Out with the Old, In With the New:
CAP Requirements to Use Current Breakpoints

Carol A. Rauch, MD, PhD, FCAP

Adjunct Associate Professor of
Pathology, Microbiology, & Immunology

First Coast ID/CM Symposium ◊ Jacksonville, FL

February 17-18, 2023

Disclosures

- Financial: I have no financial conflicts of interest to disclose.
- Related to discussion of CAP requirements:
  - Recent member CAP Microbiology Committee, current member CAP Checklists Committee
  - Member of APHL-ASM AR Laboratory Workgroup
- By habit (from my time with CDC AR Laboratory Network):
  - Opinions expressed are my own and do not necessarily reflect those of the U.S. federal government

Learning objectives

At the conclusion of this presentation, learners will be able to:

1. Recognize how using obsolete breakpoints for AST adversely impacts patient care and public health
2. Delineate steps to achieve compliance with CAP requirements to document breakpoints in use, discontinue using obsolete breakpoints, and communicate with partners in managing antimicrobial resistance
3. Make more informed choices for effective therapy using AST results

AST = antimicrobial susceptibility testing
CAP = College of American Pathologists

- Who?
  - If you generate or consume laboratory AST results, you must understand how variable use of breakpoints impacts your professional practice
- Why?
  - Efforts to care for patients and address AMR are hindered by variable laboratory practices related to a regulatory gap for AST
- How?
  - There are new breakpoint-related requirements for CAP-accredited laboratories
- When?
  - Now: you must know what breakpoints are applied in your laboratory
  - Beginning Jan 1, 2024, you may no longer use an unrecognized bp
  - You must review annually to remain current

AMR = antimicrobial resistance, bp = breakpoint

Antibiotic Resistance Threats in the United States 2019

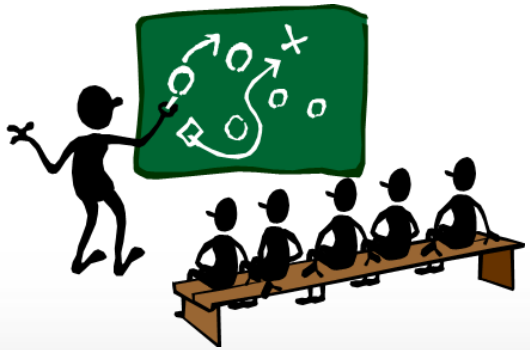
- Report updated from first version in 2013 with revised death and infection estimates
  - AR threat overall greater
  - deaths decreased
- Bottom line:
  - efforts to prevent infections and transmission are working, more effort is needed

www.cdc.gov/DrugResistance/Biggest-Threats.html
https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

The AR Threat in the United States

- Per year, more than 2,800,000 AR infections and 35,000 deaths
  - *Clostridioides difficile* infections (related to antibiotic use) accounts for more
- Rates *vs* numerators?
- Each AR infection can be devastating for individual patient, and can serve as source for transmission

You are the team that defends us



Urgent Threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris (C. auris)*
- *Clostridioides difficile (C. difficile)*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae (N. gonorrhoeae)*

Serious Threats

- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae
- Vancomycin-resistant *Enterococci* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa (P. aeruginosa)*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae (S. pneumoniae)*
- Drug-resistant Tuberculosis (TB)

Concerning Threats

- Erythromycin-resistant group A *Streptococcus*
- Clindamycin-resistant group B *Streptococcus*

Watch List

- Azole-resistant *Aspergillus fumigatus (A. fumigatus)*
- Drug-resistant *Mycoplasma genitalium (M. genitalium)*
- Drug-resistant *Bordetella pertussis (B. pertussis)*

Threats classified according to:

- Clinical and economic impact
- Incidence, 10-year projected incidence
- Transmissibility
- Availability of effective antibiotics
- Barriers to prevention

CDC Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.

International Perspective:
"Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis"

- Authors: "Antimicrobial Resistance Collaborators" (many!)
  - Bill and Melinda Gates Foundation, Wellcome Trust, UK Dept Health and Social Care
- Sources of data: systematic literature reviews, hospital systems, surveillance systems, other
- Assessment: used predictive statistical modeling to comprehensively estimate deaths and disability-adjusted life-years for all regions
- Estimates: ~ 4.95M deaths associated with bacterial AMR, with ~ 1.27M deaths directly attributable

Lancet. 2022; 399: 629-655.

"Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis"

- AMR is a leading cause of death around the world
  - Highest burden in low-resource settings
  - In high-income super-region (including U.S.), roughly half of fatal AMR burden due to *S. aureus* and *E. coli*
- Global Burden of Diseases 2019 ranking leading causes of death
  - "Counterfactual" no infection – AMR infection is 3rd (after ischemic heart dz, stroke)
  - "Counterfactual" susceptible infection – AMR infection is 12th (ahead of HIV, malaria)

Lancet. 2022; 399: 629-655.

We need you

Roles and Responsibilities

- The clinical laboratory supports patient care & public health
  - Organism identifications, susceptibility test results inform patient management
  - Results, isolates may also be analyzed in public health laboratories
  - Results may trigger action by infection prevention, health departments
- A working knowledge of partner responses is helpful
  - Infectious Diseases specialists, Infection Preventionists, Pharmacists, Epidemiologists, PHLs, CDC, APHL, others … everyone is needed
  - This team cannot effectively respond unless the initial clinical laboratory accurately recognizes and reports resistance … we start here

Do we have a problem on the front line?

RM Humphries & JA Hindler* (2016):

- "Antimicrobial resistance is discovered almost exclusively through frontline testing by the clinical laboratory…"
- "In the backdrop of these national efforts is an emerging and neglected struggle by the clinical laboratory to generate accurate and actionable antimicrobial susceptibility reports."

Q: Does your clinical laboratory report AST results correctly?

- Don't they all? What does it take to be sure?

*Note: Amid the work of many, I would especially like to acknowledge these microbiologists for their important contributions on this topic.

*RM Humphries & JA Hindler. "Emerging Resistance, New Antimicrobial Agents … but No Tests! The Challenge of Antimicrobial Susceptibility Testing in the Current US Regulatory Landscape." CID 2016: 63: 83-88.

Do we have a problem on the front line?

- College of American Pathologists Microbiology Committee members concerned about use of breakpoints in clinical laboratories
- Proficiency testing (PT) results indicated that some laboratories may be using obsolete breakpoints
  - Same organism evaluated in many laboratories, some interpret as susceptible and others as resistant
  - What is going on and does it impact patient safety?
  - Labs commonly use FDA-cleared commercial AST devices … isn't that enough?
- We needed to assess the status of participant testing practices

College of American Pathologists Investigation

- Supplemental voluntary questionnaire was distributed together with DB-2019 (Bacteriology) PT survey materials
- For seven “drug/bug” combinations, asked participant laboratories whether they were using current breakpoints
  - Combinations chosen because breakpoints had changed
  - Timing of change varied, ranging 2010 to 2019
  - If laboratory answered that they were not using current bp, they were asked to comment on reasons

CAP Investigation of Laboratory Practices for Updated Breakpoints

- Reasons for a change in breakpoints include:
  - identification of new resistance
  - updated pharmacokinetic/pharmacodynamic (PK/PD) data
  - updated dosing regimens in use
  - updated data on clinical outcomes available
- In all cases, updated breakpoints had been lowered
  - a particular result considered “S” with an old breakpoint is now considered “R” with the new breakpoint
  - if we were comparing test devices, falsely reporting as susceptible would count as a “Very Major Error”

Updated Breakpoints

- For example, carbapenem breakpoints were lowered in 2010 for Enterobacterales after carbapenemases had been detected
- "CRE" is highly significant for infected patient, need to prevent transmission
- We needed more reliable detection than phenotypic tests provided
- CLSI M100 had extra revisions in 2010 (M100-S20-U, M100-S20 June 2010 update), a long time ago

However, …

… not all the parts are synchronized or keeping up.

CRE = carbapenem resistant Enterobacterales
CLSI = Clinical and Laboratory Standards Institute

What happens with updated breakpoints?

- Standards Development Organizations (SDO) that set breakpoints include FDA, CLSI, EUCAST
- As new data becomes available and is reviewed by SDO, a breakpoint may be revised (*e.g.,* CLSI)
- FDA reviews CLSI rationale documents that support the change, they may then approve and publish revised BP on their website
  - prior BP is no longer recognized by FDA
  - "obsolete" BP is a BP that is no longer currently recognized by SDO
- FDA may/may not adopt the change, time frame may vary

FDA = Food & Drug Administration; EUCAST = European Committee on Antimicrobial Susceptibility Testing

What is the regulatory gap?

- Manufacturers of cAST are required to use FDA BPs
  - devices have been marketed for use in clinical laboratories using FDA BPs current at the time of FDA clearance of the device
- **There is currently no regulatory mechanism requiring manufacturers to update breakpoints on their devices**
- For manufacturers it is expensive to change, timing can be tricky, risks include losing clinical claims for organism groups
- Commercial panels have certain drug concentrations and systems optimized to perform for BPs at the time of (prior) clearance
  - updating may involve new dilutions, new formulations

Open Forum Infectious Diseases

MAJOR ARTICLE

Raising the Bar: Improving Antimicrobial Resistance Detection by Clinical Laboratories by Ensuring Use of Current Breakpoints

Patricia J. Simner,[1] Carol A. Rauch,[2] Isabella W. Martin,[3] Kaede V. Sullivan,[4] Daniel Rhoads,[5] Robin Rolf,[6] Rosemary She,[7] Rhona J. Souers,[6] Christina Wojewoda,[8] and Romney M. Humphries[9]

[1]Johns Hopkins Medical Institute, Baltimore, Maryland, USA, [2]Vanderbilt University, Nashville, Tennessee, USA, [3]Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA, [4]Temple University Hospital, Philadelphia, Pennsylvania, USA, [5]Cleveland Clinic, Cleveland, Ohio, USA, [6]College of American Pathologists, Chicago, Illinois, USA, [7]University of Southern California, Los Angeles, California, USA, [8]University of Vermont Medical Center, Burlington, Vermont, USA, and [9]Vanderbilt University Medical Center, Nashville, Tennessee, USA

Background. Antimicrobial resistance (AMR) is a pressing global challenge detected by antimicrobial susceptibility testing (AST) performed by clinical laboratories. AST results are interpreted using clinical breakpoints, which are updated to enable accurate detection of new and emerging AMR. Laboratories that do not apply up-to-date breakpoints impede global efforts to address the AMR crisis, but the extent of this practice is poorly understood.

Methods. A total of 1490 clinical laboratories participating in a College of American Pathologists proficiency testing survey for bacterial cultures were queried to determine use of obsolete breakpoints.

Results. Between 37.9% and 70.5% of US laboratories reported using obsolete breakpoints for the antimicrobials that were queried. In contrast, only 17.7%–43.7% of international laboratories reported using obsolete breakpoints ($P < .001$ for all comparisons). Use of current breakpoints varied by AST system, with more laboratories reporting use of current breakpoints in the US if the system had achieved US Food and Drug Administration clearance with current breakpoints. Among laboratories that indicated use of obsolete breakpoints, 55.9% had no plans to update to current standards. The most common reason cited was manufacturer-related issues (51.3%) and lack of internal resources to perform analytical validation studies to make the update (23.4%). Thirteen percent of laboratories indicated they were unaware of breakpoint changes or the need to update breakpoints.

Conclusions. These data demonstrate a significant gap in the ability to detect AMR in the US, and to a lesser extent internationally. Improved application of current breakpoints by clinical laboratories will require combined action from regulatory agencies, laboratory accreditation groups, and device manufacturers.

Keywords. antimicrobial resistance; breakpoints; laboratory testing; susceptibility testing.

CAP Investigation

Simner, *et al*. Open Forum Infectious Diseases. 2022.

Table 1. Clinical Breakpoints Evaluated by the College of American Pathologists Survey to Laboratories Participating in Bacteriology Proficiency Testing Program

Organism	Antimicrobial	Year BP Updated by CLSI[a]	Rationale for BP Update [4]	Obsolete Susceptible BP	Current Susceptible BP
Enterobacterales	Ceftazidime	2010	A public health need was identified due to the spread of AMR (ie, ESBL producers) Revised BPs simplified testing and eliminated the need for additional tests to detect AMR	≤8 µg/mL	≤4 µg/mL
Enterobacterales	Ceftriaxone	2010		≤8 µg/mL	≤1 µg/mL
Enterobacterales	Ciprofloxacin	2019	New PK/PD data indicated the previous breakpoints were set too high	≤1 µg/mL	≤0.25 µg/mL
Enterobacterales	Levofloxacin	2019	Revised BPs allowed harmonization across SDOs	≤2 µg/mL	≤0.5 µg/mL
Enterobacterales	Meropenem	2010	A public health need was identified related to recognition of a new AMR mechanism (ie, carbapenemase genes) Revised BPs simplified testing and eliminated the need for additional tests to detect AMR	≤4 µg/mL	≤1 µg/mL
Pseudomonas aeruginosa	Piperacillin-tazobactam	2012	New data demonstrated poor prediction of clinical response using existing breakpoints	≤64/4 µg/mL	≤16/4 µg/mL
Acinetobacter baumannii	Imipenem	2014	New data demonstrated poor prediction of clinical response using existing breakpoints	≤4 µg/mL	≤2 µg/mL

Abbreviations: AMR, antimicrobial resistance; BP, breakpoint; CLSI, Clinical and Laboratory Standards Institute; ESBL, extended-spectrum β-lactamase; PK/PD, pharmacokinetic/pharmacodynamic; SDO, standards development organization.

[a]US Food and Drug Administration recognition of the CLSI breakpoints was generally 1–3 years after publication by CLSI, although exact dates prior to 2018 are unavailable.

Simner, *et al*. Open Forum Infectious Diseases. 2022.

Table 3. Current Breakpoint Usage by Laboratory Location (United States Versus International)

Organism	Antimicrobial Agent	United States		International		*P* Value, Difference Between US and International
		Total No. of Laboratories	Current Breakpoints, No. (%)	Total No. of Laboratories	Current Breakpoints, No. (%)	
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

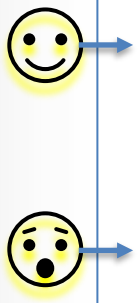
- Use of current breakpoints is variable
  - fewer labs had updated for more recent changes (*e.g.*, FQ in 2019)
- International laboratories were more likely to use current breakpoints
  - manufacturers are in a different regulatory environment

Simner, *et al*. Open Forum Infectious Diseases. 2022.

Table 5. Comment Summary for Laboratories Unsure of the Breakpoints They Applied or if They Used Obsolete Breakpoints by Location

Reason	All (N = 918)	United States (n = 835)	International (n = 83)
Efforts to use or implement current breakpoints underway	405 (44.1)	372 (44.6)	33 (39.8)
Plan to update, in progress	188 (46.4)	181 (48.7)	7 (21.2)
Not applicable because do not report, use alternate method, or send to reference laboratory	128 (31.6)	102 (27.4)	26 (78.8)
Changing panels or instruments	55 (13.6)	55 (14.8)	0 (0.0)
Validation testing not completed but underway	34 (8.4)	34 (9.1)	0 (0.0)
Ongoing use of obsolete breakpoints, no current revisions in progress	513 (55.9)	463 (55.4)	50 (60.2)
Manufacturer-related issues	263 (51.3)	232 (50.1)	31 (62.0)
Resource limitations of staff, time, organisms, guidance, laboratory information system issues, cost	120 (23.4)	112 (24.2)	8 (16.0)
Overlooked or unaware of breakpoint change or need to update	68 (13.3)	57 (12.3)	11 (22.0)
Facility does not support	30 (5.8)	30 (6.5)	0 (0.0)
Not done, under review for a variety of concerns	28 (5.4)	28 (6.0)	0 (0.0)
Do not want or intend to update	4 (0.8)	4 (0.8)	0 (0.0)

Data are presented as No. (%).



Efforts to use or implement updated breakpoints 44%

Ongoing use of obsolete breakpoints 56%

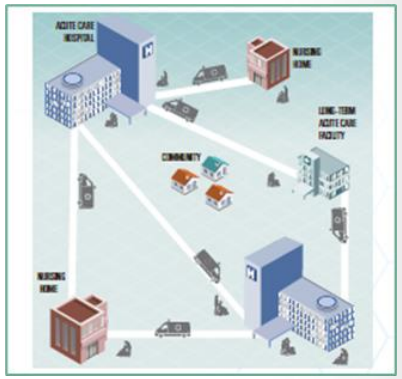
- Most common reason related to manufacturer
- Other reasons: lack of resources, support, awareness

Simner, *et al*. Open Forum Infectious Diseases. 2022.

We have some housecleaning to do!

Impact of using obsolete breakpoints

- Possible consequence of using obsolete breakpoints:
  - Therapy based on organism reported susceptible, failure to clear infection
  - Failure to trigger cascade reporting of additional AST results
  - Inaccurate cumulative antibiogram data supporting clinical practice guidelines, stewardship efforts, formulary decisions
  - Undetected resistant organism transmission to other patients due to lack of appropriate precautions
  - Patient transfer to another facility, undetected spread at new location
- Impact of clinical laboratories using different breakpoints:
  - Inaccurate rates of resistance, not comparing “apples to apples” in public health systems



AR Threats Report 2019

Improving awareness in clinical laboratories

- Published literature, webinars, newsletters, educational efforts increased over recent years, but message was not reaching everyone
- CAP included an **educational statement** in the front of PT participant summary reports, may have been overlooked or significance not clear
  - A “PSA for the PSR”
  - May have been overlooked

CAP Participant Summary Report
Bacteriology survey DB-2021 educational comment

"Clinical and Laboratory Standards Institute (CLSI) has been updating breakpoints since 2010 and a listing of the revisions can be found in the front of CLSI M100-Ed31 "Performance Standards for Antimicrobial Susceptibility Testing (AST)" (January 2021). FDA has been updating breakpoints as well; however, not all CLSI and FDA breakpoints are identical at this time. FDA breakpoints are now available on the Antibacterial Susceptibility Test Interpretive Criteria Website, https://www.fda.gov/drugs/developmentresources/antibacterial-susceptibility-test-interpretive-criteria. Federal regulations require manufacturers of AST devices to use the FDA (and not CLSI) breakpoints. For those antimicrobial agent-organism combinations that have been updated by the FDA, manufacturers are in the process of updating their system's breakpoints. Clinical laboratories should check with technical services to determine when the updated breakpoints will be available on their system's software. If the breakpoints have not been updated on their system, the laboratory can implement them following a verification study. Currently, clinical laboratories have the option to use either CLSI or FDA breakpoints and either will be acceptable to CAP."

Improving awareness in clinical laboratories

- Extensive discussions about how to improve AST results and patient safety ultimately led to laboratory accreditation requirements that were first published in the 2021 CAP microbiology checklist:

  MIC.11380 (know what breakpoints you are using)

  MIC.11385 (use current breakpoints)

***REVISED** 10/24/2022*

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

For antimicrobial susceptibility testing (AST) 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.

NOTE: This checklist item applies to all antibacterial, antifungal, and antimycobacterial agents tested in the laboratory. The same criteria applied to clinical test results must be used for proficiency testing results.

The laboratory may use interpretive criteria from standards development organizations such as Clinical and Laboratory Standards Institute (CLSI) or European Committee on Antimicrobial Susceptibility Testing (EUCAST), the FDA, or in rare instances, validated institution-specific criteria.

The source of the breakpoints applied to interpret AST results must be documented for both manual and automated antimicrobial susceptibility testing methods, including the reference with the year it was published (eg, CLSI M100-S32, 2022). For automated susceptibility testing systems, laboratories may contact the manufacturer to understand the breakpoints applied by the automated expert rules programmed into the system for the test panels in use, if not already known.

Criteria must be reviewed by the laboratory and with the antimicrobial stewardship program in the institution (if applicable) annually. The records of the review must be available.

Evidence of Compliance:

- ✓ Listing of antimicrobial susceptibility test interpretive criteria applied to test results and the specific source document for these **AND**
- ✓ Patient reports with reporting of antimicrobial agents following written protocol **AND**
- ✓ Records of annual breakpoint review **AND**
- ✓ Proficiency testing susceptibility results following written policy

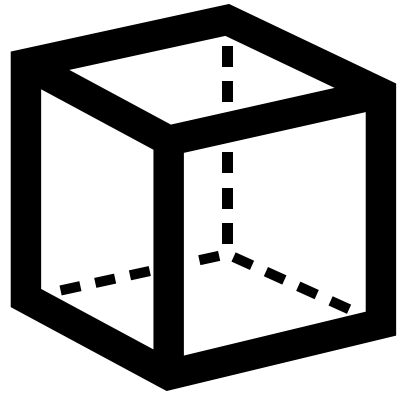
MIC.11380

"Know your breakpoints"

- Applies to bacteria, fungi, mycobacteria
- Phase II requirement
- Can use CLSI, EUCAST, FDA (or rarely, institution-specific bp's with documentation)
- Do not have to use the same source of bp's for all
- Applies to manual and automated methods
- Must be reviewed annually, including stewardship team

CAP Microbiology checklist 10/24/2022, with permission

In other words, this shouldn't be a black box



Bad news: This will take time and effort

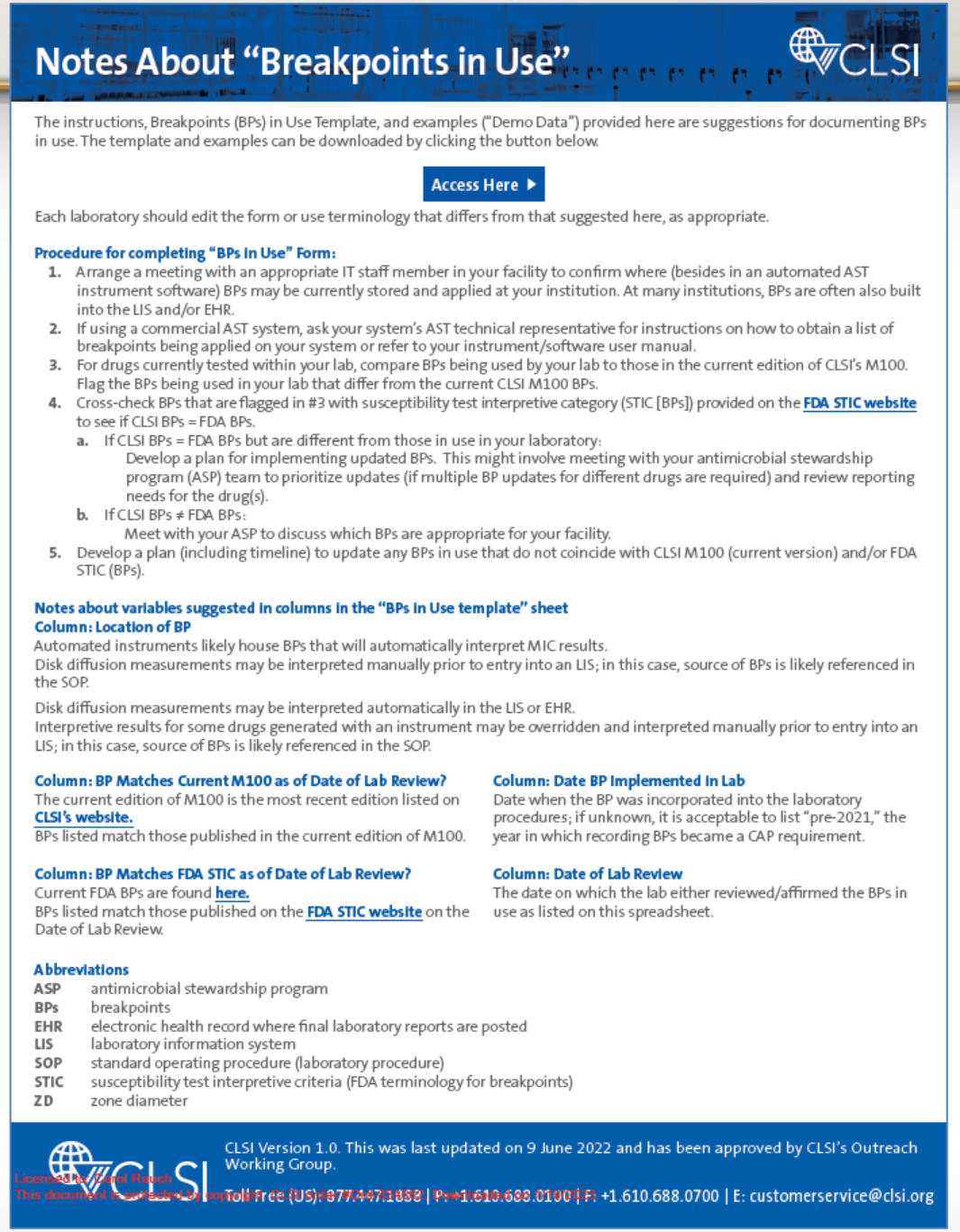
Good news: The effort is worthwhile, and there is help available

MIC.11380

"Know your breakpoints"

CLSI Outreach Working Group has prepared free step-by-step tools to assist laboratories needing to:

- Locate and identify breakpoints applied, document their source (with year)
- Determine the status of these breakpoints as current or obsolete (usually will compare CLSI M100 and FDA STIC)
- Document this review with date (CAP does not dictate how this all must be done)



Notes About "Breakpoints in Use"

CLSI

The instructions, Breakpoints (BPs) in Use Template, and examples ("Demo Data") provided here are suggestions for documenting BPs in use. The template and examples can be downloaded by clicking the button below.

Access Here ▶

Each laboratory should edit the form or use terminology that differs from that suggested here, as appropriate.

Procedure for completing "BPs in Use" Form:

1. Arrange a meeting with an appropriate IT staff member in your facility to confirm where (besides in an automated AST instrument software) BPs may be currently stored and applied at your institution. At many institutions, BPs are often also built into the LIS and/or EHR.
2. If using a commercial AST system, ask your system's AST technical representative for instructions on how to obtain a list of breakpoints being applied on your system or refer to your instrument/software user manual.
3. For drugs currently tested within your lab, compare BPs being used by your lab to those in the current edition of CLSI's M100. Flag the BPs being used in your lab that differ from the current CLSI M100 BPs.
4. Cross-check BPs that are flagged in #3 with susceptibility test interpretive category (STIC [BPs]) provided on the FDA STIC website to see if CLSI BPs = FDA BPs.
   a. If CLSI BPs = FDA BPs but are different from those in use in your laboratory:
      Develop a plan for implementing updated BPs. This might involve meeting with your antimicrobial stewardship program (ASP) team to prioritize updates (if multiple BP updates for different drugs are required) and review reporting needs for the drug(s).
   b. If CLSI BPs ≠ FDA BPs:
      Meet with your ASP to discuss which BPs are appropriate for your facility.
5. Develop a plan (including timeline) to update any BPs in use that do not coincide with CLSI M100 (current version) and/or FDA STIC (BPs).

Notes about variables suggested in columns in the "BPs in Use template" sheet

Column: Location of BP

Automated instruments likely house BPs that will automatically interpret MIC results.
Disk diffusion measurements may be interpreted manually prior to entry into an LIS; in this case, source of BPs is likely referenced in the SOP.

Disk diffusion measurements may be interpreted automatically in the LIS or EHR.
Interpretive results for some drugs generated with an instrument may be overridden and interpreted manually prior to entry into an LIS; in this case, source of BPs is likely referenced in the SOP.

Column: BP Matches Current M100 as of Date of Lab Review?

The current edition of M100 is the most recent edition listed on CLSI's website.
BPs listed match those published in the current edition of M100.

Column: Date BP Implemented in Lab

Date when the BP was incorporated into the laboratory procedures; if unknown, it is acceptable to list "pre-2021," the year in which recording BPs became a CAP requirement.

Column: BP Matches FDA STIC as of Date of Lab Review?

Current FDA BPs are found here.
BPs listed match those published on the FDA STIC website on the Date of Lab Review.

Column: Date of Lab Review

The date on which the lab either reviewed/affirmed the BPs in use as listed on this spreadsheet.

Abbreviations

ASP	antimicrobial stewardship program
BPs	breakpoints
EHR	electronic health record where final laboratory reports are posted
LIS	laboratory information system
SOP	standard operating procedure (laboratory procedure)
STIC	susceptibility test interpretive criteria (FDA terminology for breakpoints)
ZD	zone diameter

CLSI Version 1.0. This was last updated on 9 June 2022 and has been approved by CLSI's Outreach Working Group.

Toll Free (US): 877.447.1888 | P: +1.610.688.0100 | F: +1.610.688.0700 | E: customerservice@clsi.org

https://clsi.org/standards/products/microbiology/companion/bpiu/

“Breakpoints in Use” from CLSI

Instructions

Notes About “Breakpoints in Use”

CLSI

The instructions, Breakpoints (BPs) in Use Template, and examples ("Demo Data") provided here are suggestions for documenting BPs in use.

Each laboratory should edit the form or use terminology that differs from that suggested here, as appropriate.

Procedure for completing “BPs in Use” Form:

1. Arrange a meeting with an appropriate IT staff member in your facility to confirm where (besides in an automated AST instrument software) BPs may be currently stored and applied at your institution. At many institutions, BPs are often also built into the LIS and/or EHR.
2. If using a commercial AST system, ask your system’s AST technical representative for instructions on how to obtain a list of breakpoints being applied on your system or refer to your instrument/software user manual.
3. For drugs currently tested within your lab, compare BPs being used by your lab to those in the current edition of CLSI's M100. Flag the BPs being used in your lab that differ from the current CLSI M100 BPs.
4. Cross-check BPs that are flagged in #3 with BPs provided on the FDA susceptibility test interpretive category (STIC [BPs]) website to see if CLSI BPs = FDA BPs.
   https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria
   a. If CLSI BPs = FDA BPs but are different from those in use in your laboratory:
      Develop a plan for implementing updated BPs. This might involve meeting with your antimicrobial stewardship program (ASP) team to prioritize updates (if multiple BP updates for different drugs are required) and review reporting needs for the drug(s).
   b. If CLSI BPs ≠ FDA BPs:
      Meet with your ASP to discuss which BPs are appropriate for your facility.
5. Develop a plan (including timeline) to update any BPs in use that do not coincide with CLSI M100 (current version) and/or FDA STIC (BPs).

Notes about variables suggested in columns in the "BPs in Use template" sheet

Column: Location of BP

Automated instruments likely house BPs that will automatically interpret MIC results.

Disk diffusion measurements may be interpreted manually prior to entry into an LIS; in this case, source of BPs is likely

Instructions | BPs in Use template | Demo Data

Demo data using template

Antimicrobial Agent	Organism/Group	Test System	Interpretive Categories and MIC BPs (µg/mL) or Zone Diameter BPs (mm)				Location of BP (instrument/ LIS/SOP/EHR)	BP matches current M100 as of lab review date?	BP matches FDA STIC as of lab review date?	Date BPs implemented in lab	Date of lab review	Comments/Action Plan
			Susceptible, MIC ≤ or ZD ≥	Susceptible Dose-Dependent	Intermediate	Resistant, MIC ≥ or ZD ≤						
Cefepime	Enterobacterales	Commercial automated device	2	4-8	n/a	16	LIS	Yes	No	Pre-2021	5/12/2022	Instrument follows FDA STIC, categorizing 4-8 µg/mL as Intermediate. LIS converts intermediate to CLSI SDD categorization.
Cefepime	Enterobacterales	Disk diffusion	25	19-24	n/a	18	EHR	Yes	No	Pre-2021	5/12/2022	
Cefepime	*P. aeruginosa*	Commercial automated device	8	n/a	16	32	LIS	Yes	No	Pre-2021	5/12/2022	
Cefepime	*P. aeruginosa*	Disk diffusion	18	n/a	15-17	14	EHR	Yes	No	Pre-2021	5/12/2022	
Ceftazidime	Enterobacterales	Commercial automated device	8	n/a	16	32	LIS	No	No	Pre-2021	5/12/2022	Obsolete BP, must update; see validation plan. Antimicrobial not routinely reported. Currently test by disk diffusion if requested.
Ceftazidime	Enterobacterales	Disk diffusion	21	n/a	18-20	17	EHR	Yes	Yes	Pre-2021	5/12/2022	
Ceftazidime	*P. aeruginosa*	Commercial automated device	8	n/a	16	32	LIS	Yes	No	Pre-2021	5/12/2022	
Ceftazidime	*P. aeruginosa*	Disk diffusion	18	n/a	15/17	14	EHR	Yes	No	Pre-2021	5/12/2022	
Ciprofloxacin	Enterobacterales	Commercial automated device	0.25	n/a	0.5	1	LIS	Yes	Yes	Pre-2021	5/12/2022	For Enterobacterales except *Salmonella* spp. Panel concentrations not low enough for use with *Salmonella* BPs.
Ciprofloxacin	Enterobacterales	Disk diffusion	26	n/a	22-25	21	EHR	Yes	Yes	Pre-2021	5/12/2022	
Ciprofloxacin	Salmonella spp.	Gradient strip	0.06	n/a	0.12-0.5	1	SOP	Yes	Yes	Pre-2021	5/12/2022	
Ciprofloxacin	*P. aeruginosa*	Commercial automated device	0.5	n/a	1	2	LIS	Yes	Yes	Pre-2021	5/12/2022	
Ciprofloxacin (direct blood	*P. aeruginosa*	Disk diffusion	23	n/a	18-22	17	EHR	Yes	No	5/3/2022	5/12/2022	

Instructions | BPs in Use template | Demo Data

https://clsi.org/standards/products/microbiology/companion/bpiu/

Developed by CLSI Outreach Working Group, available for free

“Breakpoints in Use” from CLSI

- The BPIU is free of charge, but currently not available through a simple link
  - “Access Here” button will not work as a hot link in from the slide
- Access involves signing in to CLSI account, searching for BPIU, and going through the process to “purchase” it

Back to obsolete breakpoints:

- Obsolete breakpoints (interpretive criteria) are those that are not currently recognized by FDA or other SDO (standards development organization, CLSI or EUCAST)
- A laboratory using obsolete breakpoints likely reflects implementation a long time ago
  - before resistance was in widespread circulation
  - “set it and forget it”
  - before dosing regimens in common use changed
- **Use of obsolete breakpoints will overcall susceptibility, undercall resistance, and will no longer be acceptable in CAP-accredited labs**

***NEW/REVISED** 10/24/2022*

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. New breakpoints are implemented within three years of the date of publication by the FDA for laboratories subject to US regulations, or within three years of publication by CLSI, EUCAST or other standards development organization (SDO) for laboratories not subject to US regulations.

NOTE 1: For laboratories subject to US regulations, a breakpoint is considered obsolete three years after publication of an update by the FDA, though the laboratory may use currently accepted breakpoints from other SDOs with validation to support use. SDOs that develop breakpoints include the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Whether using breakpoints from the FDA or other SDOs, US laboratories must, at a minimum, adopt the change within three years of the official publication date of the updated breakpoint by the FDA.

NOTE 2: For laboratories not subject to US regulations, a breakpoint is considered obsolete three years after publication of an update by the SDO used by the laboratory. Laboratories must, at minimum, adopt the change within three years of the official publication date of the updated breakpoint by the SDO.

NOTE 3: Not all FDA-cleared susceptibility test systems apply current FDA-recognized breakpoints. Laboratories must determine if the breakpoints applied by their system are current and if they are not, validate changes to breakpoints as needed prior to use in patient result interpretation. Laboratories may also validate susceptibility test systems for use with alternative breakpoints (eg, those from SDOs or, more rarely, those that are institution-specific).

NOTE 4: Laboratories may choose to use CLSI, EUCAST, or FDA breakpoints. In rare instances, hospital-based laboratories may choose to use alternative breakpoints (eg, institution-derived breakpoints not recognized by SDOs or the FDA) that address unique patient and/or antimicrobial stewardship needs. In this case, the laboratory must have written documentation (eg, minutes from a pharmacy and therapeutic committee meeting, or a letter of approval signed by stakeholders) for the following:

- *Scientific and medical reasoning and institutional review/approval of institution-specific breakpoints*
- *Review and agreement to use alternative breakpoints by stakeholders (eg, chief medical officer, pharmacy, infectious diseases, and/or antimicrobial stewardship partners).*

Evidence of Compliance:

- ✓ Records of validation reports for breakpoints that differ from those included in the FDA-clearance of an instrument **AND**
- ✓ Records of the interpretive criteria used for antimicrobial susceptibility testing **AND**
- ✓ Source document (including year of publication) from which the interpretive criteria were derived **AND**
- ✓ Patient or LIS reports with interpretations matching the source document

MIC.11385

“Use current breakpoints”

- Effective Jan 1, 2024
- Phase I requirement
- Labs subject to US regulations must implement within 3 yr after FDA updated bp is published and prior bp is considered obsolete (cannot use)
- Labs can use bp from other SDO (CLSI or EUCAST) with validation study

CAP Microbiology checklist 10/24/2022, with permission

CAP eLabs Solutions Suite: Frequently Asked Questions for MIC.11385

- Must be up to date by 1/1/2024 with bp's published by SDO by 2021,
  by 1/1/2025 with bp's published by SDO in 2022, …
- Labs are not required to use the same source of bp's for all drugs tested, but should use a single breakpoint source for each drug across all methods reporting results for that drug
- If CLSI has updated but not yet FDA, labs can wait and will have 3 yrs to change after FDA update is published; labs can use either CLSI or FDA breakpoints

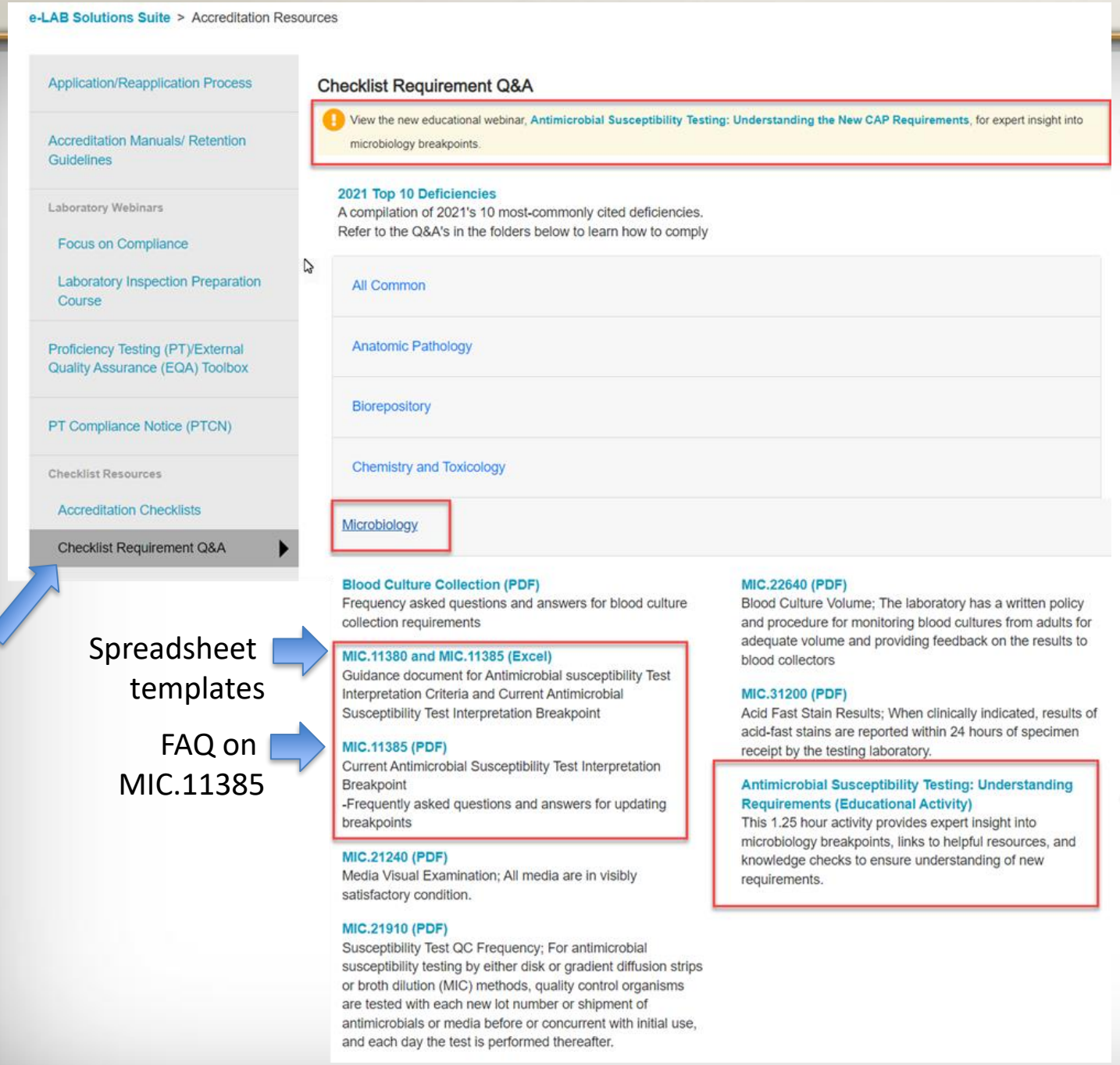
MIC.11385 FAQ in CAP eLabs Solutions Suite

- FDA breakpoints are found on “STIC website” here: https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria
- Help in finding date of FDA updates: https://www.fda.gov/drugs/development-resources/notice-updates
- CLSI breakpoints for bacteria found in free version of M100: https://clsi.org/standards/products/free-resources/access-our-free-resources/
- CLSI table of updates: “CLSI Breakpoint Additions/Revisions Since 2010” is found in frontmatter of M100 document

MIC.11385 FAQ in CAP eLabs Solutions Suite

Q: What if my test system does not have dilutions low enough to accommodate the updated breakpoints?

A: The laboratory should contact the AST manufacturer as other panel configurations may be available with expanded dilutions. The laboratory may also consider utilizing manual tests (e.g., disk diffusion) if the antimicrobial is tested rarely. Additional approaches are discussed in Humphries, *et al* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6535595/



Spreadsheet templates

FAQ on MIC.11385

Link to webinar

Link to webinar

Resources in CAP eLabs Solutions Suite

Steps to find new educational webinar (free for CAP accredited laboratories)

1. CAP.org
2. Login as member
3. Login to e-LAB Solutions Suite
4. Accreditation Resources section
5. Checklist Requirement Q&A
6. Link to webinar in top banner
7. Also, can choose Microbiology under Top 10 Deficiencies and see links to resources and webinar below

Achieving compliance with new requirements

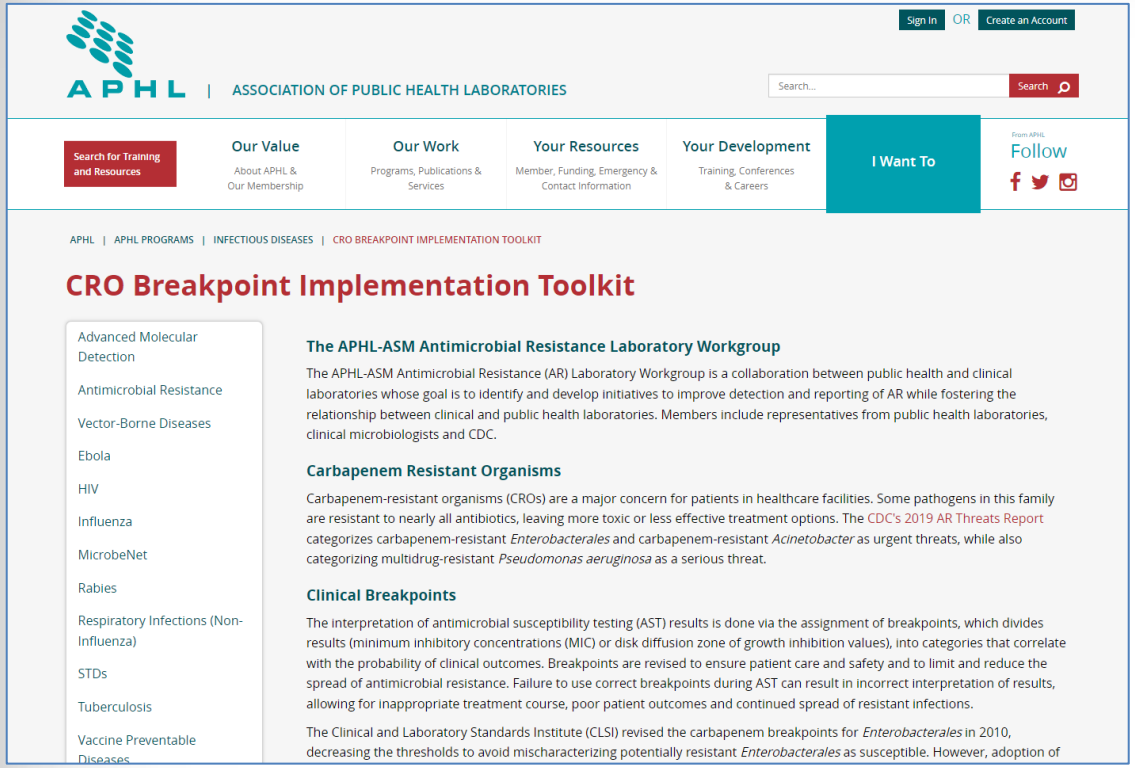
- Hunting down breakpoints applied in your laboratory will take time
  - BP may be applied in commercial AST system, LIS, middleware, HIS/EHR
  - beware of expert rules and of possible effects on cascade reporting
- If you identify an obsolete breakpoint used in your laboratory (no longer recognized by SDO or FDA), you cannot use it beginning Jan 1, 2024
  - discuss with manufacturer to assess status, their plans
  - discuss with stewardship team (is drug result needed? what is priority?)
  - evaluate options: implement new bp after verification or validation, suppress result, use alternate method, send to reference lab
  - communicate with stewardship team throughout, prepare for change (medical staff do not like surprises)

LIS = laboratory information system, HIS = hospital information system, EHR = electronic health records

Help with implementing updated breakpoints

- The Association of Public Health Laboratories and American Society for Microbiology AR Laboratory Workgroup has developed a free toolkit to assist clinical laboratories with implementation of revised carbapenem breakpoints
- "CRO Breakpoint Implementation Toolkit" provides guidance
  - Information, resources, step-by-step instructions, and verification study template

APHL-ASM AR Laboratory Workgroup CRO Breakpoint Implementation Toolkit



Sign In OR Create an Account

APHL | ASSOCIATION OF PUBLIC HEALTH LABORATORIES

Search... Search

Search for Training and Resources | Our Value (About APHL & Our Membership) | Our Work (Programs, Publications & Services) | Your Resources (Member, Funding, Emergency & Contact Information) | Your Development (Training, Conferences & Careers) | I Want To | From APHL Follow

APHL | APHL PROGRAMS | INFECTIOUS DISEASES | CRO BREAKPOINT IMPLEMENTATION TOOLKIT

CRO Breakpoint Implementation Toolkit

- Advanced Molecular Detection
- Antimicrobial Resistance
- Vector-Borne Diseases
- Ebola
- HIV
- Influenza
- MicrobeNet
- Rabies
- Respiratory Infections (Non-Influenza)
- STDs
- Tuberculosis
- Vaccine Preventable Diseases

The APHL-ASM Antimicrobial Resistance Laboratory Workgroup

The APHL-ASM Antimicrobial Resistance (AR) Laboratory Workgroup is a collaboration between public health and clinical laboratories whose goal is to identify and develop initiatives to improve detection and reporting of AR while fostering the relationship between clinical and public health laboratories. Members include representatives from public health laboratories, clinical microbiologists and CDC.

Carbapenem Resistant Organisms

Carbapenem-resistant organisms (CROs) are a major concern for patients in healthcare facilities. Some pathogens in this family are resistant to nearly all antibiotics, leaving more toxic or less effective treatment options. The CDC's 2019 AR Threats Report categorizes carbapenem-resistant *Enterobacterales* and carbapenem-resistant *Acinetobacter* as urgent threats, while also categorizing multidrug-resistant *Pseudomonas aeruginosa* as a serious threat.

Clinical Breakpoints

The interpretation of antimicrobial susceptibility testing (AST) results is done via the assignment of breakpoints, which divides results (minimum inhibitory concentrations (MIC) or disk diffusion zone of growth inhibition values), into categories that correlate with the probability of clinical outcomes. Breakpoints are revised to ensure patient care and safety and to limit and reduce the spread of antimicrobial resistance. Failure to use correct breakpoints during AST can result in incorrect interpretation of results, allowing for inappropriate treatment course, poor patient outcomes and continued spread of resistant infections.

The Clinical and Laboratory Standards Institute (CLSI) revised the carbapenem breakpoints for *Enterobacterales* in 2010, decreasing the thresholds to avoid mischaracterizing potentially resistant *Enterobacterales* as susceptible. However, adoption of

The Clinical and Laboratory Standards Institute (CLSI) revised the carbapenem breakpoints for *Enterobacterales* in 2010, decreasing the thresholds to avoid mischaracterizing potentially resistant *Enterobacterales* as susceptible. However, adoption of the updated MIC breakpoints has proved challenging for clinical microbiology laboratories that use commercial MIC susceptibility testing systems due to verification study that must be completed according to CLIA requirements.

The CRO Breakpoint Implementation Toolkit

The AR Laboratory Workgroup identified providing assistance to laboratories in the implementation of updated carbapenem susceptibility breakpoints as an important area of work. To that end they developed a toolkit laboratories can utilize to guide them through the verification study needed to implement the updated breakpoints. **The first iteration of the toolkit focuses on updating carbapenem breakpoints for *Enterobacterales***. Future iterations will expand to include additional drug-bug combinations. The toolkit components include:

- Introduction to the CRO Breakpoint Implementation Toolkit
  A one-pager providing an overview of the necessity of updating breakpoints and the toolkit
- About the AR Isolate Bank
  A document containing frequently asked questions pertaining to ordering isolate panels for verification studies from the CDC & FDA Antibiotic Resistance (AR) Isolate Bank
- Verification Template
  A template laboratories can utilize for their verification study
- Breakpoint Implementation Instructions
  Step-by-step instructions for performing the verification study
- Implementation Worksheets
  Worksheet templates to be used in conjunction with isolates ordered from the AR Isolate Bank

Bulleted items with red text are links to information, tools

https://www.aphl.org/programs/infectious_disease/Pages/CRO-Breakpoint-Implementation-Toolkit.aspx

Help for implementing updated breakpoints

- Broader guidance (beyond carbapenems) is in final stages of development, expected March 2023 release
  - CLSI Breakpoint Implementation *ad hoc W*orking Group (under CLSI Outreach WG)
  - CLSI, APHL, ASM, CAP collaboration; will be hosted on CLSI website
- Working title: "2023 BIT" (breakpoint implementation toolkit)
  - Introduction (how to use, definitions, references, resources)
  - Template for data
  - Listing of CLSI, FDA BPs
  - Workbook for data entry, calculations for assessing accuracy, precision, and analysis of discrepant results
  - CDC FDA AR Bank Isolates available for BP verification, validation studies

Stay tuned for "2023 BIT!"

- Delineates situations of BP status for CLSI, FDA, commercial AST systems
  - implications for performance assessment study required in the clinical laboratory
- Resources for updating BPs
- Videos/webinars planned to assist users

Verification? Validation?

- CLSI M52 document addresses verification, and is under revision
- A new CLSI document to address validation has been proposed
- ASM Cumitech 31A is being updated for publication in Clin Micro Reviews

"2023 BIT"
a sneak peek (still a draft)

As related to Updated CLSI BPs:

Verification is used to evaluate the performance of breakpoints which have been FDA cleared for use on a device manufacturer's AST system (i.e., the FDA recognizes the CLSI BPs, and the manufacturer obtained clearance by the FDA for the CLSI/FDA current BPs on their AST system.)

Validation refers to any other scenario not covered by verification where the laboratory is modifying an FDA cleared test (e.g., using BPs that are different from those that are FDA cleared for use on the device manufacturer's AST system.)

Note: Details regarding how AST device manufacturers implement updated breakpoints for their system can be found in Table 3.

Table 1. Situations where BP Verification or Validation is Required to Use Updated CLSI BPs

Updated BP Status	Commercial AST System Status	Performance Assessment Required [1]
CLSI = FDA	CLSI BPs are FDA cleared and available on panel/software	Verification [2] 10-15 isolates/drug
CLSI = FDA	Device manufacturer has notified customers that device has received FDA clearance with updated CLSI/FDA BPs and how to implement BPs within their panels/software, if necessary	Verification [2] 10-15 isolates/drug
CLSI = FDA	Device manufacturer has not received FDA clearance of the device with updated CLSI/FDA BPs	Validation (if desire to use CLSI BPs) 30 isolates/drug
CLSI ≠ FDA	Manufacturer must provide FDA BPs; use of CLSI BPs would be off label	Validation (if desire to use CLSI BPs) 30 isolates/drug

[1] Consensus suggestions from authors of 2023 BIT

[2] If no change to the test has been made by the AST manufacturer (e.g., no reformulation of drug dilutions), a verification of reporting may be sufficient. This would involve ensuring MIC results are interpreted correctly on patient reports.

Learning objectives and take-home

1. Recognize how using obsolete breakpoints for AST adversely impacts patient care and public health (unrecognized resistance can mean ineffective therapy, measures to prevent transmission will not be taken)
2. Delineate steps to achieve compliance with CAP requirements to document breakpoints in use, discontinue using obsolete breakpoints, and communicate with partners in managing antimicrobial resistance (go through automated and manual testing in your laboratory, hunt down breakpoints that are applied, identify obsolete bp's, discuss with stewardship partners how to manage a path forward and prepare for change)
3. Make more informed choices for effective therapy using AST results (clinicians, pharmacists need awareness of your lab's current breakpoints, help to guide change as needed, maintain communication regarding future changes)

Thank you for your attention!

Questions? Comments?

Contact: carol.a.rauch@vanderbilt.edu

Resources: webinars

- Simner PJ. “Using Clinical Breakpoints to Improve Antimicrobial Resistance Detection.” Dec 13, 2022. Fisher series. The Next Pandemic is Already Here: Addressing Antimicrobial Resistance. whitehat.com/fisher. https://www.whitehatcom.com/Fisher/Speaker_Slides/BreakPoints_to_Address_AMR_121222.pdf
- Humphries RM. “Antimicrobial Susceptibility Testing: Understanding the New CAP Requirements” www.CAP.org (path to link described in slide)
- Humphries RM, Patel J, Iarikov D, Griffin N. “Updating Breakpoints—Challenges and Solutions for Various Stakeholders.” June 25, 2022. Organized by CLSI Outreach Working Group, hosted by CLSI. https://clsi.org/standards/products/webinars/education/astedujune22wr/

Resources: webinars

- Humphries RM and Patel JB. “Breakpoints Matter: Understanding CLSI Efforts and New CAP Requirements to Ensure Appropriate Antimicrobial Treatment for All Patients.” Jan 11, 2022. CAP-CLSI webinar, hosted by CLSI. https://clsi.org/standards/products/webinars/education/astcapwr22/
- Hindler J and Humphries R. “The Breaking Point for Antimicrobial Resistance: Outdated AST Breakpoints.” Jan 20, 2021. APHL.
- Mitchell SL and Simner P. “Rational Approach to Antibacterial and Antifungal Breakpoints: What Can and Should My Laboratory Update?” Nov 20, 2019. CLSI/CAP webinar.
- California Department of Public Health, Healthcare-Associated Infections Program, California Antimicrobial Resistance Lab-Epi Alliance “Implementing updated carbapenem breakpoints.” Sept 27, 2018. https://www.cdph.ca.gov/Programs/CHCQ/HAI/Pages/CA_ARLN.aspx

Resources: selected literature

- Ambrose PG, *et al*. "Old In Vitro Antimicrobial Breakpoints Are Misleading Stewardship Efforts, Delaying Adoption of Innovative Therapies, and Harming Patients." Open Forum Infectious Diseases. 2020; 7(7): ofaa084. https://doi.org/10.1093/ofid/ofaa084.
- Antibiotic Resistance Collaborators. "Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis." Lancet. 2022; 399: 629-655. https://doi.org/10.1016/S0140-6736(21)02724-0.
- Bartsch SM, Huang SS, Wong KF, et al. "Impact of delays between Clinical and Laboratory Standards Institute and Food and Drug Administration revisions of interpretive criteria for carbapenem-resistant Enterobacteriaceae." J Clin Microbiol. 54: 2757–62. 2016.

Resources: selected literature

- CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf
- Clark RB, *et al*. 2009. Cumitech 31A. "Verification and Validation of Procedures in the Clinical Microbiology Laboratory." Coordinating Ed. SE Sharp. ASM Press, Washington, DC.
- Clinical Laboratory Standards Institute (CLSI). "Verification of commercial microbial identification and antimicrobial susceptibility testing systems." 1st ed. CLSI guideline M52. Clinical and Laboratory Standards Institute, Wayne, PA. 2015. (under revision)
- Heil EL and Johnson JK. "Impact of CLSI Breakpoint Changes on Microbiology Laboratories and Antimicrobial Stewardship Programs." 2016; J Clin Microbiol. 54(4): 840-844.
- RM Humphries & JA Hindler. "Emerging Resistance, New Antimicrobial Agents … but No Tests! The Challenge of Antimicrobial Susceptibility Testing in the Current US Regulatory Landscape." Clin Inf Dis. 2016; 63: 83-88.

Resources: selected literature

- Humphries RM, *et al*. "Carbapenem-Resistant Enterobacteriaceae Detection Practices in California: What Are We Missing?" Clin Inf Dis. 2018; 66: 1061-1067.
- Humphries RM, Ferraro MJ, Hindler JA. "Impact of 21st Century Cures Act on Breakpoints and Commercial Antimicrobial Susceptibility Test Systems: Progress and Pitfalls." J Clin Microbiol. 2018. 56(5) e00139-18. DOI 10.1128/JCM.00139-18.
- Humphries RM, Abbott AN, Hindler JA. "Understanding and Addressing CLSI Breakpoint Revisions: a Primer for Clinical Laboratories." J Clin Microbiol. 2019; 57e00203-19. https://doi.org/10.1128/JCM.00203-19.
- Humphries RM and Simner PJ. "Verification Is an Integral Part of Antimicrobial Susceptibility Test Quality Assurance." J Clin Microbiol. 2020; 58(4): e0196-19. https://doi.org/10.1128/JCM.01986-19.

Resources: selected literature

- Lutgring JD, Machado MJ, Benahmed FH, Conville P, Shawar RM, Patel J, Brown AC. "FDA-CDC Antimicrobial Resistance Isolate Bank: a Publicly Available Resource To Support Research, Development, and Regulatory Requirements." J Clin Microbiol. 2018; 56(2): e01415-17. https://doi.org/10.1128/JCM.01415-17.
- McKinnell JA, et al. "Public Health Efforts Can Impact Adoption of Current Susceptibility Breakpoints, but Closer Attention from Regulatory Bodies is Needed." J Clin Micro. 2019; 57:e01488-18. https://doi.org/10.1128/JCM.01488-18.
- Patel JB, Sharp S, and Novak-Weekley S. "Verification of Antimicrobial Susceptibility Testing Methods: A Practical Approach." Clinical Microbiology Newsletter. 35(13):103-109. 2013.
- Redell M and Tillotson GS. "The Practical Problem With Carbapenem Testing and Reporting Accurate Bacterial Susceptibilities." Frontiers in Pharmacology. 2022; 13: Article 841896. https://doi.org/10.3389/fphar.2022.841896.

Resources: selected literature

- Simner PJ, Rauch CA, Martin IW, Sullivan KV, Rhoads D, Rolf R, She R, Sours RJ, Wojewoda C, Humphries RM. "Raising the Bar: Improving Antimicrobial Resistance Detection by Clinical Laboratories by Ensuring Use of Current Breakpoints." Open Forum Infectious Diseases. 2022. https://doi.org/10.1093/ofid/ofac007
- Wojewoda CM, *et al*. "College of American Pathologists (CAP) Microbiology Committee Perspective: the Need for Verification Studies." J Clin Microbiol. 2020; 58(4). https://doi.org/10.1128/JCM.02105-19.
- Yarbrough ML, *et al*. "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 of Clin Micro & Inf Dis. 2019. https://doi.org/10.1007/s10096-019-03711-y.

Resources: professional newsletter, website discussions

- Humphries RM. "Updating Breakpoints—New Developments from CAP." CLSI AST News Update 7(1): 17-18. June 2022. https://clsi.org/media/rcqcsoad/ast-news-update-volume-7-issue-1-june-2022.pdf
- CAP Today articles
  - "AST breakpoints: a case of not aging gracefully." Titus K. April 2020. https://www.captodayonline.com/ast-breakpoints-a-case-of-not-aging-gracefully/
  - "AST and safety at core of microbiology checklist changes." Newitt VN. Oct 2021. https://www.captodayonline.com/ast-and-safety-at-core-of-microbiology-checklist-changes/
  - "Leaving behind outdated AST breakpoints." Titus K. May 2022. https://www.captodayonline.com/leaving-behind-outdated-ast-breakpoints/
- CAP Today Q&A Column. Seeking guidance on validation methods for lower bp's for carbapenems (Humphries RM and Simner PJ; March 2020), second question. https://www.captodayonline.com/qa-column-0320/

Resources: professional newsletter, website discussions

- Prinzi A. “Updating Breakpoints in Antimicrobial Susceptibility Testing.” Feb 22, 2022. https://asm.org/Articles/2022/February/Updating-Breakpoints-in-Antimicrobial-Susceptibili
- Prinzi A. “Antimicrobial susceptibility test breakpoint updates: Challenges and considerations for laboratory validation.” MLO Oct 19, 2022. https://www.mlo-online.com/diagnostics/microbiology/article/21283829/antimicrobial-susceptibility-test-breakpoint-updates-challenges-and-considerations-for-laboratory-validation
- Prinzi A. “College of American Pathologists Accreditation Program: Antimicrobial Susceptibility Testing Breakpoint Updates and Beyond.” The American Society for Clinical Laboratory Science (ASCLS). ASCLS Today. 36(5). October 2022. https://ascls.org/college-of-American-pathologists-accreditation-program-antimicrobial-susceptibility-testing-breakpoint-updates-and-beyond/

Resources

- Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing, 32nd ed. CLSI Supplement M100. Free online version https://clsi.org/standards/products/free-resources/access-our-free-resources/
- College of American Pathologists Microbiology checklists (09/22/2021, 10/24/2022) www.cap.org → Laboratory Improvement → Accreditation → Accreditation Checklists
- APHL/ASM Antimicrobial Resistance Laboratory Workgroup Carbapenem Resistant Organism Breakpoint Implementation Toolkit https://www.aphl.org/programs/infectious_disease/Pages/CRO-Breakpoint-Implementation-Toolkit.aspx
- FDA breakpoints on "STIC website" https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria
- FDA updates https://www.fda.gov/drugs/development-resources/notice-updates