The Importance of Clinical Breakpoints in Antimicrobial Resistance

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Table of Contents

Objectives

1. List the pros and cons of common antimicrobial susceptibility tests – with respect to clinical breakpoints
2. Define the type of information provided in the CLSI m100 and understand how to utilize the document
3. Describe the steps involved with implementation of new breakpoints

MICs, Zone Diameter, and Clinical Breakpoints

- Mean Inhibitory Concentration (MIC): the lowest concentration of a drug that inhibits visible growth of a bug after a defined period
- Zone diameter: measurement in mm of the zone of inhibition around an antimicrobial disc of a fixed concentration
- Breakpoint: MIC or zone diameter value used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, or nonsusceptible to a drug

Providers depend on breakpoint interpretations!!!!!!!!

Breakpoint Interpretations (STIC)

- Interpretative criteria are published by various organizations including the CLSI, EUCAST, and FDA
  - Breakpoints recognized by these organizations are not always the same
  - 21st Century Cures Act (12/13/2016) created a system to expedite the recognition of STIC
    - CLSI can submit STIC change rationale documents to the FDA for acceptance
    - FDA retains authority to accept a standard in whole or in part, or establish alternative STIC
    - FDA posts recognized STIC and updates every 6 mo: https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria
    - Manufacturers can rely on the published FDA list to support labeling changes in the IFU
    - FDA will utilize enforcement discretion regarding submission of a new 510(k) when appropriate
    - https://www.fda.gov/media/77007/download

CLSI Interpretative Category

- CLSI breakpoints are based on known serum drug concentrations unless otherwise noted (ie: urinary specific)
- S, SDD, I, I^, R, NS

What is the difference between I^ and SDD?

A. There is no difference. They both confuse me!

B. Not much difference. For both higher or more frequent dosing are required.

C. SDD means that susceptibility depends on the dosage regimen used and I^ means that the drug can concentrate in the urine.

D. It doesn't matter. I^ is for informational use only and my lab doesn't report it!

CLSI M100-ED32:2022: Table 2A *Enterobacterales*

Testing Conditions	
Medium:	Disk diffusion: MHA
	Broth dilution: CAMHB
	For cefiderocol, special media is required for testing.
	See comment (24).
	Agar dilution: MHA
Inoculum:	Broth culture method or colony suspension, equivalent to a 0.5 McFarland standard
Incubation:	35°C ± 2°C; ambient air
	Disk diffusion: 16–18 hours
	Dilution methods: 16–20 hours

Routine QC Recommendations (see Tables 4A-1 and 5A-1 for acceptable QC ranges)
Escherichia coli ATCC®* 25922
Pseudomonas aeruginosa ATCC® 27853 (for carbapenems)
Refer to Tables 4A-2 and 5A-2 to select strains for routine QC of β-lactam combination agents.
When a commercial test system is used for susceptibility testing, refer to the manufacturer's instructions for QC test recommendations and QC ranges.

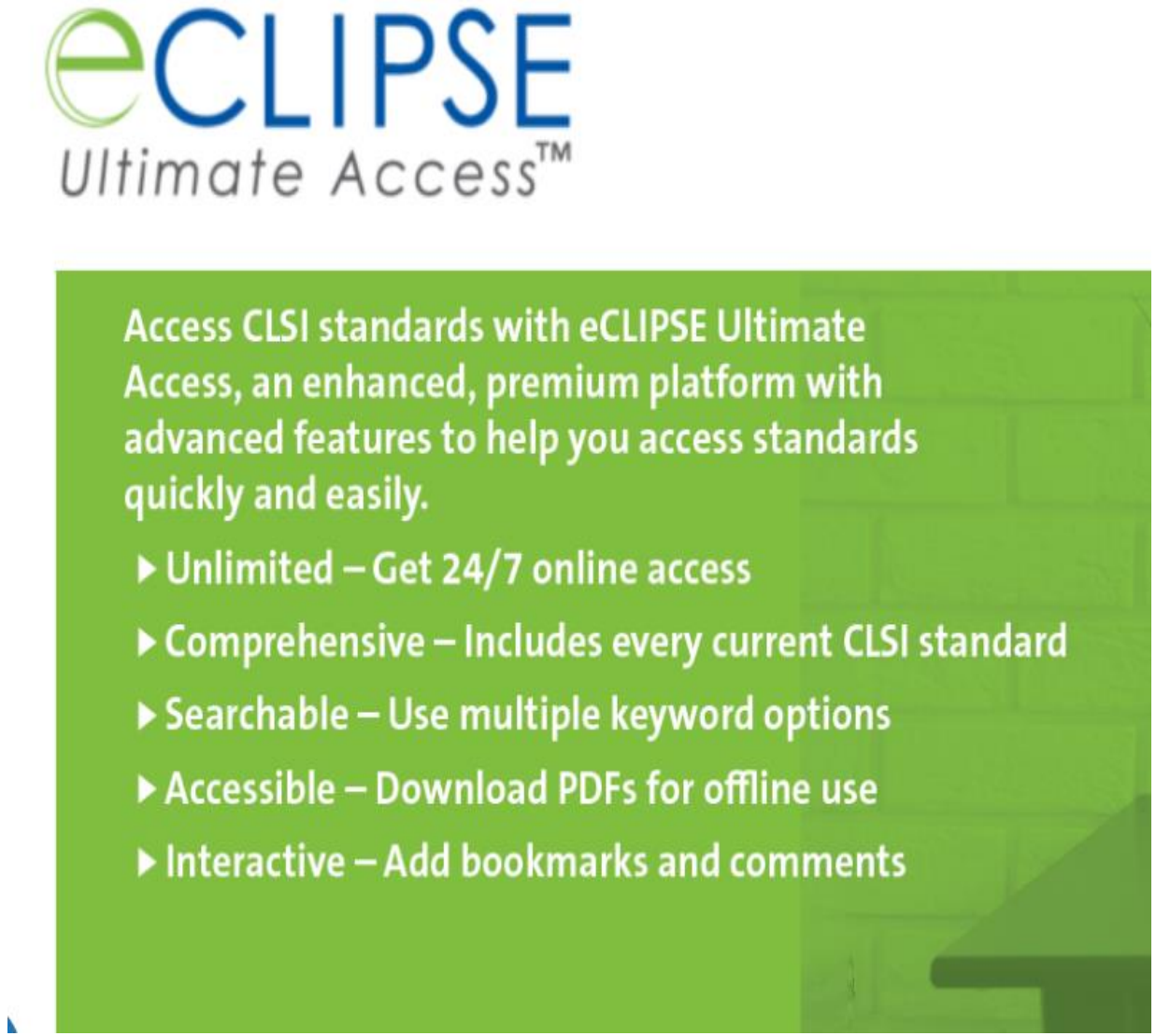
CLSI M45 ED3:2016

Infrequently Isolated or Fastidious Bacteria Including:

- *Abiotrophia* and *Granulicatella* spp.
- *Aerococcus* spp.
- *Aeromonas* spp.
- *Bacillus* spp.
- *Campylobacter jejuni/coli*
- *Corynebacterium* spp.
- *Eryspielothrix rhusiopathiae*
- *Gemella* spp.
- HACEK Group
- *Helicobacter pylori*
- *Lactobacillus* spp.
- *Lactococcus* spp.
- *Leuconostoc* spp.
- *Listeria monocytogenes*
- *Micrococcus* spp.
- *Moraxella catarrhalis*
- *Pasturella* spp.
- *Pediococcus* spp.
- *Rothia mucilaginosa*
- *Vibrio* spp.
- Potential agents of bioterrorism

CLSI Resources

- Self directed course: Using M100
  - https://clsi.org/standards/products/microbiology/companion/using-m100/
- Free M100 and M60 content
  - http://em100.edaptivedocs.net/Login.aspx
- Breakpoints in use template
  - https://clsi.org/standards/products/microbiology/companion/bpiu



Commercial AST Panels and Options

Off the Shelf Panels

E.g. Vitek cards, Microscan, Sensititre, Phoenix panels

+ Limited expertise required to choose, verify and implement panel
+ Order to receipt in days/weeks
– No control over antimicrobials or antimicrobial concentrations utilized
– May not have clearance for use with new breakpoints, even if FDA recognized
– Validation of off-label breakpoints required
– Must adhere to manufacturer limitations

Customized Panels / Options

E.g. Sensititre, KB discs, ETEST, MTS

+ Can determine which antimicrobials and which concentrations* to use in conjunction with various stakeholders
+ Implementation of new breakpoints MAY be easier than with an off the shelf panel
– Timeline from order to receipt can require many months (Sensititre)
– More expertise required to develop, validate, and implement panel
– Must adhere to manufacturer limitations

More AST method Pros and Cons

MIC Based Tests

ie: Vitek cards, Microscan, Sensititre, Phoenix panels, ETEST, MTS

+ Can be less labor intensive than discs
+ MIC can be provided if no STIC
+ Most options have software available for customized rules and labeling comments
– More costly than KB discs
– Validation/verification can be more complicated than with KB discs

KB Disc Diffusion

+ Breakpoints available for rapid AST, direct from positive blood culture
+ Inexpensive materials
+ When STIC change, the correct “concentration” is always available
+ Implementation of new STIC or new antimicrobials likely easier than with other methods
– Labor intensive if no automation
– No MICs available, STIC required
– STIC for some drug/bug combos is not available

More AST method Pros and Cons

Phenotypic AST

+ Can provide MIC and / or STIC
+ Can test bug and drug without extensive knowledge of resistance mechanisms
– MIC/STIC can be incorrect due to heteroresistance, inducible resistance, low level resistance
– Easier to forget about making changes to the protocol when STIC change

Molecular AST

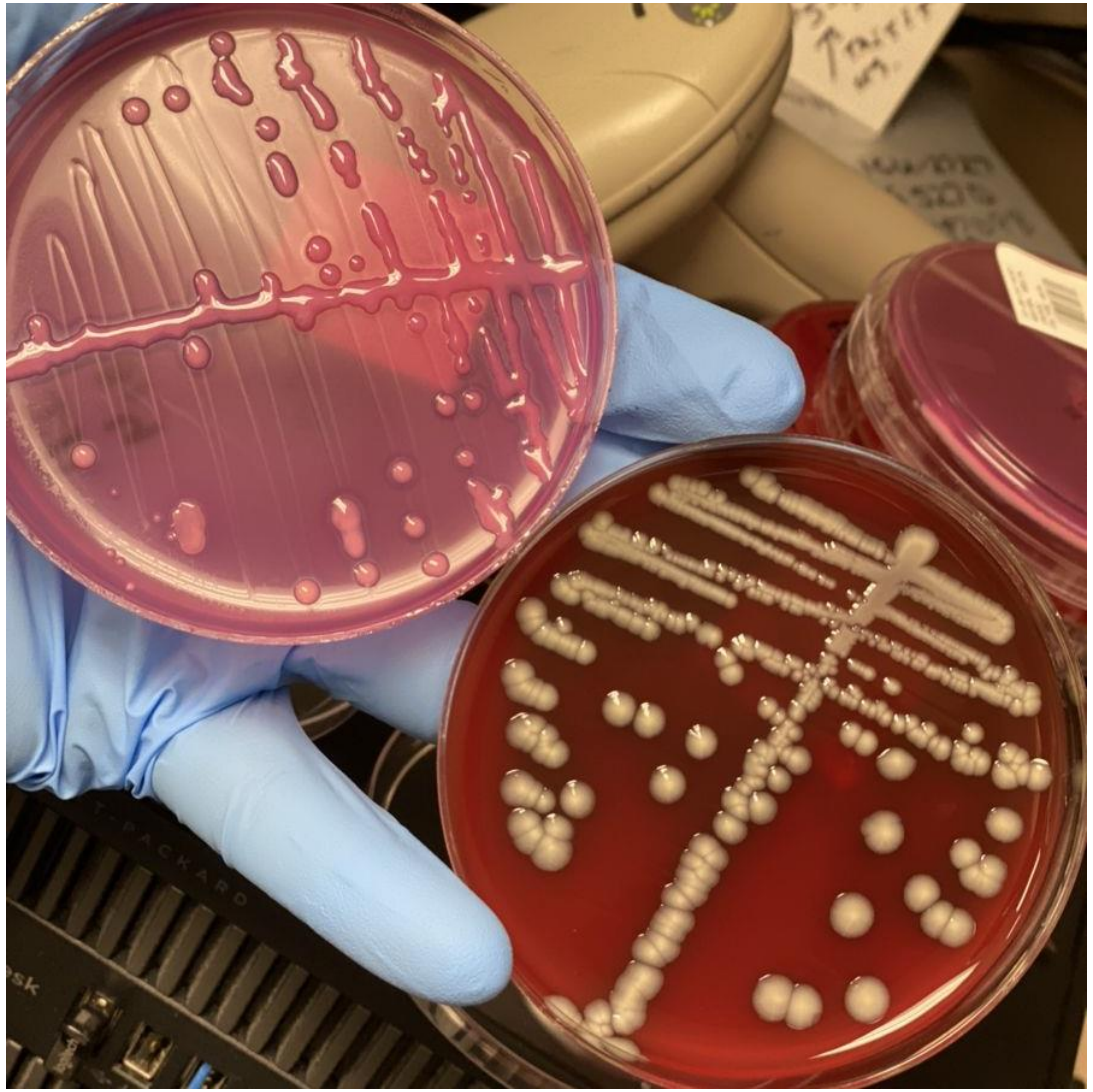
+ Can be more rapid than phenotypic because not growth based
+ Can detect resistance markers in mixed infections
+ STIC changes do not impact procedure
– Must know what gene/mutation/marker to look for or how to interpret
– In cultures with mixed populations, must be able to link gene/mutation/marker to a specific organism.

Why Breakpoints Matter: Case Study Day 1

- Typically alert 76 yo female snowbird admitted to a local hospital with increasing fatigue, painful urination, and new onset fever.
- Her son became concerned when she could not get up from her chair and called for an ambulance to take her to a local ED.
- Her son reported some mental status changes over the past day or two
- Temperature of 102.1F with tachycardia and tachypnea
- WBC 14.3, 95% neutrophils, Glucose 190, BUN 37, Creatinine 1.5, Lactate 3.3
- Urine dip: + protein, + nitrite, + leukocyte esterase, WBC > 100
- Placed on vancomycin and pip/tazo with blood and urine cultures obtained

Why Breakpoints Matter: Case Study Day 2

- Urine cultures positive for GNR (looked like Klebsiella pneumonia)
- Vancomycin discontinued and meropenem initiated
- AST/ID set up using the Vitek System
- Initial blood cultures remained negative



Why Breakpoints Matter: Case Study Day 3-6

- Urine cultures positive for Klebsiella pneumonia, sensitive to meropenem
- Patient not improving and was transferred to our facility for higher level care
- Repeat blood and urine cultures obtained
  - Day 4 = Urine positive for K. pneumo
  - Request AST data from previous hospital
    - MEROPENEM MIC $\leq$ 4!!!!
    - Regimen switched to high does meropenem and fosfomycin
  - Day 5 AST from in-house method and current breakpoints 4 = Resistant
    - Phenotypic testing set up for CRE (mCIM)
    - Day 6 + for carbapenemase production and sent to state lab for PCR
    - KPC positive at state lab

College of American Pathology (CAP) Response

- Revised MIC.11380 9/22/2021 AST Interpretation Criteria

  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.

- New MIC.11385 9/22/2021 Current AST Interpretation Breakpoints

  Effective January 1, 2024, the laboratory uses current breakpoints for interpretation of antimicrobial 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.

Breakpoints in Use

- CLSI resource: https://clsi.org/standards/products/microbiology/companion/bpiu

Which breakpoints does your lab utilize for carbapenems (2010), fluroquinolones (2019) and piperacillin/tazobactam (2022)?

A. Your guess is as good as mine!

B. We use allllllll the current breakpoints!

C. Current carbapenem and fluroquinolone breakpoints but outdated for pip/tazo.

D. Current carbapenem breakpoints but outdated for fluroquinolone and pip/tazo

E. All our breakpoints are outdated

Breakpoints in Use

- CLSI resource: https://clsi.org/standards/products/microbiology/companion/bpiu

Where can you find out which breakpoints are used in your lab?

A. I'm sure someone knows that answer, but it's not me
B. It's in my SOP
C. It's programmed into my LIS
D. It's within my AST instrument's software
E. Our processes are manual. It's in the m100 or m45.

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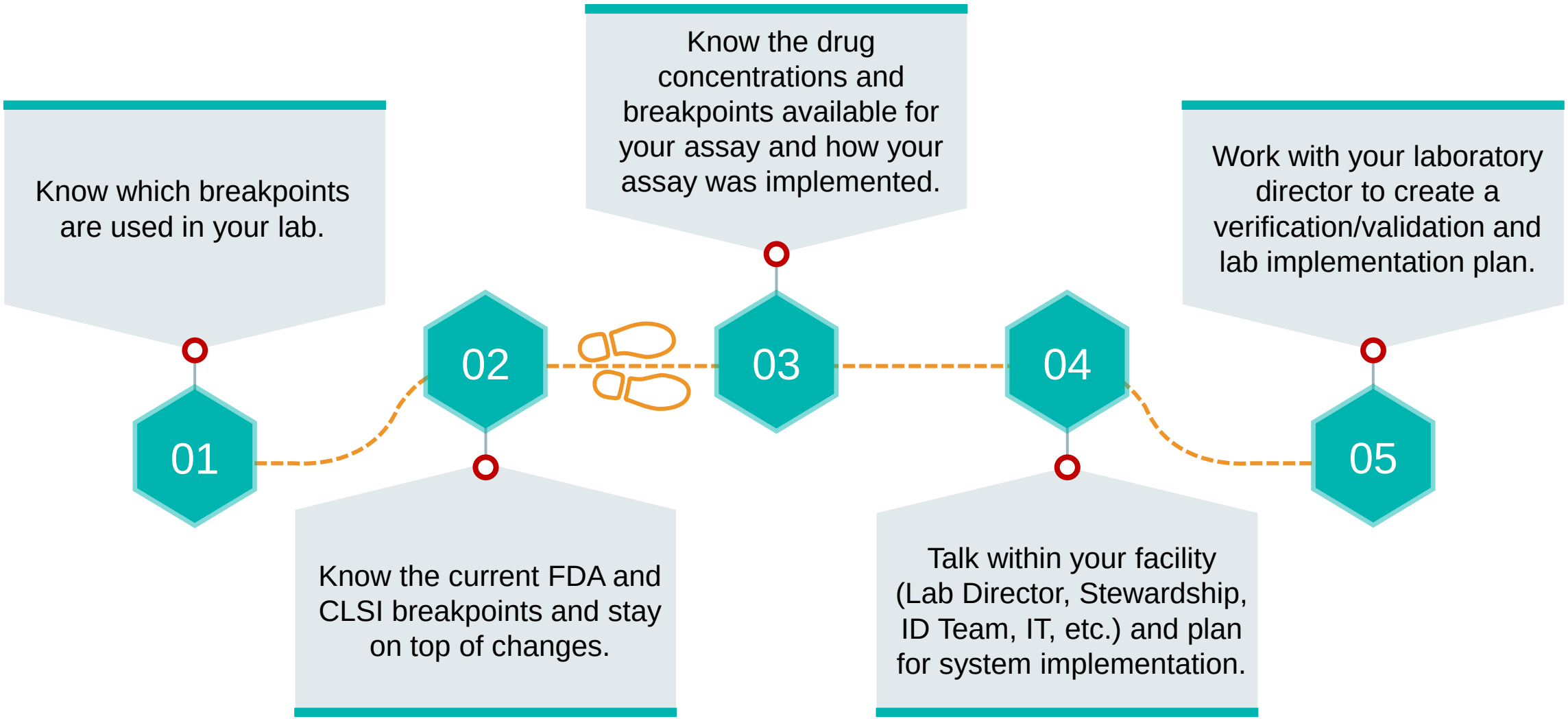
Implementing Updated Breakpoints



Study Design and Logistics

Verification

- FDA cleared test
  - FDA recognized breakpoints
  - Manufacturer has FDA clearance with the breakpoints
- IMO: if initial implementation of test was via validation and only updating STIC
- M52
  - Accuracy 10 isolates
  - CA > 90%
  - VME/ME < 3%
  - Reproducibility 3 x 5 QC strains

Validation

- No FDA clearance or a modification of a cleared test
  - To include STIC that is not recognized by either FDA or test manufacturer
- M52
  - Accuracy 30 isolates
  - CA >90% CA
  - 0 VME, ≤1 ME
  - Reproducibility 3 x 5 QC strains
  - Remember analytical sensitivity (ie: LOD) does NOT apply to AST testing

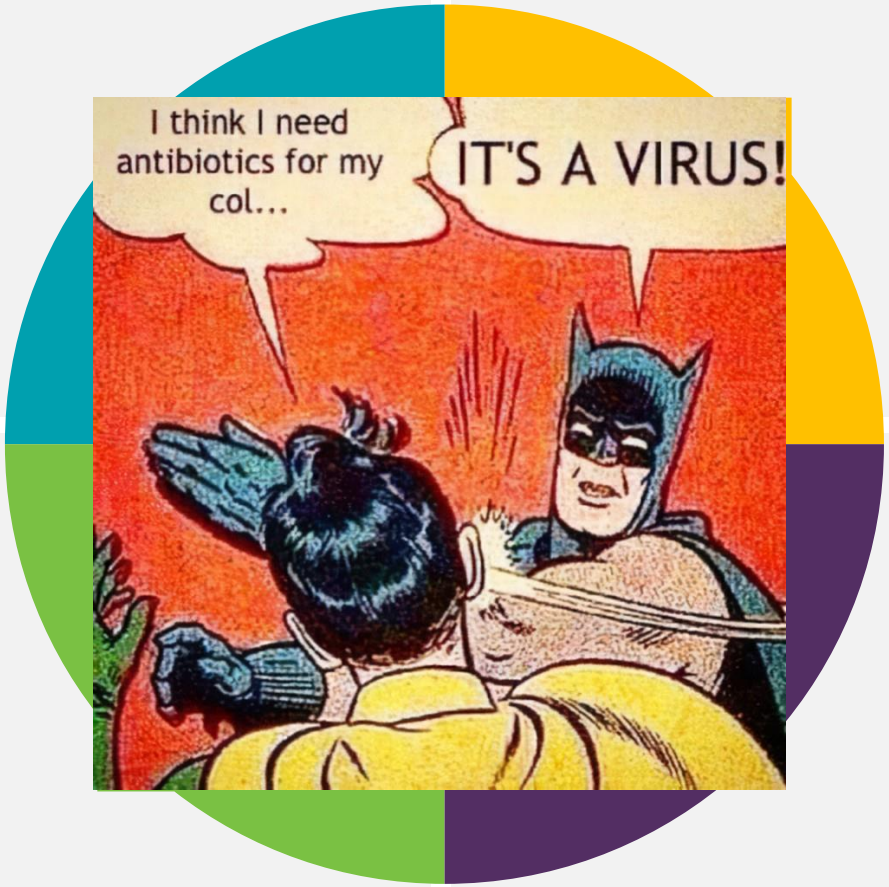
Antimicrobial Stewardship

Laboratory

- Test appropriate drugs
- Utilize cascade reporting
- Provide relevant data including annual antibiograms
- Assist or lead education efforts

Pharmacy

- Compose and appropriate formulary
- Provide interventions when necessary
- Implement appropriate guidance
- Assist or lead education efforts



Physicians (MVP: ID Team)

- Prescribe antibiotics when needed
- Prescribe appropriate therapy
- Reassess Rx based on results
- Assist or lead education efforts

Infection Prevention

- Lead surveillance efforts
- Evaluate and present relevant data
- Utilize date to garner C Suite support
- Observational rounding
- Assist or lead education efforts

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