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# MicroFocus

## A Macro Look at Micro Issues

Winter 2010

Answers for life.



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## Introduction

The Fall 2010 issue of MicroFocus is devoted to a discussion about the recent interpretive guideline changes from the Clinical and Laboratory Standards Institute (CLSI) for *Enterobacteriaceae* and beta-lactam drugs. There is significant conversation among many laboratorians regarding how to manage these changes—what to do if test options for your system don't contain the right dilutions for all of the drugs for which breakpoints changed; if lower dilutions are available, can reporting with the new breakpoints be implemented and how? How do these changes impact clinical decisions? How may these changes impact infection control management?

These concerns are affecting almost everyone performing automated antimicrobial susceptibility testing. Even though CLSI reached consensus, this continues to be a contentious issue with opinion leaders. I refer you to two papers posted on the American Society for Microbiology website.<sup>1</sup> Written by Drs. Stephen Jenkins and Paul Schreckenberger, these papers present opposing positions on the subject. Each provides valid and compelling reasons for their perspective.

For just over a decade, CLSI has recommended reporting penicillins, cephalosporins, and aztreonam as

resistant for extended-spectrum beta-lactamase (ESBL) producing strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and later, *Proteus mirabilis*. This conservative measure was based on the observation that some molecularly characterized ESBL-producing isolates had elevated but still susceptible MICs, and there were also limited reports of poor patient outcomes in some of these cases. When the standards were proposed, these strains were almost all susceptible to another class of beta-lactam drugs, the carbapenems, so alternate treatment options were readily available. It seemed appropriate to discourage use of drugs that may result in treatment failures. As antimicrobial resistance continued to evolve and additional resistance mechanisms were identified, treatment options became less clear cut. Carbapenems have not remained active against all of these strains.

Dr. Jenkins' view supports the perspective that we should no longer over-call results to be resistant for ESBL-positive isolates when today's treatment options are diminishing. Furthermore, there is no current evidence that these isolates will fail treatment with every cephalosporin. In his view the latest CLSI breakpoints

## Introduction

(continued from page 1)

better represent the clinical effects and current dosing regimens of these antibiotics.<sup>2</sup> Unfortunately since these antibiotics have routinely been reported as resistant, there is little clinical outcome data available to support the changes. But based on scientific evidence and better alignment with breakpoints recommended by other international breakpoint-setting agencies, he believes the new CLSI breakpoints and interpretive guidance provide better information for those making clinical care decisions.

Alternately, Dr. Schreckenberger is concerned that reporting MICs without regard to resistance mechanism may result in patients receiving inappropriate therapy.<sup>3</sup> Some resistant pathogens may still appear susceptible based solely on *in vitro* antimicrobial susceptibility testing. He cites a number of clinical studies documenting failed patient outcomes when an ESBL was present, in spite of the use of antibiotics with susceptible *in vitro* MICs. In addition, he illustrates a number of technique- and method-based conditions which may lead to false susceptibility. In his opinion, discontinuation of confirmation testing will not provide the best information for clinical decisions.

In this issue, Dr. Barbara L. Zimmer, Director of Clinical and Scientific Affairs at Siemens, a voting member of the CLSI Antimicrobial Susceptibility Testing Subcommittee and the diagnostic industry representative, provides background on how breakpoints are established and a discussion of the changes published in the CLSI M100 documents. It is fair to say that these changes will not be the last made by CLSI. Discussions about cefazolin breakpoints, as well as other organisms and antimicrobial agents, continue and are under review.

Readers who use any Siemens analyzer in their laboratory are eligible to obtain one hour of continuing education credit for successful online completion of the competency assessment following Dr. Zimmer's article. Look for instructions accompanying the questions on page 10. Also included in this issue is an Antibiotic Reference Guide. The first version was published a few years ago, and based on your requests we have updated the piece for this issue.

Please continue to provide feedback on MicroFocus and suggestions for future topics. If you have an interest in becoming an author, please email me directly.

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3. Schreckenberger, P.C. 2010. Changing MIC Breakpoints: Do Mechanisms Count? Available at <http://www.asm.org/index.php/policy/clsi-meeting-summaries.html?title=CLSI+Meeting+Summaries>

# Evolving *Enterobacteriaceae* Beta-Lactam Antibiotic Interpretive Breakpoints

Navigating and Understanding New CLSI Recommendations

## Background

As long as there have been antibiotics, there has been a need to know whether or not an antibiotic works against a specified microorganism. The January 2010 Clinical and Laboratory Standards Institute (CLSI) document M100-S20, Performance Standards for Antimicrobial Susceptibility Testing; Twentieth Informational Supplement, and the M100-S20 Update, Performance Standards for Antimicrobial Susceptibility Testing; Update<sup>8,9</sup> contain much-discussed and long-debated modified interpretive breakpoints for susceptibility testing for certain cephalosporins and carbapenems, with *Enterobacteriaceae*. Why did CLSI do this? This article will discuss what a "breakpoint" is, and give a brief summary of how these revised CLSI breakpoints were decided. Some of these breakpoints are not what currently exist on the FDA-approved label (package insert) for the antibiotics themselves. What does it mean for manufacturers of susceptibility testing devices such as the MicroScan® system? How do the latest recommendations impact the laboratory?

Alexander Fleming's significant contribution to microbiology was not just as the discoverer of penicillin, but he also published a macrobroth dilution technique using turbidity as an endpoint determination,<sup>15</sup> essentially the forerunner of modern MIC techniques.<sup>21</sup> Early antimicrobial susceptibility testing (AST) procedures had no real criteria to judge success. In 1966 Bauer and colleagues published a procedure on disk diffusion<sup>1</sup> and thus described a standardized methodology available to all. In 1975, this procedure became the basis for the National Committee on Clinical Laboratory Standards, NCCLS (now known as CLSI; the 10th edition of the disk standard,<sup>7</sup> the 8th edition of the MIC method,<sup>6</sup> as well as current editions on AST procedures for other

microorganisms). After publication of the first standardized method, the laboratory was now able to determine reproducibly and the antibiotic/microorganism interaction for a variety of antimicrobial agents. (The interested reader is referred to reference 29 for a brief history of antimicrobial susceptibility testing.)

## What is a Breakpoint?

A standardized procedure also gives the laboratory the ability to determine "breakpoints." The word breakpoint can mean several things. First, it is used as a microbiological or wild-type breakpoint. It is the "MIC for any given antibacterial (agent) that distinguishes wild-type populations of bacteria from those with resistance mechanisms. A wild-type strain is defined as a strain of a bacterium which does not harbor any acquired or selected resistance to the particular class of antibiotic being examined."<sup>24</sup>

A breakpoint, however, also can interpret the results of susceptibility tests.

To do this, susceptibility test interpretive categories were defined by CLSI. The definition of a "category" is found in CLSI document M-23—a "classification based on an *in vitro* response of an organism to an antimicrobial agent at levels corresponding to blood or tissue levels attainable with usually prescribed doses of that agent." The definitions of each category are also found there. A "susceptible" category means that isolates are inhibited by the usually achievable concentrations of antimicrobial agent when the recommended dosage is used for the site of infection. An "intermediate"



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Clinical pharmacology links medical practice to laboratory science. The intent of this science is to promote the safety of a drug, with the goal of maximizing its action while minimizing unnecessary side effects. The two main areas of study are pharmacokinetics and pharmacodynamics.

category includes isolates with antimicrobial agent MICs that approach usually attainable blood and tissue levels and for which response rates may be lower than for susceptible isolates. This category also includes a buffer zone, which should prevent small, uncontrolled technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins. A resistant antimicrobial susceptibility test implies that isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules.<sup>5</sup> Following this definition, the breakpoints are the MIC values corresponding to each category (e.g. resistant is defined as having MIC values above a certain level). Thus, CLSI (and other standards organizations such as EUCAST<sup>13</sup> or the Japanese Society for Chemotherapy) have standardized both testing and interpretive categories.

All standardized procedures that provide interpretations now integrate the pharmacology of the antibiotic, susceptibility patterns of a population of bacteria including a minimal inhibitory concentration (MIC), and ultimately, clinical success.

**Table 1: Comparison of CLSI and FDA Breakpoints for *Enterobacteriaceae* and Select Beta-lactam Agents<sup>23</sup>**

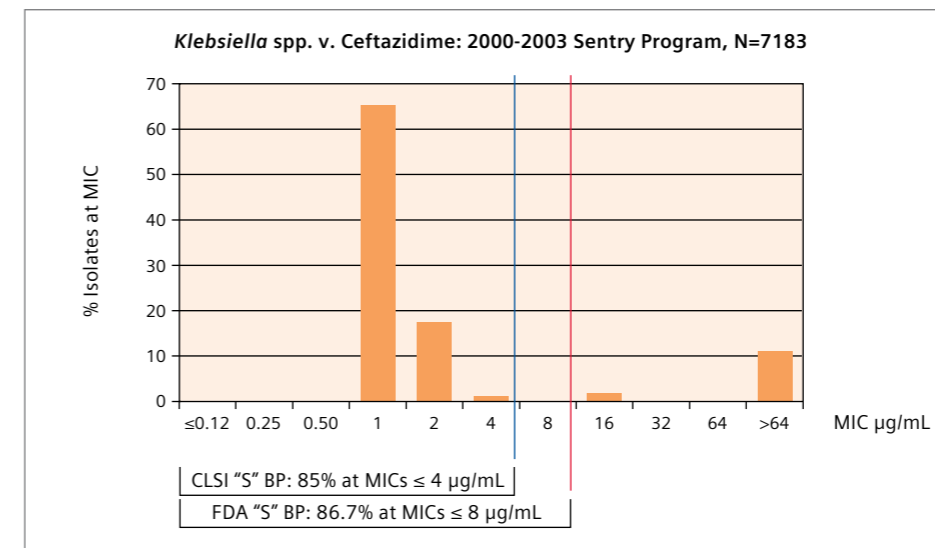
Antimicrobial Agent	Old CLSI M100-S19 and/or Current FDA Breakpoints (µg/mL)			New/Revised MIC Breakpoints CLSI M100-S20-U (µg/mL)		
	S	I	R	S	I	R
Cefazolin	≤ 8	16	≥ 32	≤ 1	2	≥ 4
Cefotaxime	≤ 8	16 – 32	≥ 64	≤ 1	2	≥ 4
Ceftriaxone	≤ 8	16 – 32	≥ 64	≤ 1	2	≥ 4
Ceftazidime	≤ 8	16	≥ 32	≤ 4	8	≥ 16
Aztreonam	≤ 8	16	≥ 32	≤ 4	8	≥ 16
Doripenem	≤ 0.5	–	–	≤ 1	2	≥ 4
Ertapenem	≤ 2	4	≥ 8	≤ 0.25	0.5	≥ 1
Imipenem	≤ 4	8	≥ 16	≤ 1	2	≥ 4
Meropenem	≤ 4	8	≥ 16	≤ 1	2	≥ 4

**Reevaluating Breakpoints – Why Now?**

Reassessment of interpretive criteria becomes necessary when and if new information becomes available. One of the major microbiology pieces of information is evolving resistance. When resistant strains develop to an antimicrobial agent, or when organisms with new mechanisms of resistance are not reliably detected using current breakpoints, it indicates a reassessment may be necessary.<sup>5</sup> Breakpoints for many of the cephalosporins with *Enterobacteriaceae* were set years ago (before we all knew that the abbreviation “ESBL” meant “extended-spectrum beta-lactamase”), and those for the carbapenems were set before there were any resistant strains. Today’s laboratory deals with multi-drug resistant bacteria that not only Fleming, but microbiologists just 20 years ago, could not imagine. This new information was a critical component of the decision to examine breakpoints for these drugs.

The following CLSI MIC breakpoints (and associated disk diffusion breakpoints, not listed here) were revised in the M100-S20 and M100-S20 Update documents.

**Figure 1: Assessment of *Klebsiella* spp. wild-type distribution against Ceftazidime using FDA and CLSI Susceptible breakpoints<sup>17</sup>**



Drug	Stat	Total	≤0.12	0.25	0.50	1	2	4	8	16	32	64	>64
Ceftazidime	n	7,183	–	–	–	4,712	1,264	129	122	165	–	–	791
	%	100.0	–	–	–	65.6	17.6	1.8	0.02	2.3	–	–	11.0
	Cumulative %	100.0	–	–	–	65.6	83.2	85.0	86.7	89.0	–	–	100.0

The CLSI breakpoints were revised to correspond to how particular antibiotics work in treating infections with today’s organisms. Revising breakpoints not only required a review of microbiology data, but review of clinical and pharmacologic data. For cepheims and *Enterobacteriaceae*, the history with ESBL-producing organisms was important. Initial CLSI recommendations for screening and confirmation testing, and the subsequent changing of all penicillin, cephalosporin, and aztreonam interpretive criteria to “R” for selected genera with a positive ESBL confirmation test were based on the elevated (but not yet resistant) MICs obtained with ESBL producers and clinical observations of poor outcome in patients.<sup>20</sup> But beta-lactamases in *Enterobacteriaceae* continued to evolve with both changes in ESBLs (e.g. the CTX-M class),

recognition of ESBLs in genera of the *Enterobacteriaceae* other than *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis*, and multiple beta-lactamases in resistant organisms, including ampC enzymes which tend to mask phenotypic ESBL confirmation results.<sup>2,3,4,16,19,22</sup> Since many of the cepheims are older antimicrobial agents, there was additional reliance on pharmacokinetic/pharmacodynamic (PK/PD) data, including the use of Monte Carlo simulations (data are not summarized here) and published clinical literature. Surveillance studies showed that lowering breakpoints would have minimal impact on the percentage susceptible for the third-generation cephalosporins (Figure 1). In addition, the new CLSI breakpoints are based on specific dosing, using the lowest or medium FDA-approved dosages.

Pharmacokinetics relates to what the body does with a drug. Dosing distribution and half-life of an antibiotic are factors impacting the achievable concentration of the drug at the site of infection.

Pharmacodynamics relates to what a drug does to the body, or bacteria within the body. With antibiotics, it is a measure of the inhibitory and killing ability of a drug relative to its mode of action and concentration at the site of the infection. Two pharmacodynamic concepts that are most important are time-dependent and concentration-dependent killing.

Ultimately in 2010, new breakpoints for cefazolin, cefotaxime, ceftizoxime, ceftriaxone, ceftazidime, and aztreonam were published. Cefepime breakpoints were not revised based upon both clinical and PK/PD data. Cefuroxime breakpoints were not revised, but information about dosage regimens was included. Breakpoints for cepheids generally not used or available in the USA including cefamandole, cefonicid, cefoperazone, and moxalactam were not reevaluated. Corresponding disk diffusion breakpoints were reviewed and delineated for all except cefazolin. Initial studies with cefazolin did not have clear correlation between zone diameter and M100-S20 MIC breakpoints. Finally, the need for ESBL confirmation and subsequent change of interpretive criteria for penicillins, cephalosporins and aztreonam was no longer recommended as necessary using the M100-S20 breakpoints—the interpretation given by the MIC with the new breakpoints should be retained and no other overriding changes made. ESBL testing may be needed for infection control and other non-reporting uses.

CLSI carbapenem breakpoint changes also followed this process; however, more recent data were generally available (Figure 2). Detailed information can be found in the *Enterobacteriaceae* section of the CLSI agenda book.<sup>12</sup>

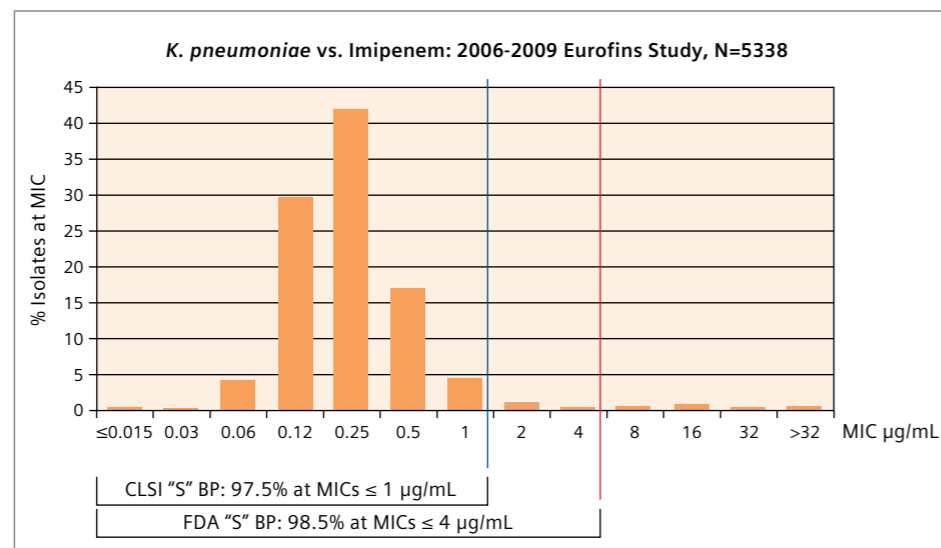
In brief, resistance in the form of carbapenemases began emerging, particularly the KPC type (*Klebsiella pneumoniae* carbapenemases,

unfortunately not restricted to *Klebsiellae*).<sup>14</sup> The Modified Hodge Test (MHT) was developed and shown to be able to detect these. However, the interpretive question remained. Was an organism that was positive for the MHT test susceptible or resistant? Could a patient with an infection with a MHT-positive organism be treated with one but not another carbapenem? Thus, there was a need for interpretive criteria for Modified Hodge Test-positive organisms, and the *Enterobacteriaceae* Working Group wanted to avoid a screening test paradigm. Clinical data were available from studies for the new carbapenem, doripenem, as well as older comparator carbapenems. MIC distributions and PK/PD exposure-response and simulation data were reviewed. All data included

carbapenemase-producing organisms. Ultimately, breakpoints for ertapenem, imipenem, and meropenem were changed, and the new breakpoint for doripenem assigned.

The primary goals for these new recommendations from CLSI are both to better detect resistance without the need for routine use of ESBL confirmation and offline modified Hodge tests, and to facilitate wider treatment options. Reporting recommendations when using the lower breakpoints no longer force all cephalosporins, penicillins, and aztreonam to resistant; but rather they are reported as tested. To put the changes in perspective, see the comparison of CLSI M100-S20-U breakpoints vs. the original FDA-cleared breakpoints (Table 1).

**Figure 2: Assessment of *Klebsiella pneumoniae* wild-type distribution against Imipenem using FDA and CLSI Susceptible breakpoints<sup>23</sup>**



Drug	Stat	Total	≤ 0.015	0.03	0.06	0.12	0.25	0.50	1	2	4	8	16	32	>32
Imipenem	n	5338	7	4	218	1,591	2,238	900	246	45	10	19	27	13	20
	%	100.0	0.1	0.1	4.1	29.8	41.9	16.9	4.6	0.8	0.2	0.4	0.5	0.2	0.4
	Cumulative %	100.0	0.1	0.2	4.3	34.1	76.0	92.9	97.5	98.3	98.5	98.9	99.4	99.6	100

There are several methods to set breakpoints (the reader is referred to reference 24 for a comprehensive review). In all deliberations regarding breakpoint determinations and changes, CLSI followed a consensus process whereby all stakeholders were heard. Since the need for reassessment was from a source other than the manufacturer of the antibiotic, the pharmaceutical manufacturers were notified, with time to prepare relevant data, as needed. Input was also sought from clinicians, laboratories, PK/PD specialists, and regulators. Most importantly for this review, we gave input on behalf of the Susceptibility Testing Manufacturers Association (STMA), a group of all AST manufacturers, including Siemens Healthcare Diagnostics, the maker of MicroScan panels.

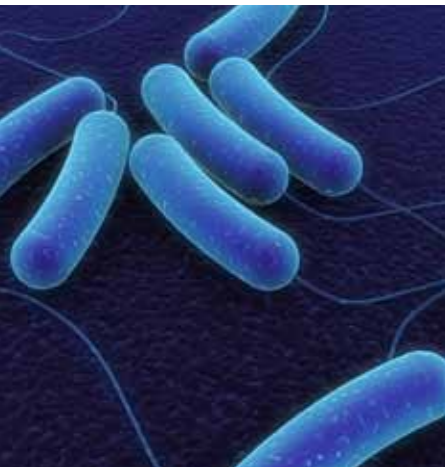
#### How Straightforward is Implementation?

What is the impact on AST manufacturers when long-standing breakpoints are changed? The purpose of the STMA June 2003 presentation,<sup>11</sup> which has subsequently been presented to other regulatory agencies, was to inform CLSI and others about the process required by FDA-regulated device manufacturers. It is a lengthy process with several regulatory steps, including a required new submission and clearance by the FDA. The study must follow design described in Class II Special Controls Guidance Document; AST Systems, use a similar group of organisms that provided the original category agreement (breakpoint) or essential agreement (+/- 1 doubling dilution) results, and include a representative number from all groups of organisms that might be

affected by modifications to the device.<sup>27</sup> Regulatory submission is only a small part of the work required for AST devices when interpretive criteria are changed. New test development for microbiologic and software is required if the new interpretive breakpoint is very different than current product configurations. The total product commercialization changes are extensive and include new software releases, LIS software updates, new product configurations, and labeling changes. It is important to note that disk diffusion manufacturers submit labeling only to the regulatory agencies; however, their package insert must also reflect new breakpoints.

But AST device manufacturers cannot legally change their system breakpoints in FDA-regulated countries when CLSI changes breakpoints until a key predecessor happens. This key predecessor is a change to the label for the antibiotic. When a new antimicrobial agent—the drug itself—is approved by the FDA, it is approved for certain indications of use and with certain breakpoints that reflect the information from the clinical trial for that agent. CLSI breakpoints for an antimicrobial agent may differ from those approved by the FDA for many reasons—among them, different databases, differences in dosages utilized in different parts of the world, and also the fact that CLSI has historically proactively evaluated the need for changing breakpoints.





When CLSI changes an existing breakpoint, the FDA may also review data in order to determine how that change may affect the safety and effectiveness of the antimicrobial agent for the approved indications of use. If the FDA decision from this review is to change the breakpoint for the antimicrobial agent, then the agency notifies the pharmaceutical manufacturer (or the most significant generic manufacturer for older drugs) and the label is changed. Then and only then can commercial (AST) device manufacturers, including Siemens Healthcare Diagnostics, as the manufacturer of MicroScan panels, initiate processes to evaluate product performance using a revised breakpoint. Thus, formal implementation of revised breakpoints by device manufacturers is a regulated process that may take several months to years to complete.

At this time, FDA has not made revisions to any drug labels based upon the M100-S20 and M100-S20-U breakpoint changes; however, they are reviewing the revisions made by CLSI, and are committed to ongoing review and update of breakpoints. The Food and Drug Administration Amendments Act (FDAAA) of 2007<sup>26</sup> specifically guides the FDA to update breakpoints. The FDA issued a guidance document for industry for updating labeling of susceptibility test information in systemic antibacterial drug products and antimicrobial susceptibility testing devices.<sup>28</sup> The FDA has also conducted an advisory group meeting to have the ability to use a standard-setting organization to assist in monitoring the need for changes. However, this has not yet been enacted into law. Consequently, manufacturers of commercial AST systems cannot proceed with any modification to their systems until and if FDA revises breakpoints.

It is very important that the laboratory have a plan in place for these breakpoint changes. The laboratory confer with infectious disease practitioners, pharmacy, infection control groups, and others as needed.

### Impact to Clinical and Laboratory Practice

The most important part of AST interpretive criteria is letting the physician know that an organism is susceptible, intermediate, or resistant to selected antimicrobial therapy. If the laboratory uses new breakpoints recommended by CLSI for *Enterobacteriaceae* with selected cepheims and carbapenems, some susceptibility test results will change from susceptible to resistant. These changes will also be seen with organisms that produce ESBLs in that results for other cephalosporin and penicillin antibiotics will not be overridden to resistant. It is very important that the laboratory have a plan in place for these breakpoint changes. The laboratory should confer with infectious disease practitioners, pharmacy and infection control groups, and others as needed. Excellent informational material regarding implementation of new breakpoints, as well as Q&A, is available.<sup>10</sup> Because commercial AST systems cannot yet legally provide the new breakpoints in their system software, the laboratory may find selected situations where the new interpretive criteria may be important for patient care. In addition, ESBL confirmation testing may continue to be appropriate in some situations. The laboratory can implement new breakpoints immediately if they are using the CLSI reference broth micro dilution method, or reference disk testing, or if appropriate concentrations are available on the commercial AST panel and an in-house validation is performed, similar to what would be done for in-house or investigational use only tests. Laboratories should be aware of CLIA requirements for verification and validation of these tests.<sup>25</sup>

It is acceptable to clinical laboratory accrediting bodies to use either FDA or CLSI breakpoints. A text box that has appeared in M100 documents since –S16

Table 2: Reference Chart for Laboratory Testing Options

Purpose		If using	
		Old CLSI M100-S19 & FDA Breakpoints	Revised CLSI M100-S20/S20-U Breakpoints
<b>For Patient Management</b>			
ESBL	Perform screen and/or confirmatory tests	Yes	No
	Edit "S" to "R" for cephalosporins, penicillins, and aztreonam for ESBL confirmation-positive organisms	Yes	No
Carbapenemase	Evaluate results: Perform MHT if "R" to $\geq$ one third-generation cephalosporin + any carbapenem with elevated MIC (Ertapenem: 2 – 4 $\mu$ g/mL, Imipenem: 2 – 8 $\mu$ g/mL, Meropenem: 2 – 8 $\mu$ g/mL)	Yes	N/A
	• If MHT positive and S to a carbapenem, report the carbapenem MIC without an interpretation	Append comment	N/A
	• If MHT negative, report carbapenems as tested	Yes	N/A
	Evaluate results: if all carbapenems are "I" or "R", no MHT confirmation test required; report agents as tested	Yes	Yes
<b>For Infection Control</b>			
ESBL	Perform screen and/or confirmatory tests	Yes, if requested	Yes, if requested
	Edit "S" to "R" for cephalosporins, penicillins, and aztreonam for ESBL confirmation-positive organisms	Yes	N/A
Carbapenemase	Evaluate results: Perform MHT if "R" to $\geq$ one third-generation cephalosporin + any carbapenem MIC elevated (Etp: 2 – 4 $\mu$ g/mL, Imp: 2 – 8 $\mu$ g/mL, Mer: 2 – 8 $\mu$ g/mL)	Yes, if requested	Yes, if requested
	• If MHT positive and S to a carbapenem, report the carbapenem MIC without an interpretation	Append comment	N/A

(and is on page 18 of M100-S20) also reiterates that "laboratories that use FDA-approved susceptibility testing devices are allowed to utilize existing FDA interpretive breakpoints. Either FDA or CLSI susceptibility interpretive breakpoints are acceptable to clinical laboratory accrediting bodies." The current FDA breakpoints are reflected in CLSI document M100-S19. However, do note—if using the old breakpoints, laboratories should continue to follow the M100-S19 ESBL testing and reporting rules. The table above provides a snapshot of testing options for *Enterobacteriaceae* using either CLSI or FDA breakpoints.

Setting of breakpoints is both a science and an art, and there are interdisciplinary inputs and impacts to interpretation decisions made. There are pros and cons to any change, but as microorganisms continue to evolve resistance mechanisms, laboratory testing regimens will need to continue to change to better detect such resistance. Susceptibility testing is but one facet in an array of diagnostic tools available to assist in better patient care and the appropriate use of antimicrobial agents.

It is acceptable to clinical laboratory accrediting bodies to use either FDA or CLSI breakpoints.

CLSI recommended report comment when MHT positive but S to a carbapenem:

This isolate demonstrates carbapenemase production. The clinical efficacy of the carbapenems has not been established for treating infections caused by *Enterobacteriaceae* that test carbapenem susceptible but demonstrate carbapenemase production *in vitro*.<sup>7</sup>

## Questions for Continuing Education Credit

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Once you have entered the site, select: > Fall 2010 MicroFocus CEU Assessment.

### 1. It is acceptable for laboratories to use either FDA or CLSI breakpoints.

- a. True      b. False

### 2. To what does the term "wild-type" population refer?

- a. A strain of bacteria that has naturally picked up a form of resistance from a similar microorganism in the wild  
b. A strain of bacteria that has naturally mutated due to use of antibacterial agents  
c. A strain of bacteria that represents the normal, non-mutated version existing in the wild  
d. A strain of bacteria that represents the normal, beta-lactam profile existing in a given geography

### 3. KPC-type resistance is seen only in strains of *Klebsiella pneumoniae*.

- a. True      b. False

### 4. For detection of ESBL- and KPC-producing strains using FDA (and the old CLSI M100-S19) breakpoints, the user

- a. Should perform confirmation and change interpretations accordingly  
b. Is not required to perform confirmation testing and should report antimicrobial results as they originally tested  
c. Should perform confirmation tests when all cephalosporins and carbapenems are elevated  
d. Is only required to perform confirmation testing upon request

### 5. When can susceptibility test manufacturers implement new CLSI breakpoints?

- a. The FDA may review data to determine if any changes affect the safety and effectiveness of an antibiotic  
b. The FDA notifies pharmaceutical manufacturers of breakpoint changes  
c. Labeling for affected antibiotics is changed to be the same as CLSI breakpoints  
d. All of the above  
e. Answers a and b only

### 6. Study data reviewed by CLSI indicate that lower breakpoints have very little impact on the percentage of susceptible isolates for third-generation cephalosporins.

- a. True      b. False

### 7. All standardized procedures that provide interpretations now integrate which of the following aspects in the process?

- a. Clinical outcome  
b. Pharmacology of the antibiotic  
c. Inhibition likelihood based on bacterial species  
d. Susceptibility patterns and MICs of a population of bacteria  
e. All of the above  
f. A, B and D

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