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TREATMENT OF EXTENDED-SPECTRUM BETALACTAMASE ENTEROBACTERIACEAE WITH CEFEPIME: THE DOSE MATTERS, TOO

TO THE EDITOR—We read Lee et al’s article in the 15 February 2013 issue of Clinical Infectious Diseases with great interest [1]. In this retrospective cohort, Lee et al showed that 17 propensity-score-matched patients had increased mortality when treated with cefepime, as compared to carbapenems, as definitive therapy for extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae. This finding was only relevant to organisms with minimum inhibitory concentrations (MICs) in the 2–8 µg/mL range. Based on their results, the authors conclude that cefepime therapy may only be appropriate to treat ESBL-producing organisms when the MIC is ≤1 µg/mL. Although we agree that there are limited data supporting the clinical use of cefepime for ESBL-producing organisms, we cannot entirely dismiss the efficacy of cefepime for pathogens with elevated but susceptible MICs based on these results.

With the recent change in the Clinical and Laboratory Standards Institute recommendations to simply report MICs instead of performing confirmatory phenotypic testing for ESBL production, the assumption is that the organism’s β-lactamase gene is irrelevant as long as pharmacodynamic targets remain attainable with the most commonly utilized dose of the drug [2]. Indeed, Andes and Craig have shown that maintaining a free cephalosporin concentration above the MIC for 70% of the dosing interval is associated with optimal microbial killing in both non-ESBL- and ESBL-producing organisms in the neutropenic mouse model, irrespective of genotype [3]. As Lee et al point out, several authors have described the difficulty in achieving meaningful pharmacodynamic probability of target attainment (PTA) for cefepime with organisms in the higher (2–8 µg/mL) MIC ranges. As shown in the Monte Carlo simulation performed by Roos et al, a dose of 2 g every 12 hours resulted in insufficient PTA for pathogen MICs of 4–8 µg/mL in the critically ill population, whereas 2 g every 8 hours was able to achieve meaningful PTA [4]. These data are in concordance with the findings of Bhat et al, who showed that a group of bacteremic patients with organism MICs of 8 µg/mL treated with cefepime 1–2 g every 12 hours had higher mortality compared to those with lower MICs [5]. As the present study only included 11 patients (5 of whom had died at 30 days) with MICs in the 2–8 µg/mL range [1], it is difficult to conclude that cefepime is ineffective, especially without specification of the MIC distribution and dosing regimens utilized. For instance, were all 5 failures treated with 1 g every 8 hours for organisms with an MIC of 8 µg/mL?

Given the recent increase in prevalence of carbapenemase-producing organisms, it is essential to minimize the use of carbapenems whenever possible. There are data suggesting that traditional doses of cefepime (1 g every 8 hours or 2 g every 12 hours) may be inadequate to treat infections due to Enterobacteriaceae with elevated cefepime MICs (≥4 µg/mL), including ESBL-producing organisms; however, we are not aware of any trials evaluating aggressive cefepime doses (2 g every 8 hours, 1 g every 6 hours, or extended infusion strategies) to optimize the chances of achieving PTA and treat infections due to Enterobacteriaceae with higher cefepime MICs. Although carbapenems remain the drug of choice for ESBL-producing organisms, further clinical research evaluating cefepime dosing with pharmacodynamic optimization should be performed.

NOTE

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