# Antimicrobial Stewardship News

Volume 10, Number 2

February 2022


## Use of Current Breakpoints by Clinical Laboratories - Mission Critical for Accurate Detection of Antimicrobial Resistance

Antimicrobial resistance is an urgent and serious public health threat. More than 2.8 million antibiotic-resistant infections occur in the United States each year.[1] In a recent comprehensive evaluation of the global burden of antimicrobial resistance (AMR), an estimated 4.95 million deaths were associated with bacterial AMR in 2019.[2] Growing awareness of this issue has sparked several initiatives, such as the National Report on Combating Antimicrobial Resistant Bacteria and the Centers for Disease Control and Prevention's Antibiotic Resistance Solutions Initiative. Yet little attention has been directed to clinical laboratories and the ability to accurately implement up-to-date practices. Curbing AMR will take coordinated, multi-faceted processes of change, but critical to doing so is the accurate detection of antibiotic resistance in clinical laboratories.

### Establishing breakpoints

In the United States, antimicrobial susceptibility testing (AST) interpretive criteria, or breakpoints, are established by two separate entities, the Food and Drug Administration (FDA) and the Clinical Laboratory Standards Institute (CLSI). The FDA provides breakpoints for a new drug application or upon request of the drug manufacturer for older agents. Notably, drug manufacturers are under no legal obligation to submit a request for revised breakpoints as they become available for older drugs.[3] Alternatively, CLSI establishes consensus breakpoints through the analysis of microbiologic information, pharmacokinetic and pharmacodynamic data, and the results of clinical studies performed prior to FDA approval of an antibiotic.[4,5] Independent of drug manufacturers' requests, CLSI may re-evaluate breakpoints and publish these updates annually in the M100 reference. Importantly, laboratories must use FDA-approved breakpoints for any commercial AST (cAST) device.[6]

Analysis of AST testing according to breakpoints enables the reporting of "susceptible," "susceptible-dose-dependent," "intermediate," and "resistant," and, in turn, guides clinical decision-making. Misinterpretation of a microorganism as susceptible when it is, in fact, resistant based on outdated breakpoints has significant implications for patient care and safety.[7] Additionally, failure to detect resistant microorganisms hinders accurate surveillance and reporting of AMR trends necessary for infection control measures and effective public health responses.

For more information on commonly-used antibiotic susceptibility testing methods, please see the January 2014 newsletter.

### Antimicrobial susceptibility testing devices

The performance of cAST devices, including automated systems (e.g., Vitek2, Phoenix, MicroScan) or Etest, are compared to broth microdilution and must yield similar categorical (i.e., susceptible, intermediate, resistant) and essential (i.e., MIC) agreement for FDA approval.[8] Clinical laboratories must use cAST devices according to the manufacturer's instructions, and any change in susceptibility testing requires a new review process and clearance by the FDA. Similar to drug manufacturers and antibiotic breakpoints, the FDA has no legal authority over commercial device manufacturers to review device performance and update cAST platforms. So, although a cAST device must use current FDA-approved breakpoints at the time of initial application, manufacturers have no regulatory requirement to update systems as breakpoints change and new antibiotics are developed. Any deviation from the manufacturer's instructions or manual override by a clinical laboratory requires internal verification of the accuracy, reproducibility, and

reliability of the modifications, a process that few clinical laboratories have the resources and ability to perform.[6]

**Obsolete breakpoints**

The processes between the FDA, CLSI, and cAST manufacturers can be quite disjointed, and contribute to the use of obsolete breakpoints within many laboratories. In a recent survey of nearly 1500 College of American Pathologist (CAP)-accredited facilities, 37.9-70.5% of US laboratories reported using obsolete breakpoints for antimicrobial susceptibility testing, a significantly lower proportion relative to international laboratories. More laboratories reported use of current Enterobacterales breakpoints for cephalosporins and carbapenems compared to fluoroquinolones, which were updated in 2010 and 2019, respectively **(Table 1).** The most common reasons for continued use of outdated breakpoints were manufacturer-related issues (51.3%) and lack of resources to perform analytical validation within the responding clinical laboratory (23.4%).[9]

Due to the potential negative impact of using obsolete breakpoints, CAP-accredited clinical laboratories are required to update their AST processes to include the current breakpoints by January 1, 2024. A step-by-step checklist can be found here.[10]

**Summary**

With improved understanding of antibacterial resistance mechanisms, pharmacokinetics, and pharmacodynamics, AST criteria have evolved accordingly. However, several limitations have halted more widespread, timely adoption of new breakpoints within clinical laboratories. These challenges include, 1) delays between the update of breakpoints and subsequent clearance on commercial AST devices, 2) FDA regulation over which antibiotic/bacteria combinations can be used on commercial AST platforms, in turn limiting availability of newer drugs or organisms not originally included in testing, and 3) lack of periodic review of the AST devices.[6] Given the complexities of AST testing, increased oversight and regulation is needed to ensure timely and accurate application of current breakpoints. The ability to detect AMR within a clinical laboratory has critical implications for patient care, antimicrobial stewardship, infection prevention, and disease surveillance.

**Table 1.** Breakpoint Usage by Laboratory Location[9]

| | | United States | | International | | |
|---|---|---|---|---|---|---|
| Organism | Antimicrobial Agent | Total No. of Laboratories | Current Breakpoints, No. (%) | Total No. of Laboratories | Current Breakpoints, No. (%) | *P* Value, Difference Between US and International |
| Enterobacterales | Ceftazidime | 1046 | 620 (59.3) | 201 | 164 (81.6) | <.001 |
| Enterobacterales | Ceftriaxone | 1124 | 694 (61.7) | 186 | 153 (82.3) | <.001 |
| Enterobacterales | Ciprofloxacin | 1058 | 312 (29.5) | 206 | 122 (59.2) | <.001 |
| Enterobacterales | Levofloxacin | 1019 | 306 (30.0) | 160 | 90 (56.3) | <.001 |
| Enterobacterales | Meropenem | 982 | 610 (62.1) | 187 | 149 (79.7) | <.001 |
| *Pseudomonas aeruginosa* | Piperacillin-tazobactam | 1064 | 559 (52.5) | 197 | 150 (761) | <.001 |
| *Acinetobacter baumannii* | Imipenem | 784 | 367 (46.8) | 182 | 139 (76.4) | <.001 |

**References**

1. Centers for Disease Control and Prevention (U.S.). *Antibiotic Resistance Threats in the United States, 2019*. Centers for Disease Control and Prevention (U.S.); 2019.
2. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet Lond Engl*. 2022;399(10325):629-655.
3. Research C for DE and. Antibacterial Susceptibility Test Interpretive Criteria. *FDA*. Published online October 14, 2021. Accessed February 28, 2022. https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria
4. Jorgensen JH, Ferraro MJ. Antimicrobial susceptibility testing: a review of general principles and contemporary practices. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2009;49(11):1749-1755.
5. Weinstein MP, Lewis JS. The Clinical and Laboratory Standards Institute Subcommittee on Antimicrobial Susceptibility Testing: Background, Organization, Functions, and Processes. *J Clin Microbiol*. 2020;58(3):e01864-19.
6. Humphries RM, Hindler JA. Emerging Resistance, New Antimicrobial Agents … but No Tests! The Challenge of Antimicrobial Susceptibility Testing in the Current US Regulatory Landscape. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2016;63(1):83-88.
7. Yarbrough ML, Wallace MA, Potter RF, D'Souza AW, Dantas G, Burnham CAD. Breakpoint beware: reliance on historical breakpoints for Enterobacteriaceae leads to discrepancies in interpretation of susceptibility testing for carbapenems and cephalosporins and gaps in detection of carbapenem-resistant organisms. *Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol*. 2020;39(1):187-195.
8. Health C for D and R. Antimicrobial Susceptibility Test (AST) Systems - Class II Special Controls Guidance for Industry and FDA. *FDA*. Published online March 22, 2021. Accessed February 28, 2022. https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/antimicrobial-susceptibility-test-ast-systems-class-ii-special-controls-guidance-industry-and-fda
9. Simner PJ, Rauch CA, Martin IW, et al. Raising the Bar: Improving Antimicrobial Resistance Detection by Clinical Laboratories by Ensuring Use of Current Breakpoints. *Open Forum Infect Dis*. 2022;9(3):ofac007.
10. Updating Breakpoints in Antimicrobial Susceptibility Testing. ASM.org. Accessed February 28, 2022. https://asm.org/Articles/2022/February/Updating-Breakpoints-in-Antimicrobial-Susceptibili