CLSI Changes for Cephalosporin / Enterobactericaeae breakpoints

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Rationale Supporting CLSI Changes in Interpretive Criteria (Breakpoints) for Several Cephalosporins and Aztreonam When Testing Enterobacteriaceae

Since 1999, the CLSI Subcommittee on Antimicrobial Susceptibility Testing has recommended that extended spectrum β-lactamase producing (ESBL+) members of the Enterobacteriaceae be reported as resistant to aztreonam and to all cephalosporins (1). This decision was based upon very limited medical evidence. In fact, the data indicating that ESBL+ isolates will fail treatment with all cephalosporins is nonexistent. The original approach recommended by the CLSI seemed reasonable at the time the decision was made as it was conservative (errning on the side of over-calling resistance) and because carbapenems were available for treatment. The initial CLSI recommendations to conduct ESBL screening and confirmatory testing and to amend penicillin, cephalosporin, and aztreonam results from susceptible to resistant for isolates with a positive ESBL confirmatory test were predicated on: 1) observations that antibiotic MICs for some ESBL-producing isolates were elevated but still within the susceptible range, and 2) limited numbers of clinical reports of poor outcomes among patients with infections caused by isolates expressing ESBLs when treated with cephalosporins and aztreonam. The ESBL testing recommendations were intended to be a short term solution to address a newly recognized resistance mechanism. Subsequently, additional mechanisms of resistance were identified (e.g., new ESBLs including CTX-M types, AmpC-like enzymes, KPCs, etc.). Additionally, with increasing frequency, multiple enzymes were being identified in single isolates, confounding ESBL testing (2). Phenotypic tests for ESBL detection and confirmation can be inaccurate when multiple enzymes are present (e.g., false-negative results occur when isolates express both ESBLs and AmpC-type enzymes) (3), and the presence of multiple enzymes is more frequently common in contemporary isolates (4, 5).

As the carbapenems are no longer routinely active against all isolates of Enterobacteriaceae, the practice of over-calling resistance in the absence of clinical outcome data is no longer an option. To address this, the CLSI chose to rely upon scientific evidence to adjust the interpretive criteria (breakpoints) for several of the cephalosporins and aztreonam. These breakpoints were revised in order to better represent the clinical effects these compounds might have with currently recommended antibiotic dosage regimens when used to treat infections caused by contemporary bacterial isolates. Knowledge garnered from ESBL-producing isolates played a significant role in the decision making process. These issues coupled with an improved understanding of the pharmacokinetic and pharmacodynamic (PK/PD) determinants of efficacy with cephalosporins and aztreonam resulted in the decision to modify the breakpoints. The information considered by the group was primarily PK/PD in nature, supplemented by animal study results. The MIC of an isolate correlates better with clinical outcome than knowledge of resistance mechanisms (e.g., ESBLs) (6). Unfortunately, there were only limited clinical outcome data to support these changes. This was in large part due to the fact that laboratories were routinely reporting ESBL-producing isolates as resistant to all cephalosporins and aztreonam, irrespective of the antibiotic MICs. Resultantly, these drugs were only infrequently employed for treatment of infections caused by ESBL-producing organisms. Carbapenems were prescribed as alternatives, a practice
that may have been a driving force in the ongoing evolution and dissemination of carbapenem resistant Enterobacteriaceae. The breakpoints for cefepime were not revised because PK/PD evaluations and patient outcome data supported the current interpretive criteria. Clinical trial data indicated cefepime efficacy for patients infected with organisms that tested cefepime susceptible (MIC ≤8 µg/mL), yet produced ESBLs. PK/PD evaluations demonstrated that daily doses of cefepime exceeding 3 g per day (i.e., 1 g every 8h or 2 g every 12h) would result in cefepime levels meeting target exposure criteria as used in the interpretive criteria revision decisions. These updated CLSI breakpoints are predicated on the best available scientific evidence, and obviate the need for laboratories to perform ESBL screening and confirmatory tests for directing treatment decisions. Additionally, the breakpoints are largely consistent with those currently recommended by other international breakpoint-setting organizations, such as EUCAST (www.eucast.org). The CLSI believes that the new breakpoints will provide improved information for directing patient care and result in less uncertainty and work for clinical microbiology laboratories.

References


Supplemental References


