Do Patient Data Really Support the Clinical and Laboratory Standards Institute Recommendation for Lowering Third-Generation Cephalosporin Interpretive Breakpoints?

TO THE EDITOR—Dudley and colleagues recently reviewed the rationale for revising the Clinical and Laboratory Standards Institute (CLSI) breakpoints for cephalosporins against Enterobacteriaceae [1]. As we witness a rise in organisms with increased minimum inhibitory concentrations (MICs) to existing β-lactam agents, this work is very timely. We are concerned, however, that the bulk of the data to inform these changes is related to pharmacokinetic-pharmacodynamic studies. Although this information is indeed hypothesis generating, it is in need of confirmation from clinical outcomes data as MIC changes can significantly impact patient care.

A 3-fold lowering of breakpoints of third-generation cephalosporins against Enterobacteriaceae means that clinicians would increasingly prescribe broad-spectrum antibiotics to treat common gram-negative infections, in direct conflict with the need to conserve the effectiveness of existing agents. We observed a >300% increase in Enterobacteriaceae isolates no longer “susceptible” to third-generation cephalosporins based on the revised breakpoints [2]. The patient data used by CLSI to demonstrate poorer clinical outcomes with elevated MICs consisted of 52 patients infected with extended-spectrum beta-lactamase (ESBL)-producing organisms treated with cephalosporins (with cephalosporin MICs in the susceptible range using pre-2010 breakpoints) [3, 4]. Favorable outcomes declined with increasing MICs. What was missing, however, was adjustment for underlying characteristics of patients that may have confounded this association. Patients with elevated MICs inherently differ from those with lower MICs on factors that are independent predictors of worse outcomes [5]; elevated MICs may be a marker for (rather than causal) in poorer outcomes as demonstrated by work in which patients had worse outcomes with higher MICs to a drug they never received [6]. Patient demographic and clinical characteristics should be analyzed in studies evaluating the role of MICs in patient outcomes. Such data are available for justifying the lowering of breakpoints for piperacillin-tazobactam against Pseudomonas aeruginosa; however, existing data are lacking for third-generation cephalosporins against Enterobacteriaceae [2, 7, 8]. If the concern is to capture ESBL-producing Enterobacteriaceae with MICs between 2 µg/mL and 8 µg/mL (organisms previously considered susceptible using pre-2010 breakpoints), then we need better diagnostics for ESBLs rather than lowering the breakpoints on all Enterobacteriaceae and further limiting already narrowed treatment options. As clinical microbiology laboratories do not routinely test for AmpC β-lactamase producers and third-generation cephalosporins are generally avoided in serious infections with potential AmpC producers, their role is less important in changing breakpoints.

We are also concerned with the CLSI recommendation to forgo confirmatory ESBL testing. In vitro testing for ESBLs may indicate susceptibility to cefepime and piperacillin [9], which is in contrast to in vivo data demonstrating poorer outcomes of patients infected with ESBL-producing organisms treated with these agents [10, 11]. In the absence of
confirmatory ESBL testing, organisms will not be identified as ESBL producers, susceptibility testing may reveal in vitro susceptibility to piperacillin-tazobactam and cefepime, and clinicians may prescribe suboptimal agents to treat serious, life-threatening infections. Additionally, confirmatory ESBL testing can help understand institutional and national ESBL trends to optimize infection control practices. The absence of epidemiologic data on ESBLs can hamper efforts to decrease spread within healthcare institutions [12].

We appreciate the efforts of the CLSI and realize they are constrained by the limited available clinical data. However, we believe the CLSI should encourage the undertaking of well-designed clinical studies to ensure that changing breakpoints are truly in the best interest of patients.

**Note**

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**Pranita D. Tamma¹ and John H. Powers²**

¹Division of Pediatric Infectious Diseases, Department of Pediatrics, Johns Hopkins Medical Institutions, Baltimore, and ²Division of Clinical Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

**References**


Correspondence: Pranita D. Tamma, MD, MHS, Division of Pediatric Infectious Diseases, Department of Pediatrics, Johns Hopkins Medical Institutions, 200 N Wolfe St, Ste 3155, Baltimore, MD 21287 (ptamma1@jhmi.edu).

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