Impact of Revised Cefepime CLSI Breakpoints on *Escherichia coli* and *Klebsiella pneumoniae* Susceptibility and Potential Impact If Applied to *Pseudomonas aeruginosa*

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The CLSI reduced the cefepime *Enterobacteriaceae* susceptibility breakpoint and introduced the susceptible-dose-dependent (S-DD) category. In this study, MICs were determined for a Gram-negative collection to assess the impact of this change. For *Enterobacteriaceae*, this resulted in <2% reduction in susceptibility, with 1% being S-DD. If applied to *Pseudomonas aeruginosa*, the % susceptibility (%S) dropped from 77% to 43%, with 34% being S-DD. The new breakpoints did little to the *Enterobacteriaceae* %S, but for *P. aeruginosa*, a profound reduction was seen in %S. The recognition of a S-DD response to cefepime should alert clinicians to the possible need for higher doses.

Cefepime is a commonly utilized antimicrobial for empirical and directed therapy against infections involving both *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Prior to 2014, the Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoint for cefepime was ≤8 μg/ml for both *Enterobacteriaceae* and *P. aeruginosa* (1). As a result of the changing phenotypic profiles to a variety of antimicrobials, including cefepime, used to treat *Enterobacteriaceae*, as well as changes in the doses commonly utilized for this agent, the *Enterobacteriaceae* breakpoint for cefepime was reduced to ≤2 μg/ml in January 2014. Along with this breakpoint revision, the CLSI introduced the *Enterobacteriaceae* susceptible-dose-dependent (S-DD) category of 4 to 8 μg/ml in order to encourage clinicians to use higher doses for organisms with higher MICs (2). The purpose of this study was to determine the impacts of these new susceptibility criteria on the reported cefepime profile for *Enterobacteriaceae*, and since these new criteria may subsequently be extended to include *P. aeruginosa*, we also assessed effect on the % susceptibility (%S) of cefepime for this pathogen.

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The MIC distribution for all organisms is displayed in Fig. 1. When these new cefepime breakpoints were applied to *E. coli* and *K. pneumoniae*, 1% and 2% reductions in %S, respectively, were recognized for these organisms. The majority of *Enterobacteriaceae* with MICs in the S-DD range were *Enterobacter* and *Citrobacter* species. A comparison of the cefepime %S, S-DD, and resistant (/H11350 16 /H9262 g/ml) categories for all organisms is shown in Fig. 2. Overall, 9% (n = 14) of the phenotypically confirmed ESBL-positive *E. coli* isolates (n = 156) and 19% (n = 22) of the ESBL-positive *K. pneumoniae* isolates (n = 118) had a cefepime MIC of 2 μg/ml, whereas the majority of the ESBL-positive *E. coli* (86%) and *K. pneumoniae* (62%) isolates had a cefepime MIC of 16 μg/ml (Fig. 3). Sixty-five of the 72 CarbaNP-positive *Enterobacteriaceae* were *K. pneumoniae*, and only a single *K. pneumoniae* isolate displayed an MIC of 2 μg/ml; all other isolates were defined as resistant (data not shown).

The cefepime MIC distribution for *P. aeruginosa* is displayed in Fig. 1. When the new 2-μg/ml breakpoint was applied to *P. aeruginosa*, the overall %S was reduced from 77% to 43% (P < 0.01), as the S-DD limit of 4 μg/ml at 17% and the S-DD limit of 8 μg/ml at 17% comprised the remaining portion. The susceptibility of *P. aeruginosa* as defined by both sets of breakpoint values is shown in Fig. 2.

Cefepime is a commonly used broad-spectrum cephalosporin.
with potent activity against a wide variety of Gram-negative bacteria, including *P. aeruginosa* (5). The interpretive susceptibility criteria are determined by several different organizations, including the U.S. Food and Drug Administration (FDA), CLSI, and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Although these criteria are generally determined at the time of registration or shortly thereafter, periodic adjustments in these breakpoint values have been undertaken for a number of antimicrobials by these organizations in the postmarketing period. Recently, the FDA also changed the *Enterobacteriaceae* interpretive susceptibility criteria for cefepime to the same values as those of the CLSI (i.e., ≤2 μg/ml, 4 to 8 μg/ml, and ≥16) but with the 4- to 8-μg/ml category defined as intermediate, not S-DD. While the susceptibility range of 4 to 8 μg/ml is defined as intermediate for *Enterobacteriaceae*, the recommendation in the cefepime package insert is for the use of a 2-g dose every 8 h in a patient with normal renal function (6) when organisms with MICs of 4 to 8 μg/ml are identified. The criteria for *P. aeruginosa* remained unchanged at ≤8 (susceptible) and ≥16 μg/ml (resistant) in this most recently revised package insert.

Since the cefepime MIC distribution of these *Enterobacteriaceae* is overwhelmingly ≤2 or ≥16 μg/ml, the recently revised breakpoints did very little to change the overall %S for these organisms. However, since the MIC distribution of *P. aeruginosa* is heavily weighted to 4 and 8 μg/ml, the application of these revised breakpoints might have a profound effect on the reporting of the %S for this organism. Moreover, our group investigated cefepime exposures in patients infected with *P. aeruginosa* to identify the pharmacodynamic relationship that is predictive of a microbiologic response (7). In that report, cefepime doses of 2 g every 8 h in patients with normal renal function were required to achieve adequate exposures and ultimately increase the probability of microbiologic success against pathogens with cefepime MICs of 8 μg/ml.

The application of these CLSI susceptibility and S-DD breakpoints to *P. aeruginosa* appears to be important, because it will encourage clinicians to use higher cefepime doses for the substantial population of organisms having MICs of 4 or 8 μg/ml which require higher cefepime exposures to optimize the pharmacodynamic profile of the compound in an attempt to maximize the clinical and microbiologic outcomes for the infected patient.

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**REFERENCES**


