Rationale for the 2010 Revised Susceptibility Breakpoints for Cephalosporins, Aztreonam, and Carbapenems for Enterobacteriaceae

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Scenario

The antimicrobial susceptibility breakpoints for Enterobacteriaceae were revised downward in 2010 for selected β-lactam antimicrobial agents. What were the driving forces behind this change? What types of data were used to inform these new recommendations? How do the old and new breakpoints compare?

β-Lactam antimicrobial agents are mainstays for treatment of infections due to many members of the Enterobacteriaceae. Since the introduction of these agents into clinical use in the 1970s and 1980s, there have been considerable changes in the potency of these drugs against clinical isolates of Enterobacteriaceae, largely due to the evolution and dissemination of extended spectrum β-lactamases (ESBLs) that hydrolyze penicillins, cephalosporins, and monobactams. The worldwide dissemination of these ESBLs played a major role in the first revision of susceptibility breakpoints (minimum inhibitory concentrations [MICs]) for these drugs by the Clinical Laboratory Standards Institute in June 2010.

The increasing problem of β-lactamase-mediated resistance has recently extended to the carbapenem class of antimicrobial agents. The serine carbapenemase KPC (for Klebsiella pneumoniae carbapenemase) has been detected in Enterobacteriaceae from several major population regions in the United States, and is problematic in many institutions in Europe. More recently, a metallo β-lactamase (NDM-1) that hydrolyzes carbapenems and most β-lactams has spread rapidly from Asia to the United Kingdom and other regions in the world. The Centers for Disease Control and Prevention has issued alerts for both of these carbapenemases and recommendations for limiting its spread in hospitals [1, 2].

Carbapenemases of the KPC type produced a situation similar to that for ESBLs; strains producing KPC or ESBLs were often classified as susceptible using breakpoints established in the former era. Thus, new lower breakpoints for cephalosporins and carbapenems against Enterobacteriaceae were established to ensure optimal exposures with US Food and Drug Administration (FDA)-approved dosage regimens, and would also classify these isolates as nonsusceptible.

Clinical, pharmacokinetic-pharmacodynamic (PK-PD), and MIC distribution data were considered in revising the breakpoints [3, 4]. While highly desirable, clinical data were difficult to acquire. Critical information concerning MIC, concomitant drug treatment, site of infection, and cephalosporin dosage regimen was generally not available in studies of ESBL-producing isolates. Thus, other analyses were required.

PK-PD analyses were conducted to determine whether usual FDA-approved dosage regimens of the
cephalosporins, aztreonam, and carbapenems would be expected to provide target levels of drug exposures that are associated with bacterial killing in vivo for organisms with MICs at and below the selected susceptibility breakpoint [5, 6]. The strength of this approach is that a consistent target level of exposure (eg, $T > \text{MIC}$ of 50% for cephalosporins; $T > \text{MIC}$ of 30%–40% for carbapenems) could be compared across FDA-approved dosage regimens for several agents with different pharmacokinetic properties [7].

Table 1 shows the previous and revised MIC breakpoints for cephalosporins and carbapenems, respectively. In most cases, the susceptible breakpoints were reduced 2–4-fold from pre-2010 values. Notably, changes in breakpoints were referenced to a dosage regimen for the drug used for treatment of infection. In contrast to previous breakpoints, approximately 90% of patients receiving the indicated dosage regimen would be expected to have free serum drug concentrations exceeding the new susceptibility breakpoints for at least 50% of the dosing interval for cephalosporins, and 30% of the dosing interval for carbapenems.

Inspection of MIC distributions and PK-PD breakpoints for cephalosporins showed that for most drugs, the shifts in breakpoints resulted in placement of most ESBL-positive strains into the nonsusceptible category; this is not surprising since most of the PK-PD breakpoints also centered around the MICs used for the ESBL screening test. For key extended-spectrum cephalosporins (i.e., ceftiraxone, ceftazidime) and aztreonam, the mode for the MIC distribution remained below the new susceptible breakpoints identified by the PK-PD analysis (eg, MIC < 2 or 4 mg/L). Similarly, KPC-producing Enterobacteriaceae were correctly classified as nonsusceptible to carbapenems by the new lower breakpoints.

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### References


