For Physicians:

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

What Changed?
In January 2014, the CLSI-Antimicrobial Susceptibility Testing Subcommittee 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)	≥ 18mm	15-17mm	≤ 14mm

Revised - 2014

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

Abbreviation: MIC, minimal inhibitory concentration.

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. Isolates in the susceptible-dose-dependent category would be expected to have the same clinical response as isolates in the susceptible category if higher cefepime exposure is achieved either by using higher doses or more frequent doses or both, up to approved maximum dosing regimens.

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 drug label should be consulted for recommended doses and adjustment for organ function.

Why were the cefepime breakpoints reconsidered and why S-DD?
The issue of new breakpoints for cefepime became apparent for several reasons:

- SDD is preferred to "intermediate" when reporting cefepime results for *Enterobacteriaceae* isolates because there are multiple approved dosing options for cefepime and SDD highlights that higher doses can be successfully used to treat infections caused by isolates with cefepime MIC is 4 or 8 µg/mL or zone is 19 to 24 mm.
- 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
- There is a growing need to refine susceptibility reporting to maximize the use of available drugs.
- "Intermediate" is often interpreted as "Resistant". SDD conveys that a higher dose can be used for isolates with MICs (or zones) that fall in this interpretive category, maximizing cefepime as a treatment option.
- Antibiotic Stewardship Programs can assist clinicians with optimal dosing regimens and duration of therapy options for an SDD result for cefepime.

Additional Q & A's:

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, the CLSI recommends the following: "The interpretive criterion for susceptible is based on a dosage regimen of 1 g every 12 h. The interpretive criterion 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 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 (e.g., other extended-spectrum cephalosporins).

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: 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. 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. M100-S24 Appendix F lists these dosing regimens.