Antibiotic Breakpoints:
How Redefining Susceptibility Preserves Efficacy and Improves Patient Care
Mark Redell, PharmD, and Glenn Tillotson, PhD

Guiliano and colleagues\(^1\) provided an excellent overview in the April 2019 issue of P&T on how to interpret culture and susceptibility results from the microbiology laboratory. A critical lesson described in their article is the application of susceptibility data to daily clinical practice. As P&T readers are aware, antibiotic resistance is a global health crisis. Consequently, The Joint Commission mandated standards (standard MM.09.01.01) on antibiotic stewardship programs (ASP) on January 1, 2017, published as the New Antimicrobial Stewardship Standard, applicable to acute care hospitals and critical access hospitals for use in managing resistance.\(^2,3\) An important component of ASP is the provision of timely antibiograms. These data sets are frequently used to construct empiric antibiotic selection guidelines, which enable clinicians to prescribe antibiotics appropriately. The development of antibiograms is dependent on accurate and reproducible susceptibility testing using current antibiotic breakpoints established by the Clinical and Laboratory Standards Institute (CLSI).\(^4\) Because antibiograms reflect susceptibility data acquired from large populations, generalizations should be used cautiously when developing institution-specific, empiric antibiotic guidelines. More narrowly, the individual patient pathology report informs clinicians of potential choices in drug selection. Accurate susceptibility information relies on laboratory utilization of appropriate antibiotic breakpoints for both the broader antibiogram and patient-specific reports.

The recognition of new bacterial resistance mechanisms within the Enterobacterales (formerly, Enterobacteriaceae) family, such as 
*Klebsiella pneumoniae*, represented a signal suggesting that the original breakpoints and susceptibility categories for carbapenems no longer met clinical needs. For example, Patel and colleagues\(^5\) found that a group of patients infected by an organism within the Enterobacterales family, with carbapenem minimum inhibitory concentrations (MICs) of 2 mg/Liter to 8 mg/Liter, had a significantly higher 30-day mortality than the group with carbapenem MICs of ≤ 1 mg/Liter (38.9% vs. 5.6%, \(P = 0.04\)). At the time of this study, the FDA susceptible breakpoint for meropenem was 4 mg/Liter. From 2009 to 2010, CLSI carried out an investigation to determine whether breakpoint revisions were in order. Because little clinical evidence was available to reassess carbapenem breakpoints, pharmacokinetico-pharmacodynamic (PK/PD) analyses were conducted. These focused on determining whether FDA-approved dosage regimens of carbapenems would be expected to provide target drug exposures that are associated with bacterial killing in vivo with MICs that are at and below a susceptibility breakpoint. The resulting analysis showed that a breakpoint of 1 mg/Liter provided a consistent target level of exposure in humans and excluded bacterial isolates with MICs greater than this new breakpoint. The overall effect of the two-dilution lowering of imipenem and meropenem breakpoints was to prevent interpreting isolates with “carbapenem-resistance mechanisms” as “susceptible.”\(^6\)

The historic (pre-2010) and revised breakpoints are shown in Table 1.\(^7\) It is apparent that utilizing historic breakpoints can lead to “false susceptibility.”

Laboratories that use revised carbapenem breakpoints detect significantly more carbapenem-resistant Enterobacterales than laboratories that use historical breakpoints. The studies in Table 2 illustrate a decrease in cumulative susceptibility between pre-2010 and current breakpoints.\(^8,9\) Critically, it was estimated in 2018 that around one-third of laboratories do not implement current CLSI breakpoints for carbapenems and Enterobacterales. For example, one study performed in California demonstrated that using obsolete carbapenem breakpoints for a collection of carbapenemase-producing Enterobacterales resulted in an increase of 16% of isolates being incorrectly interpreted as susceptible to meropenem.\(^10\) Moreover, some laboratories have taken more than four years to implement the CLSI updates.\(^7\) Indeed, there is an assumption among those using the automated systems that the manufacturer automatically updates them, although this is not always the case.\(^7\)

Significantly, there are several major consequences of failing to update breakpoints that are relevant to the clinical microbiology laboratory, consequences that can have significant implications. First, the quality of data emanating from the laboratory is compromised. As errors in susceptibility interpretation originate within the microbiology department, quality improvements must be addressed by experts in the institution’s laboratories. McKinnell and colleagues conducted a survey of 128 laboratories and discovered that only 72% of laboratories employed current CLSI carbapenem breakpoints and that time to implementation varied from 0 to 68 months (mean, 41 months; median, 55 months).\(^11\) Implementing those changes is time-consuming, and it may not be feasible for some laboratories due to the interruption of workflow, lack of test strains, and lack of adequate resources needed to verify the new breakpoints. Validation of the new carbapenem breakpoints should be immediate, given the time that has elapsed since the 2010 revisions. In addition, the ASP team and infectious disease practitioners should liaise with their laboratory regarding breakpoint changes, and update the antibiogram issued to prescribers to guide empiric therapy.

Second, patient morbidity and mortality can be affected by reporting incorrect susceptibility results. Antibiotics that are

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Antibiotic Breakpoints

Table 1 CLSI/FDA Carbapenem Breakpoints (mg/Liter) for Enterobacterales

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Historical (pre-2010)</th>
<th>Current (2010 and later)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>≤ 2</td>
<td>4</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≤ 4</td>
<td>8</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤ 4</td>
<td>8</td>
</tr>
</tbody>
</table>

CLSI = Clinical and Laboratory Standards Institute; FDA = Food and Drug Administration
Current FDA and CLSI breakpoints are listed on the FDA Susceptibility Test Interpretive Criteria (STIC) website: https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria.

Table 2 Effect of a Two-Dilution Decrease in Meropenem MIC Breakpoint in Two Large Surveillance Studies of Carbapenem-Resistant Enterobacterales

<table>
<thead>
<tr>
<th>Study</th>
<th>Cumulative susceptibility to meropenem of clinical enterobacterales isolates</th>
<th>Decrease in cumulative % susceptibility between pre-2010 and current breakpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC ≤ 1 mg/Liter</td>
<td>MIC ≤ 4 mg/Liter</td>
</tr>
<tr>
<td>CRE worldwide</td>
<td>1.9%</td>
<td>26.0%</td>
</tr>
<tr>
<td>n = 265 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KPC worldwide</td>
<td>0%</td>
<td>12.0%</td>
</tr>
<tr>
<td>n = 991 (9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRE = carbapenem-resistant Enterobacteriaceae; KPC = Klebsiella pneumoniae carbapenemase; MIC = minimum inhibitory concentration; n = number

selected for specifically chosen therapy based on an individual patient culture and susceptibility report might be inappropriate and could lead to clinical failure. It has been shown that such inappropriate antibiotic therapy increases morbidity and mortality, as demonstrated by longer lengths of hospitalization and intensive care unit (ICU) days, a greater number of days on antibiotics, and higher costs of therapy. Competition for resources such as ventilators, non-antibiotic medications, and IV pumps may increase. Furthermore, inappropriate antibiotic usage leads to the necessity for additional therapeutic agents, prolongs the number of days of therapy, and increases potential exposure to nephrotoxic agents. Sequelae of prolonged antibiotic use include an increased risk for infection and colonization by opportunistic and invasive pathogens, such as Clostridium difficile infection, vancomycin-resistant enterococci, and Candida spp., which exert a significant cost burden.

Finally, and what is often overlooked, is the potential for the spread of resistant pathogens when infection-control specialists cannot identify emerging resistance trends. Reliance on the accurate identification of carbapenemase-producers is necessary to institute appropriate management strategies that will address the potential for intra-hospital spread. For example, using a simulation model, Bartsch and colleagues found that a 32-month delay in changing carbapenem-resistant Enterobacteriaceae (CRE) breakpoints resulted in 1,821 additional carriers in Orange County, California—an outcome that could have been avoided by identifying CRE and initiating the appropriate isolation or contact precautions. The authors suggest that a policy aimed at minimizing delay in the adoption of new breakpoints for antimicrobials against emerging pathogens should be implemented when the containment of spread is paramount. A delay of no more than 1.5 years would have the most impact in slowing the spread of carbapenemase-producing Enterobacterales. Failure to identify resistant pathogens can result in their dissemination throughout the hospital environment, leading to colonization and infections in other patients.

The story for carbapenem breakpoints is now being repeated for drugs within the fluoroquinolone class, specifically levofloxacin and ciprofloxacin, against members of Enterobacterales and Pseudomonas aeruginosa. Fluoroquinolone resistance can arise through mutations in defined regions of DNA gyrase or topoisomerase IV—termed the Quinolone-Resistance Determining Regions (QRDRs)—decreased outer-membrane permeability, dysregulation of efflux pumps, and plasmid-mediated resistance mechanisms. Revised breakpoints were published in January 2019 by CLSI. Following a similar process for carbapenems—rising resistance to fluoroquinolones—PK/PD analyses provided the basis for lower breakpoints for ciprofloxacin and levofloxacin. As the infectious disease community is gaining experience in antibiotic susceptibility breakpoint adjustments, two recently published reports provide laboratory staff and clinicians guidance in validating these new fluoroquinolone breakpoints.

In summary, ASP practices require an understanding of the interplay between mechanisms of antibiotic resistance, MICs, breakpoints defining susceptibility, and PK/PD—important components that synergize to optimize the chances for positive clinical success. The consequences of failing to adopt revised breakpoints include the following:

1. Laboratory quality assurance is compromised and antibiograms are incorrect;
2. Historical breakpoints provide “false security” and lead clinicians to prescribe inappropriate empiric and definitive therapies;
3. Early infection-control strategies cannot be implemented to contain potential outbreaks and endemcity; and
4. Inappropriate treatment leads to longer lengths of stay in the ICU and hospital, higher inpatient costs, and increased mortality.

Carbapenems are primary therapeutic agents for the treat-
ment of infections caused by multidrug-resistant bacterial pathogens. To maintain their efficacy and to control the emergence of further resistance, breakpoints corresponding to recommended doses that provide appropriate PK/PD target attainment are essential. The implementation of revised breakpoints is vital to the practice of diagnostic stewardship and leads to improved patient care.

REFERENCES