For Microbiology Laboratories:

Cefepime Breakpoint Change for *Enterobacteriaceae* and Introduction of the Susceptible-Dose Dependent (SDD) Interpretive Category

What Changed?

The CLSI Subcommittee on Antimicrobial Susceptibility Testing revised the cefepime interpretive criteria (breakpoints) and is introducing the susceptible-dose dependent (SDD) category with this breakpoint revision. Below is a summary of the changes.

Previous – 2013

Method	Susceptible	Intermediate	Resistant
MIC	≤8 µg/mL	16 µg/mL	≥32 µg/mL
Zone Diameter (Disk Diffusion)	≥18 mm	15–17 mm	≤14 mm

Revised – 2014

Method	Susceptible	Susceptible-Dose Dependent	Resistant
MIC	≤2 µg/mL	4–8 µg/mL	≥16 µg/mL
Zone Diameter (Disk Diffusion)	≥25 mm	19–24 mm	≤18 mm

Abbreviation: MIC, minimal inhibitory concentration.

Why were the cefepime breakpoints reconsidered?
The issue of new breakpoints for cefepime became apparent for several reasons:

- Previous breakpoints were based on a higher dose of cefepime than is often used.
- Clinical failures were noted for isolates with cefepime MICs of 4 and 8 µg/mL, especially when lower doses of cefepime were used.
- There are limited new drugs in the pipeline that show activity against multidrug-resistant gram-negative bacteria; thus, there is a need to optimize use of drugs currently available. Designing susceptibility reports to correlate better with dosages of the drug used is one way to help accomplish this goal.

What does "susceptible-dose dependent" (SDD) mean?
SDD interpretation is a new interpretive category for antibacterial susceptibility testing, although it has been applied for interpretation of antifungal susceptibility test results for several years.

Definition:

The "susceptible-dose dependent" category implies that susceptibility of an isolate is dependent on the dosing regimen that is used in the patient. In order to achieve levels that are likely to be clinically effective against isolates for which the susceptibility testing results (either MICs or disk diffusion) are in the SDD category, it is necessary to use a dosing regimen (ie, higher doses, more frequent doses, or both) that results in higher drug exposure than the dose that was used to establish the susceptible breakpoint. Consideration should be given to the maximum approved dosage regimen, because higher exposure gives the highest probability of adequate coverage of an SDD isolate. The dosing regimens used to set the SDD interpretive criterion are provided in Appendix E. The drug label should be consulted for recommended doses and adjustment for organ function.

NOTE: The SDD interpretation is a new category for antibacterial susceptibility testing, although it has been previously applied for interpretation of antifungal susceptibility test results (see CLSI document M27-S4). The concept of SDD has been included within the intermediate category definition for antibacterials. However, this is often overlooked or not understood by clinicians and microbiologists when an intermediate result is reported. The SDD category may be assigned when doses well above those used to calculate the susceptible breakpoint are approved and used clinically, and where sufficient data to justify the designation exist and have been reviewed. When the intermediate category is used, its definition remains unchanged.

SDD is recommended instead of "intermediate" when reporting cefepime results for *Enterobacteriaceae* isolates because there are multiple approved dosing options for cefepime, and SDD highlights the option of using higher doses to treat infections caused by isolates when the cefepime MIC is 4 or 8 µg/mL or the zone is 19 to 24 mm.

Why is SDD being used now?

- It has become apparent that there is a growing need to refine susceptibility reporting to maximize clinicians' use of available drugs.

- Intermediate too often means "resistant" to clinicians because they do not appreciate the full definition of "intermediate."

- SDD is more specific and it conveys what we know—a higher dose can be considered for isolates with MICs (or zones) that fall in this interpretive category.

- SDD is already well established for use in antifungal susceptibility testing.

- It is anticipated that reporting a cefepime SDD result will encourage clinicians to consider the possibility that cefepime may be an option for treatment.

- Antibiotic stewardship programs, which emphasize dosing regimen and duration of therapy options, are increasing awareness of appropriate use of antibiotics. Personnel from these programs should be able to describe the significance to clinicians of an SDD result for cefepime.

How should this change be implemented?

- Meet with the appropriate practitioners at your institution (members of the antimicrobial stewardship team, infectious disease staff, pathology group, pharmacy, etc.) to inform them of these changes and agree on a plan to inform your clinicians of this change.

- Talk to the manufacturer of your antimicrobial susceptibility testing device to determine how to implement the revised breakpoints on your device.

  – **NOTE:** Because the US Food and Drug Administration (FDA) has not revised the cefepime breakpoints and commercial manufacturers must use FDA breakpoints, the manufacturer cannot adopt the new CLSI cefepime breakpoints. However, for most systems, you can manually change the breakpoints and implement following a verification study.

- Work with your laboratory information system staff to report "SDD" or "D" for *Enterobacteriaceae* when the cefepime MIC is 4 or 8 µg/mL. Make certain that SDD will be transmitted to the hospital information system and appropriately displayed on reports viewed by clinicians.

- Distribute user-specific educational materials to laboratory staff and clinicians receiving antimicrobial susceptibility testing results from your laboratory. Examples of these materials can be found on the CLSI Subcommittee on Antimicrobial Susceptibility Testing webpage at www.clsi.org.

Additional Questions and Answers:

Q: Does CLSI recommend a comment to be reported with the new cefepime breakpoints?
A: If a laboratory chooses to report a comment explaining the SDD range, CLSI recommends the following: "The interpretive criterion for susceptible is based on a dosage regimen of 1 g every 12 h. The interpretive criterion for susceptible-dose dependent is based on dosing regimens that result in higher cefepime exposure, either higher doses or more frequent doses or both, up to approved maximum dosing regimens."

Q: Will all intermediate ranges become SDD?
A: No, the SDD category will be implemented for drug/organism combinations only when there is sufficient evidence to suggest alternative approved dosing regimens may be appropriate for organisms that have MICs or zone diameters between the susceptible and resistant categories.

Q: Will SDD be applied to other antimicrobial agents?
A: CLSI will examine the SDD category possibility for additional drug/organism combinations where multiple dosing options exist (eg, other extended-spectrum cephalosporins).

Q: How do we perform a verification study before implementing the new cefepime breakpoints on our antimicrobial susceptibility testing device?
A: Guidelines for performance of such a verification study are provided in the following publication:
Clark RB, Lewinski MA, Loeffelholz MJ, Tibbetts RJ. Cumitech 31A: verification and validation of procedures in the clinical microbiology laboratory. Washington, DC: ASM Press; 2009.

Q: Does SDD apply to all patients and specimen types (eg, pediatric, geriatric, immunosuppressed)?
A: Yes, in terms of laboratory reporting. Clinicians must decide how to use an SDD result for a specific patient in consideration of all other clinical and physiological parameters for that patient.

Q: Do the new cefepime breakpoints apply to *Pseudomonas aeruginosa* and other gram-negative bacteria also?
A: No, currently they are only applicable to members of the *Enterobacteriaceae.*

Q: Is any special QC required once the SDD breakpoints are implemented?
A: No, currently recommended routine QC is sufficient.

Q: Will we be required to report SDD on proficiency testingsurvey samples?
A: Sponsors of proficiency testing surveys are aware of the difficulties encountered by clinical laboratories in implementing newer CLSI breakpoints. It is highly unlikely that there will be a mandate to report SDD in the near future, but it would be best to check with your proficiency testing survey provider.

Q: If we can implement the revised cefepime breakpoints but cannot facilitate reporting of SDD, can we report "intermediate" instead of SDD?
A: A decision related to this question should be made following consultation with your laboratory director, antibiotic stewardship team (if available), infectious disease practitioners, pharmacists, and infection control practitioners.

Q: If we can implement the revised cefepime breakpoints but cannot facilitate reporting of SDD, can we report an MIC or zone diameter without an MIC?
A: A zone diameter should never be reported without an interpretation because there is a high risk of misinterpretation of this value and this poses patient safety issues. There is a lesser danger of reporting an MIC without an interpretation, but this should not be done without an accompanying qualifying comment. See answer to question above.

Q: If we are still doing extended-spectrum β-lactamase (ESBL) testing and implement the new cefepime breakpoints, do we change a susceptible or SDD result to resistant for ESBL-positive isolates?
A: No. When CLSI changed the other cephem breakpoints in 2010, the recommendation to perform routine ESBL testing was eliminated. When using the new cefepime breakpoints, there is no need to perform routine ESBL testing for patient reporting purposes. However, ESBL testing might be done for infection control or epidemiological purposes.

Q: What does the dosing information that is given with breakpoints mean?
A: The evolving science of pharmacokinetics-pharmacodynamics has become increasingly important in recent years in determining MIC interpretive criteria. Recently approved susceptible or SDD interpretive criteria for a number of agents have been based on a specific dosing regimen(s); these dosing regimens are listed in Appendix E of M100-S24. Proper application of the interpretive criteria requires drug exposure at the site of infection that corresponds to or exceeds the expected systemic drug exposure, at the dose listed, in adult patients with normal renal function. This information should be shared with pharmacists, infectious disease staff, and others making dosing recommendations for the institution.