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Navigating Through Microbiology Changes That Impact Your Antimicrobial Stewardship Program

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Disclosures

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Learning Objectives

At the end of this session, participants should be able to:

1. Recall recent changes to performance standards for antimicrobial susceptibility testing
2. Identify the impact of changes in antibiotic breakpoints on antimicrobial use
3. Recognize cascade and selective reporting rules in collaboration with microbiology and antimicrobial stewardship teams to optimize patient care

Abbreviations

CLSI	Clinical & Laboratory Standards Institute	**MIC**	Minimum inhibitory concentration
CRE	Carbapenem resistant Enterobacterales	**PD**	Pharmacodynamic
ECV	Epidemiological cutoff value	**PK**	Pharmacokinetic
EHR	Electronic health record	**R**	Resistant
ESBL	Extended spectrum beta-lactamase	**S**	Susceptible
I	Intermediate	**SDD**	Susceptible dose-dependent
ID	Infectious diseases	**TMP/SMX**	Trimethoprim/sulfamethoxazole
KB	Kirby Bauer	**UTI**	Urinary tract infection
MDRO	Multidrug resistant organism		

Outline

Breakpoints	Background & Significant Updates in 2023–2024	J. Cowper
	Microbiology Perspective	R. Philogene
	Antimicrobial Stewardship Perspective	L. Cwengros
Selective & Cascade Reporting	Selective & Cascade Reporting	J. Cowper
	Microbiology Perspective	R. Philogene
	Antimicrobial Stewardship Perspective	L. Cwengros
HCA Process in 2023–2024	Breakpoints & Standardized Cascade Rules	R. Philogene & J. Cowper
	Antimicrobial Stewardship & Microbiology Collaboration	L. Cwengros

BREAKPOINTS

Source: Getty Images. Used with permission from HealthTrust.

Breakpoints / Susceptibility Test Interpretive Criteria (STIC)

- Breakpoints
  - Susceptibility test interpretive criteria (STIC)
  - Informs clinicians about a given antimicrobial's potential efficacy against an isolated pathogen
- Food & Drug Administration (FDA) and Clinical & Laboratory Standards Institute (CLSI)
  - Recognized standards development organizations allowed to set or revise STIC
- Prior to 2024, challenges in implementing new breakpoints frequently led to delays in adoption by clinical labs
- As of 1/1/2024, current breakpoints must be used to meet regulatory requirements

Sources:
1. Clinical and Laboratory Standards Institute. 2023 Breakpoint Implementation Toolkit (2023 BIT). Available at: https://clsi.org/bit-toolkit/. Accessed 5/6/2024.
2. Humphries R. AST News Update June 2022: Updating Breakpoints-New Developments from CAP. August 2, 2022. Available at: https://clsi.org/about/blog/ast-news-update-june-2022-updating-breakpoints-new-developments-from-cap/. Accessed 5/6/2024.

Breakpoints – Why are they updated?

Breakpoints are based on 3 data sources:

Microbiologic

- MIC distribution & epidemiological cutoff values

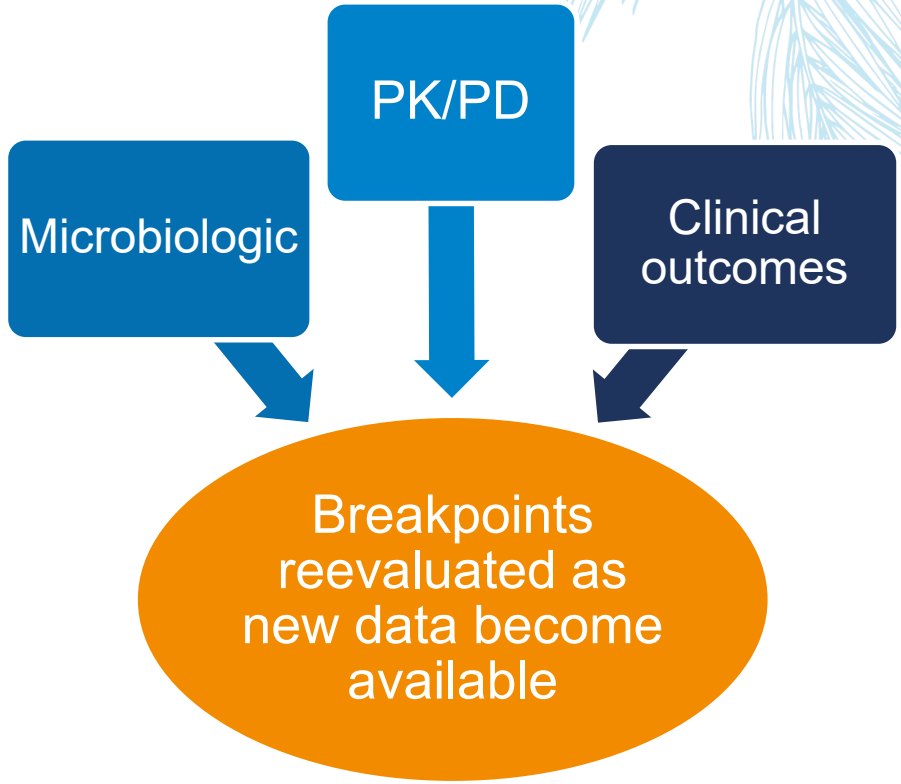
Pharmacokinetic & pharmacodynamic (PK/PD)

- Antibiotic exposures & “probability of target attainment”

Clinical outcomes

- Correlation of microbiologic & PK/PD with patient outcomes

CLSI monitors the need for updates & publishes updated breakpoints in their annual M100 standards



Sources:
1. Tamma PD, Harris PNA, Mathers AJ, Wenzler E, Humphries RM. Breaking down the breakpoints: rationale for the 2022 Clinical and Laboratory Standards Institute revised piperacillin-tazobactam breakpoints against Enterobacterales. *Clin Infect Dis* 2022: ciac688.
2. Tamma PD, Harris PNA, Mathers AJ, Wenzler E, Humphries RM. Deconstructing the 2023 Clinical and Laboratory Standards Institute revised piperacillin-tazobactam breakpoints against Pseudomonas aeruginosa. *Clin Infect Dis* 2023: ciad012.

CLSI Significant Breakpoint Updates

2023

- Aminoglycosides & Enterobacterales
- Aminoglycosides & *Pseudomonas aeruginosa*
- Piperacillin/tazobactam & *P. aeruginosa*
- Levofloxacin comment for *Stenotrophomonas maltophilia*

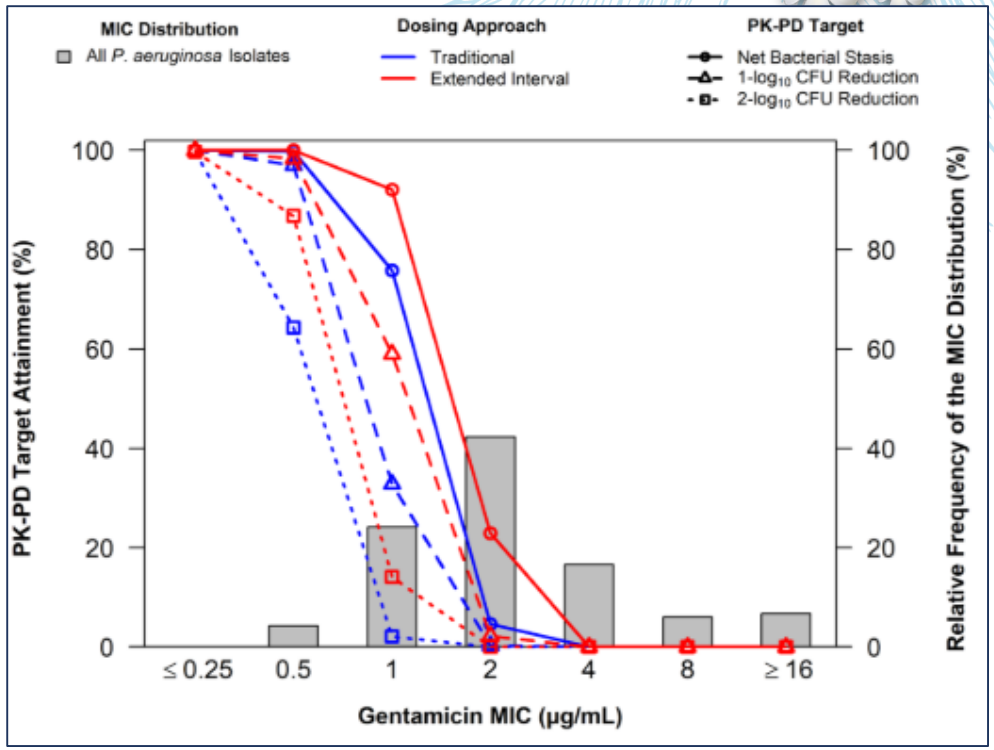
2024

- Ceftazidime & *S. maltophilia*
- TMP/SMX comment for *S. maltophilia*
- Minocycline & *S. maltophilia*

Source: CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 34th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2024.

Aminoglycoside Breakpoint Changes

- No aminoglycoside safely predicted to achieve bactericidal activity
- Bacterial stasis achievable with extended-interval dosing – only at MICs less than the pre-2023 susceptible breakpoints
- Epidemiological cutoff value (ECV) for gentamicin & *P. aeruginosa* was 8 mg/L
  - ECV is upper end of reference strain distribution – isolates with MICs above EVC expected to have acquired or mutational resistance mechanisms
  - Bacterial stasis only possible at MICs ≤0.5 mg/L



Source: The United States Committee on Antimicrobial Susceptibility Testing. 2023 USCAST Virtual Public Meeting: Updates on Aminoglycoside Breakpoints. February 8, 2023. https://www.uscast.org/. Accessed 5/6/2024.

Source: Humphries RM. AST News Update June 2023: New! CLSI M100-Ed33: Updated Aminoglycoside Breakpoints for Enterobacterales and Pseudomonas aeruginosa. 6/21/2023. Available at: https://clsi.org/about/blog/ast-news-update-june-2023-new-clsi-m100-ed33-updated-aminoglycoside-breakpoints-for-enterobacterales-and-pseudomonas-aeruginosa/. Accessed 5/6/2024.

Aminoglycoside Breakpoint Changes

Antibiotic	Breakpoint Change	New Breakpoints (mg/L)			Breakpoint Change	New Breakpoints (mg/L)		
Organism	**Enterobacterales**	**S**	**I**	**R**	***P. aeruginosa***	**S**	**I**	**R**
Gentamicin	Lowered	≤ 2	4	≥ 8	Deleted	---	---	---
Tobramycin	Lowered	≤ 2	4	≥ 8	Lowered	≤ 1	2	≥ 4
Amikacin	Lowered	≤ 4	8	≥ 16	Changed to urine only	≤ 16	32	≥ 64

New comments:

- Monotherapy use should be limited to UTIs
- Consider combination therapy for indications other than UTIs
- Consultation with ID specialist recommended
- Breakpoints based on extended-interval dosing (7 mg/kg every 24 hours for gentamicin/tobramycin & 15 mg/kg every 24 hours for amikacin)

Source: CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 34th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2024.

Piperacillin/Tazobactam Breakpoints for *P. aeruginosa*

Pip/Tazo breakpoints for Enterobacterales were changed in 2022

S	I	R
≤ 16/4	32/4-64/4	≥ 128/4

S	SDD	R
≤ 8	16	≥ 32

- ECV is 16 mcg/mL
  - ECV is upper end of reference strain distribution
  - Breakpoints below ECV are discouraged – high error rates
- PK/PD data showed:
  - Standard infusions (30 min) were adequate at MICs ≤8 mg/L
  - Extended infusions (3 hours) given every 6 hours needed for MICs=16 mg/L
- Clinical outcomes data indicate increased mortality at MICs ≥32 mg/L
  - No data available on extended-infusion & patient outcomes by MIC

Source: Tamma PD, Harris PNA, Mathers AJ, Wenzler E, Humphries RM. Deconstructing the 2023 Clinical and Laboratory Standards Institute revised piperacillin-tazobactam breakpoints against Pseudomonas aeruginosa. *Clin Infect Dis* 2023; 76(10): 1868-70.

Piperacillin/Tazobactam Breakpoints for *P. aeruginosa*

- Intermediate & resistant breakpoints were lowered
- Susceptible breakpoint did not change

S	I	R
≤ 16/4	32/4-64/4	≥ 128/4

S	I	R
≤ 16	32	≥ 64

New comments:

- Breakpoint for susceptible based on dose of 4.5 grams every 6 hours
- Breakpoint for intermediate only to provide buffer zone to prevent small uncontrolled technical factors from causing major discrepancies in interpretations

Source: CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 34th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2024.

S. maltophilia Changes

	• Not considered appropriate for testing, reporting or for treatment
Ceftazidime • Breakpoints removed	• No high-quality clinical outcomes data • Major error rates in susceptibility testing • MIC distribution • Intrinsic beta-lactamases that render ceftazidime ineffective
Minocycline • Breakpoints lowered	• Susceptible breakpoint ≤1 mg/L
	• MIC distribution • PK/PD data with higher dose of 200mg IV/PO every 12 hours
Levofloxacin • Comment added	• Should not be used alone for therapy
TMP/SMX • Comment added	• Added to align with IDSA 2023 Guidance on Treatment of Antimicrobial Resistant Gram-Negative Infections

Sources:
1. CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 34th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2024.
2. Bixby ML, Zheng D, Hirsch EB. Long story short: establishing breakpoints for antimicrobials and 2023 updates. *Curr Infect Dis Rep* 2024; 26: 47-55.

Assessment Question #1

Based on recent changes to performance standards for antimicrobial susceptibility testing, which of the following antibiotics are no longer considered an effective treatment option for Pseudomonas aeruginosa?

a. Piperacillin/tazobactam

b. Ceftazidime

c. Gentamicin

d. Tobramycin

Answer: Assessment Question #1

Based on recent changes to performance standards for antimicrobial susceptibility testing, which of the following antibiotics are no longer considered an effective treatment option for Pseudomonas aeruginosa?

a. Piperacillin/tazobactam

b. Ceftazidime

c. **Gentamicin**

d. Tobramycin

Why is it challenging for clinical labs?

- Major CLSI changes began in 2010
  - CLSI vs. FDA breakpoints not aligned
  - Antimicrobial susceptibility testing (AST) devices must follow FDA
    - 2023 CAP required laboratories to update breakpoints

- FDA vs. AST devices updates
  - Prior to 2007, both FDA & CLSI breakpoints could be reported
  - 2007 – FDA class II special guidance
    - Required AST devices report FDA-recognized breakpoints
    - CLSI breakpoints only allowed for instruments with clearance in 2007 or earlier
  - 2009 – FDA revision
    - AST devices should follow antimicrobial's instructions for use & only report breakpoints for organisms with in vivo efficacy

Source: Regulatory Hurdles for Updating Breakpoints: What to Know (asm.org)

Other Factors Impacting Breakpoint Updates

- Updating breakpoints can be complicated
  - Pharmacy requests vs. FDA Indication For Use vs. Pharma labeling
  - Validation & manual testing
  - Communication/collaboration needed
    - FDA vs. CLSI vs. Pharmaceutical label vs. clinical need
    - Clinical labs are trying to figure it out & provide quality results
- Other challenges for clinical labs
  - Staffing
    - Continue to heavily impact laboratories
    - Experienced techs are retiring
    - Learning GAP
  - Other resources are limited
    - LIS/IT
      - Needed to make updates
      - AST updates are manual – challenging to automate
      - Requires close collaboration with clinical labs

Overcoming Challenges With Updating Breakpoints

Recent breakpoint updates
- Aminoglycosides
- Piperacillin/tazobactam
- *S. maltophilia*

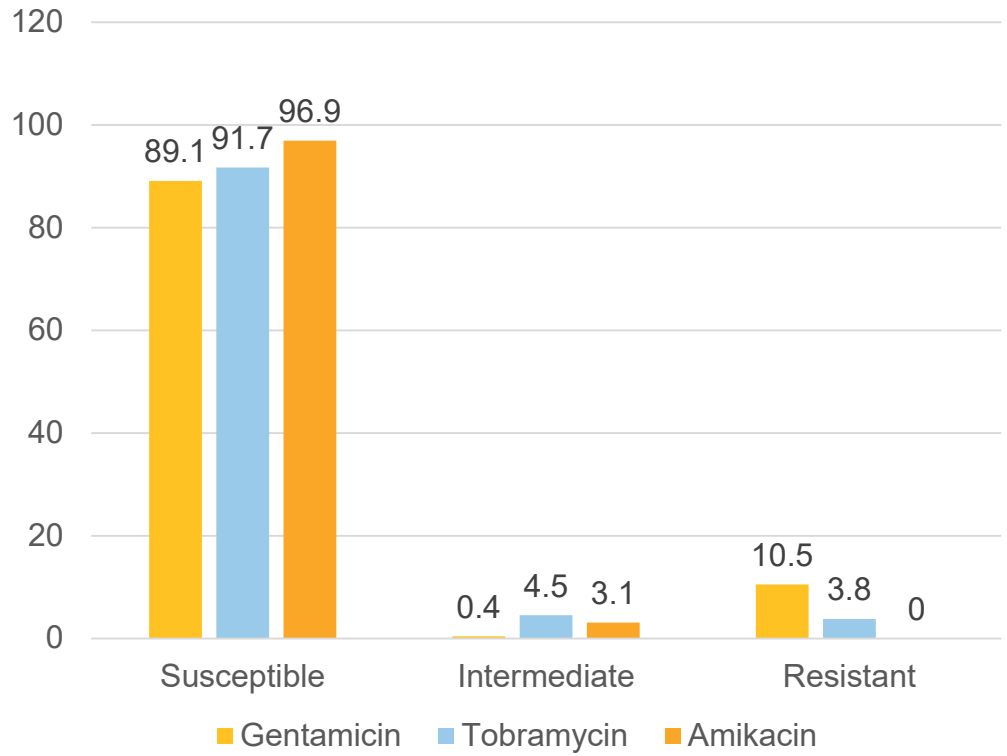
TEAMWORK

AST device company	Pharmacy & other stakeholders	Outline a plan for success
Determine breakpoints gaps What's new?	Discuss FDA indications for use vs. off-label testing,	Panel types
Last time agents were submitted for clearance	Choose the right panel, cascade, etc.	Finalize standardized cascade
Roadmap to align with updated breakpoints	Limitations	Build standardized antibiotics & panels in LIS
Off-label testing	FDA vs. CLSI breakpoints	Create calculations/rules
New organism claims		Create verification/ validation plan
FDA indications for use		Create communication plans Set target date

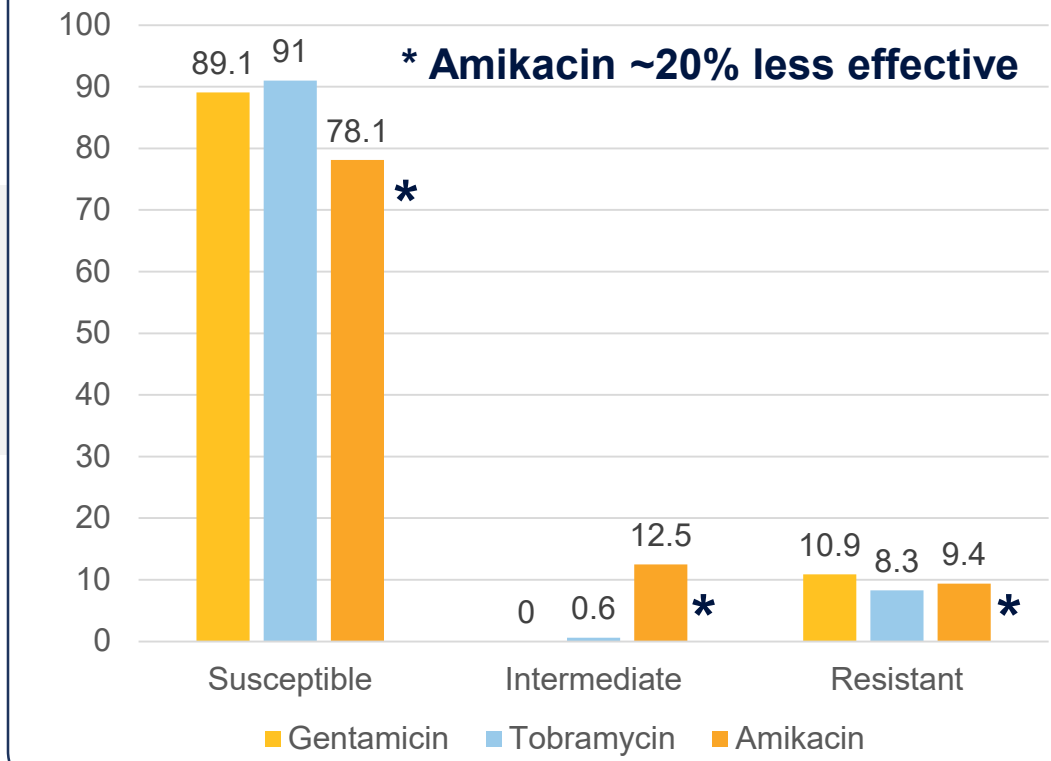
Source: Regulatory Hurdles for Updating Breakpoints: What to Know (asm.org)

Aminoglycoside Activity Against Enterobacterales

Pre-CLSI Breakpoint Changes at JW



Impact of Breakpoint Changes at JW

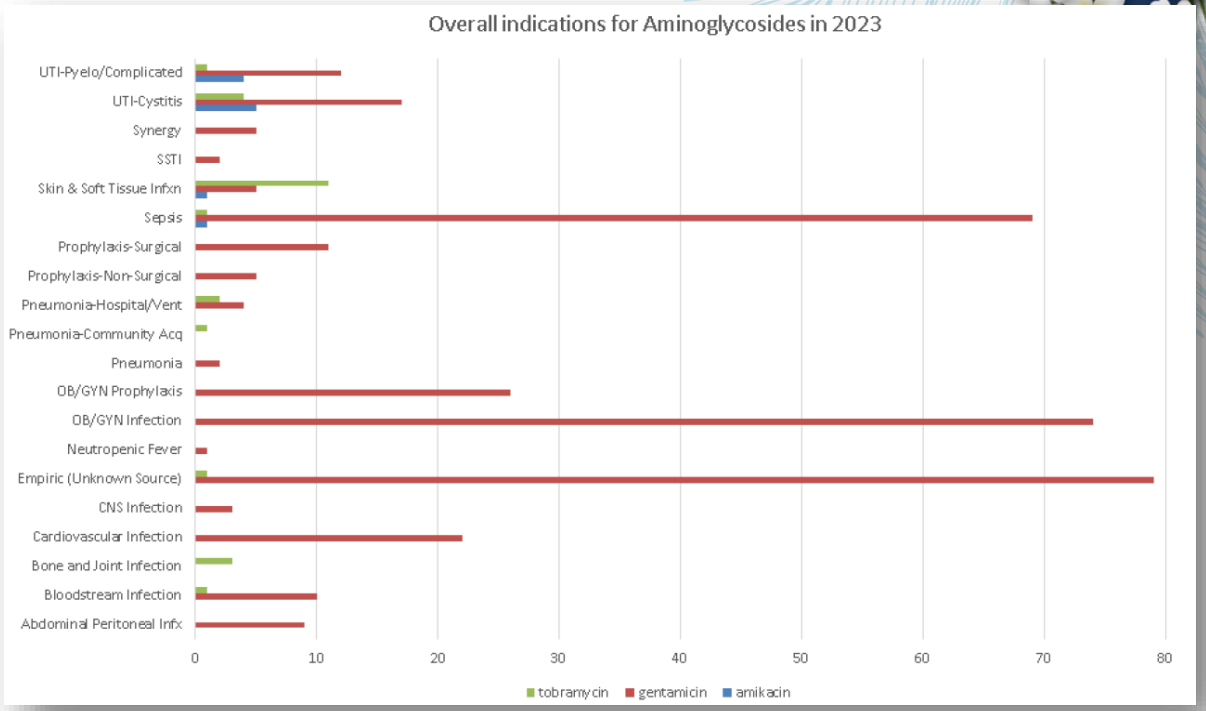


JW = Johnston-Willis Hospital

Source: CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 34th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2024.

Review Antibiotics Impacted by Breakpoint Update

- Use of aminoglycosides in sepsis & septic shock for *P. aeruginosa*
- CLSI removed gentamicin breakpoints for *P. aeruginosa*
- Update antibiogram (remove gentamicin for *P. aeruginosa* use)
- Sepsis order sets
  - Change gentamicin to tobramycin
  - Change facility-order sets



CLSI Breakpoints	Pre-	Post-	Pre-	Post-
Tobramycin susceptibility	CMC (n=196)		JW (n=94)	
	98.5%	96.9%	98.9%	96.8%

JW = Johnston-Willis Hospital
CMC = Chippenham Medical Center

How do breakpoints impact empiric selection?

Dosing (susceptible-dose dependent or MDRO)

Monotherapy vs. combination therapy

Avoidance (breakpoint removed)

Infusion time (line access)

Assessment Question #2

Changes in antibiotic breakpoints on antimicrobial use may have which of the following impacts?

A. Empiric antibiotic selection for sepsis
B. Susceptibility rate on antibiogram
C. Limited use to a certain site of infection (i.e. cystitis)
D. All of the above

Assessment Question #2

Changes in antibiotic breakpoints on antimicrobial use may have which of the following impacts?

A. Empiric antibiotic selection for sepsis

B. Susceptibility rate on antibiogram

C. Limited use to a certain site of infection (i.e. cystitis)

D. All of the above

SELECTIVE & CASCADE REPORTING

Source: Getty Images. Used with permission from HealthTrust.

Selective & Cascade Reporting

Selective Reporting

- Reporting results for specific antibiotics based on defined criteria that are unrelated to susceptibility results

Examples

- Nitrofurantoin is only reported on urine isolates
- Daptomycin is not reported on respiratory isolates

Cascade Reporting

- Reporting results for specific antibiotics based on overall susceptibility profile of that isolate
- Results for secondary or broader-spectrum agents only reported if isolate is resistant to primary or narrower-spectrum agents

Examples

- *E. coli* that is susceptible to cefazolin would have results suppressed for cefepime
- *P. aeruginosa* that is susceptible to cefepime or piperacillin/tazobactam would have results suppressed for meropenem & imipenem

Source: CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 34th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2024.

Selective & Cascade Reporting – Advantages & Evidence

Study	Results
Simon 2023	↓ broad-spectrum antibiotics, driven by ↓ in 3rd generation cephalosporins (P<0.001)
Hernando 2022	↑ testing appropriateness (P<0.0001)
Munting 2022	↓ meropenem use (P<0.001)
Daley 2018	↑ appropriate treatment (P=0.002)
Langford 2016	↓ ciprofloxacin use (P<0.001) & ↓ *E. coli* resistance at 12 & 24 months
Heireman 2022	↓ piperacillin/tazobactam use (P=0.049) & ↓ ESBLs (P<0.001) & carbapenemase-positive Enterobacterales (P=0.009)
Liao 2019	↓ cefepime use (P<0.001)
Vissichelli 2020	↓ meropenem (P=0.005), piperacillin/tazobactam (P=0.002) & ciprofloxacin (P<0.001)
Overall	↓ use of broad-spectrum, costly, less effective and/or more toxic antibiotics ↓ resistance to suppressed antibiotics ↑ use of narrow-spectrum & more appropriate antibiotics ↑ testing appropriateness

Sources: see table above and list of references at end of slide deck.

Selective & Cascade Reporting – CLSI M100 Tables 1A-1J

Why the change

- New antimicrobials
- New mechanisms of resistance
- Increasing prevalence of multidrug resistance
- Additional emphasis & requirements for antimicrobial stewardship programs

What changed

- Vertical to horizontal format to help facilitate cascade reporting
- “Groups” changed to “tiers”
- New tier (tier 3)
- Definitions & guidance for use of tiers

Tier 1	Tier 2	Tier 3	Tier 4
Appropriate for routine, primary testing & reporting	Appropriate for routine, primary testing but may be reported following cascade rules	Appropriate for routine, primary testing in sites that serve patients at high risk for MDROs but only report following cascade rules	May warrant testing & reporting by clinician request if antibiotics in other tiers are not optimal

Sources:
1. “Partnering Laboratory with Stewardship to Navigate Breakpoint Updates and Other New CLSI Recommendations to Enhance Clinical Practice,,” Society of Infectious Diseases Pharmacist, American College of Clinical Pharmacy, and Clinical and Laboratory Standards Institute. https://www.sidp.org/SIDPEC. Accessed 5/10/2024.
2. CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 34th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2024.

Example: CLSI M100 Table 1B-1 for *P. aeruginosa*

Antimicrobials by Tier Group That Should be Considered for Testing & Reporting for *P. aeruginosa*

Tier 1 Appropriate for routine, primary testing & reporting	**Tier 2** Appropriate for routine, primary testing but may be reported following cascade rules	**Tier 3** Appropriate for routine, primary testing if high MDRO rates but only report following cascade rules	**Tier 4** May warrant testing & reporting by clinician request if antibiotics in other tiers are not optimal
Ceftazidime	Imipenem, meropenem	Cefiderocol	
Cefepime		Ceftazidime-avibactam	
Piperacillin-tazobactam		Ceftolozane-tazobactam	
		Imipenem-relebactam	
Tobramycin			
Ciprofloxacin, levofloxacin			
			Aztreonam
Urine Only			
	Amikacin		

Source: CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 34th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2024.

Example: CLSI M100 Table 1B-1 for *P. aeruginosa*

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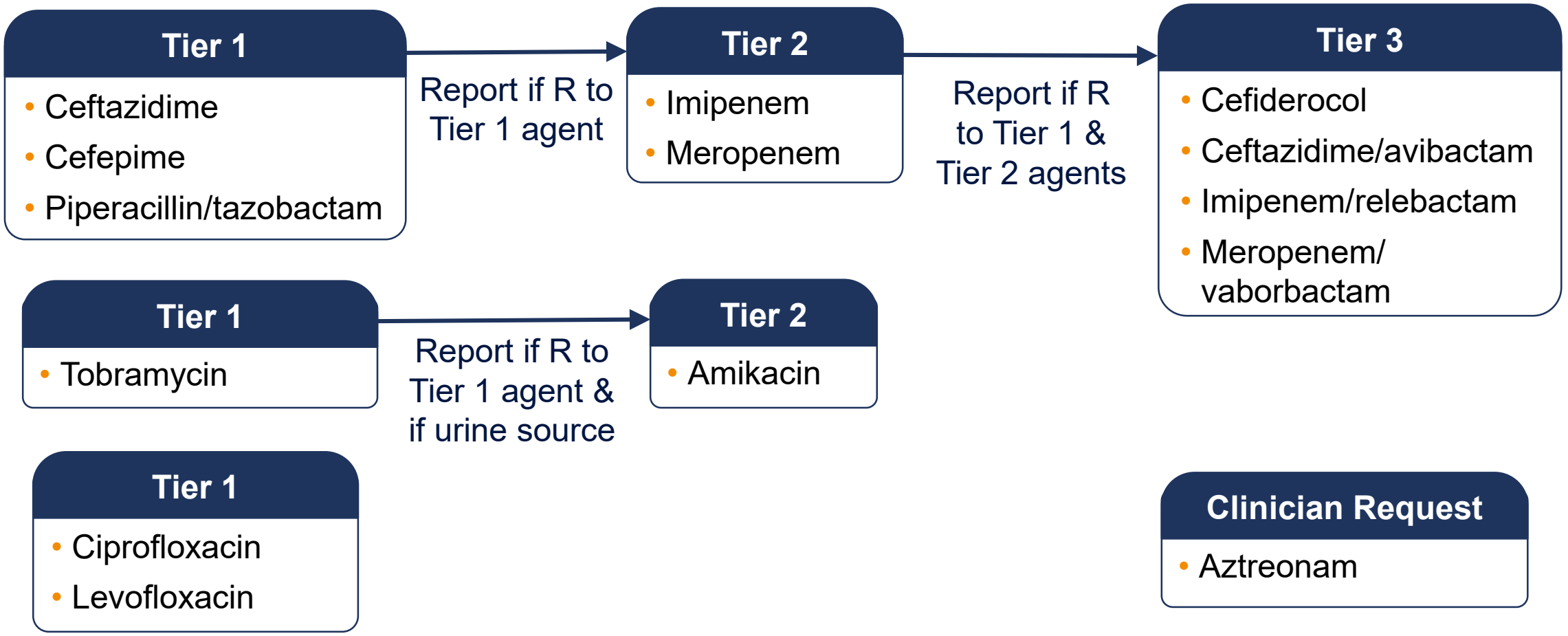

Source: CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 34th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2024.

Selective & Cascade Reporting

- Panel type
  - Formulary needs & updated breakpoints
    - Pros & cons
    - Automated vs. Manual testing
- Education
  - Training
    - Laboratory staff – understanding the why
    - Stewardship team – communicate with pharmacy/providers
    - Utilize AST device for flags/comments for reminders
- LIS/IT
  - Create rules in LIS to automate
    - Do not utilize AST device for cascade rules if possible
    - Opportunity to automate antibiogram in LIS
  - Determine a pilot site if standardizing more than one site
    - Test rules/cascade with pilot site
- Feedback/Revisions:
  - Outline a plan to track feedback & requests
    - Laboratory will receive a lot of calls/requests
    - Partner with pharmacy to escalate/assist
  - Edits to the cascade impacts laboratory
    - Additional verification/validation may be needed
    - IT/LIS resources may be needed

Case Study: Prior to Selective Reporting

- 35-year-old male is admitted to the ICU & is started on ceftriaxone for septic shock
- Blood & urine cultures obtained. Blood cultures grew polymicrobial *E. coli* & ESBL *K. oxytoca*

	ESCHERICHIA COLI		KLEBSIELLA OXYTOCA-ESBL	
	INTERP	M.I.C.	INTERP	M.I.C.
AMOXICILLIN/CLAVULANATE	S	<=2		
AMPICILLIN/SULBACTAM	S	<=2		
CEFTRIAXONE	S	<=0.25	R	>=64
CEFOXITIN	S	<=4	S	<=4
CEFEPIME			I	4
CIPROFLOXACIN	S	<=0.06	R	1
GENTAMICIN	S	<=1	S	<=1
LEVOFLOXACIN	S	<=0.12	S	1
MEROPENEM			S	<=0.25
SULFAMETHOXAZOLE/TRIMETHOPRIM	S	<=20	R	>=320

	ESCHERICHIA COLI	KLEBSIELLA OXYTOCA-ESBL
	INTERP	INTERP
AMPICILLIN	S	
CEFAZOLIN	I	R

Source: HCA Healthcare data. Not for reuse without permission of HCA Healthcare.

ESBLs: Impact of Selective Cascade Reporting

Without cascade reporting (blood)

- Ceftriaxone
- Cefoxitin

× Markers for ESBL, cefoxitin: *in vitro activity*

- Cefepime

× *In vitro* activity, use only in cystitis

- Gentamicin
- Meropenem
- Ciprofloxacin
- Levofloxacin
- TMP/SMX

✓ Drugs of choice

With cascade reporting (blood)

- Gentamicin
- Meropenem
- Ciprofloxacin
- Levofloxacin
- TMP/SMX
- Ertapenem (only if I or R)

✓ Drugs of choice

Source: HCA Healthcare LSL antibiotic susceptibility testing panels. Feb 2024 version. Not for reuse without permission of HCA Healthcare.

De-escalating Based on Susceptibilities

- The intensivist reviewed the susceptibilities for the ESBL (more resistance)
- De-escalated to cefoxitin (narrowest) susceptible option

	ESCHERICHIA COLI		KLEBSIELLA OXYTOCA-ESBL	
	INTERP	M.I.C.	INTERP	M.I.C.
AMOXICILLIN/CLAVULANATE	S	<=2		
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CEFEPIME			I	4
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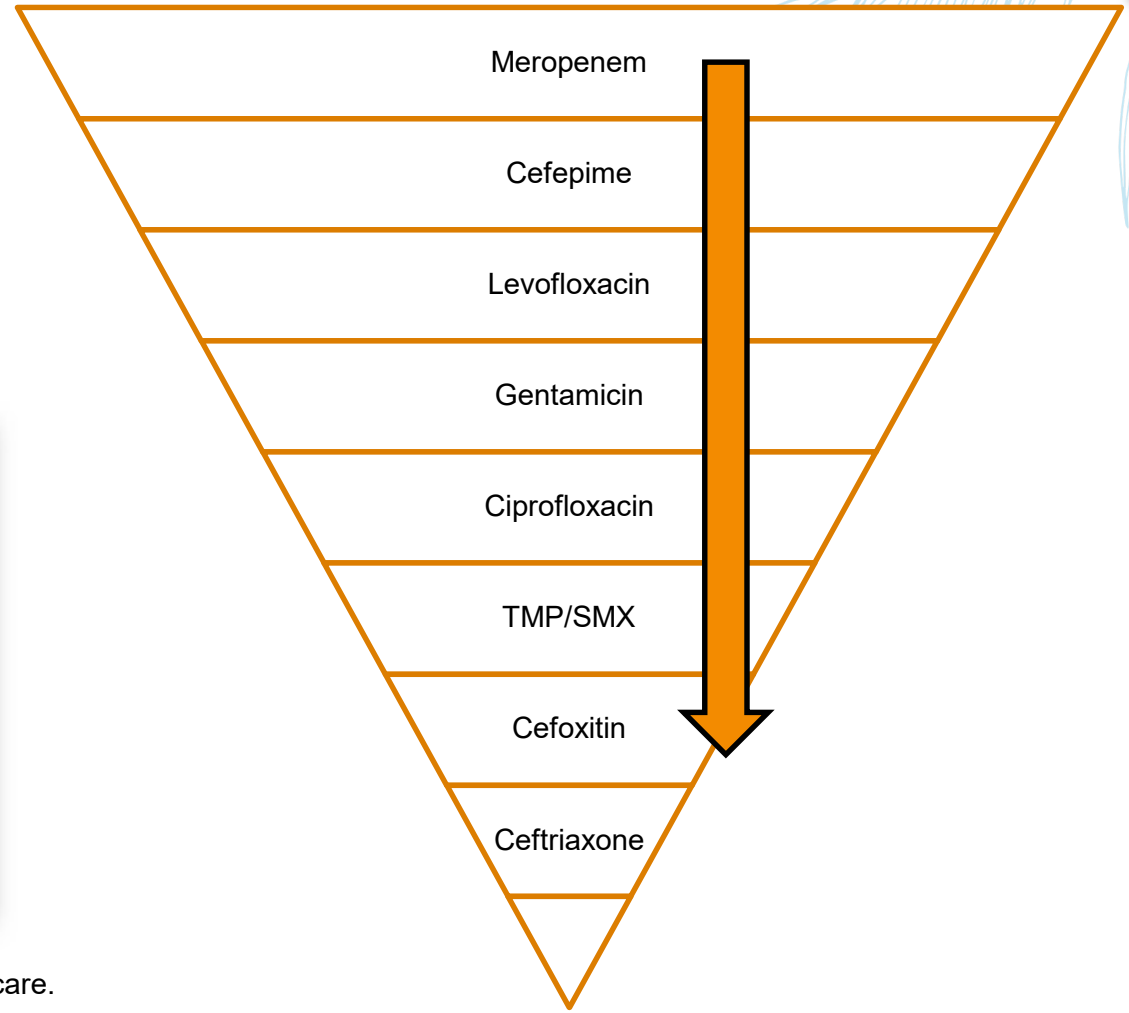
	ESCHERICHIA COLI	KLEBSIELLA OXYTOCA-ESBL
	INTERP	INTERP
AMPICILLIN	S	
CEFAZOLIN	I	R



Source: HCA Healthcare data. Not for reuse without permission of HCA Healthcare.

Current Evidence-based Medicine & Guidelines

Preferred antibiotics for systemic ESBL infections

- Critically ill: carbapenems (i.e., meropenem)
- After clinical response: oral (TMP/SMX, ciprofloxacin or levofloxacin)

Antibiotics with *in vitro* activity to avoid

- Cefepime:
  - Hydrolyzed by ESBLs
  - MIC testing can be inaccurate
- Cefoxitin (cephamycins):
  - “Stable” against ESBLs
  - Higher mortality rate compared to carbapenems in bacteremias

Sources:

1. Tamma PD, et al. Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections. *Clin Infect Dis.* 2023;, ciad428.
2. Yang CC, et al. Discrepancy between effects of carbapenems and flomoxef in treating nosocomial hemodialysis access-related bacteremia secondary to extended spectrum beta-lactamase producing Klebsiella pneumoniae in patients on maintenance hemodialysis. *BMC Infect Dis*. 2012; 12:206.
3. Lee CH, et al. Comparative effectiveness of flomoxef versus carbapenems in the treatment of bacteremia due to extended-spectrum beta-lactamase producing Escerichia coli or Klebsiella pneumoniae with emphasis on minimum inhibitory concentration of flomoxef: A retrospective study. *Int J Antimicrob Agents*. 2015; 46(6): 610-5.

Assessment Question #3

You are rounding with the intensivist team & notice the provider has narrowed ceftriaxone to cefoxitin for patient in septic shock

QTc 580, Scr 2.5 (baseline 1)

What do you recommend?

A. Continue cefoxitin

B. Escalate to levofloxacin

C. Escalate to gentamicin

D. Escalate to meropenem

QTc = corrected QT interval
Scr = serum creatinine

	ESCHERICHIA COLI		KLEBSIELLA OXYTOCA-ESBL	
	INTERP	M.I.C.	INTERP	M.I.C.
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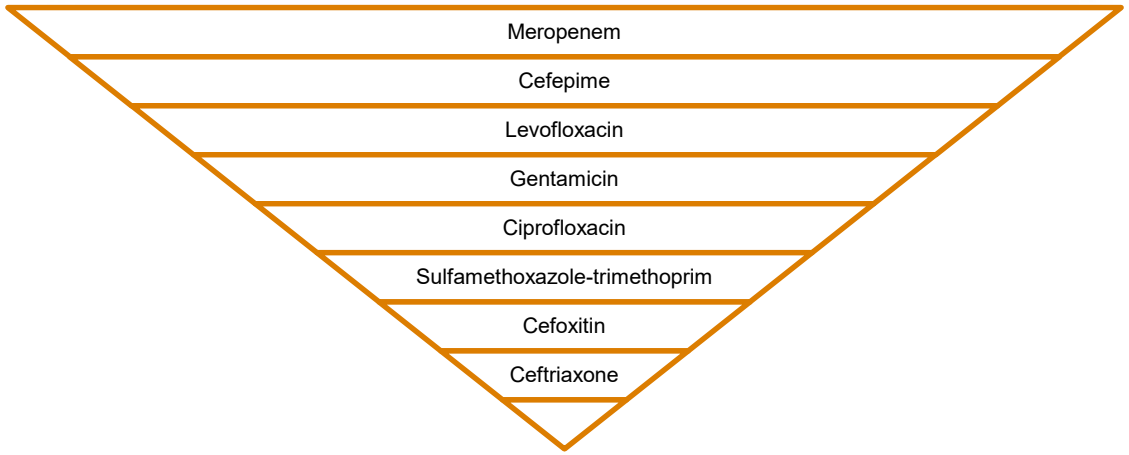
	INTERP	INTERP
AMPICILLIN	S	
CEFAZOLIN	I	R



Assessment Question #3

You are rounding with the intensivist team & notice the provider has narrowed ceftriaxone to cefoxitin for patient in septic shock

QTc 580, Scr 2.5 (baseline 1)

What do you recommend?

A. Continue cefoxitin

B. Escalate to levofloxacin

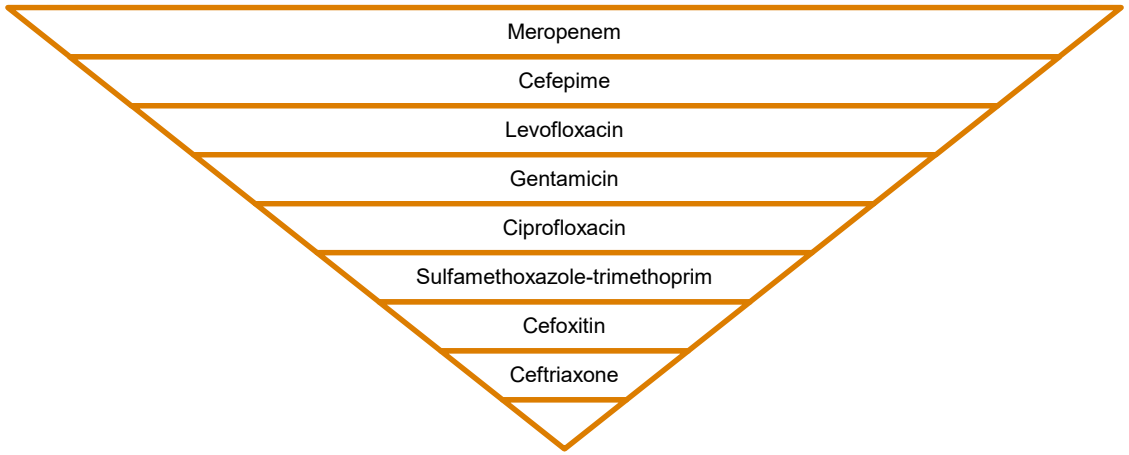
C. Escalate to gentamicin

D. Escalate to meropenem

QTc = corrected QT interval
Scr = serum creatinine

	ESCHERICHIA COLI		KLEBSIELLA OXYTOCA-ESBL	
	INTERP	M.I.C.	INTERP	M.I.C.
AMOXICILLIN/CLAVULANATE	S	<=2		
AMPICILLIN/SULBACTAM	S	<=2		
CEFTRIAXONE	S	<=0.25	R	>=64
CEFOXITIN	S	<=4	S	<=4
CEFEPIME			I	4
CIPROFLOXACIN	S	<=0.06	R	1
GENTAMICIN	S	<=1	S	<=1
LEVOFLOXACIN	S	<=0.12	S	1
MEROPENEM			S	<=0.25
SULFAMETHOXAZOLE/TRIMETHOPRIM	S	<=20	R	>=320

	ESCHERICHIA COLI	KLEBSIELLA OXYTOCA-ESBL
	INTERP	INTERP
AMPICILLIN	S	
CEFAZOLIN	I	R



Case Study: CRE Infections

Urine culture

ESCHERICHIA COLI-CRE

	INTERP	M.I.C.
CEFTAZIDIME	R	>=64
CEFEPIME	R	>=32
CIPROFLOXACIN	R	>=4
NITROFURANTOIN	S	<=16
GENTAMICIN	S	<=1
LEVOFLOXACIN	R	>=8
MEROPENEM	R	>=16
PIPERACILLIN/TAZOBACTAM	R	>=128
SULFAMETHOXAZOLE/TRIMETHOPRIM	S	<=20

ESCHERICHIA COLI-CRE

	INTERP	M.I.C.
CEFTAZIDIME	R	>=64
NITROFURANTOIN	S	<=16
GENTAMICIN	S	<=1
MEROPENEM	R	>=16
SULFAMETHOXAZOLE/TRIMETHOPRIM	S	<=20
MEROPENEM-VABORBACTAM	R	32
CEFTAZIDIME/AVIBACTAM	R	>=16
TETRACYCLINE	S	2

Blood culture

Organism 1 ESCHERICHIA COLI-CRE
ADDITIONAL SUSCEPTIBILITY TO FOLLOW
1 SET POSITIVE OUT OF 2 SETS COLLECTED

ESCHERICHIA COLI-CRE

	INTERP	M.I.C.
CEFTAZIDIME	R	>=64
CIPROFLOXACIN	R	>=4
GENTAMICIN	S	<=1
LEVOFLOXACIN	R	>=8
MEROPENEM	R	>=16
SULFAMETHOXAZOLE/TRIMETHOPRIM	R	>=320
MEROPENEM-VABORBACTAM	R	>=64
CEFTAZIDIME/AVIBACTAM	R	>=16
TETRACYCLINE	S	2

ESCHERICHIA COLI-CRE

	INTERP	M.I.C.
IMIPENEM RELEBACTAM	R	>=32

S
R (cascade testing)

Source: HCA Healthcare LSL antibiotic susceptibility testing panels. Feb. 2024 version. Not for reuse without permission of HCA Healthcare.

Multi-step Process for Microbiology

Multi-drug resistant organism detected

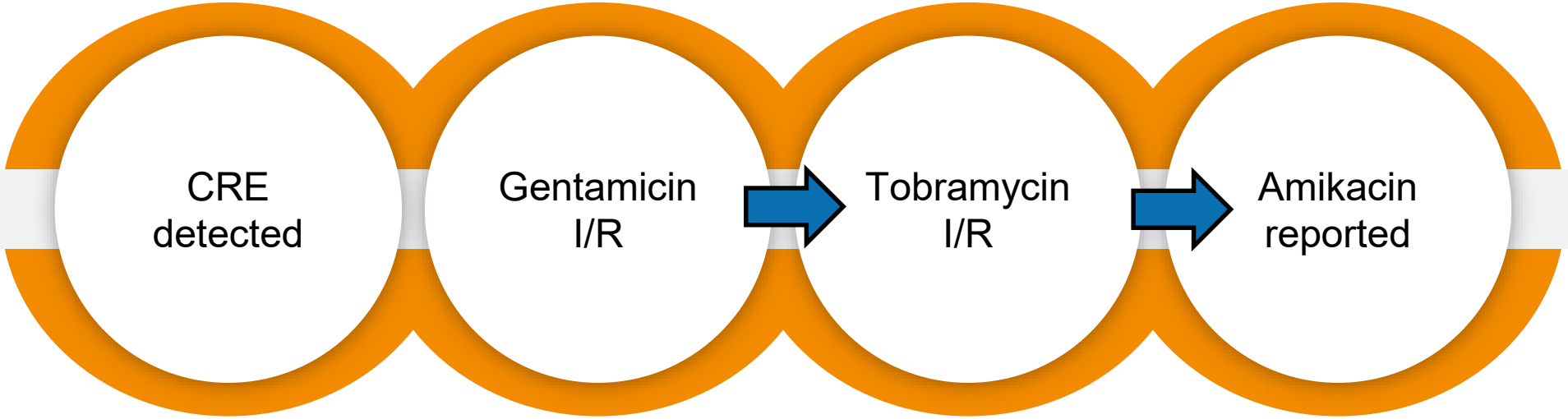
Selectively report for urine cultures

Additional testing by request only

Kirby Bauer or E-test if certain antibiotics are intermediate/resistant

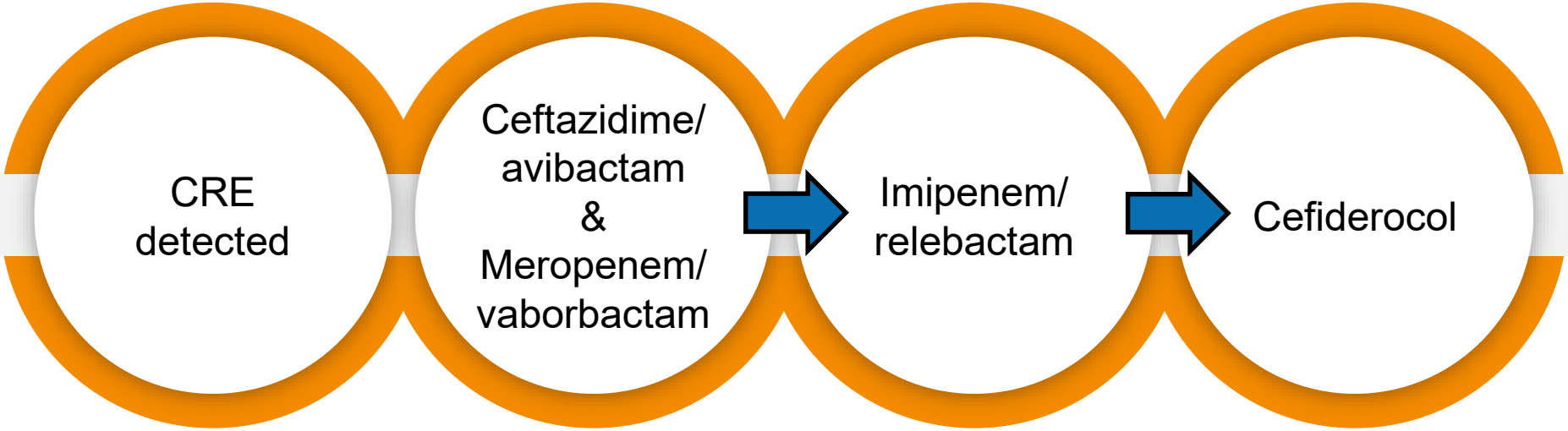
Source: HCA Healthcare LSL antibiotic susceptibility testing panels. Feb. 2024 version. Not for reuse without permission of HCA Healthcare.

Cascade Reporting to Help the Clinician



Source: HCA Healthcare LSL antibiotic susceptibility testing panels. Feb. 2024 version. Not for reuse without permission of HCA Healthcare.

Cascade Reporting When Resistance Is Detected



Source: HCA Healthcare LSL antibiotic susceptibility testing panels. Feb 2024 version. Not for reuse without permission of HCA Healthcare.

HCA PROCESS IN 2023-2024

Source: Getty Images. Used with permission from HealthTrust.

HCA Process in 2023–2024

- HCA standardized AST reporting across HCA to:
  - Phase out obsolete breakpoints
  - Comply with CAP/regulatory requirements
  - Support HCA Clinical Pharmacy Services stewardship initiatives by:
    - Standardizing antibiotic test panels used by HCA microbiology laboratories
    - Standardizing antibiotic suppression & cascade rules used across HCA laboratories using Table 1 in CLSI M100 as a guide
    - Aligning with formulary- and guideline-recommended antibiotics

HCA Process in 2023–2024

- Implementation plan for clinical labs

Source: HCA Healthcare. Not for reuse without permission of HCA Healthcare.

HCA Process in 2023–2024

- **Challenges**
  - Staffing
  - IT/LIS resources
    - Dictionary not standardized by all sites
      - Created standardized antibiotics & panels
      - Unable to standardize organism dictionary
  - AST devices not standardized across HCA
    - Need to update software – additional $$ or new analyzers needed
    - Rules & flags not standardized across platforms
  - Pharmacy/providers
    - Special requests
    - Increased phone calls to the lab

- **We are in a better place**
  - ✓ Standardized cascade & AST reporting for the enterprise
  - ✓ Great Laboratory, Pharmacy & IT/LIS collaboration/alignment
  - ✓ Aligned in antibiotic stewardship

HCA Standardized Cascade Rules – Goals

Goals

Establish a standard set of cascade rules that will be implemented across all HCA facilities

Ensure appropriate antibiotics are tested for susceptibilities

Report results that will encourage use of the most effective & narrow-spectrum antibiotic

Display susceptibility results that help clinicians provide the best patient care

- (SUSCEPTIBILITY,N802 and XN15) Pseudomonas aeruginosa sensitivities:
- CEFEPIME - S (4)
- CIPROFLOXACIN - I (2)
- LEVOFLOXACIN - R (4)
- PIPERACILLIN/TAZOBACTAM - S (<=4)
- TOBRAMYCIN - S (<=1)

- (SUSCEPTIBILITY,N802 and XN15) Escherichia coli sensitivities:
- AMOXICILLIN/CLAVULANATE - R (>=32)
- AMPICILLIN/SULBACTAM - R (>=32)
- CEFTRIAXONE - S (<=0.25)
- CEFOXITIN - S (<=4)
- CIPROFLOXACIN - S (<=0.06)
- GENTAMICIN - S (<=1)
- LEVOFLOXACIN - S (<=0.12)
- SULFAMETHOXAZOLE/TRIMETHOPRIM - R (>=320)

HCA Standardized Cascade Rules – Initial Steps

Review & feedback between enterprise Lab & Pharmacy teams

Finalization of standardized cascade

Communication & education with Divisions & facilities

Establish implementation date with Divisions & facilities based on IT support

Collaboration between enterprise Lab service line & ID Pharmacy team

HCA Standardized Cascade Rules

Gram-negative rods – Enterobacterales

Enterobacterales	Ciprofloxacin/Levofloxacin: Suppress for urine isolates
ESBL & CRE	Ciprofloxacin/Levofloxacin: Do not suppress for urine isolates
	Non-urine isolates: Suppress cefazolin, ceftriaxone, cefoxitin, cefepime, piperacillin/tazobactam, aztreonam, ampicillin, ampicillin/sulbactam
	Urine isolates: suppress cefazolin, ceftriaxone, cefoxitin, aztreonam, ampicillin, ampicillin/sulbactam
	Tetracycline: Routinely report
CRE	Report ceftazidime/avibactam & meropenem/vaborbactam
Ertapenem	Report if ertapenem is I or R & meropenem is S

HCA Standardized Cascade Rules

Gram-negative rods – Non-fermenter

Pseudomonas aeruginosa	Meropenem: Report when cefepime or piperacillin/tazobactam is I/R
	Tobramycin: Test by KB when cefepime OR piperacillin/tazobactam is I/R
	Ceftolozane/tazobactam: Report when I/R to cefepime & ceftazidime & piperacillin/tazobactam & meropenem
	Ceftazidime/avibactam: Report when I/R to cefepime & ceftazidime & piperacillin/tazobactam & meropenem & ceftolozane/tazobactam
	Imipenem/relebactam: report when I/R to meropenem & ceftolozane/tazobactam & ceftazidime/avibactam
	Amikacin: Suppress for non-urine isolates
Burkholderia cepacia	Report TMP/SMX, ceftazidime & meropenem routinely by Etest
Other Non-Enterobacterales	Report cefepime, gentamicin, piperacillin/tazobactam & TMP/SMX routinely by Etest

HCA Standardized Cascade Rules

Gram-positives

Methicillin-resistant *S. aureus* (MRSA)	Linezolid	Sterile sources: Routinely report
		Non-sterile sources: Report when TMP/SMX is I/R or when tetracycline is I/R
	Daptomycin	Sterile sources: Routinely report
Enterococcus	Linezolid	Routinely report on sterile sources
		For all other sources, report when ampicillin is I/R or when vancomycin is I/R
	Daptomycin	Report when ampicillin is I/R or when vancomycin is I/R
		Do not report on isolates from respiratory sources

HCA Standardized Cascade Rules

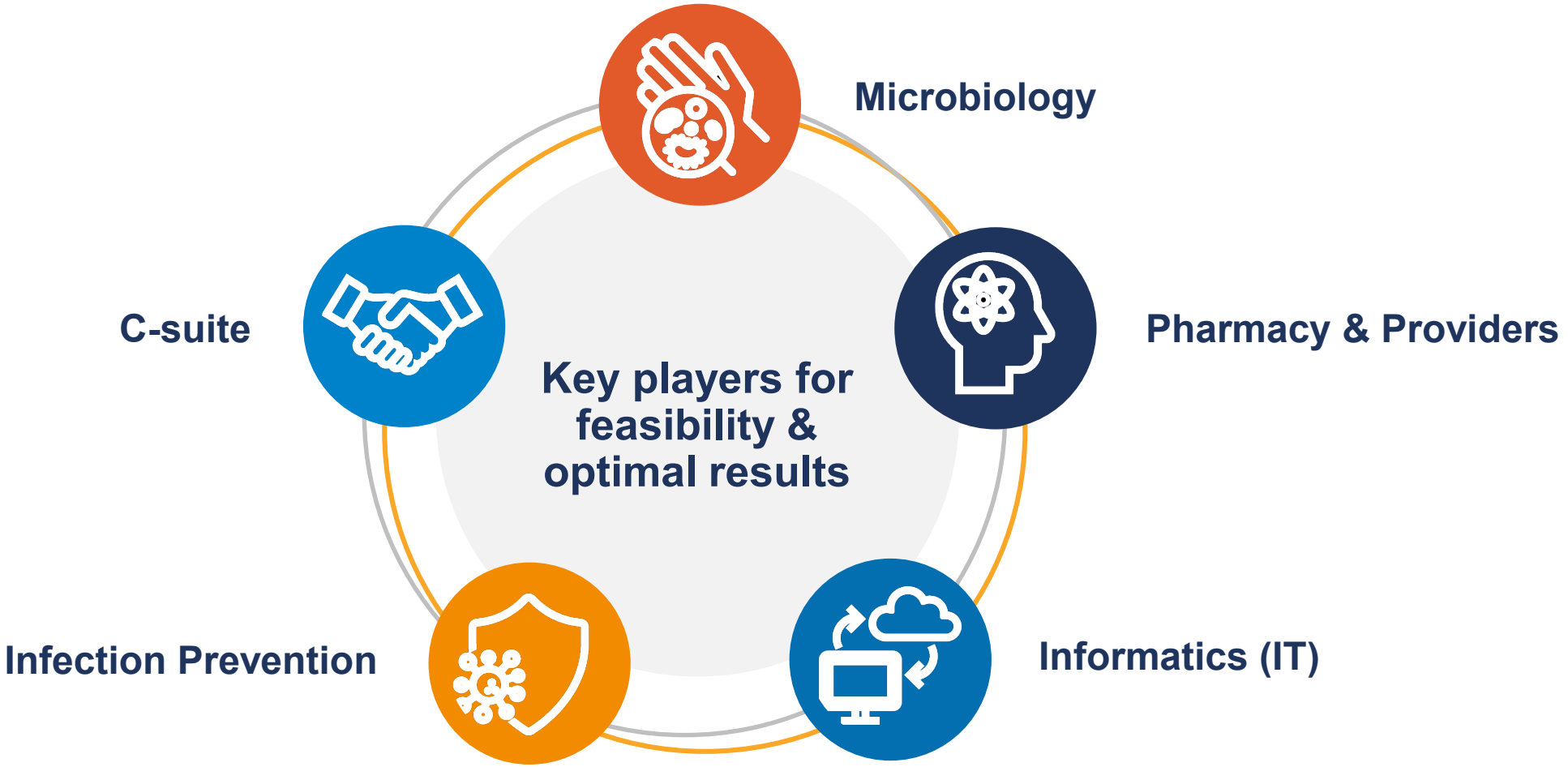
Challenges

- HCA facilities use 1 of 3 AST panels/cards: Vitek, MicroScan MIC & MicroScan Combo
- IT support for rule building & troubleshooting
- Different levels of antimicrobial stewardship support & initiatives
- Facilities with existing cascade rules more or less restrictive than others
- Gaps in communication

Future State

- Measuring the impact
- Feedback from frontline stewardship teams
- Requests for changes
- Continued collaboration to update breakpoints & AST panels/cards
- Make updates when necessary based on antimicrobial stewardship goals, resistance rates & pharmacy formulary

Interdisciplinary Collaboration



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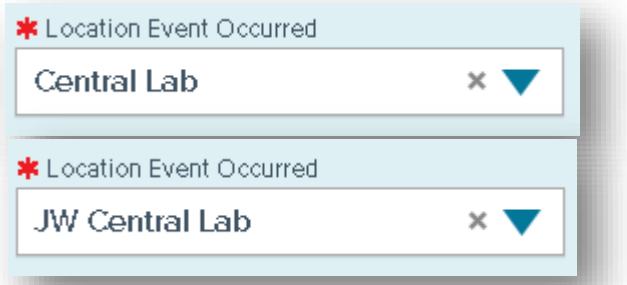
Educating Frontline Providers

Emergency Department	Culture call backs Adjusting treatment empirically
Expectations	Selective reporting & cascade testing Instrumentation limitations
Errors or delays	Shortage of testing Limitation on susceptibilities
Reporting	Escalation to leadership or lead steward Real-time submission into tracking platform

Quality Improvement

Track Issues

- Standardized reporting system



- Review trends
  - Gram stains
  - Turn-around-times
  - MDROs

Educate & Optimize

- New hires
- Cascade updates
- IT cross-over from central lab to EHR
- Escalation to leadership

2024 Antibiograms: Creation & Validation

- Need data from antimicrobial susceptibility testing
- Electronic health record limitation (cascade rules)
- Compare with prior year
  - Number of isolates
  - Susceptibility rates
- Organism standardization reporting
  - MDROs or organism nomenclature change
  - Removes duplicates
  - 1st organism per patient per year/timeframe (routine/MDRO)
  - Query by organism group (remove duplicates)

CHIPPENHAM HOSPITAL — **All Isolates**

January – December 2022 Data	% Susceptible (A blank box means the drug is not reported for that bacteria)															
GRAM NEGATIVE	**# ISOLATES**	**AMPICILLIN**	**CEFAZOLIN**	**CEFTRIAXONE**	**CEFTAZIDIME**	**CEFEPIME**	**AMP/ SULBACTAM**	**PIP/TAZOBACTAM**	**MEROPENEM**	**CIPROFLOXACIN**	**LEVOFLOXACIN**	**GENTAMICIN**	**TOBRAMYCIN**	**AMIKACIN**	**NITROFURANTOIN**	**TMP/SMX**
Escherichia coli	510	50	74	88			59	97	100	74	69	90	91	100	97	72
Klebsiella pneumoniae	186		74	83			68	89	100	80	72	90	88	96	27	82
Proteus mirabilis	104	80	83	98			92	100	100	81	81	95	96			86
Enterobacter cloacae	48			71		98		79	100	94	92	100	100		45	92
Klebsiella (Enterobacter) aerogenes	[a]39			74		100		79	100	97	92	97	97			100
Serratia marcescens	31			94					100	94	94	97	71			100
Morganella morganii	[a]35			77		91	9	97	100	77	89	97	97			97
Pseudomonas aeruginosa	175					93		78	89	87	78	95	99	99		
Acinetobacter baumannii	[a]39				38		79	45	49	46	46	74	67			59
Stenotrophomonas maltophilia	[a]39				39						92					85

GRAM POSITIVE	**# ISOLATES**	**PENICILLIN**	**AMPICILLIN**	**OXACILLIN**	**CEFTRIAXONE**	**ERYTHROMYCIN**	**LEVOFLOXACIN**	**GENTAMICIN SYNERGY**	**STREPTOMYCIN SYNERGY**	**CLINDAMYCIN**	**LINEZOLID**	**NITROFURANTOIN**	**RIFAMPIN (do not use alone)**	**TETRACYCLINE**	**TMP/SMX**	**VANCOMYCIN**
Staph aureus (MRSA only)	177			0		9		97		61			99	87	92	100
Staph aureus (MSSA only)	232			100		56		99		73			100	92	95	100
Staphylococcus epidermidis	99			25		26		90					97		54	100
Strep pneumoniae:	[a]28					64	100							89	86	100
Meningitis		64			89											
Non-meningitis [c]		100			100											
Enterococcus faecalis	157		99					75	90			99		23		99
Enterococcus faecium	[a]67		13					97	30			16		13		30
Enterococcus faecium (VRE)	[a]47		0					96	13		100	21		7		0
Enterococcus faecium (VSE)	[a]20		45					100	70			0		30		100

[a] Includes combined data from both Chippenham and Johnston-Willis
Antibiotics with ≥ 80% activity can be used for empiric treatment of suspected (or known) pathogen, streamline based on susceptibilities

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Future Directions for Optimizing Therapy

- Automated comments
  - *H. influenzae*: beta-lactamase negative vs. positive
  - Guidance for interpretation
    - Susceptible-dose dependent (SDD)
    - Vancomycin-resistant Enterococcus (different species)
- Cascade optimization
  - New FDA-approved drugs
  - Turn-around time with results
- Annual CLSI updates

Assessment Question #4

Which of the following best describes the purpose of developing cascade and selective reporting rules in collaboration with microbiology and antimicrobial stewardship teams?

a. Encourage the use of narrow-spectrum antibiotics

b. Reduce the risk of treatment failure

c. Ensure formulary and preferred antibiotics are being tested and reported

d. All of the above

Answer: Assessment Question #4

Which of the following best describes the purpose of developing cascade and selective reporting rules in collaboration with microbiology and antimicrobial stewardship teams?

a. Encourage the use of narrow-spectrum antibiotics

b. Reduce the risk of treatment failure

c. Ensure formulary and preferred antibiotics are being tested and reported

d. All of the above

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Thank you…

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