Clinical and Laboratory Standards Institute Antimicrobial Susceptibility Testing Updates

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Ochsner Health

Disclosures

- Gilead Sciences – Advisory board, speakers bureau
- Melinta Therapeutics – Speakers bureau
- Theratechnologies – Advisory board

Objectives

- Review antimicrobial susceptibility testing (AST) updates
- Discuss pharmacokinetic/pharmacodynamic data supporting AST updates
- Outline clinical implications of AST

Susceptibility Testing Basics

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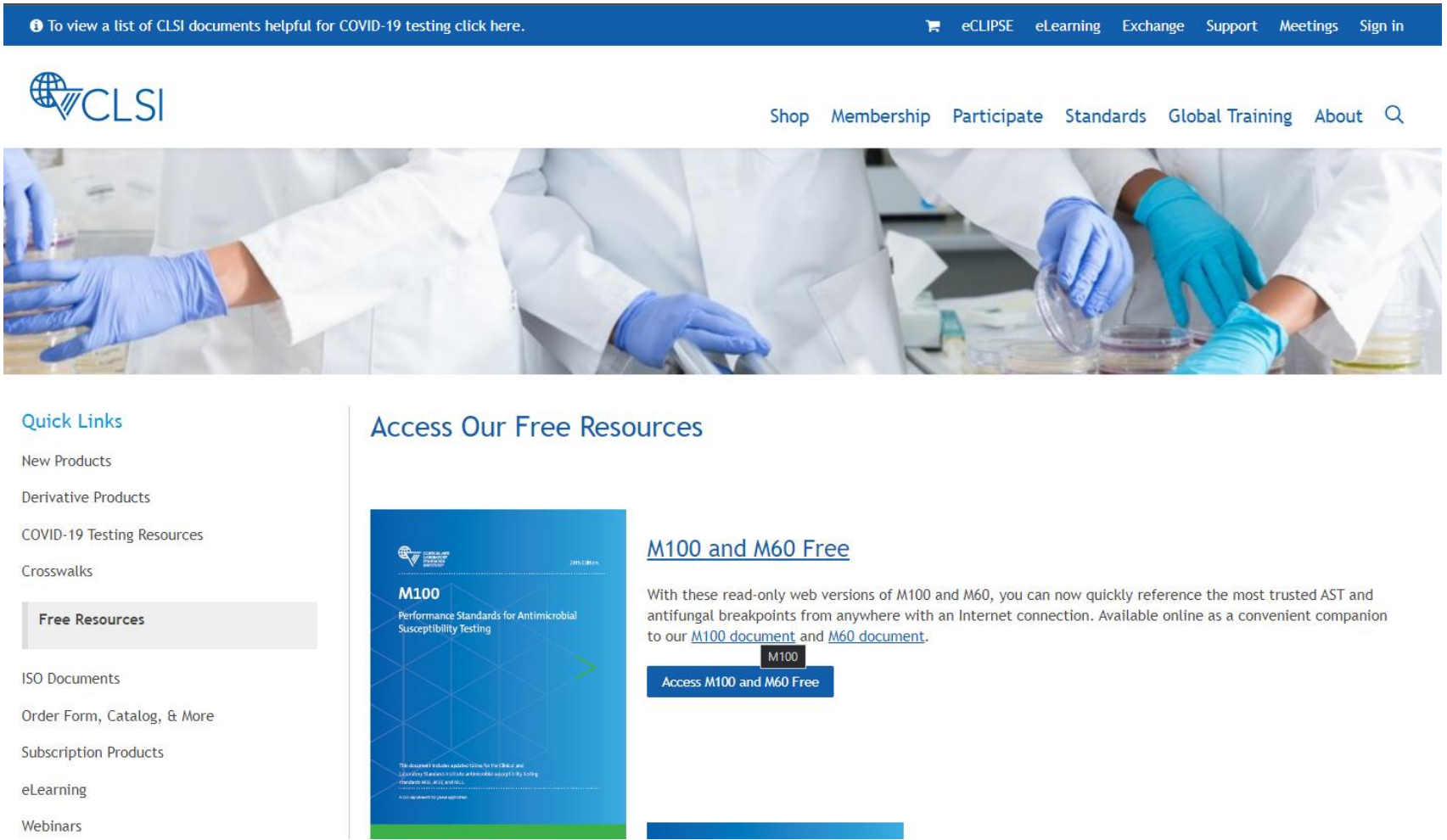
Susceptibility Testing Resources

- https://clsi.org/standards/products/free-resources/access-our-free-resources/



Microbes are susceptible…not sensitive

Susceptibility Testing

- Minimum Inhibitory Concentration (MIC)
  - Lowest concentration of antibiotic that prevents visible growth
  - Feasible to operationalize at a macro/clinical lab level
  - Clinically applied for most PK/PD analyses
- Minimum Bactericidal Concentration (MBC)
  - Lowest concentration of antibiotic that kills 99.9% of organism
  - Exceptionally laborious outside of research setting

Quantity vs Quality??

MIC-Based Testing**

Broth Microdilution

- Organism suspended in liquid media
- Varying concentrations of drug tested
- Lowest effective concentration reported as MIC
- Standard method for reporting MICs correlated with S, I, R interpretation

Etest ®

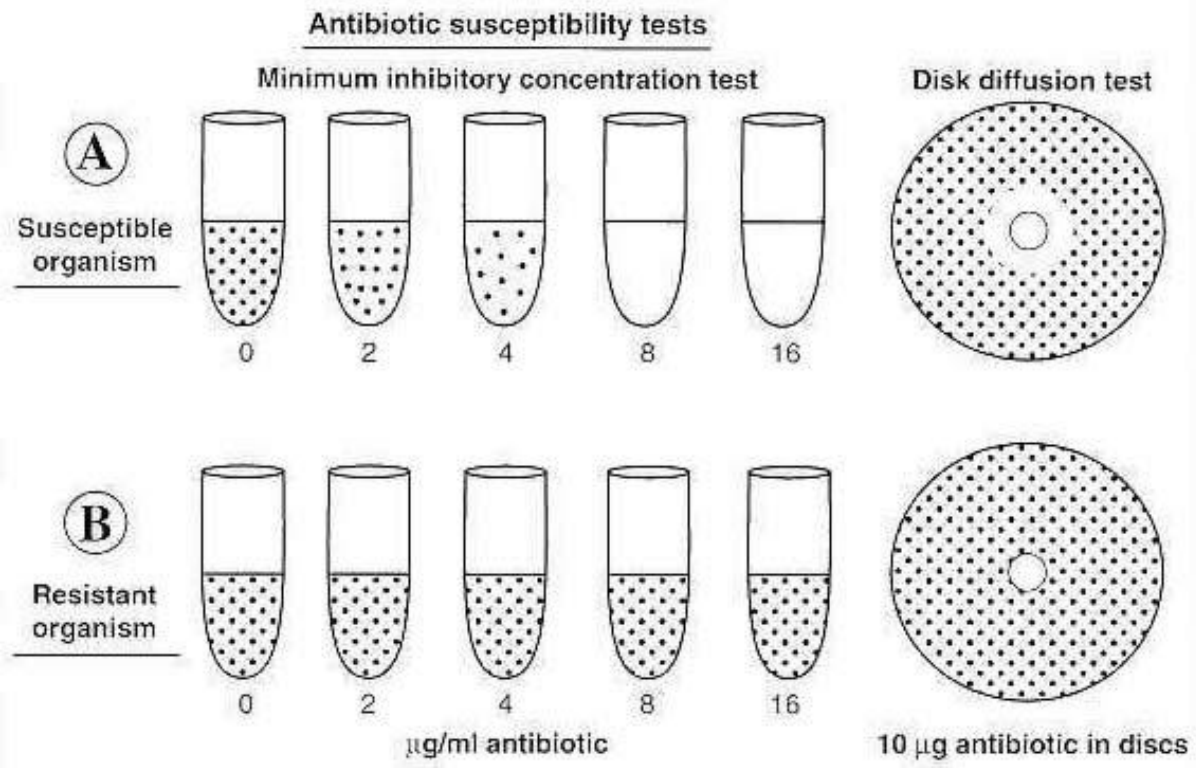
- Organism plated on Mueller-Hinton agar
- Nitrocellulose strip with escalating drug concentrations applied to agar
- Point where growth crosses strip read as MIC

Qualitative Testing

Disk Diffusion (Kirby-Bauer)

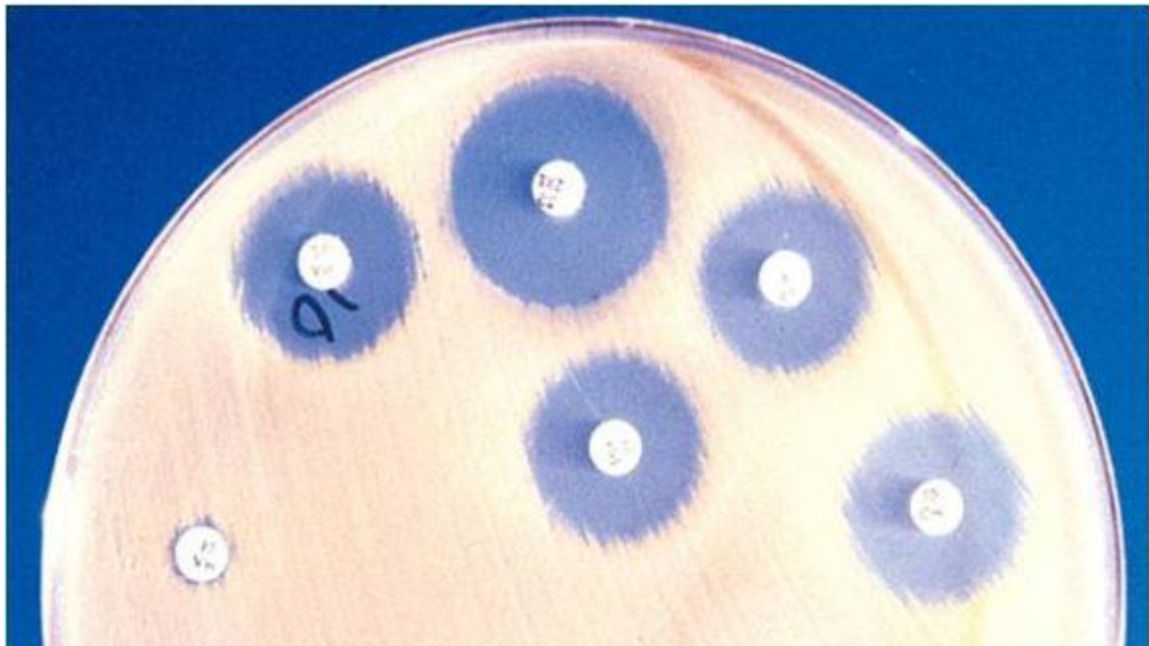
- Organism plated on Mueller-Hinton agar
- Drug-impregnated disk applied to agar → drug diffuses across agar
- Zone of inhibited growth measured in millimeters (mm)
- Larger the zone…more active the drug
- Zone of inhibition correlated with S, I, R interpretation...*or should*

**Modified versions utilized by standard automated platforms



Broth Microdilution

Kirby-Bauer (Disk Diffusion)



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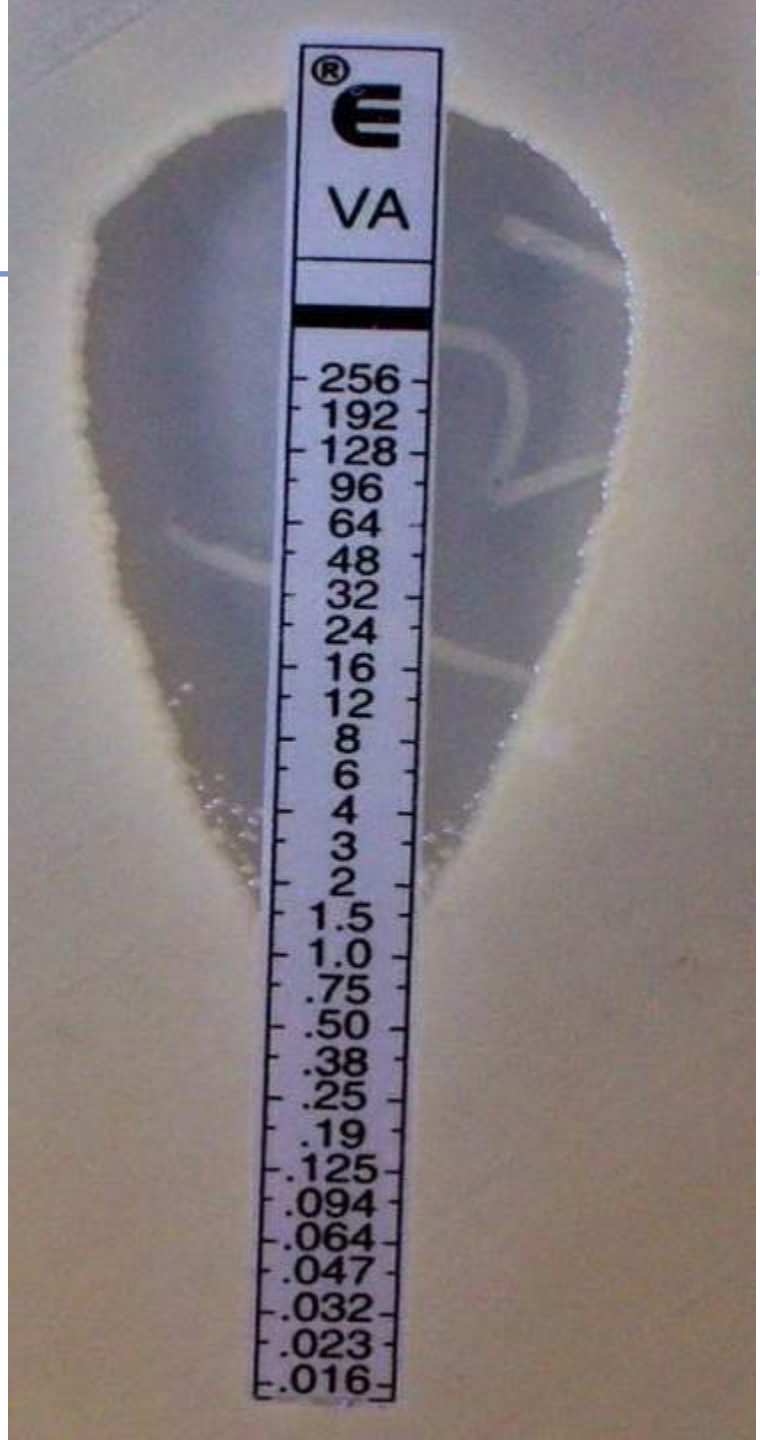
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Pharmacodynamic Targets

- **Time > MIC (concentration-INdependent)**
  - Time that drug concentration exceeds MIC
  - Expressed as % of dosing interval
  - *Ex:* Beta-Lactams
- **Peak concentration to MIC (concentration-dependent)**
  - Peak drug concentration achieved after dose related to MIC
  - *Ex:* Aminoglycosides
- **Area Under Concentration Curve (AUC) > MIC**
  - Relationship of total drug exposure to MIC
  - *Ex:* Vancomycin

Clinical Breakpoints

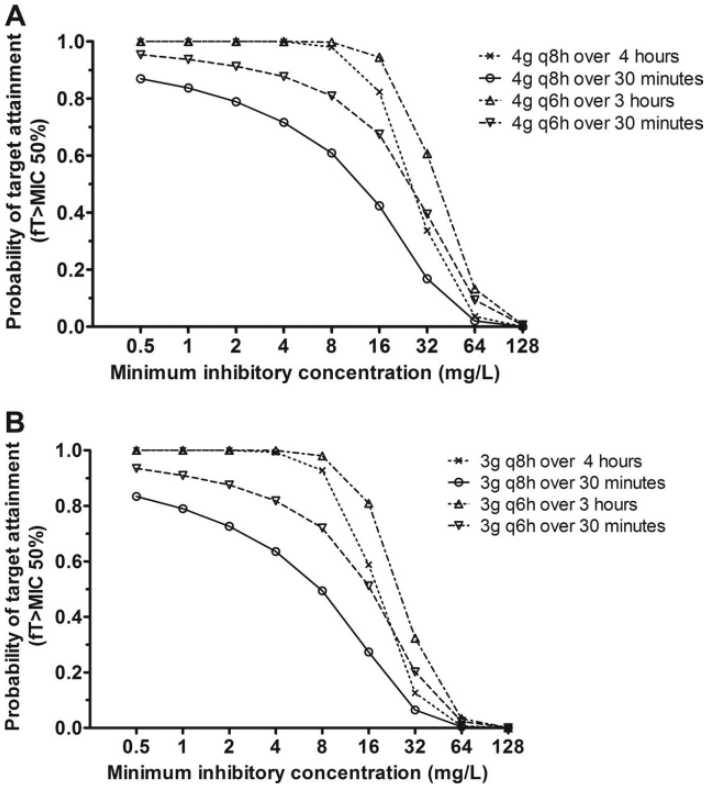
- Surrogayr for prediction of therapeutic success
- Classic Susceptible/Intermediate/Resistant structure
  - Shifting towards S/SDD*/R
- Based on:
  - MIC distributions (wildtype or nah…)
  - PK/PD models
  - Animal data
  - Human data
  - Clinical testing capabilities

*Susceptible-dose dependent

Piperacillin-Tazobactam

Hello…Is It Me You're Looking For?

- Everyone's go-to
- Antiquated dosing strategies
- High loss of PTA at MICs > 16 mcg/mL
  - Old BP ≤ 16 mcg/mL
  - Based on 30 min infusions
- Increased prevalence of narrow OXAs
  - 37.4% in MERINO surveillance
  - Associated with elevated but "S" MICs



Felton TW et al. AAC 2012 Aug; 56(8): 4087–4094

All the enzymes

Heavy heterogeneity across MIC spectrum

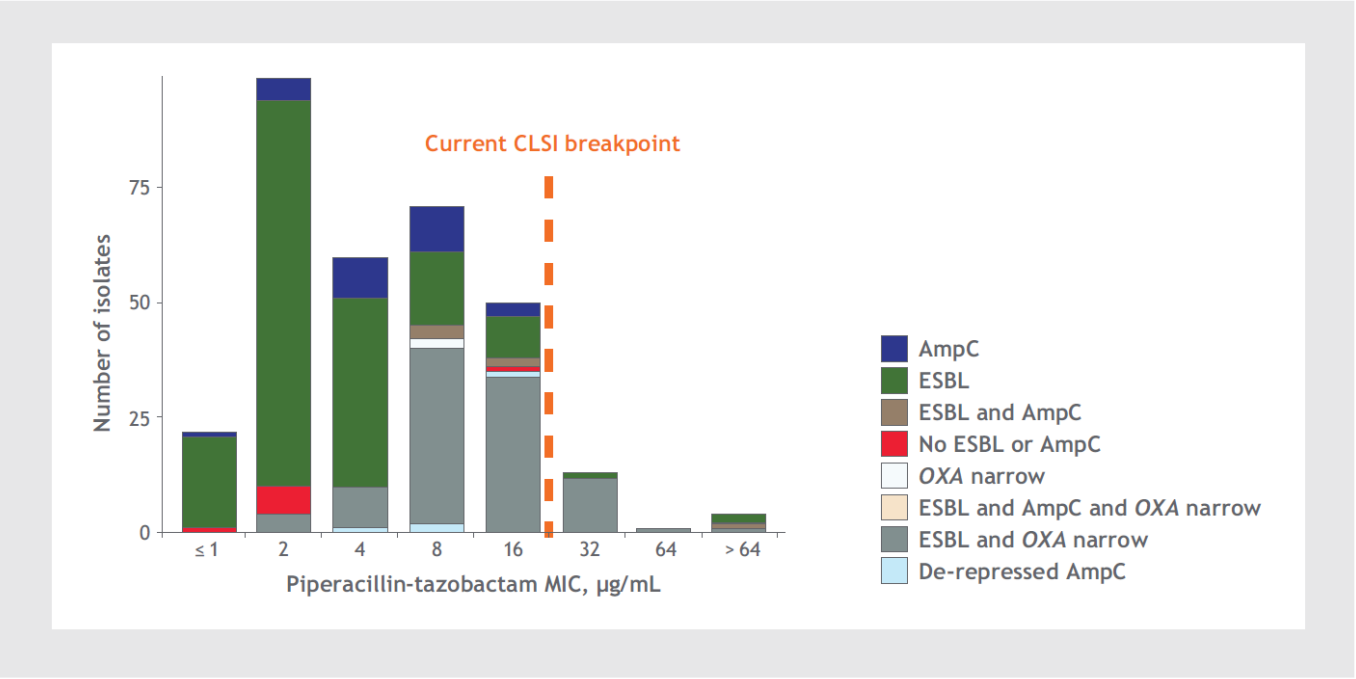


Figure 3. Piperacillin-Tazobactam MIC Distribution for *Escherichia coli* and *Klebsiella pneumoniae* Isolated in the MERINO Trial[9]

CLSI. Piperacillin-Tazobactam Breakpoints for Enterobacterales. 1st Ed. CLSI Rationale Document MR14. Clinical and Laboratory Standards Institute; 2022

Importance of the Infusion

- Demonstrable dose/infusion dependency
- Outcomes worse with MICs > 16 in MERINO

Table 5. Summary of Studies Investigating Piperacillin-Tazobactam PK and PD Data

Dosage	Infusion Time	MIC With ≥ 90% PTA[a]
3.375 g every 6 h	30 min	≤ 8 µg/mL[10-12]
4.5 g every 6 h	30 min	≤8 µg/mL[12-15]
3.375 g every 8 h	4 h	≤8 µg/mL[14-17]
4.5 g every 8 h	4 h	≤8 µg/mL[12-15]
4.5 g every 8 h	4 h	≤16 µg/mL[12,14,17,18]
4.5 g every 6 h	3 h	≤16 µg/mL[12,13,18,19]

- *CrCL ≤ 120 mL/min *(augmented clearance is problematic)*

CLSI. Piperacillin-Tazobactam Breakpoints for Enterobacterales. 1st Ed. CLSI Rationale Document MR14. Clinical and Laboratory Standards Institute; 2022

Piperacillin-Tazobactam 2022 Updates

Table 6. Excerpt From CLSI document M100[2] Table 2A, Zone Diameter and MIC Breakpoints for Enterobacterales[a]

Test/ Report Group	Antimicrobial Agent	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm[b]			Interpretive Categories and MIC Breakpoints, µg/mL		
		S	SDD	R	S	SDD	R
B	Piperacillin-tazobactam	≥ 25	21–24	≤ 20	≤ 8/4	16/4	≥ 32/4

Abbreviations: MIC, minimal inhibitory concentration; R, resistant; S, susceptible, SDD, susceptible-dose dependent.
[a] Breakpoints for susceptible are based on a dosage regimen of 3.375-4.5 g administered every 6 hours as a 30-minute infusion. Breakpoints for SDD are based on a dosage regimen of 4.5 g administered every 6 hours as a 3-hour infusion or 4.5 g administered every 8 hours as a 4-hour infusion.
[b] Disk content 100/10 µg.

- "S" BPs based on PTZ dosing of 3.375-4.5 g q6h over 30 min
- "SDD" BPs based PTZ dosing of 4.5 g q6h over 3h ***OR*** 4.5 g q8h over 4h

*****NOTE: Shift from S/I/R to S/SDD/R***

*****Prior BP: ≤ 16 mcg/mL***

CLSI. Piperacillin-Tazobactam Breakpoints for Enterobacterales. 1st Ed. CLSI Rationale Document MR14. Clinical and Laboratory Standards Institute; 2022

Clinical Considerations with PTZ

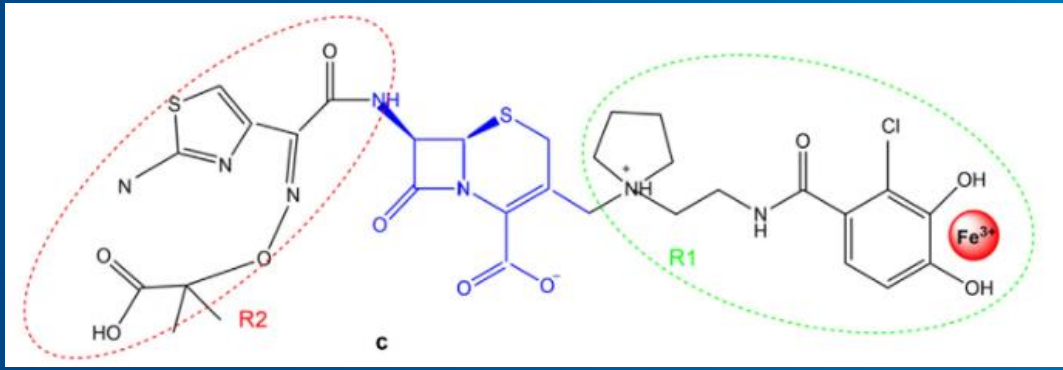
- If concerned for ESBL…..carbapenem (see MERINO universe)
- Explore extended infusion dosing schemes…may help mitigate inability to “call” below 16 mcg/mL
- Work with local microbiology to explore alternative AST options

Cefiderocol

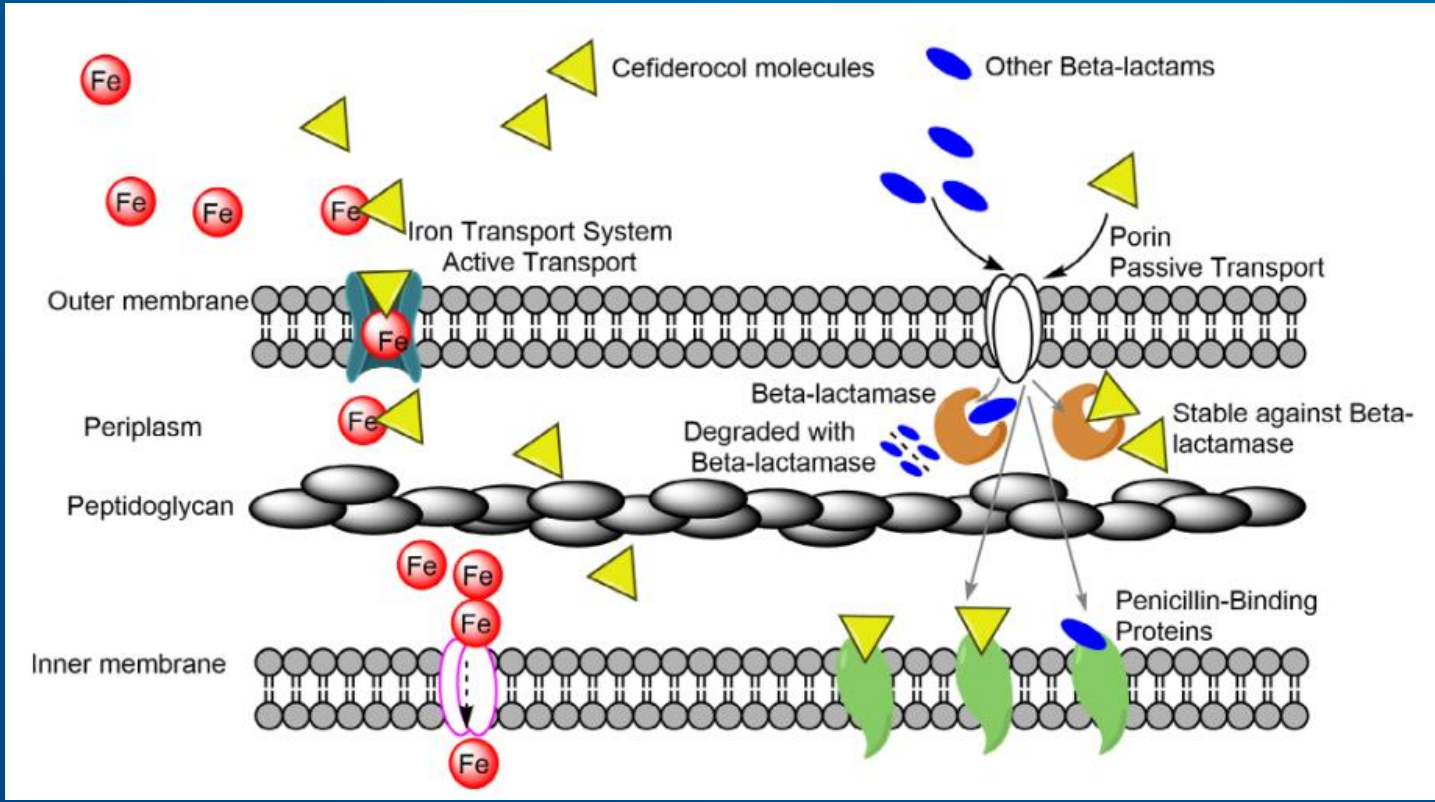
Cefidercol (Fetroja®)

- Iron chelating antimicrobial (siderophore)
- Chelating property facilitates “sneaky” entry into bacteria via iron transport system
- Improved stability against beta-lactamases (including Class B)
- Broad activity
  - Carbapenem-resistant Enterobacteriaceae
  - Carbapenem-resistant *Acinetobacter baumanii (A. baumanii)*
  - Carbapenem-resistant *Pseudomonas aeruginosa (P. aeruginosa)*
  - *Stenotrophomonas maltophilia (S. maltophilia)*

Abdul-Mutakabbir JC et al. Pharmacotherapy 2020;40(12):1228–1247



Red: increased permeabilty
Blue: cephalosporin pharmacophore
Green: Increased stability to B-lactamases



Abdul-Mutakabbir JC et al. Pharmacotherapy 2020;40(12):1228–1247

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Cefiderocol breakpoints

Organism		CLSI	
	MIC	Disc diffusion (DD)	MIC
Enterobacterales	≤ 4	≥ 16	≤ 4
P. aeruginosa	≤ 1	≥ 18	≤ 4
A. baumanii	≤ 1	≥ 15	≤ 4
S. maltophilia	None	≥ 15	≤ 1

- Note discrepancy between FDA and CLSI
  - Not uncommon but improving
  - Discomfort with activity against non-fermenters (*P. aeruginosa/A. baumanii*)
    - CREDILBLE-CR study showed numerically higher mortality in cefiderocol group
  - Lack of available robust data supporting use (*S. maltophilia*)

Bassetti M et al. Lancet Infect Dis 2021;21:226-240

Cefiderocol 2022 Updates

- Acinetobacter DD breakpoints
  - High discordance between MIC and DD measurements
  - Multiple isolates with DD of ≤ 14 mm in all S/I/R categories
  - If using DD, confirm “S” for isolates with zones ≤ 14 mm
- S. maltophilia MIC breakpoint of ≤ 1 mcg/mL
  - Few isolates in trials
  - Lack of firm PK/PD data
  - Refer to reference lab for isolates with MIC above 1 mcg/mL
- Manufacturer has resources for reference lab testing if not available in house
  - Always note time delays when referring

Fluoroquinolones

Quinolone Breakpoints – New and Old

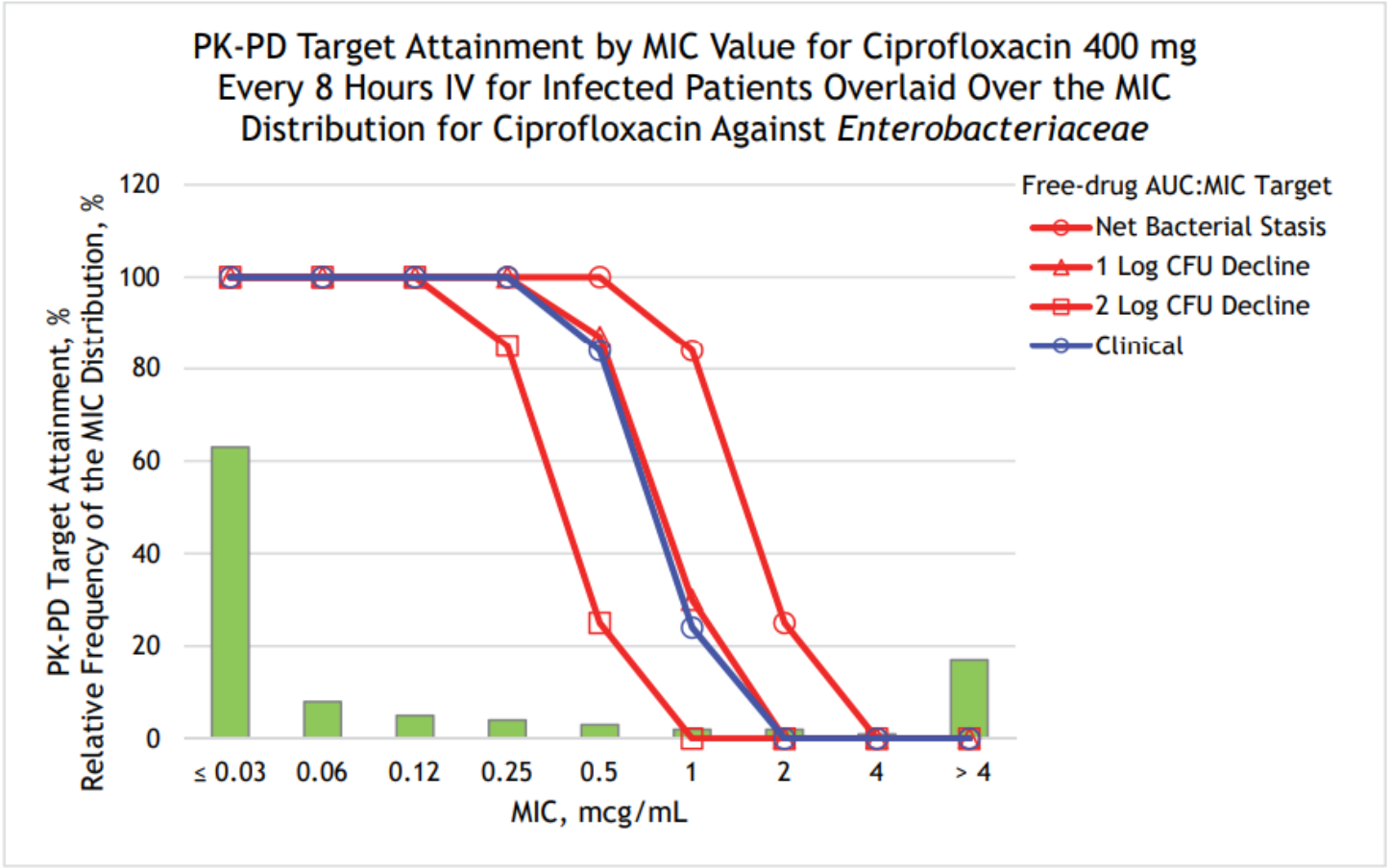
Old…

Organism	Antimicrobial	"S" MIC
Enterobacterales	Ciprofloxacin	≤ 1
	Levofloxacin	≤ 2
P. aeruginosa	Ciprofloxacin	≤ 1
	Levofloxacin	≤ 2

New…

Organism	Antimicrobial	"S" MIC
Enterobacterales	Ciprofloxacin	≤ 0.25
	Levofloxacin	≤ 0.5
P. aeruginosa	Ciprofloxacin	≤ 0.5
	Levofloxacin	≤ 1

Dosing Matters…



Abbreviations: AUC, area under the curve; CFU, colony-forming unit; IV, intravenous; MIC, minimal inhibitory concentration; PK-PD, pharmacokinetic-pharmacodynamic; PO, oral.

https://clsi.org/media/3011/mr02ed1.pdf?utm_source=rm&utm_medium=landingpage&utm_content=MR02&utm_campaign=rationaldocument

Quinolone Take-Homes

- Work with microbiology to determine ability to “call” MICs
- If you cant…re-address dosing strategies with FQs to target PK/PD
  - Consider high-dose quinolones as a standard (**for Gram negatives**)
    - CPX: 750 PO BID/400 IV q8h
    - LVX: 750 PO/IV q24h
- Cautionary notes for high-dose (or any) quinolone use (new age PPIs)
  - *C. difficile*
  - Aneurysms/dissections
  - Glycemic concerns
  - Neuropsychiatric complications
  - Drug interactions
  - Tendon ruptures
  - Fluoroquino-don’t
- Great antibiotics…Very Effective…troubled class
- **USE STRATEGICALLY**

https://clsi.org/media/3011/mr02ed1.pdf?utm_source=rm&utm_medium=landingpage&utm_content=MR02&utm_campaign=rationaldocument

Update Miscellany

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Other Updates

- Amoxicillin-Clavulanate v *Haemophilus infulenzae*
  - New BP of ≤ 2/1 mcg/mL….MIC of 4 mcg/mL not reliably achieved with current dosing
  - Concern for emerging beta-lactamase negative, AMP-resistant strains
    - PBP3 mutation

- Direct from blood AST
  - Work with our lab on capabilities
  - Opportunities for early results/optimized treatment
  - Excellent opportunity for Gram-negatives

- Look forward to….
  - Revised BPs for aminoglycosides
  - Further updates for *S. maltophilia*
  - Ceftazidime-avibactam-aztreonam AST

http://em100.edaptivedocs.net/Login.aspx

Travis's Lab/ASP Advice

- Review your current AST panel's ability to detect lowered BPs
  - Update your AST panels whenever possible
  - Have contingency plans to detect (Etest, disc internal validation)
- Explore alternate dosing regimen implementation
  - Sometimes takes a village (system vs. single institution)
  - Don't forget your nursing colleagues for alternative infusion schemes
  - Consider aggressive antimicrobial dosing when lowered BPs can't be detected (FQ's)
- Consider rapid diagnostic platforms for resistance detection
  - Validation required
  - Requires action/interpretation/communication…have a process!
- Buy doughnuts often…

Last point…Retrain your brain

Intermediate doesn't = Resistant

Dose-Dependency

Thank you!!

Questions?

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