exact proportions of these two pathogens among isolates from nonsurvivors for which MICs were ≥8 µg/ml.

However, Bhat et al. observed a high odds ratio (OR) for mortality among *P. aeruginosa* bacteremic patients through a subgroup analysis that compared outcomes associated with MICs of ≥8 µg/ml versus MICs of ≤4 µg/ml (mortality, 20.8%; 5 of 24 patients died), and when a reconstituted population excluding *P. aeruginosa* was analyzed on the basis of MICs of ≥8 µg/ml versus MICs of ≤4 µg/ml, the analysis did not reveal statistical significance (4 of 9 patients [44.4%] with isolates for which MICs were ≥8 µg/ml died, and 30 of 121 [24.8%] with isolates for which MICs were <8 µg/ml died; OR = 2.4; 95% CI, 0.6 to 9.6). It seems quite reasonable to reconsider the current breakpoint MIC of cefepime (8 µg/ml) for *P. aeruginosa*. However, additional verification is required to resettle the cefepime MIC breakpoint for gram-negative pathogens other than *P. aeruginosa* and *Acinetobacter* spp. We believe that this verification may be accomplished through a subgroup analysis excluding *P. aeruginosa* and *Acinetobacter* spp. and providing statistical evidence.

In 2006, the probability of target attainment (PTA) for the conventional dose of cefepime (2 g every 12 h) against common intensive care unit (ICU) pathogens in ICU patients was estimated (2). According to the results of the study, higher doses of cefepime (>4 g/day) are required to achieve the required PTA expectation value for *P. aeruginosa*, and even a higher dose (6 g/day) failed to achieve the bactericidal target for *Acinetobacter baumannii*, unlike that for other pathogens. Like various MIC distributions, we suppose that MIC breakpoint resettlement requires verifications for different pathogens.

**REFERENCES**


**Authors’ Reply**

Chin and Seo question whether breakpoint MICs for cefepime should be reassessed for organisms other than *P. aeruginosa*. In particular, they ask whether a subgroup analysis excluding *P. aeruginosa* or *Acinetobacter* spp. allows us to generalize a change in breakpoints for all gram-negative bacilli.

Breakpoints should be reassessed when new mechanisms of antibiotic resistance are detected at some time after the breakpoints were originally determined (5). With respect to gram-negative organisms other than *P. aeruginosa*, a number of mechanisms of antibiotic resistance have been discovered which elevate the MICs of cefepime. Foremost among these are a variety of beta-lactamases which can hydrolyze cefepime, thereby compromising its activity (2). The MIC for at least 10% of extended-spectrum beta-lactamase (ESBL)-producing klebsiellae, for example, is 8 µg/ml (3), which is precisely the MIC of interest in this discussion.

Reevaluation of breakpoints should be via evaluation of clinical data and pharmacokinetic/pharmacodynamic (PK/PD) data (5). Our clinical data showed that 56.3% of patients with a bloodstream infection due to a gram-negative organism for which the cefepime MIC was 8 µg/ml died, compared to 24.1% of those infected with an organism for which the cefepime MIC was <8 µg/ml (1). Our original purpose was to study gram-negative bacilli in toto rather than subgroups. However, the subgroup of *P. aeruginosa* dominates this discussion because *P. aeruginosa* is the most common organism for which the cefepime MIC is 8 µg/ml. Formal statistical analysis of organisms other than *P. aeruginosa* is impossible because of small numbers. With respect to the *Enterobacteriaceae*, only six patients had a bloodstream infection with an organism for which the MIC was 8 µg/ml or higher. Of those infected with an organism for which the cefepime MIC was 8
μg/ml, two survived and one died. (The patient who died had a polymicrobial infection with Enterobacter cloacae, for which the cefepime MIC was 8 μg/ml, and P. aeruginosa, for which the cefepime MIC was 1 μg/ml).

Evaluation of PK/PD data has suggested that a cefepime dosing regimen of 1 to 2 g every 12 h risks a suboptimal probability of attaining important PK/PD targets (1). These targets are not specific for P. aeruginosa but are shared by the Enterobacteriaceae (1). Chin and Seo cite the study by Roos et al. (4) in their letter. The analysis by Roos et al. (4) in fact showed that the probability of target attainment for any gram-negative organism for which the cefepime MIC is 8 μg/ml is less than 30% when 1 to 2 g of cefepime is administered every 12 h. This finding supports the concept that it is inappropriate to interpret a cefepime MIC of 8 μg/ml to indicate susceptibility for any organism.

Certainly, it would be optimal for a large amount of clinical data to be available to support breakpoint revisions. In a case where clinical data are sparse, if the PK/PD data are compelling for the inadequacy of a dosing regimen for a certain MIC, it is appropriate either to change breakpoints based on the PK/PD analysis or to screen for the presence of mechanisms of resistance that would increase the MIC (5). We do not believe that screening for mechanisms of resistance solves the issue in this circumstance. We observed 11 patients infected with ESBL-producing Enterobacteriaceae. Mortality data were available for 10 of these patients, and 50% died. Importantly, 8 of these 10 patients had infections caused by isolates that would currently be reported as susceptible on the basis of the cefepime MIC (MIC ≤ 8 μg/ml). The majority of ESBL-producing organisms in our study were species of Enterobacter, a genus for which ESBL detection methods are not widely available. Thus, if diagnostic microbiology laboratories cannot aggressively test for ESBL production, then these cases of hidden resistance will go undetected by the microbiologist and the clinician, with the potential for untoward consequences. For this reason alone, we feel that cefepime breakpoints for Enterobacteriaceae should be lowered, removing the risk of organisms with hidden ESBLs resulting in MICs that PK/PD analyses suggest would not be adequately achieved by commonly used cefepime doses. Breakpoint change for cefepime and the Enterobacteriaceae would remove this risk.

REFERENCES

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