Understanding New CAP Requirements for Antimicrobial Susceptibility Testing 2022

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Overview

In 2021, new CAP requirements added to Microbiology Checklist:

MIC.11380 – AST interpretive criteria

MIC.11385 – Updated AST interpretive criteria

We will discuss:

1. Who sets BPs
2. Why BPs are updated
3. How labs can become compliant with new MIC requirements

CAP, College of American Pathologists; AST, antimicrobial susceptibility testing; BP, breakpoints

Abbreviations used in this workshop

AST – Antimicrobial susceptibility testing
BPs – breakpoints
CAP – College of American Pathologists
CLSI – Clinical and Laboratory Standards Institute
EMR – electronic medical record (e.g., EPIC)
FDA – U.S. Food and Drug Administration
    FDA CDER – center for drug evaluation and research
    FDA CDRH – center for devices and radiological health
LIS – laboratory information system (e.g., Cerner, Sunquest)
SDO – standards development organization (e.g., CLSI)
STIC – susceptibility test interpretive criteria (refers to FDA)

Breakpoints in the US

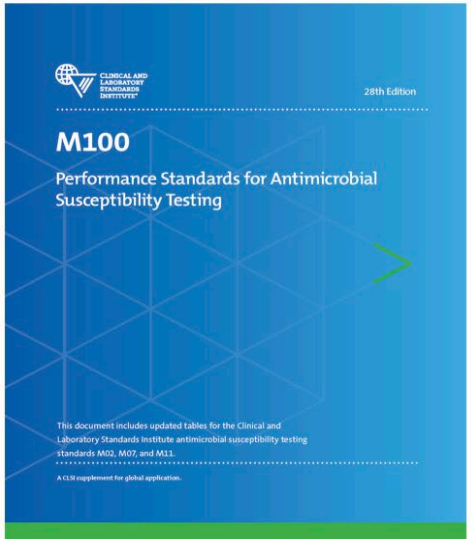
Two primary* groups:

US FDA CDER	CLSI
Regulatory	Standards Organization
Breakpoints used by pharma companies and commercial AST companies	Breakpoints used by labs and clinicians
Generally, breakpoints based on: - FDA approved doses - FDA approved organisms	Breakpoints can be based on: - Off-label doses - Off-label organisms
Data: - From Pharma - From CLSI (or other SDO) - Additional submissions to docket	Breakpoints set by: - Consensus process - Based on clinical need

*USCAST also sets BPs for U.S.

Where do I find CLSI breakpoints for bacteria?

Access Our Free Resources



M100 and M60 Free

CLSI Breakpoint Additions/Revisions Since 2010

Previous breakpoints can be found in the edition of M100 that precedes the document listed in the column labeled "Date of Addition/Revision (M100 edition)." For example, previous breakpoints for aztreonam are listed in M100-S19 (January 2009).

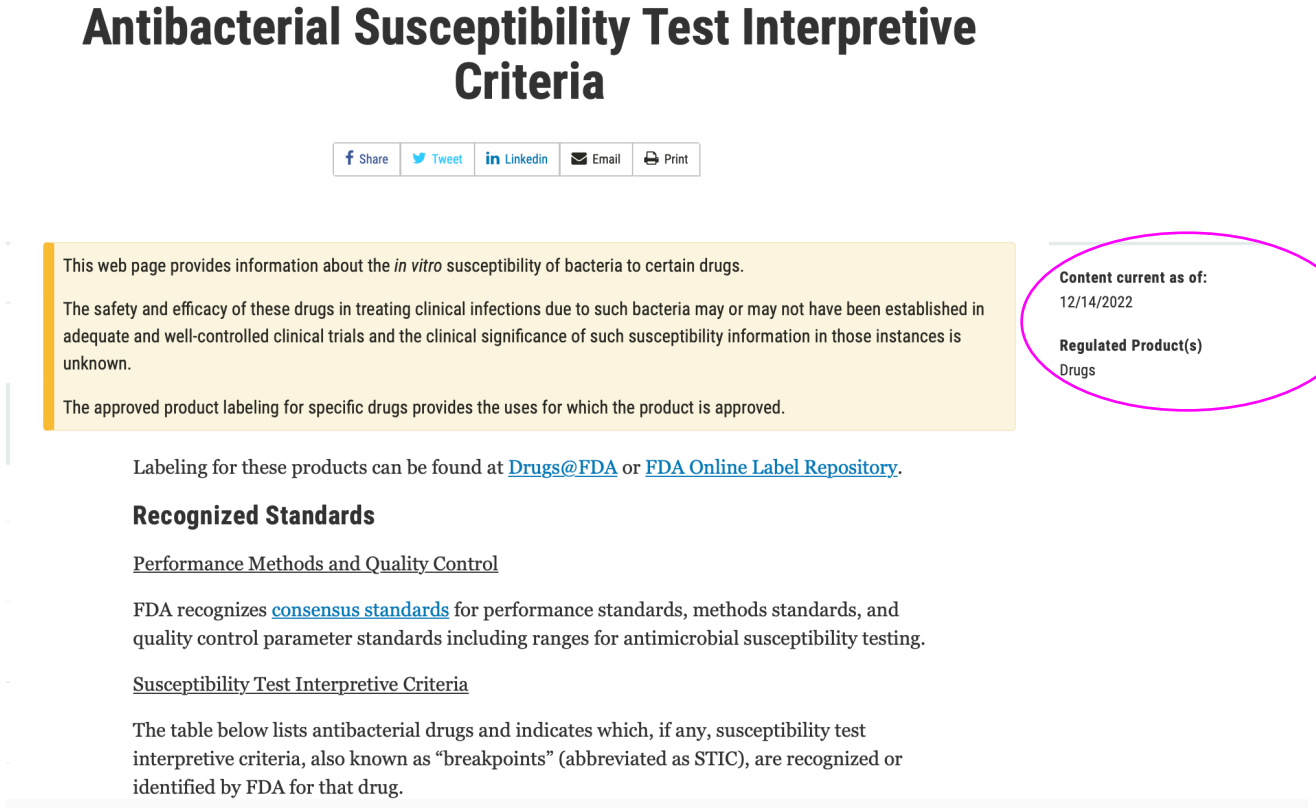
Antimicrobial Agent	Date of Addition/Revision (M100 edition)	Disk Diffusion Breakpoints		MIC Breakpoints		Comments
		New[a]	Revised[b]	New[a]	Revised[b]	
Enterobacterales						
Azithromycin	January 2015 (M100-S25)	X		X		*S. enterica* ser. Typhi only
	March 2021 (M100-Ed31)	X		X		*Shigella* spp. Previously assigned an ECV
Aztreonam	January 2010 (M100-S20)		X		X	
Cefazolin (parenteral)	January 2010 (M100-S20)				X	Removed disk diffusion breakpoints January 2010 (M100-S20)
	January 2011 (M100-S21)	X			X	
	January 2016 (M100-S26)	X		X		For uncomplicated UTIs

Google "M100 Free."

Page xxiii is a listing of all updates since 2010 for reference

Also available from CLSI as handout 1, which includes FDA status for the updates

Where do I find current FDA breakpoints?



Antibacterial Susceptibility Test Interpretive Criteria

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This web page provides information about the *in vitro* susceptibility of bacteria to certain drugs.

The safety and efficacy of these drugs in treating clinical infections due to such bacteria may or may not have been established in adequate and well-controlled clinical trials and the clinical significance of such susceptibility information in those instances is unknown.

The approved product labeling for specific drugs provides the uses for which the product is approved.

Content current as of:
12/14/2022

Regulated Product(s)
Drugs

Labeling for these products can be found at Drugs@FDA or FDA Online Label Repository.

Recognized Standards

Performance Methods and Quality Control

FDA recognizes consensus standards for performance standards, methods standards, and quality control parameter standards including ranges for antimicrobial susceptibility testing.

Susceptibility Test Interpretive Criteria

The table below lists antibacterial drugs and indicates which, if any, susceptibility test interpretive criteria, also known as "breakpoints" (abbreviated as STIC), are recognized or identified by FDA for that drug.

Current as of 12/14/2022

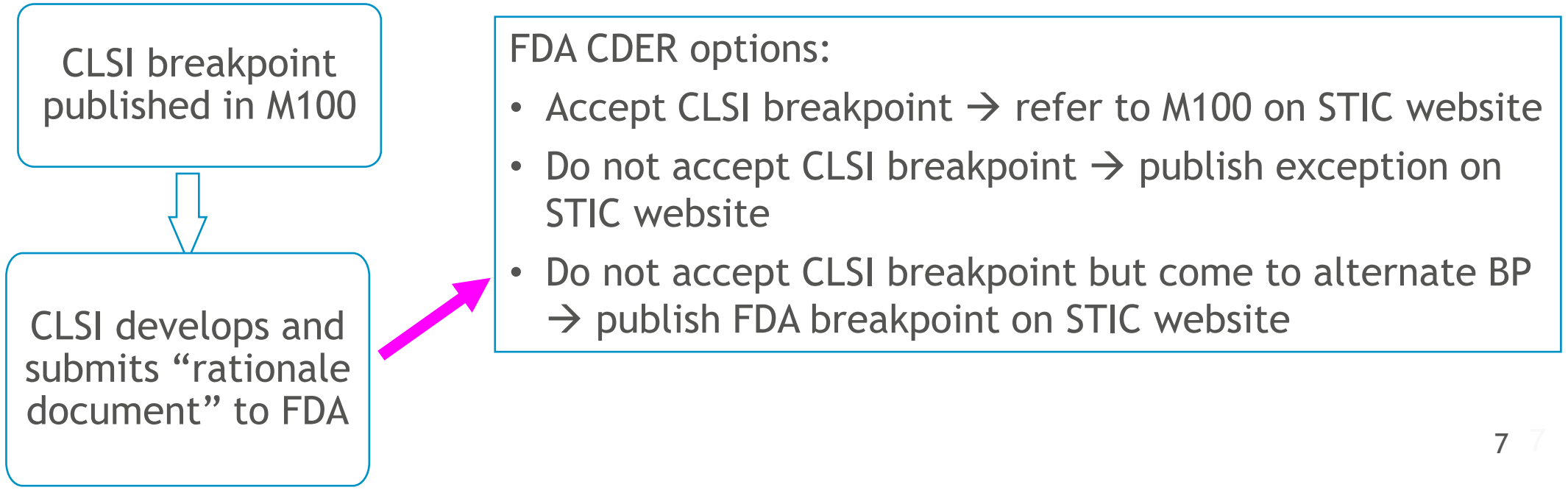
Google "FDA STIC."

Current Process: FDA and CLSI BPs

FDA CDER and CLSI independently set BPs for new drugs

- FDA - as part of New Drug Approval process → listed on STIC website
- CLSI - if the drug sponsor requests CLSI breakpoints (optional) → listed in M100

When BPs are updated, CLSI requests FDA recognize CLSI BPs via Rationale Document submission



What about the tests I use in my lab?

Commercial test systems include:

- Vitek2, MicroScan, Phoenix, Sensititre
- PhenoTest BC
- Etest, MTS strips

These are cleared by FDA, Using BPs on FDA STIC website

NOT evaluated by CLSI, who use reference broth microdilution

Disks are considered “reference”, but do achieve FDA clearance

What if I want to test an organism / drug with no FDA STIC BPs?

… it depends

AST devices in USA

Pre- 2009: Manufacturers obtain AST FDA clearance using CLSI BPs

2009: Manufacturers must use FDA BP

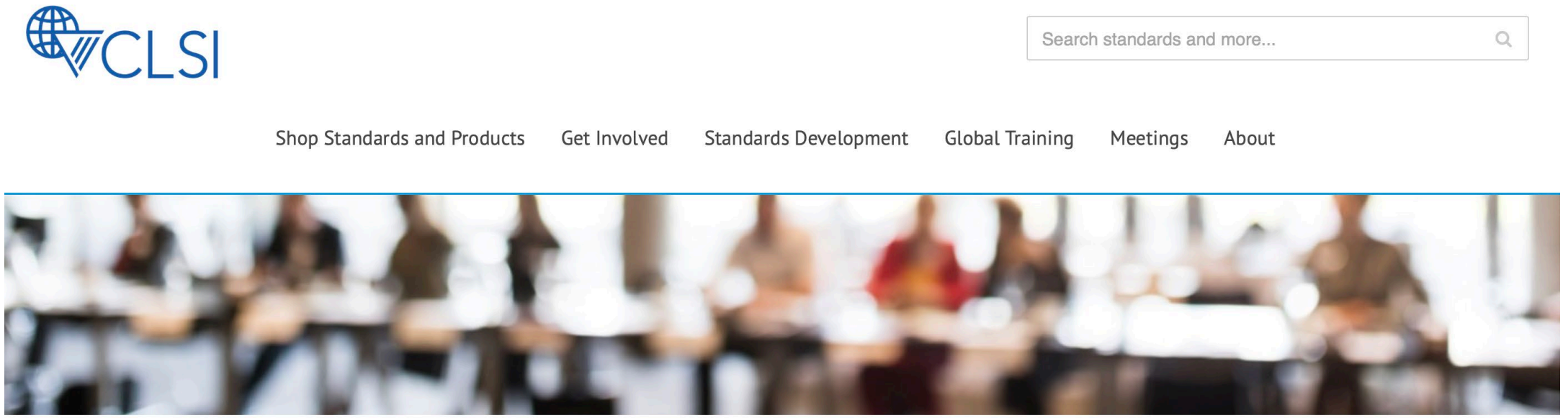
Systems cleared pre-2009, "grandfathered" (i.e., can keep using 2009 CLSI BP)
If system updated, must use FDA breakpoint going forward

2010: CLSI starts updating BPs

2016: 21st Century Cures Act Allows FDA to Recognize CLSI BPs

2022: Many CLSI BPs updated between 2009-2021 recognized by FDA, but some are not (see CLSI handout)

Rationale documents: Free online



https://clsi.org/meetings/ast/rationale-documents/

Current Process: AST Devices

When submitting to FDA CDRH for clearance of an AST:

- Must use version of BPs published on FDA STIC website at time of submission

- If STIC is subsequently updated by FDA, device is not required to be updated (i.e., no regulatory need to stay current)

Updating BPs is at high cost for manufacturers:

may require new development / reformulations

may require new clinical trials for test

significant software logistical challenges

may lose claims for old ”pre-2009” testing if BPs not recognized by FDA

= opportunity cost for other work

Today:
possible BPs scenarios on AST devices in USA

Test* FDA cleared pre-2009

- Applies 2009 CLSI BPs
  - Some of these may be the same as 2022 FDA BPs
  - Some of these may be obsolete BPs
  - Need to check!

Test FDA cleared post-2009

- Applies FDA BPs current on date of clearance
  - Could be same as CLSI BPs
  - Could be unique FDA BPs
  - May be current in 2022
  - May be obsolete in 2022
  - Need to check!

Laboratory adoption of breakpoint updates will differ:

- If test system is FDA cleared with update (i.e., current FDA) = verification of FDA cleared system
- If test system is NOT FDA cleared with update = validation of modified FDA cleared system

* AST devices are cleared drug-by-drug. In this case, test refers to individual antimicrobial

Why update BPs anyway?

Why are BPs updated?

Criterion	Example
new resistance mechanism(s)	Carbapenems / Enterobacteriaceae
new PK/PD data	Fluoroquinolones / Enterobacteriaceae and P. aeruginosa
dose used in clinical practice changes	Cefazolin / Enterobacteriaceae
new dose/route leads to new PK	Ceftaroline / S. aureus
common use of abx changes	Penicillin / Streptococcus pneumoniae
poor prediction of clinical response	Daptomycin / Enterococcus spp.
public health need	Colistin / P. aeruginosa and Acinetobacter spp.
MIC and disk diffusion breakpoints off	Ceftaroline / S. aureus
simplify testing	Cephalosporins / Enterobacteriaceae (ESBLs)
differences between CLSI and EUCAST	Fluoroquinolones / Enterobacteriaceae and P. aeruginosa

Adapted from M23 Guideline

14

Case 1

6 YO male,
5 days fever, abdominal pain, leg pain
No diarrhea, elevated AST/ALT
Imaging shows no osteomyelitis
Treated with ceftriaxone IV

15 h

Blood culture **rapid test**
Salmonella spp.

Day 2

AST report, day 2

Ampicillin	32 µg/mL	R
Ceftriaxone	0.5 µg/mL	S
Ciprofloxacin	1.0 µg/mL	S
SXT	>4 µg/mL	R

Patient started on oral levofloxacin based on AST

Case 1

AST report, day 2

Ampicillin	32 µg/mL	R
Ceftriaxone	0.5 µg/mL	S
Ciprofloxacin	1.0 µg/mL	S
SXT	>4 µg/mL	R

MIC interpreted with obsolete BP

Ciprofloxacin Oral, Injection products

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Recognized Interpretive Criteria

Additional FDA-identified interpretive criteria

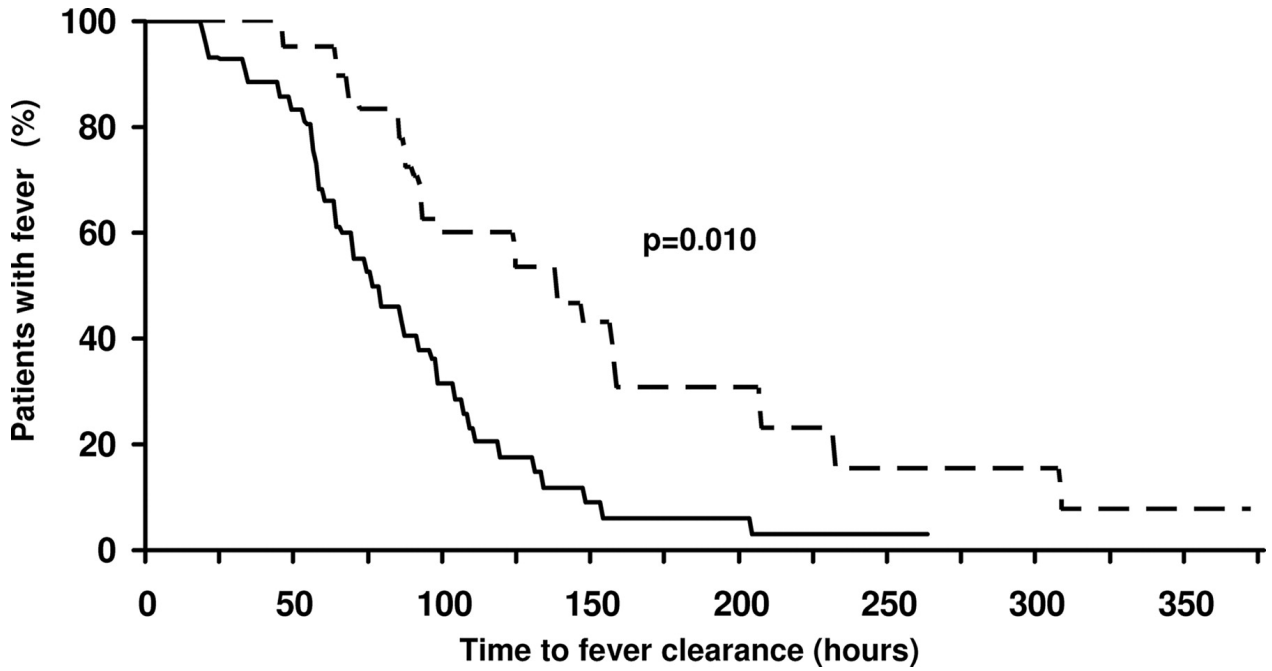
	Minimum Inhibitory Concentrations (mcg/mL)		Disk Diffusion (zone diameter in mm)		
		R	S	I	R
Enterobacteriaceae	M100 standard is recognized				
***Salmonella* spp.**	M100 standard is recognized				

Table 2A. Enterobacterales (Continued)

Test/Report Group	Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm				Interpretive Categories and MIC Breakpoints, µg/mL				Comments
			S	SDD	I	R	S	SDD	I	R	
QUINOLONES AND FLUOROQUINOLONES for *Salmonella* spp. (Please refer to Glossary I.) (Continued)											
B	Ciprofloxacin	5 µg	≥31	-	21-30^	≤20	≤0.06	-	0.12-0.5 ^	≥1	(64) Isolates of *Salmonella* spp. that test not susceptible to ciprofloxacin, levofloxacin, ofloxacin, or pefloxacin may be associated with clinical failure or delayed response in fluoroquinolone-treated patients with salmonellosis.
B	Levofloxacin	-	-	-	-	-	≤0.12	-	0.25-1^	≥2	

CLSI M100 32nd Ed., FDA STIC website

Ciprofloxacin MIC >0.06 µg/mL associated with poor outcomes for ciprofloxacin rx in typhoid fever



Dashed line, ciprofloxacin MIC >0.06 µg/mL

17% of patients treated with a fluoroquinolone experienced treatment failure if MIC >0.125 µg/mL

Vs.

4% if MIC ≤0.06 µg/mL

2012: CLSI updates MIC breakpoints

Recognized by FDA

Crump et al. 2008 AAC. 52:1278

Case (1 month later)

Increasing fever, abdominal pain, blood culture is + for *S.* Typhi

Clinically well, no foci identified

Laboratory review: isolate was actually "I" to fluoroquinolones

BPs applied by lab : historical CLSI Enterobacterales BPs

CLSI comment 64 (Table 2A)

"Isolates of *Salmonella* spp. that test not susceptible to fluroquinolones may be associated with clinical failure or delayed response."

Antimicrobial	MIC	Interp. With obsolete breakpoint	Interp. with current breakpoint
Ciprofloxacin	1	S	R

Note from clinical team on discharge:

"At this time, it seems most likely that *S.* Typhi resistance to fluoroquinolones resulted in a partially treated infection. "

Note from ID team on discharge:

"*Salmonella* typhi is difficult to eradicate with common (~20%) recurrence. Therefore, this recurrence may be multifactorial."

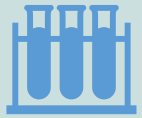
The CAP Checklist Change

2019: CAP recognizes many US labs have not updated BPs

Organism	Antimicrobial Agent	US Laboratory Responses to Use of Current BP	
		Total no. of labs responding to question	Proportion using current CLSI/FDA breakpoints
Enterobacterales	Ceftazidime	1046	59.3%
Enterobacterales	Ceftriaxone	1124	61.7%
Enterobacterales	Ciprofloxacin	1058	29.5%
Enterobacterales	Levofloxacin	1019	30.0%
Enterobacterales	Meropenem	982	62.1%
Pseudomonas aeruginosa	Piperacillin/tazobactam	1064	52.5%
Acinetobacter baumannii	Imipenem	784	46.8%

Simner et al. 2021. OFID. Data from CAP 2019 D-B supplemental questions.

CAP Concerns and Response



Many laboratories do not know which breakpoints are applied by their laboratory.

Concern regarding patient safety if obsolete breakpoints applied

CAP efforts to improve quality of AST results reported by laboratories:

MIC.11380, revised (Phase II)

MIC.11385, new (Phase I)

CAP Checklist MIC.11380 (Revised)

REVISED* ***09/22/2021***

MIC.11380 **Antimicrobial Susceptibility Test Interpretation Criteria** **Phase II**

For antimicrobial susceptibility testing systems, there are written criteria for determining and interpreting minimal inhibitory concentration (MIC) or zone diameter sizes as susceptible, intermediate, resistant, non-susceptible, or susceptible dose-dependent. These criteria are reviewed annually.

Key points:

- You must know which breakpoints are in use in your laboratory.
- You may choose to use CLSI, EUCAST, or FDA breakpoints.
- You may choose to use (in rare instances) institution-specific breakpoints.
- You must review the breakpoints applied by your laboratory annually.

Previously MIC.21930 (Susceptibility Test Endpoint Determination)

CAP Checklist MIC.11385

NEW* ***09/22/2021***

MIC.11385 **Current Antimicrobial Susceptibility Test Interpretation Breakpoints** **Phase I**

Effective January 1, 2024, the laboratory uses current breakpoints for interpretation of antimicrobial minimum inhibitory concentration (MIC) and disk diffusion test results, and implements new breakpoints within three years of the date of official publication by the FDA or other standards development organization (SDO) used by the laboratory.

Key points:

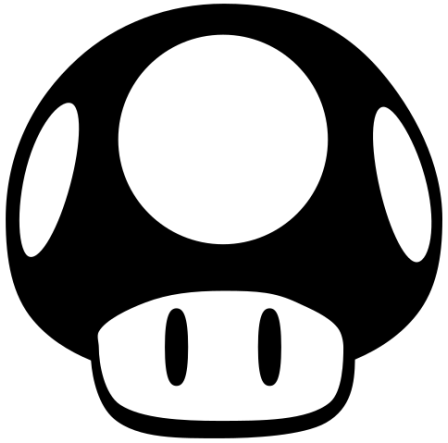
Effective January 1, 2024 laboratory must use current breakpoints for MIC and disk diffusion tests.

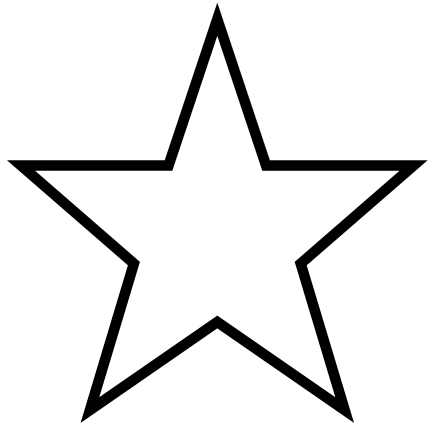
Minimum requirement = FDA breakpoint (US laboratories); may also use current CLSI or EUCAST BPs.

UNACCEPTABLE to use breakpoints no longer recognized by CLSI, EUCAST, FDA .

Exception: laboratory can use alternative breakpoints (including old breakpoints), if justified (requires documentation).

CAP Requirements: The Combined Process





IDENTIFY (MIC.11380)	LEVEL UP (MIC.11385)	MAINTAIN (MIC.11380 + 11385)
Determine which breakpoints are applied by lab for MIC and disk diffusion tests. Document this as your "baseline"	Identify obsolete breakpoints. Make plan and update. By 2024: must update any that were updated prior to 2021 by FDA	Annual review- Identify updates in breakpoints. Implement within 3 years of FDA.

Strategies to Comply With CAP Checklist Requirements

MIC.11380 (VUMC Approach)

Identify	What is driving MIC or disk diffusion interpretation? (Instrument, LIS, EMR, manual?)
Record	Record breakpoint criteria applied and date of review.
Check	Check laboratory breakpoints against current CLSI documents (eg, M100 S31).
Cross-Check	If breakpoints different than CLSI, cross check FDA STIC Website.

MIC.11380 – What do I document?

- Location of BPs – Commercial AST system, LIS, EMR, SOP, other?
- Record BPs
- What is the source document for these BPs?
  - CLSI M100, which version?
  - FDA
  - Other/unknown
- What is the date of review?
- Any notes and plans?
- Have examples of proficiency tests and patient reports ready to show inspector to prove you're using the documented BPs.

Example: VUMC Review, Enterobacterales

See Handout 1 (Breakpoint Review, 2021)

HANDOUT 1. VUMC Example for MIC.11380

Test System	Panel	Organism/Group	Antimicrobial Agent	Source Document for BP	Location of breakpoint (LIS/instrument/S	Susceptible, MIC ≤ DD≥	Intermediate	Resistant MIC ≥ DD≤	Match M100 S31?	Match STIC 12/21?	Date of last update	Date of last review	Rationale for alternative breakpoint or action plan
Phoenix	NMIC-306	Enterobacterales	amikacin	CLSI M100 S31	Epicenter	16	32	64	yes	yes	pre-2021	December 16 2021	
Disk diffusion	manual	Enterobacterales	amikacin	CLSI M100 S31	Cerner	≥17	15-16	≤14	yes	yes	pre-2021	December 16 2021	
Phoenix	NMIC-306	Enterobacterales	amox-clav	CLSI M100 S31	Epicenter	8	16	32	yes	yes	pre-2021	December 16 2021	
Phoenix	NMIC-306	Enterobacterales	amp-sulbactam	CLSI M100 S31	Epicenter	8	16	32	yes	yes	pre-2021	December 16 2021	
Disk diffusion	manual	Enterobacterales	amp-sulbactam	CLSI M100 S31	Cerner	≥15	12-14	≤11	yes	yes	pre-2021	December 16 2021	
Phoenix	NMIC-306	Enterobacterales	ampicillin	CLSI M100 S31	Epicenter	8	16	32	yes	yes	pre-2021	December 16 2021	
Disk diffusion	manual	Enterobacterales	ampicillin	CLSI M100 S31	Cerner	≥17	14-16	≤13	yes	yes	pre-2021	December 16 2021	
Phoenix	NMIC-306	Enterobacterales	aztreonam	CLSI M100 S31	Epicenter	4	8	16	yes	yes	pre-2021	December 16 2021	
Disk diffusion	manual	Enterobacterales	aztreonam	CLSI M100 S31	Cerner	≥21	18-20	≤17	yes	yes	pre-2021	December 16 2021	
Phoenix	NMIC-306	Enterobacterales	cefazolin	Laboratory (2020 FDA)	Epicenter	1	2	4	No	No	2021	December 16 2021	See justification discussion with ASP and memo dated December 10 2020
Disk diffusion	manual	Enterobacterales	cefazolin	CLSI M100 S31	Cerner	≥23	20-22	≤19	yes	yes	pre-2021	December 16 2021	
Etest	Manual	Enterobacterales	Cefazolin	CLSI M100 S19	Cerner	8	16	32	no	no	pre-2021	December 16 2021	Obsolte BP - test not used; delete from Cerner
Phoenix	NMIC-306	Enterobacterales	Cefazolin - urine only	CLSI M100 S31	Epicenter	16	-	32	yes	no	pre-2021	December 16 2021	No FDA breakpoint - using CLSI

What test are BPs applied to?

What is source document for BPs?

Where are the BPs housed?

Are BPs current?

When were the last BPs updated?

When were BPs reviewed?

FDA Breakpoints

Antibacterial Susceptibility Test Interpreti Criteria

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Recognized Standards

Performance Methods and Quality Control

FDA recognizes consensus standards for performance standards, methods standards, quality control parameter standards including ranges for antimicrobial susceptibility testing.

Susceptibility Test Interpretive Criteria

The table below lists antibacterial drugs and indicates which, if any, susceptibility test interpretive criteria, also known as "breakpoints" (abbreviated as STIC), are recognized or identified by FDA for that drug.

With certain exceptions and additions, identified in the table, FDA recognizes the standard published in:

- Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing. 31st ed. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2021. (CLSI M100)

M100 Standard recognized ("2021")

Ceftazidime – Injection products

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Date of update

Recognized Interpretive Criteria

Exceptions to the recognized standard of CLSI M100

Content current as of: 06/14/2019

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameter in mm)		
Pathogen	S	I	R	S	I	R
Enterobacteriaceae	M100 standard is recognized					
Pseudomonas aeruginosa [a]	≤ 8	-	≥ 16	≥ 18	-	≤ 17

CLSI BPs recognized

CLSI BP not recognized & FDA-specific BPs

For the bacteria listed below, susceptibility test interpretive criteria are not recognized at this time:

Acinetobacter spp. disk diffusion interpretive criteria (Interpretive criteria for MIC are recognized.)

Burkholderia cepacia complex disk diffusion interpretive criteria (Interpretive criteria for MIC are recognized.)

Other Non-*Enterobacteriaceae*

CLSI BPs not recognized, no FDA BPs

VUMC, Phoenix NMIC-306 Enterobacterales BPs

	Location of BP	S (≤)	I	R (≥)	Current with M100 S31?	Current with FDA STIC 2021	Date of review	Notes
Ceftriaxone	Epicenter	1	2	4	Yes	Yes	12/16/21	Ok
Ceftazidime	Epicenter	8	16	32	No	No	12/16/21	Must update by 1/1/2024

Phoenix NMIC-306 has FDA clearance for ceftriaxone breakpoint, but not ceftazidime

FDA STIC recognizes CLSI M100 S31 Enterobacterales ceftazidime breakpoint (last update, 2017).

CAP MIC.11385: Must update by January 1, 2024 at minimum.

Plan: Check with commercial AST manufacturer on pending updates: manufacturer has already obtained clearance for current BPs, can update with minimal verification!

Case 1. Ceftazidime BP issue

16 YO boy with relapse of pre-B cell acute lymphocytic leukemia

On chemotherapy, neutropenic.

Feeling tired, weak and has diarrhea.

Spikes fever at home to 102.7°F.

In ER:

-In shock

-WBC <0.1 K

-Urine, sputum and blood grow *K. pneumoniae*

-Negative for *CTX-M*

-Hospital protocol: cefepime, but shortage

Alternative - ceftazidime? meropenem?

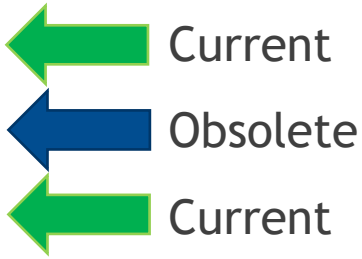
Agent	MIC (µg/ml)	
Amikacin	8	S
Amikacin	≤8	S
Amox/Clav	>16	R
Ampicillin	>16	R
Cefepime	**≤1**	**S**
Ceftazidime	**8**	**S**
Ceftriaxone	**8**	**R**
Ciprofloxacin	≤0.25	S
Gentamicin	≤2	S
Levofloxacin	≤0.5	S
Pip/tazo	≤2/4	S
SXT	≤0.5	S

- Hospital policy:
  Only report meropenem if cefepime is “R.”
- Patient started on ceftazidime quickly escalated (thankfully) by ASP to meropenem.

K. pneumoniae - Ceftazidime (cont.)

Agent	MIC (µg/ml)	
Cefepime	≤1	S
Ceftazidime	8	S
Ceftriaxone	8	R

Breakpoints Used:



Enterobacterales MIC BPs (µg/ml):

Agent	Current			Obsolete		
	S	I	R	S	I	R
Cefepime	≤1	2-4	8	≤8	16	32
Ceftazidime	≤4	8	16	≤8	16	32
Ceftriaxone	≤1	2	4	≤8	16-32	64

Updated by CLSI in 2010

Last updated by FDA in 2017 per STIC website

VUMC: Fluoroquinolones BPs for Enterobacterales/*P. aeruginosa*

CLSI Updated in January 2019[1]

FDA Updated June 10, 2019[2]

Per MIC.11385, laboratory must update by January 1, 2024 (ie, effective date of checklist as BP update will be more than 3 years old by then).

VUMC performs:

- Phoenix MIC test → BPs in Epicenter
- Etest → BPs in Cerner
- Disk diffusion → BPs in Cerner

[1]M100 Ed 31, Table on page xxv
[2]https://www.federalregister.gov/documents/2020/10/22/2020-23439/21st-century-cures-act-annual-compilation-of-notices-of-updates-from-the-susceptibility-test

VUMC Fluoroquinolone Review

HANDOUT 1. VUMC Example for MIC.11380

Test System	Panel	Organism/Group	Antimicrobial Agent	Source Document for BP	Location of breakpoint (LIS/instrument/S	Susceptible, MIC ≤ DD≥	Intermediate	Resistant MIC ≥ DD≤	Match M100 S31?	Match STIC 12/21?	Date of last update	Date of last review	Rationale for alternative breakpoint or action plan
Phoenix	NMIC-306	Enterobacterales	ciprofloxacin	CLSI M100 S31	Epicenter	0.25	0.5	1	yes	yes	pre-2021	December 16 2021	
Disk diffusion	manual	Enterobacterales	ciprofloxacin	CLSI M100 S31	Cerner	≥26	22-25	≤21	yes	yes	2020	December 16 2021	
Etest	manual	Enterobacterales	ciprofloxacin	CLSI M100 S31	Cerner	0.25		1	yes	yes	2020	December 16 2021	
Phoenix	NMIC-306	Enterobacterales	levofloxacin	CLSI M100 S31	Epicenter	0.5	1	2	yes	yes	pre-2021	December 16 2021	
Disk diffusion	manual	Enterobacterales	levofloxacin	CLSI M100 S31	Cerner	≥21	17-20	≤16	yes	yes	2020	December 16 2021	
Etest	manual	Enterobacterales	Levofloxacin	CLSI M100 S31	Cerner	0.5	0.75-1.5	2	yes	yes	2020	December 16 2021	
Phoenix	NMIC-306	P. aeruginosa	ciprofloxacin	CLSI M100 S31	Epicenter	0.5	1	2	yes	yes	pre-2021	December 16 2021	
Disk diffusion	manual	P. aeruginosa	ciprofloxacin	CLSI M100 S28	Cerner	≥21	16-20	≤15	no	no	pre-2021	December 16 2021	Update to 2021 breakpoint. See Handout 4
Etest	manual	P. aeruginosa	Ciprofloxacin	CLSI M100 S31	Cerner	0.5	1	2	Yes	yes	pre-2021	December 16 2021	
Phoenix	NMIC-306	P. aeruginosa	levofloxacin	CLSI M100 S31	Epicenter	1	2	4	yes	yes	2020	December 16 2021	
Disk diffusion	manual	P. aeruginosa	levofloxacin	CLSI M100 S28	Cerner	≥17	14-16	≤13	no	no	pre-2021	December 16 2021	Update to 2021 breakpoint. See Handout 4

BPs are up to date, EXCEPT:

- Disk diffusion BPs for *P. aeruginosa* and ciprofloxacin.
- Disk diffusion BPs for *P. aeruginosa* and levofloxacin.

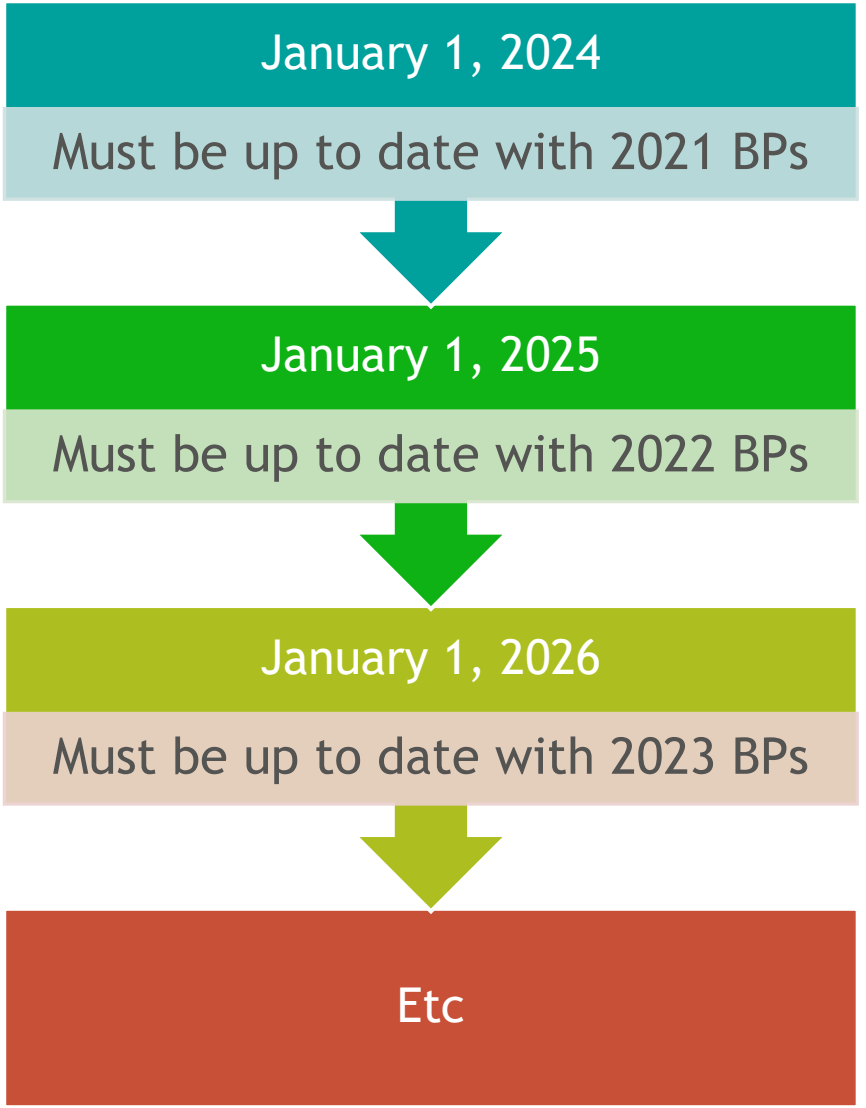
Disk diffusion used routinely for cystic fibrosis patients and mucoid isolates.

MIC.11380: Lessons learned (RMH)

- Most BPs were current on AST test system.
- Incorrect BPs were identified in AST expert rules software.
  - Did not align with FDA or CLSI (current or obsolete) - unclear of the source for these (lab error?)
- One antimicrobial may have BPs applied to results at AST, LIS, or EMR– sometimes these conflict.
- “Cleanup” needed in LIS:
  - Occasionally forgot to update disk diffusion BPs in LIS.
  - Several old BPs in system – delete to avoid accidental reporting
- This takes time! Give yourself plenty of time to document everything

MIC.11385: Updating Breakpoints

- MIC.11385 requires laboratory update:
  - Effective January 1, 2024
  - Must be done within 3 years of most recent update by FDA (US labs) or CLSI/EUCAST
  - In US, if CLSI updates but FDA does not, update not required of laboratory, but optional.
  - Laboratory can use FDA, CLSI, or EUCAST BPs.
- Laboratories should start now.
  - Determine what breakpoints do not match CLSI/FDA (identify process).
  - Plan to be updated to at least 2021 BPs by January 1, 2024.



Example for complying with MIC.11385

Levofloxacin for *Enterobacterales*

1998: levofloxacin BPs first published. → 2019: CLSI Updates BPs. → 2019: FDA recognizes CLSI BPs. → FDA/CLSI BPs the same. Labs must update to 2019 BPs. Cannot use 1998 BPs after 1/1/24.

Ceftazidime for *Pseudomonas aeruginosa*

Pre-1990: ceftazidime BPs first published. → ~ 2013: FDA updates BPs (CLSI does not update). → Two current BPs: CLSI and FDA → Either CLSI or FDA BPs acceptable for use.*

*If laboratory opts to use CLSI BPs, and AST system is cleared with current FDA BPs, must validate CLSI BPs (check with manufacturer!)

More examples for complying with MIC.11385

Ceftaroline for *S. aureus*

2013: Initial CLSI BPs published → 2019: CLSI updates BPs → 2020: FDA reviews CLSI rationale, does not adopt BPs → Two current BPs, CLSI and FDA. Either acceptable for use

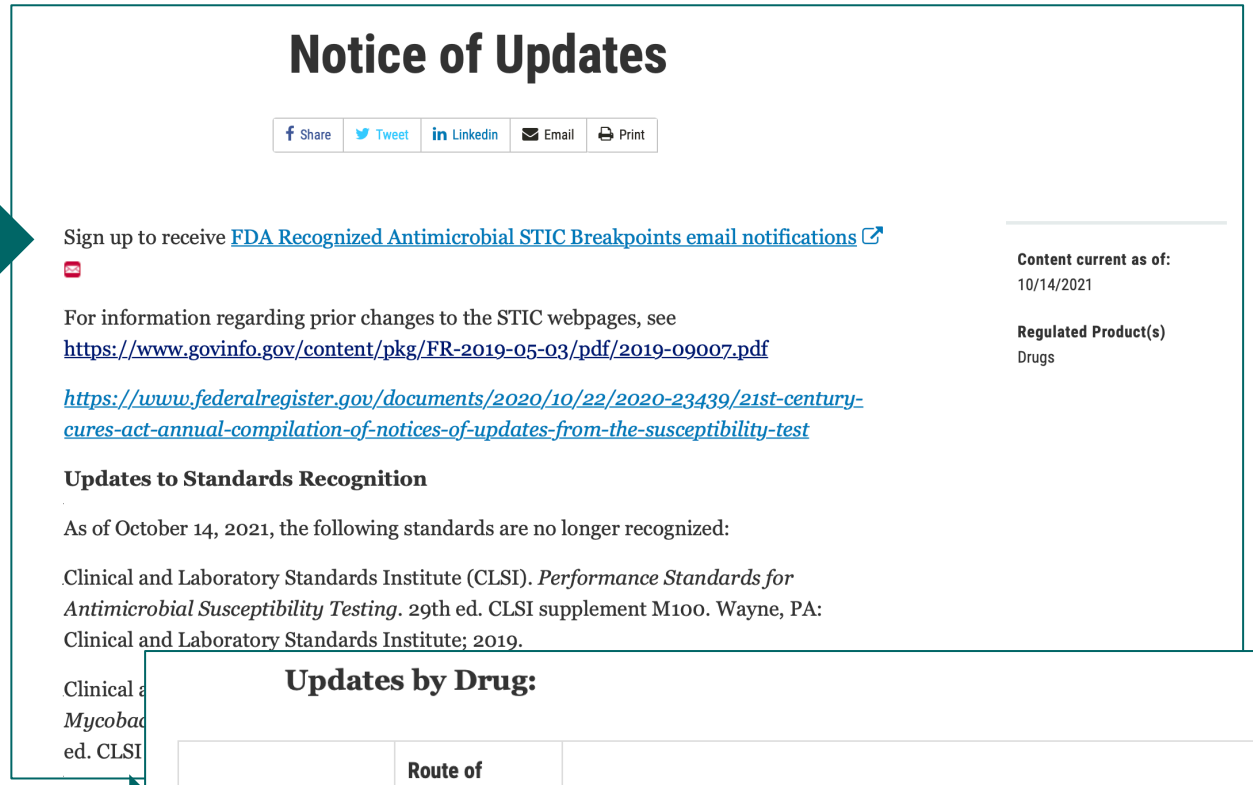
Daptomycin for *E. faecium*

2005: Initial CLSI BPs published. No FDA BPs. → 2017: FDA recognizes CLSI BPs. → 2019/2020: CLSI updates BPs. → 2020: FDA does not accept CLSI BPs. No FDA BPs. → One current BPs (CLSI). Labs cannot use 2017 FDA/CLSI BPs after 1/1/2024

How do I know the date of an FDA update?

Sign up for email updates

During annual review of BPs (MIC.11380), review Notice of Updates



Notice of Updates

Share | Tweet | Linkedin | Email | Print

Sign up to receive FDA Recognized Antimicrobial STIC Breakpoints email notifications

For information regarding prior changes to the STIC webpages, see https://www.govinfo.gov/content/pkg/FR-2019-05-03/pdf/2019-09007.pdf

https://www.federalregister.gov/documents/2020/10/22/2020-23439/21st-century-cures-act-annual-compilation-of-notices-of-updates-from-the-susceptibility-test

Updates to Standards Recognition

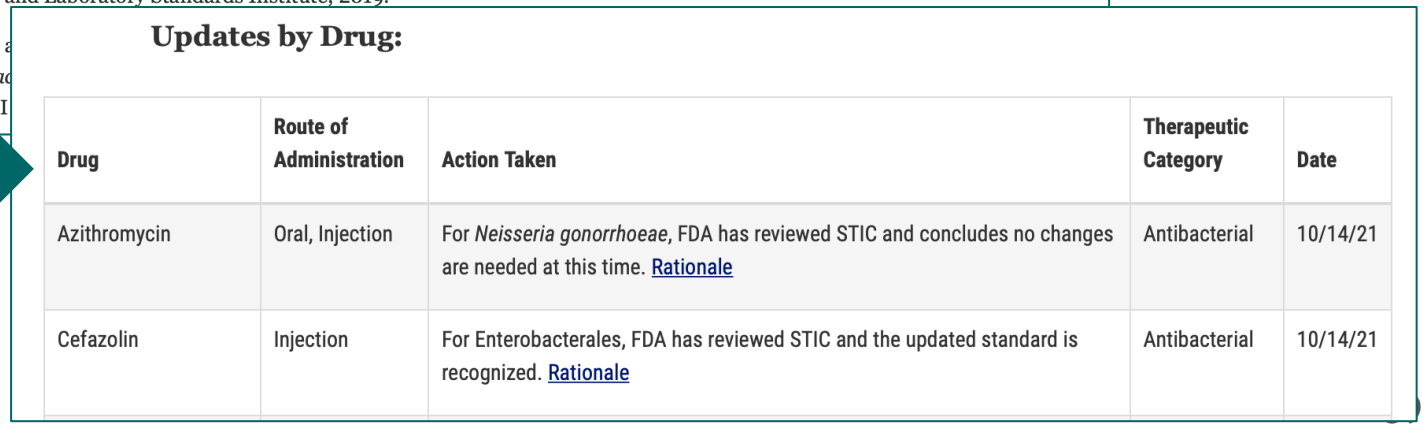
As of October 14, 2021, the following standards are no longer recognized:

Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing*. 29th ed. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2019.

Clinical a
Mycobac
ed. CLSI

Content current as of:
10/14/2021

Regulated Product(s)
Drugs



Updates by Drug:

Drug	Route of Administration	Action Taken	Therapeutic Category	Date
Azithromycin	Oral, Injection	For *Neisseria gonorrhoeae*, FDA has reviewed STIC and concludes no changes are needed at this time. Rationale	Antibacterial	10/14/21
Cefazolin	Injection	For Enterobacterales, FDA has reviewed STIC and the updated standard is recognized. Rationale	Antibacterial	10/14/21

https://www.fda.gov/drugs/development-resources/notice-updates

How do I know the date of an FDA update (cont.)?

Notice of Updates

Share | Tweet | Linkedin | Email | Print

Sign up to receive FDA Recognized Antimicrobial STIC Breakpoints email notifications

For information regarding prior changes to the STIC webpages, see https://www.govinfo.gov/content/pkg/FR-2019-05-03/pdf/2019-09007.pdf

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Clinical and Laboratory Standards Institute (CLSI). *Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard*. 2nd ed. CLSI guideline M24-A2. Wayne, PA: Clinical and Laboratory Standards Institute; 2011.

Content current as of:
10/14/2021

21st Century Cures Act: Annual Compilation of Notices of Updates From the Susceptibility Test Interpretive Criteria Web Page; Request for Comments

A Notice by the Food and Drug Administration on 10/22/2020

PUBLISHED DOCUMENT

Table 1—Notices of Updates to Recognized or Updated Susceptibility Test Interpretive Criteria (STIC) by Drug

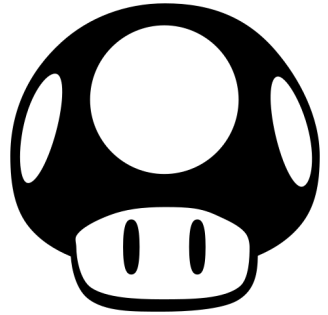
Drug	Route of administration	Action taken	Therapeutic category	Date
Azithromycin	Oral, Injection	For *Neisseria gonorrhoeae*, STIC are not recognized at this time. FDA review of these STIC is ongoing	Antibacterial	6/10/19
Cefiderocol	Injection	Added drug to antibacterial Susceptibility Test Interpretive Criteria web page. FDA identified STIC	Antibacterial	11/18/19
Ceftaroline fosamil	Injection	Typographical error corrected	Antibacterial	8/29/19
Ceftolozane Tazobactam	Injection	For Enterobacteriaceae, an exception to the recognized standard is provided for Disk Diffusion. For *Haemophilus influenzae*, the FDA-identified STIC are provided. STIC are based on dosing regimens that differ by the serious infection being treated, and this information is provided	Antibacterial	6/10/19

Updates prior to the most current BPs are available online, as a notice to the federal register.

If laboratory keeps up to date (ie, annual review), no need to dig back into these records.

https://www.fda.gov/drugs/development-resources/notice-updates

MIC.11385 (VUMC Approach)



Identify	Determine all breakpoints that do not meet CLSI or FDA standards, from MIC.11380 process.
Discuss	With commercial AST manufacturer, determine which BPs above are FDA cleared/not FDA cleared.
Plan	Is this a drug we need to test? Do we need to validate updated breakpoints? Or is verification appropriate?
Execute	Perform testing, update breakpoints.

How can the laboratory approach these?

1. Prioritize!

   What drugs are on formulary?
   How are drugs used clinically at your institution?
   What are your ASP initiatives?
   What are your resistance challenges?

   Most important:

   Discuss, discuss, discuss

VUMC and Enterobacterales BPs

VUMC identified the following Enterobacterales BPs issues:

Antimicrobial	Test System	Issue	Plan
Cefazolin (IV)	Phoenix	Use of non-FDA or CLSI BPs	IV cefazolin used often, Update
Cefazolin (IV)	Etest	Use of obsolete BPs	Discontinue test – rarely used
Cefepime	Phoenix	Use FDA BPs, differs from CLSI	Ok to use FDA BPs – only difference is "I" vs. "SDD" name to category
Ceftazidime	Phoenix	Use of obsolete BPs, system wasn't cleared by FDA for current FDA/CLSI BPs	Update to current CLSI/FDA BPs
Cefuroxime	Phoenix	Use of obsolete BPs, Phoenix not cleared by FDA for current FDA/CLSI BPs	Suppressed antimicrobial – not reported. No action.
Pip-tazo	Phoenix, Etest, Disk	Use of FDA BPs, differ from CLSI	Ok to use FDA BPs, but ASP desire to use CLSI → update!

For pip-tazo, utilized CDC/FDA AR Bank isolates (n=30) to validate BP → implemented.

VUMC and *P. aeruginosa* BPs

VUMC identified the following BP issues:

Antimicrobial	Test System	Issue	Plan
Cefepime	Phoenix	Use of current FDA BPs, differs from CLSI	OK to use FDA BPs – no action
Ciprofloxacin	Disk diffusion	Use of obsolete BPs (2018 CLSI)	Update to current CLSI/FDA BPs*
Levofloxacin	Disk diffusion	Use of obsolete BPs (2018 CLSI)	Update to current CLSI/FDA BPs*

*For ciprofloxacin and levofloxacin, disks not cleared with current FDA/CLSI BPs. Utilized CDC/FDA AR Bank isolates (n=30) to validate BPs → implement.

Part II: Making the updates

VUMC examples needing updates

Breakpoints	Primary Test system	FDA cleared on system?	Plan
Cefazolin Enterobacterales	Phoenix	No	Validate BPs
Ceftazidime Enterobacterales	Phoenix	Yes as of mid-2022	Verify BPs
Piperacillin-tazobactam Enterobacterales	Phoenix	No (not possible as FDA does not recognize CLSI)	Validate BPs
Ciprofloxacin and levofloxacin P. aeruginosa	Disk diffusion	Yes*	Verify BPs

Verify… Or validate Updated BPs?

Verification

- When updating BPs that are FDA cleared on your AST system
- Only possible for FDA BPs
- ”On label use" of AST system
- Minimal evaluation

Validation

- When updating BPs that are *not* FDA cleared on your AST system
- FDA BPs if AST system not yet cleared
  CLSI BPs if FDA does not recognize
- “Off label use” of AST system
- More extensive evaluation

Scenarios for Updating Breakpoints

(for drug previously verified/validated on your commercial AST system)

	Scenario	Your Action (suggestion)…
1	cASTs manufacturer updates BPs & clears through FDA by revising software; no changes to panel/card	Make appropriate changes to software and downstream activities (LIS, EHR)
2	cASTs manufacturer updates BPs & clears through FDA by adding dilutions and/or revising drug formulations	• **Verification** • Make appropriate changes to software and downstream activities (LIS, EHR)
3	cASTs manufacturer has NOT updated BPs (use of updated BPs by the laboratory would be “off-label”)	• **Validation** • Make appropriate changes to software and downstream activities (LIS, EHR)

Commercial AST system must use FDA BPs.

Check with manufacturer of your cASTs card/panel/software for breakpoint status.

Example validation plan

- Selected n=30 isolates of Enterobacterales with desired MIC ranges
  - We chose clinical isolates and did our own BMD
  - Forthcoming! CDC AR Bank Panel for validation purposes with known BMD MICs
- Score BMD results (CDC or other) by current CLSI BPs
- Score your system results by current CLSI BPs
- Evaluate:
  - VME (R by BMD, S by your system) → desire <3%
  - ME (S by BMD, R by your system) → desire <3%
  - mE (SDD by either but not by the other) → desire 10%

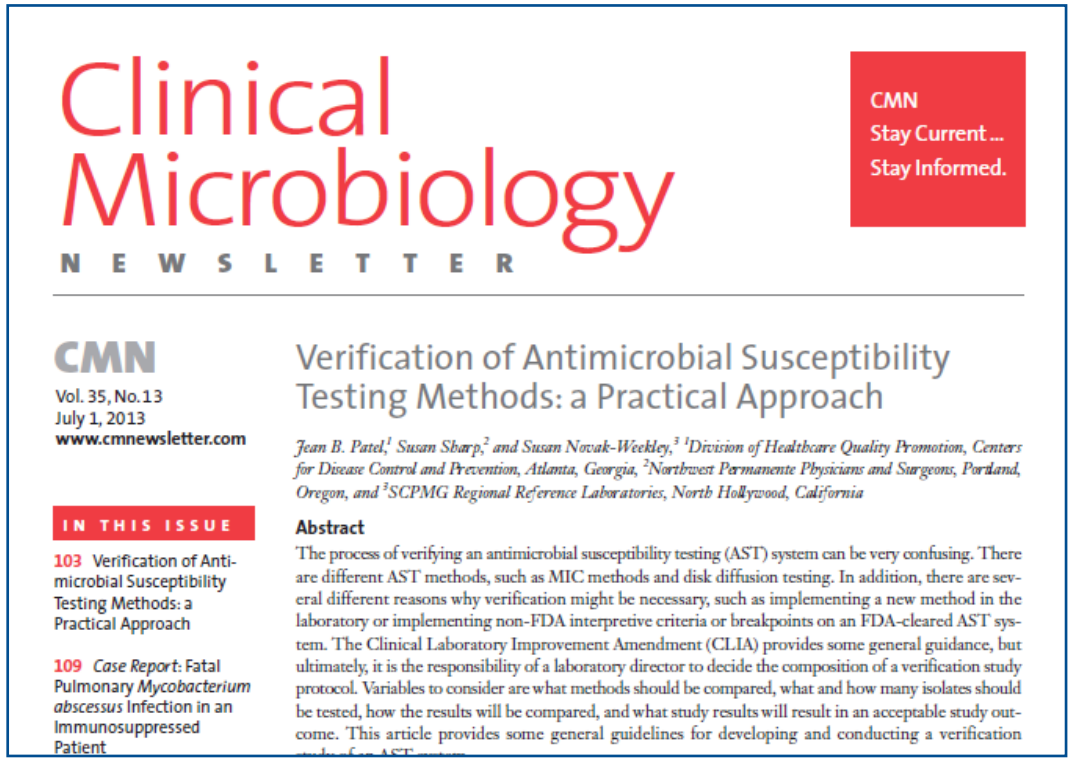
Thank you!

Questions?

Romney.Humphries@vumc.org

Resources for Verification

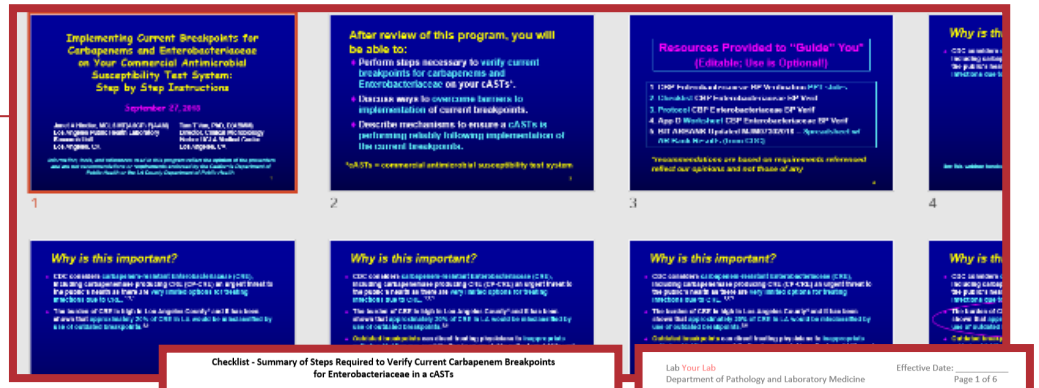
CLSI M52, 1st edition. Clinical Laboratory Standards Institute; 2016.

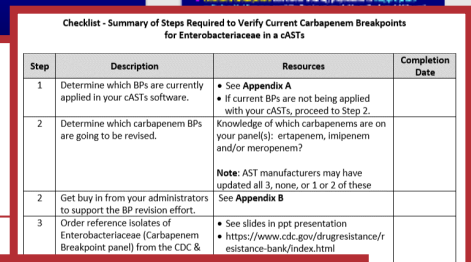


Patel, J.B., S. Sharp, and S Novak-Weekley. 2013. Clinical Microbiology Newsletter. Vol. 35 No. 13:103.

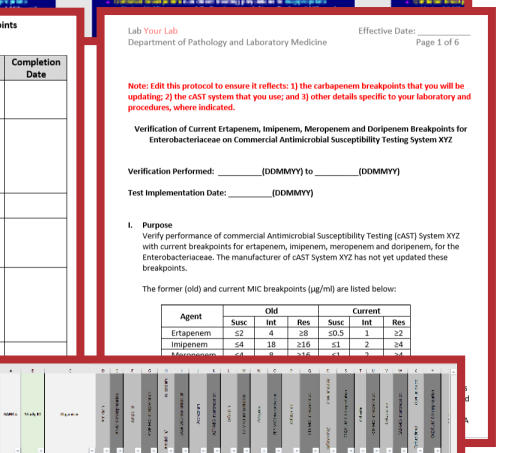
Resource for Verification of Current Breakpoints for Carbapenems and Enterobacterales

1. CBP Enterobacterales BP Verif_D PPT slides/audio
2. Checklist CBP Enterobacterales BP Verif_D
3. Protocol CBP Enterobacterales BP Verif_D
4. App D Worksheet CBP Enterobacterales BP Verif_D
5. BIT ARBANK Updated MJM07302018_D – Spreadsheet w/ AR Bank Results (from CDC)




Checklist - Summary of Steps Required to Verify Current Carbapenem Breakpoints for Enterobacteriaceae in a cASTs

Step	Description	Resources	Completion Date
1	Determine which BPs are currently applied in your cASTs software.	• See **Appendix A** • If current BPs are not being applied with your cASTs, proceed to Step 2.	
2	Determine which carbapenem BPs are going to be revised.	Knowledge of which carbapenems are on your panel(s): ertapenem, imipenem and/or meropenem? **Note**: AST manufacturers may have updated all 3, none, or 1 or 2 of these	
2	Get buy in from your administrators to support the BP revision effort.	See **Appendix B**	
3	Order reference isolates of Enterobacteriaceae (Carbapenem Breakpoint panel) from the CDC &	• See slides in ppt presentation • https://www.cdc.gov/drugresistance/resistance-bank/index.html	


Lab Your Lab
Department of Pathology and Laboratory Medicine
Effective Date: _____
Page 1 of 6

Note: Edit this protocol to ensure it reflects: 1) the carbapenem breakpoints that you will be updating; 2) the cAST system that you use; and 3) other details specific to your laboratory and procedures, where indicated.

Verification of Current Ertapenem, Imipenem, Meropenem and Doripenem Breakpoints for Enterobacteriaceae on Commercial Antimicrobial Susceptibility Testing System XYZ

Verification Performed: _____(DDMMYY) to _____(DDMMYY)

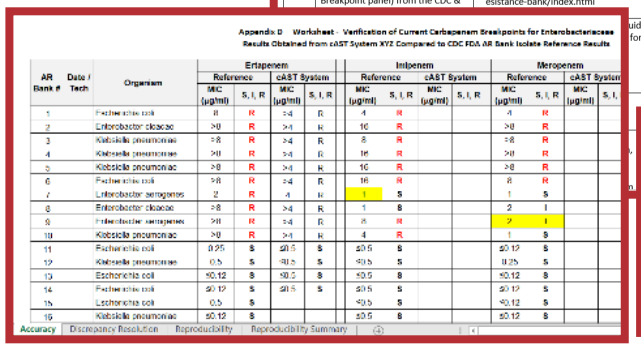
Test Implementation Date: _____(DDMMYY)

I. Purpose

Verify performance of commercial Antimicrobial Susceptibility Testing (cAST) System XYZ with current breakpoints for ertapenem, imipenem, meropenem and doripenem, for the Enterobacteriaceae. The manufacturer of cAST System XYZ has not yet updated these breakpoints.

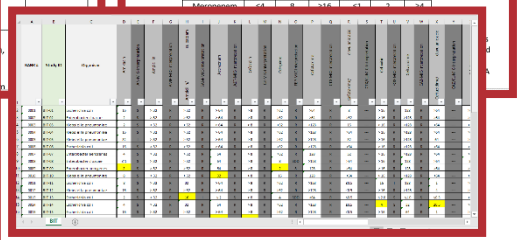
The former (old) and current MIC breakpoints (µg/ml) are listed below:

Agent	Old			Current		
	Susc	Int	Res	Susc	Int	Res
Ertapenem	≤2	4	≥8	≤0.5	1	≥2
Imipenem	≤4	18	≥16	≤1	2	≥4
Meropenem	≤4	8	≥16	≤1	2	≥4


Appendix D Worksheet - Verification of Current Carbapenem Breakpoints for Enterobacteriaceae
Results Obtained from cAST System XYZ Compared to CDC FDA AR Bank Isolate Reference Results

AR Bank #	Date / Tech	Organism	Ertapenem Reference MIC (µg/ml)	Ertapenem Reference S, I, R	Ertapenem cAST System MIC (µg/ml)	Ertapenem cAST System S, I, R	Imipenem Reference MIC (µg/ml)	Imipenem Reference S, I, R	Imipenem cAST System MIC (µg/ml)	Imipenem cAST System S, I, R	Meropenem Reference MIC (µg/ml)	Meropenem Reference S, I, R	Meropenem cAST System MIC (µg/ml)	Meropenem cAST System S, I, R
1		Escherichia coli	8	R	>4	R	4	R			4	R		
2		Enterobacter cloacae	>8	R	>4	R	16	R			>8	R		
3		Klebsiella pneumoniae	≤8	R	>4	R	8	R			≤8	R		
4		Klebsiella pneumoniae	>8	R	>4	R	16	R			>8	R		
5		Klebsiella pneumoniae	>8	R	>4	R	16	R			>8	R		
6		Escherichia coli	>8	R	>4	R	16	R			8	R		
7		Enterobacter aerogenes	2	R	4	R	1	S			1	S		
8		Enterobacter cloacae	>8	R	>4	R	1	S			2	I		
9		Enterobacter aerogenes	>8	R	>4	R	8	R			2	I		
10		Klebsiella pneumoniae	>8	R	>4	R	4	R			1	S		
11		Escherichia coli	0.25	S	≤0.5	S	≤0.5	S			≤0.12	S		
12		Klebsiella pneumoniae	0.5	S	≤0.5	S	≤0.5	S			0.25	S		
13		Escherichia coli	≤0.12	S	≤0.5	S	≤0.5	S			≤0.12	S		
14		Escherichia coli	≤0.12	S	≤0.5	S	≤0.5	S			≤0.12	S		
15		Escherichia coli	0.5	S			≤0.5	S			≤0.12	S		
16		Klebsiella pneumoniae	≤0.12	S			≤0.5	S			≤0.12	S		

Accuracy | Discrepancy Resolution | Reproducibility | Reproducibility Summary



California Department of PublicHealth

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Home | Programs | Center for Health Care Quality | Healthcare Associated Infections | CA_ARLN

HEALTHCARE-ASSOCIATED INFECTIONS (HAI) PROGRAM

California Antimicrobial Resistance Lab-Epi Alliance

Can be used as guide for verification of other BPs.

https://www.cdph.ca.gov/Programs/CHCQ/HAI/Pages/CA_ARLN.aspx

Resources to laboratories from CAP

Webinars

- On-Demand CLSI and CAP Webinar 2022 (Jan 11, 2022)
- Upcoming webinar from CAP

MIC.11385 FAQs and templates

- Accessible in e-LAB Solutions Suite → Accrediation Resources → Checlist Requirement Q&A → Microbiology