Education Session

Standard Reference Methods for AST

Perspectives From Various Stakeholders

June 3, 2023

Reference Antimicrobial Susceptibility Testing: The Perspective from Drug Development

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Disclosure

JMI Laboratories was contracted to perform services in 2022 for

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Contents

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Early Drug Discovery and Development Guidelines: For Academic Researchers, Collaborators, and Start-up Companies

Jeffrey Strovel, Sitta Sittampalam, Nathan P. Coussens, Michael Hughes, James Inglese, Andrew Kurtz, Ali Andalibi, Lavonne Patton, Chris Austin, Michael Baltezor, Michael Beckloff, Michael Weingarten, and Scott Weir.

Author Information and Affiliations

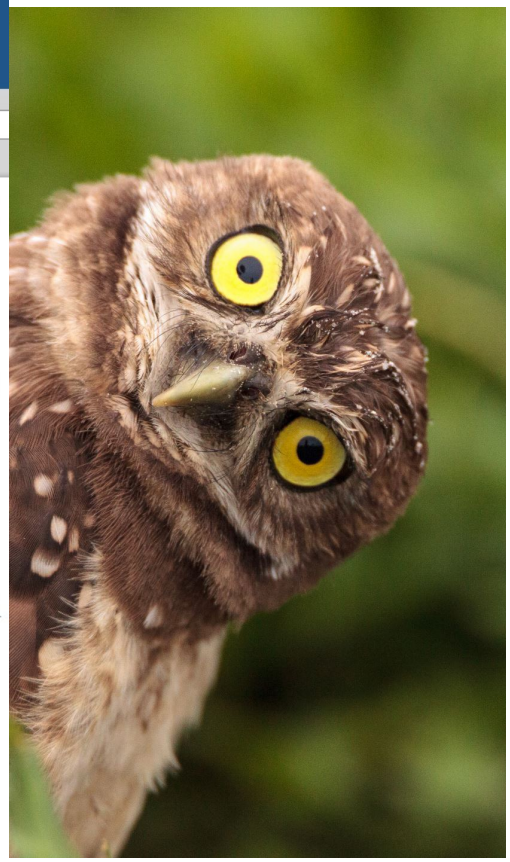
Published May 1, 2012; Last Update: July 1, 2016.

Abstract

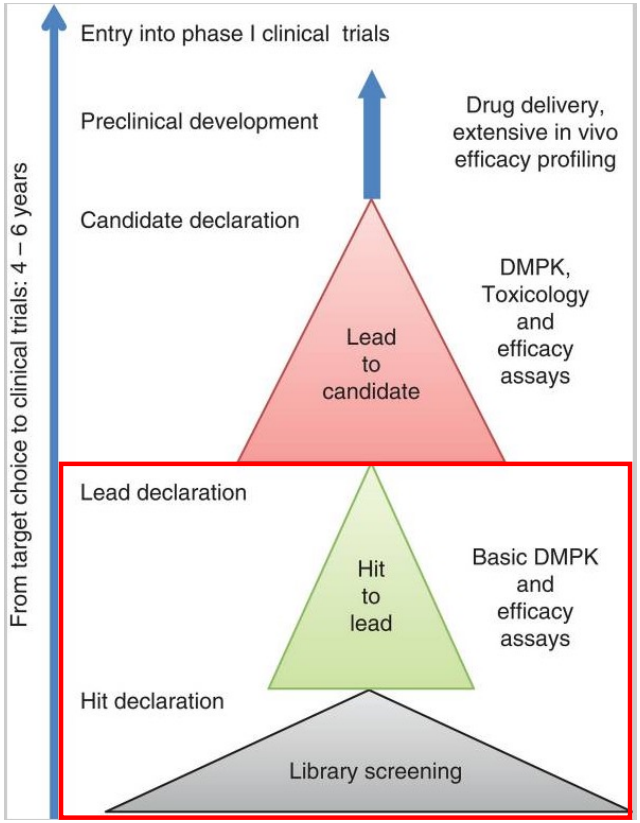
Go to:

Setting up drug discovery and development programs in academic, non-profit and other life science research companies requires careful planning. This chapter contains guidelines to develop therapeutic hypotheses, target and pathway validation, proof of concept criteria and generalized cost analyses at various stages of early drug discovery. Various decision points in developing a New Chemical Entity (NCE), description of the exploratory Investigational New Drug (IND) and orphan drug designation, drug repurposing and drug delivery technologies are also described and geared toward those who intend to develop new drug discovery and development programs.

Note: The estimates and discussions below are modeled for an oncology drug New Molecular Entity (NME) and repurposed drugs. For other disease indications these estimates might be significantly higher or lower.



Initial development



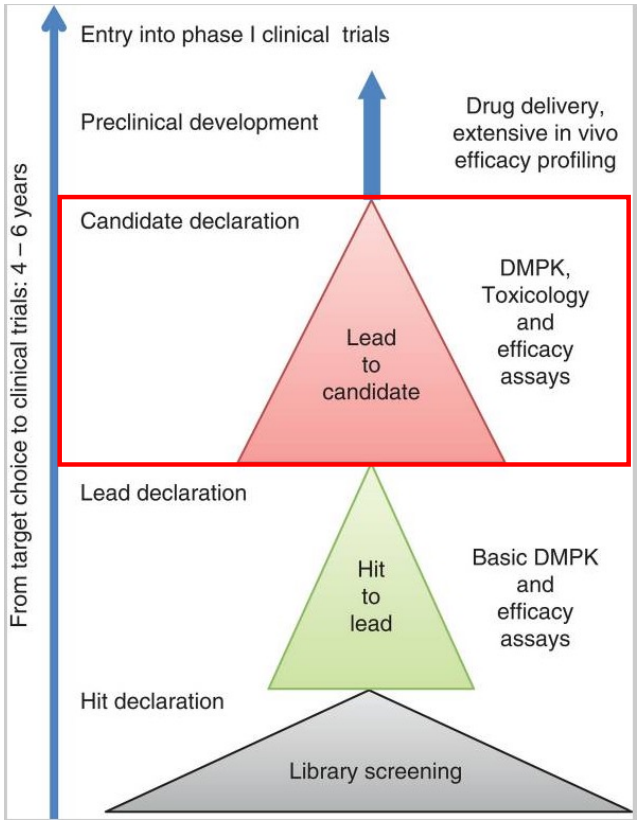
DMPK = drug metabolism and pharmacokinetics

Hughes & Karlén, Ups J Med Sci. 2014; 119:162-9.

- Library screening and hit to lead – not reference broth microdilution (rBMD)
- Need high throughput
  - Easy set up and reading endpoints
  - Small volumes

Bio-Rad website

Initial development

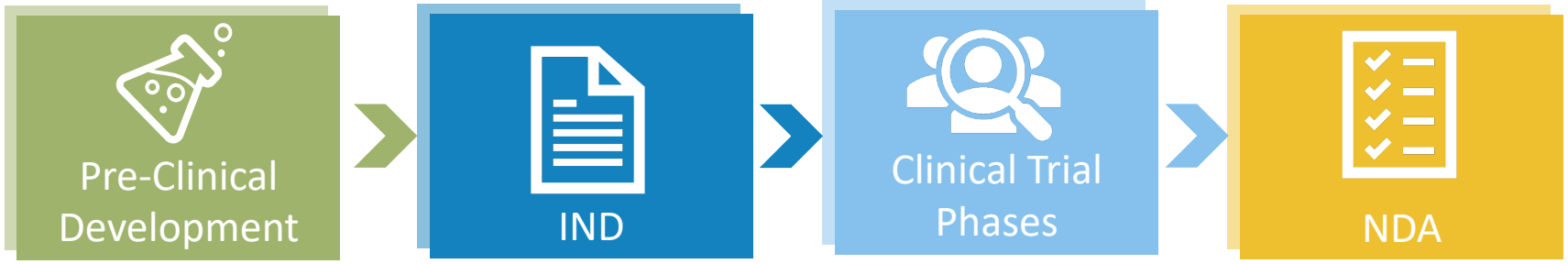


DMPK = drug metabolism and pharmacokinetics

- Candidate selection
  - Some chemical modifications/optimization
  - Same method throughout but still doesn't need the rBMD

  Some companies might choose at this stage to use rBMD
- Interest in rBMD usually occurs after selection of lead candidate

Hughes & Karlén, Ups J Med Sci. 2014; 119:162-9.

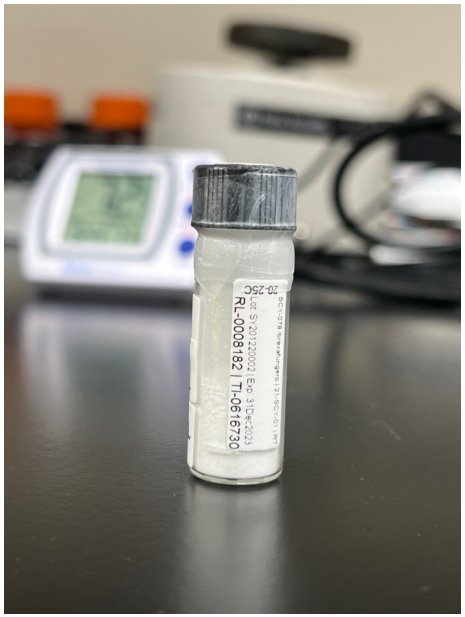


Pathway for Development of New Agent

When we get a new drug powder…

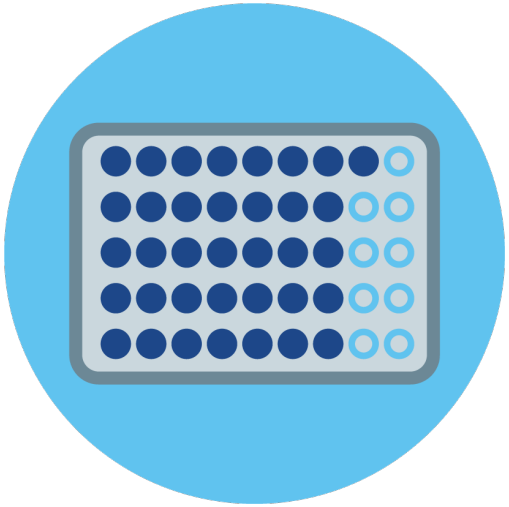
We ask about experience with rBMD – answers are variable

- Is it a new class?
- What solvent and diluent can be used?
- What are concentrations that should be tested?
- Is there internal QC data?
- Stability of panels?
- How were endpoints read?
- Is BMD or the rBMD the appropriated method?



Initial pre-clinical MIC studies

- Is it a new class?
  - Use similar conditions for known classes
- What solvent and diluent can be used?
  - DMSO often used in screening (=<1.0%, CLSI, M100)
  - Water or phosphate buffer work?
  - Cation-adjusted Mueller Hinton broth (CAMHB)
    - Indicated by CLSI, EUCAST, and ISO
- What are concentrations that should be tested?
  - Broader range for initial analysis



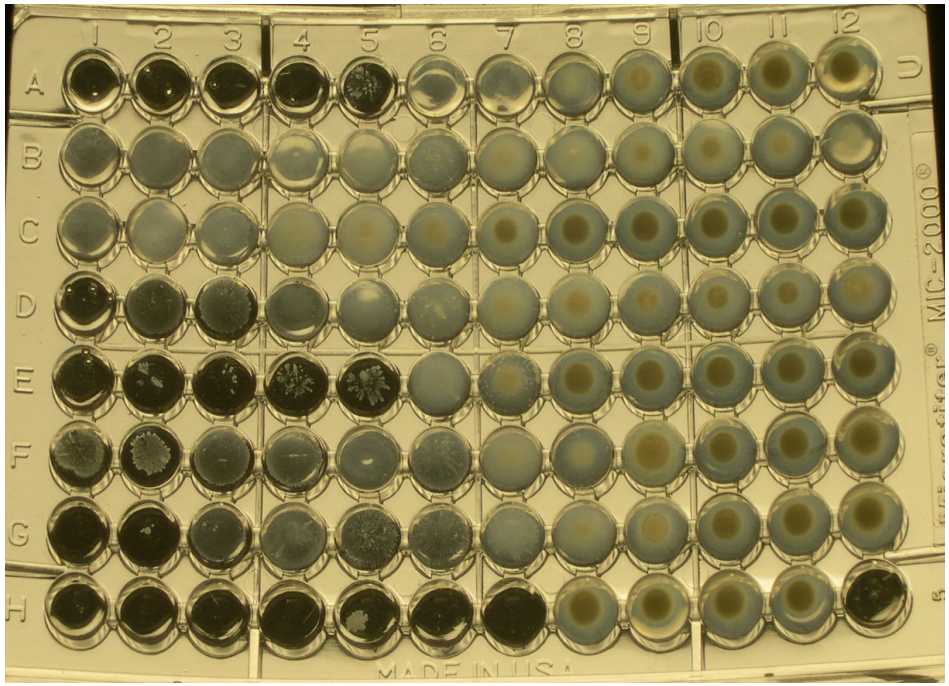
Initial pre-clinical MIC studies

- Is there internal QC data?
  - Variability in responses (important to make sure expectations are met)
  - Expand to more relevant QC
- Stability of panels?
  - Many sponsors have asked for stability studies

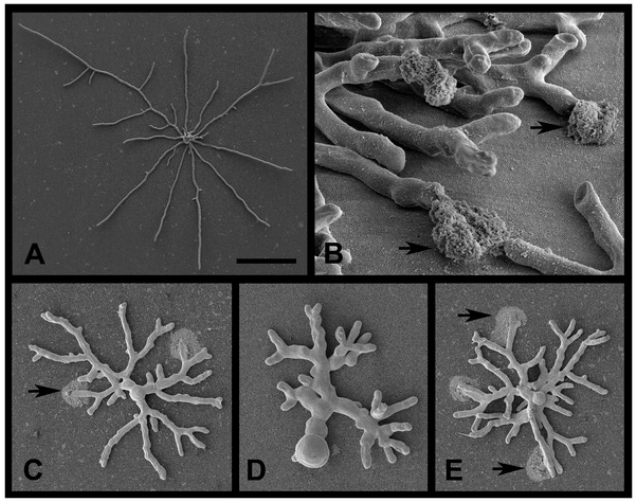
More difficult questions

Goal is to have a reproducible method that correlates to clinical success

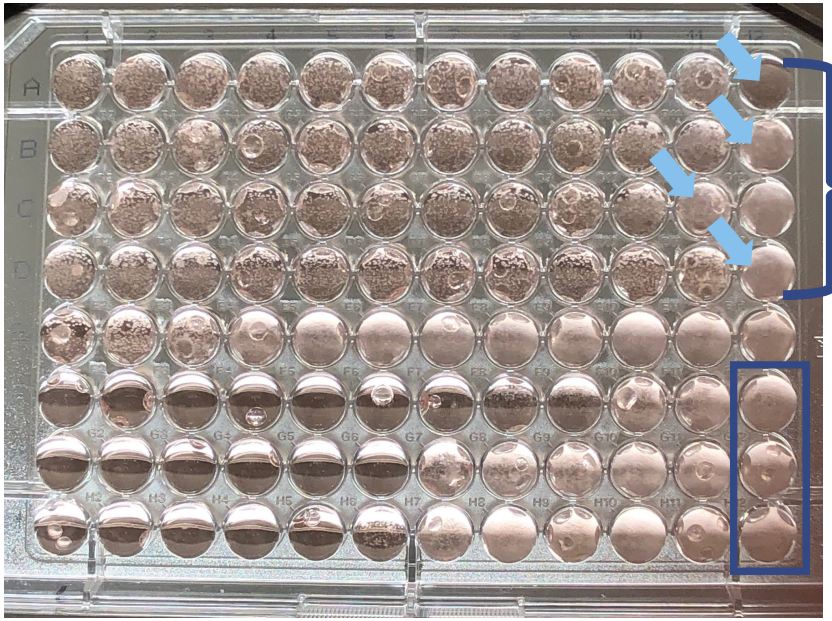
- How were endpoints read?
  - Ignore trailing
  - Major reduction in growth
  - First clear well



Minimal Effective Concentration (MEC)



Ingham & Schneeberger, PLOS ONE 2012



Subjective and requires a lot of training and reading guidelines

Is BMD or the rBMD the appropriated method?

- Cefiderocol: iron-depleted (ID) CAMHB
- Daptomycin: CAMHB + additional Ca^{2+}
- Fosfomycin and mecillinam: agar dilution
- Lipoglycopeptides: CAMHB + P-80 (0.002%)
  - Telavancin: CAMHB + P-80 (revision, with lowered breakpoints)
- Oxacillin: CAMHB + 2% NaCl
- Tigecycline: fresh medium
- Exebacase: CAMHB + 25% serum + 0.5mM DL-dithiothreitol (CAMHB-HSD)

Cefiderocol and ID-CAMHB

In Vivo Pharmacodynamic Study of Cefiderocol, a Novel Parenteral Siderophore Cephalosporin, in Murine Thigh and Lung Infection Models

Rio Nakamura,[a] Tsukasa Ito-Horiyama,[a] Miki Takemura,[a] Shinsuke Toba,[a] Shuhei Matsumoto,[a] Tatsuya Ikehara,[a] Masakatsu Tsuji,[a] Takafumi Sato,[a] Yoshinori Yamano[a]

TABLE 1 MICs of cefiderocol, cefepime, and meropenem against the tested strains

Organism	Type of carbapenemase	Infection model applied in this study	MIC (μg/ml) Cefiderocol ID-CAMHB	Cefiderocol CAMHB
E. coli				
ATCC 25922	—[d]	Thigh	0.125	0.25
AB	NDM-4	Lung	4	8
IR-5	NDM-1	Lung	4	4
K. pneumoniae				
ATCC 13883	—	Thigh	0.25	0.5
1478266	—	Thigh	0.5	1
1478677	—	Thigh	0.25	0.25
VA-357[a]	KPC-2	Thigh, lung	2	8
VA-361[a]	KPC-2	Lung	4	16
VA-384[a]	KPC-2	Thigh, lung	4	16
VA-391[a]	KPC-3	Thigh, lung	4	16
6560-MAR[b]	NDM-1	Thigh, lung	2	2
KI2[c]	NDM-1	Thigh, lung	8	32
NCTC 13443	NDM-1[c]	Thigh, lung	16	256
P. aeruginosa				
SR27016	—	Thigh	0.25	0.25
ATCC 27853	—	Thigh, lung	0.5	2
SR27001	IMP-1	Thigh, lung	2	32
NCTC 13437	VIM-10	Lung	1	8
A. baumannii				
BEN ST BRI	OXA-24	Lung	0.25	2
1485247	—	Lung	2	32
NCTC 13301	OXA-23	Lung	1	32
S. maltophilia				
1146824	Not tested	Lung	0.125	0.125
1371071	Not tested	Lung	0.125	0.125
1392567	Not tested	Lung	0.25	0.25
1444463	Not tested	Lung	0.25	0.125

[a]ST258.
[b]ST15.
[c]ST14.
[d]—, not detected.

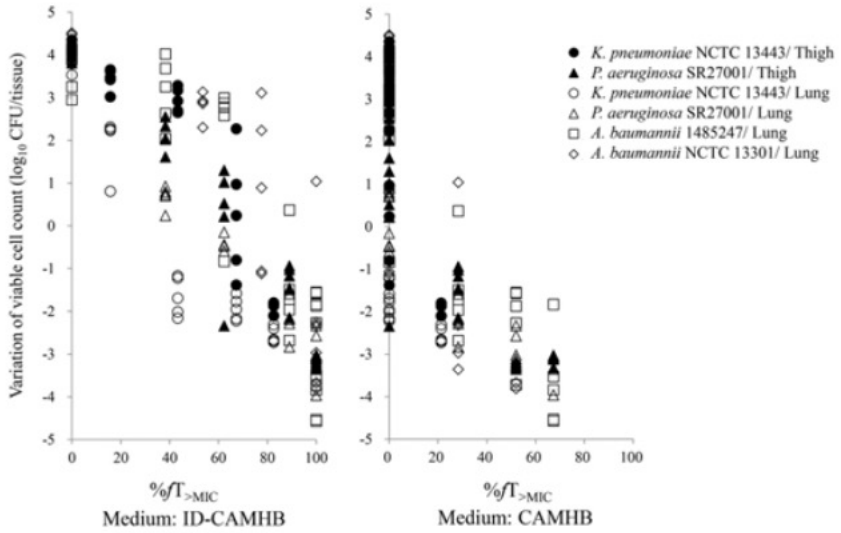


FIG 2 Comparison of the %$fT_{>MIC}$ of cefiderocol between MIC values in ID-CAMHB and CAMHB in neutropenic murine thigh and lung infection models.

https://doi.org/10.1128/AAC.02031-18

Exebacase (lysin) and CAMHB-HSD

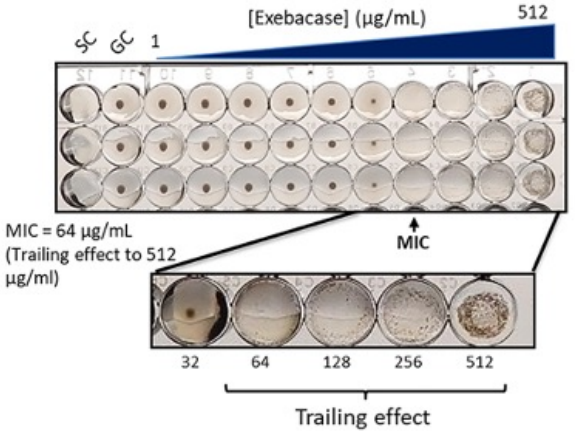
Development of a Broth Microdilution Method for Exebacase Susceptibility Testing

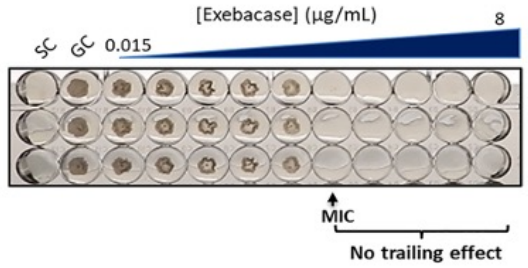
Jun T. Oh,[a] Jane E. Ambler,[a] Cara Cassino,[a] Raymond Schuch[a]

TABLE 1 Impact of BMD assay modifications and supplements on exebacase MICs against 25 *S. aureus* isolates[a]

Supplementation/modification	MIC (μg/ml)			Trailing effect
	50%	90%	Range	
None	32	64	2–128	Yes
0.002% polysorbate 80	64	64	8–64	Yes
50 μg/ml Ca^{2+}	32	64	1–128	Yes
2% NaCl	128	128	32–128	Yes
2.5% laked horse blood	32	64	4–256	Yes
5% laked horse blood	32	64	4–256	Yes
10% laked horse blood	16	32	2–128	Yes
25% laked horse blood	8	16	2–128	Yes
Polypropylene plates	16	128	4–128	Yes
0.1% BSA (polypropylene plates)	8	32	1–32	Yes
0.1% BSA	8	32	4–32	Yes
0.1% BSA, 2% NaCl, 200 rpm	32	128	8–>256	Yes
0.1% BSA, 2% NaCl	32	64	16–128	Yes
CO_2 atmosphere	32	64	32–128	Yes
0.5 mM DTT	128	128	8–256	Yes
50% horse serum	0.5	2	0.125–2	No
25% horse serum	0.5	2	0.125–2	No
12.5% horse serum	1	4	0.125–4	No
6.25% horse serum	4	8	1–8	No

[a]MICs were determined by broth microdilution in 96-well, round-bottom, polystyrene microtitration plates (unless otherwise indicated) according to the method described in CLSI document M07-A11 (9), with the indicated supplements and modifications.





https://doi: 10.1128/AAC.02587-20

Tigecycline and Fresh CAMHB

Tigecycline MIC Testing by Broth Dilution Requires Use of Fresh Medium or Addition of the Biocatalytic Oxygen-Reducing Reagent Oxyrase To Standardize the Test Method

Patricia A. Bradford,[1]* Peter J. Petersen,[1] Mairead Young,[2] C. Hal Jones,[1] Mark Tischler,[2] and John O'Connell[1]

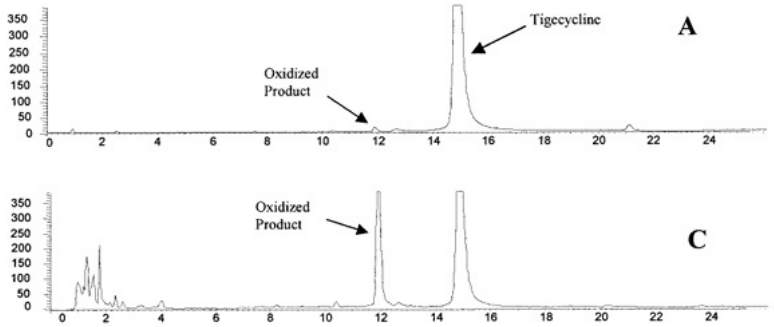


FIG. 2. HPLC chromatographs comparing the stability of tigecycline in distilled H_20, aged Mueller-Hinton II broth (MHB), and fresh MHB in the presence and absence of the biocatalytic oxygen-reducing reagent Oxyrase. Tigecycline at a concentration of 1 mg/ml was incubated for 24 h at RT in various media prior to HPLC analysis. (A) Distilled H_2O; (B) distilled H_2O supplemented with 2% Oxyrase; (C) aged MHB; (D) aged MHB supplemented with 2% Oxyrase; (E) fresh MHB; (F) fresh MHB supplemented with 2% Oxyrase.

TABLE 5. Stability of the in vitro activity of tigecycline in frozen microdilution MIC panels and stored at −70°C

Week	Tigecycline MIC (μg/ml) for:		
	E. coli ATCC 25922	*S. aureus* ATCC 29213	*E. faecalis* ATCC 29212
1	0.06 ($n = 3$)[a]	0.12 ($n = 2$)	0.03 ($n = 2$)
2	0.06–0.12 ($n = 4$)	0.12 ($n = 2$)	0.03 ($n = 2$)
3	0.06 ($n = 4$)	0.12 ($n = 2$)	0.03 ($n = 2$)
4	0.06 ($n = 4$)	ND	0.06 ($n = 1$)
5	0.06 ($n = 4$)	0.12 ($n = 3$)	0.03 ($n = 1$)
6	ND[b]	0.12 ($n = 2$)	0.03 ($n = 2$)

[a] One to four plates were removed from frozen storage at each week and MICs determined.
[b] ND, not tested.

https://doi: 10.1128/AAC.49.9.3903-3909.2005

Variable Effect on *In vitro* MIC Testing

- Purpose
  - Study common variables and their effect on MIC values
  - Understand how robust your MIC test is
- Standard method
  - CAMHB microdilution
  - Triplicate testing
- Method variations
  - Inoculum: low, standard (10^5 CFU/mL), high
  - Incubation atmosphere: ambient, CO_2, microaerophilic, and anaerobic
  - Incubation time: 16, 18, or 24 hours
- Compare broth microdilution and agar dilution

Variable Effect on *In vitro* MIC Testing, continued

- pH
  - Low (pH 6), standard (pH 7.2), or high (pH 8)
- Calcium and magnesium (lower and higher) vs standard CAMHB
  - Effect of other cations on compound activity might be useful
- Polysorbate-80
  - Addition of polysorbate-80 up to 0.002%
- CAMHB
  - MIC values can vary between MHB manufacturers
  - Compare 3 different MHB sources, if possible
  - MHB must meet ISO criteria for use in susceptibility testing

Variables on *in vitro* MIC Testing

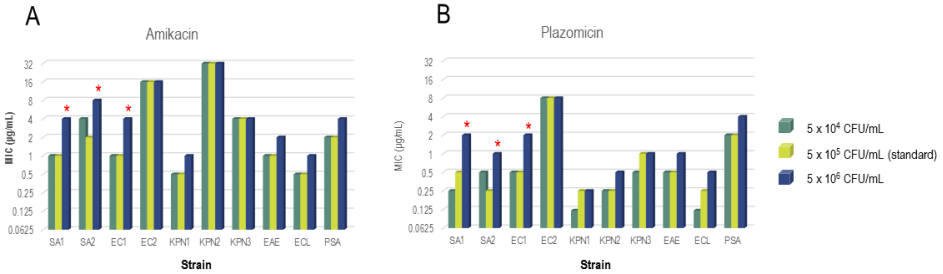


Figure 1 Effect of inoculum size on MIC values

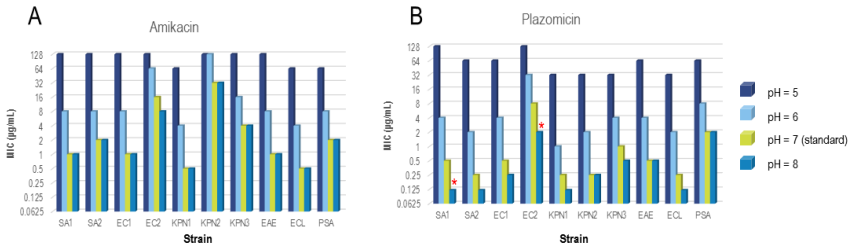


Figure 2 Effect of broth medium pH on MIC values

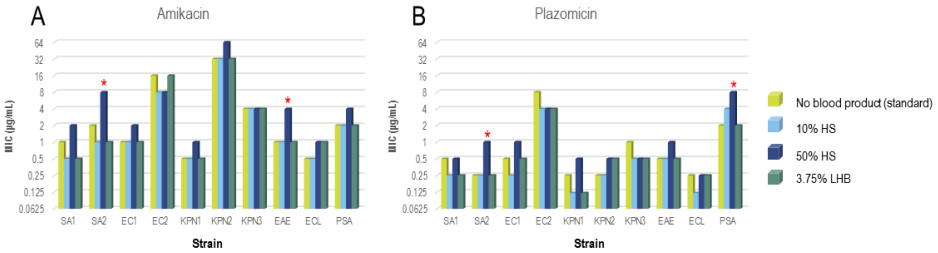


Figure 3 Effect of human serum (HS) and lysed horse blood (LHB) on MIC values

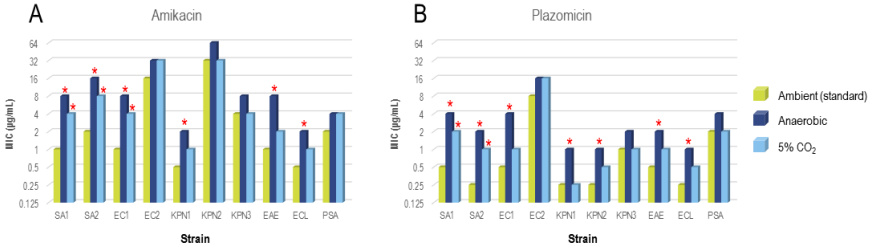


Figure 4 Effect of different growth atmospheres on MIC values

https://www.jmilabs.com/publications/impact-changes-growth-medium-inoculum-density-incubation-conditions-vitro-antimicrobial-activity-plazomicin/

Conclusions

To develop a reproducible susceptibility test that correlates with the clinical/animal data for chance of success treating infections

- When determining MIC values, start with rBMD and CAMHB first
  - If *in vitro* activity with reference broth microdilution doesn't correlate with *in vivo*
    - MIC method variation studies
    - An alternate MIC method is an option, but should be the last option
- The test should clearly identify susceptible versus resistant isolates
- If MIC endpoints are less than clear-cut to read
  - Discuss how to read endpoint with external experts and SDOs (CLSI/EUCAST)
  - Develop reading guidelines with photos

References not cited in slides

- CLSI. M07Ed11. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. 2018.
- CLSI. M23Ed5. Development of *in vitro* susceptibility testing criteria and quality control parameters. 2018.
- CLSI M100Ed33. Performance standards for antimicrobial susceptibility testing. 2023.
- EUCAST. Breakpoint tables for interpretation of MICs and zone diameters. V13. 2023.
- ISO 16782. 2016. Clinical laboratory testing– Criteria for acceptable lots of dehydrated Mueller-Hinton agar and broth for antimicrobial susceptibility testing.
- ISO 20776. Part 1, 2019. Broth micro-dilution reference method for testing the in vitro activity of antimicrobial agents against rapidly growing aerobic bacterial involved in infectious diseases.
- US FDA. Guidance for industry, microbiology data for systemic antibacterial drugs– development, analysis, and presentation. 2018.
- GARPD Talk by Shortridge and Canton (https://revive.gardp.org/susceptibility-testing-in-antibacterial-drug-rd/)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What Does Reference AST Mean to Me?

Perspectives of an AST Device Manufacturer & Past Chair of the CLSI AST Subcommittee

CLSI Educational Symposium
June 3, 2023

Jean B. Patel, PhD, D(ABMM)
Scientific Affairs, Beckman Coulter Microbiology

Summary

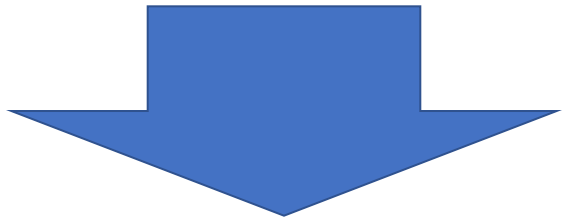
- Reference broth microdilution (BMD) AST is truth to an AST device manufacturer
  - When agar dilution is the preferred method for a bug/drug, then MICs from this method becomes truth
- Performance criteria:

Criteria	FDA	ISO
Essential Agreement	≥ 90%	≥ 90%
Categorical Agreement	≥ 90%	N/A
Major Error Rate	≤ 3%	N/A
Very Major Error Rate	≤ 2%	N/A
Bias	≤ 30%	≤ 30%
Reproducibility	≥ 95%	≥ 95%
Quality control	≥ 95%	≥ 95%
Qualitative tests	≥ 95%	≥ 95%
No-growth	≤ 10%	N/A

Antimicrobial Susceptibility Test (AST) Systems - Class II Special Controls Guidance for Industry and FDA | FDA
ISO 20776-2:2021

Performance Criteria are Established in a Clinical Trial

- Testing at 3 sites
- Frozen reference BMD and commercial AST from a single inoculum
- Challenge isolates (i.e., stock isolates)
- Efficacy isolates (i.e., fresh clinical isolates)
- Reproducibility
- QC testing



Regulatory Submission

Reference BMD for a Clinical Trial

- MicroScan manufacturers this in house and ships panels to clinical trial sites

- Performance of reference BMD is measured using QC (2 to 3 QC strains) performed at the beginning, middle, and end of a study in house and daily at each testing site.

Inherent Variability of Reference AST

- Even under the best controlled conditions, the isolate's inherent biological variability and other factors may lead to a range of MIC values similar to what is observed with replicate testing with QC strains. CLSI M07, 2018.

- "Under the best of circumstances, an MIC of 1.0 mg/L should be considered as a value between 0.5 and 2.0 mg/L." EUCAST Breakpoint tables for interpretation of MICs and zone diameters Version 13.0

A Reference AST Method MIC

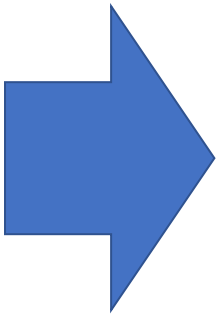
- An MIC is a convenient numerical value that can be used to measure relative susceptibility of an isolate to a drug and correlate this susceptibility to data indicating likelihood of clinical success or failure of the drug when used to treat infections at the body site in which this isolate is causing an infection.

- An MIC should be standardized, reproducible and generated from a non-proprietary method.

- An MIC should be generated under *in vitro* conditions that most closely reflect drug/bug interactions *in vivo*.

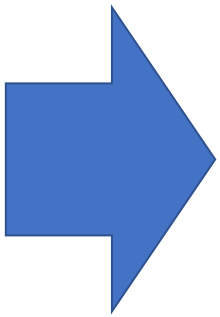
Examples of CLSI Reference Method Decisions

- Colistin MIC testing (surfactant or no surfactant)
  - Surfactants were commonly used in polymyxin AST method to reduce drug binding to the panel plastic
  - MICs are significantly lower with surfactant
  - Surfactant also increases permeability of bacteria, creating an artificial increase in susceptibility



No change in reference method

- Cefiderocol testing (chelation or no chelation)
  - The drug is active in a low iron environment
  - To obtain drug activity expected at the body site, media chelation to remove iron is needed



Change in reference method

Are There Drugs or Dilutions with Increased Variability?

- Example: *Enterobacterales* piperacillin-tazobactam MIC = 16 µg/mL

Enterobacterales *

EUCAST Clinical Breakpoint Tables v. 13.0, valid from 2023-01-01

Expert Rules and Expected Phenotypes

For abbreviations and explanations of breakpoints, see the Notes sheet

Penicillins	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
	S ≤	R >	ATU		S ≥	R <	ATU	
indications)[1]								
Piperacillin	8	8		30	20	20		
Piperacillin-tazobactam	8[5]	8[5]	16	30-6	20	20	19	
~~Ticarcillin~~								
Ticarcillin-clavulanic acid	8[4]	16[4]		75-10	23	20		

*"The ATUs are **warnings to laboratory staff** that there is an uncertainty that needs to be addressed before reporting AST results to clinical colleagues."*

ATU, area of technical uncertainty

Reproducibility Data for Reference BMD

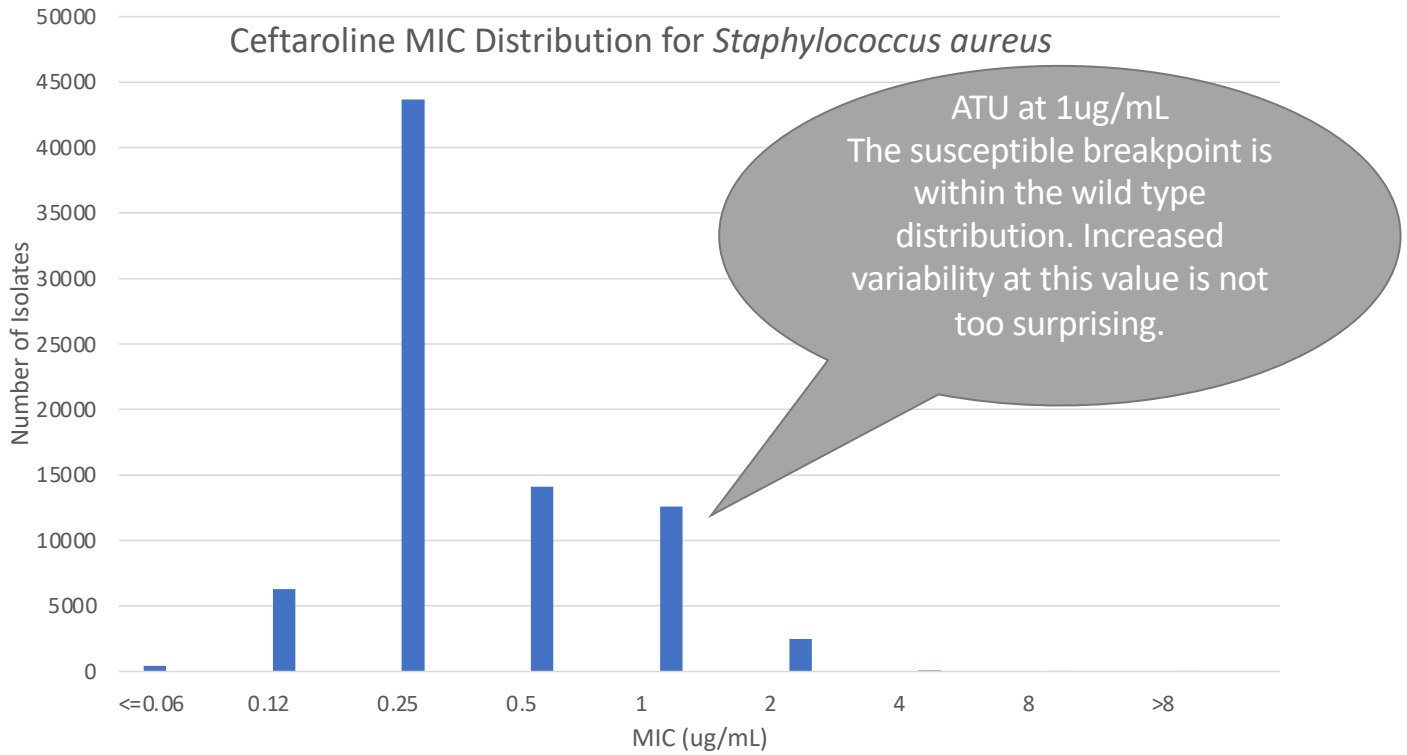
Enterobacterales vs Piperacillin-Tazobactam

Strain	1	4	8	16	32	64	128	256
A					30	24		
B	54							
C		54						
D*	6			48				
E			36	18				
F*		46		8				
G		36	18					
H					34	6	14	
I							48	6
J						4	6	44

*Result variability because of changes in resistance expression? Likely a bug problem, not an assay problem

Another ATU Issue - Ceftaroline

Project: SENTRY Public
All years: All Regions
Ceftaroline



Other Variable Drugs

- Plazomycin – Variability in reference BMD was noted at MicroScan. No source of the variability was noted.
    - Variability in reference BMD also seen at CDC. It was related to early drug powder lots. Drug obtained from a hospital pharmacy did not exhibit this variability. The problem was solved when pharma company manufactured new lots (David Lonsway, CDC, personal communication)
- Cefiderocol – Variability addressed with a more robust chelation procedure.

Should the current reference method be changed for improved performance?

Precision or Reproducibility

We could probably find a method with more precision but may be proprietary. Even if not proprietary, we need data indicating that this feature improves breakpoint decisions and therapeutic outcomes.

Accuracy

The ability to separate isolates where therapy success is likely from isolates where therapy success is unlikely. This is a hard question to answer. Consider ceftazidime susceptible ESBL-producers. Is it really the MIC or the mechanism that drives therapeutic success? Would a different MIC method be able to answer this question definitely?

Would Less MIC Variability Drive Better Patient Outcomes?

Three sources of data used to predict therapy success. All data come with significant sources of variability.

1. MIC distribution data
2. **Monte Carlo simulation of PK-PD data**
3. Clinical outcome by MIC data

Would a more precise MICs overcome the variability of PK-PD data, which is commonly used as the data to set breakpoints?

FDA vs ISO Performance Measures

- FDA: Essential Agreement & Category Agreement
- ISO: Essential Agreement & Bias
- For a manufacturer: two different design intents.
- CA is a challenge when breakpoints are within or at the upper limit of the normal MIC distribution.
- ISO criteria work best when different breakpoints can be applied
- FDA criteria work when only one breakpoint is applied

Summary

- Changing a reference method is a big deal
- For a manufacturer
  - Adds cost
  - Slows work
  - Can impact the type of tests available
- Decisions for methods need to be data driven
- The goal of adjusting methods – better outcomes for patients
  - Improve detection of therapeutic success vs therapeutic failure

“Reference” AST Methods for the Clinical Laboratory

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Associate Professor, University of North Carolina

Director of Bacteriology and Susceptibility Testing, UNC Medical Center

What might a clinical lab consider “reference” AST testing?

- Broth microdilution (BMD) panels prepared and read in accordance to M07
- Disk diffusion testing done in accordance with M02
- Manually read commercial BMD panels
- Results from another validated commercial AST method (including gradient diffusion)
- Results from a commercial referral lab

When does a clinical lab need “reference” AST testing?

- When CLSI says so
  - Appendix A (Confirming AST Results) suggests use of a reference method to confirm unusual results
  - Appendix H (Using Molecular Assays for Resistance Detection) specifically says confirm some conflicting results with a reference method
  - Some drugs say confirm some disk results with MIC test (e.g. ceftazidime-avibactam and Enterobacterales)
- When doing verification or validation of new AST tests, drugs, or breakpoints
  - M52 mentions using reference or comparator method testing

Using other methods as “reference”

- To implement new commercial panels or use CLSI breakpoints when they differ from the FDA, a clinical laboratory must first do a verification or validation
- They need to have a reference or comparator method to do so
  - **Reference method** - a thoroughly investigated method in which exact and clear descriptions of the necessary conditions and procedures are given for the accurate determination of one or more property values, and in which the documented accuracy and precision of the method are commensurate with the method’s use for assessing the accuracy of other methods for measuring the same property values or for assigning reference method values to reference materials. (M52 definition)
  - **Comparator method** –method against which a new system is evaluated; NOTE: Comparator methods may include reference methods or a previously verified US Food and Drug Administration-cleared commercial system. (M52 definition)
- In the absence of availability of M07 reference BMD testing many labs use disk diffusion

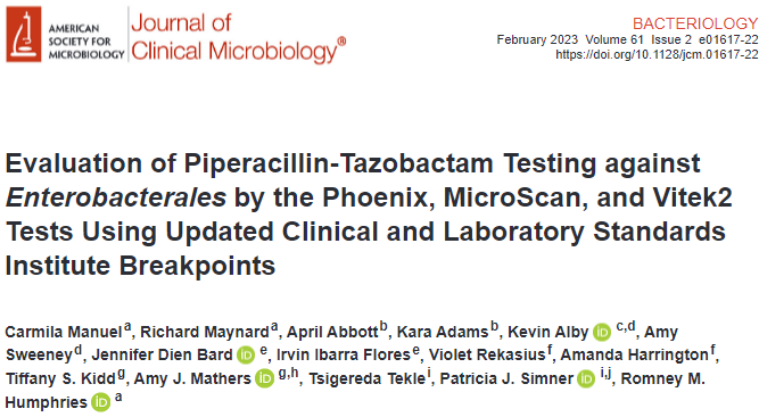
Implementation of new breakpoints: A tale of two drugs

- Tobramycin
  - 41 consecutive isolates tested – 4 R, 3 I, and 34 S by disk diffusion
  - 3% ME, 5% mE using a commercial panel
  - Validation passes

- Piperacillin-Tazobactam
  - 31 consecutive isolates tested – 4 R, 4 I, and 23 S by disk diffusion
  - 50% VME, 13% mE using a commercial panel
  - High error mE and VME call the validation into question

- Is the problem the commercial panel or disk diffusion or something else?
  - How are we going to figure out the answer?

You find a group of likeminded individuals to try and answer the question



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Evaluation of Piperacillin-Tazobactam Testing against *Enterobacterales* by the Phoenix, MicroScan, and Vitek2 Tests Using Updated Clinical and Laboratory Standards Institute Breakpoints

Carmila Manuel[a], Richard Maynard[a], April Abbott[b], Kara Adams[b], Kevin Alby[c,d], Amy Sweeney[d], Jennifer Dien Bard[e], Irvin Ibarra Flores[e], Violet Rekasius[f], Amanda Harrington[f], Tiffany S. Kidd[g], Amy J. Mathers[g,h], Tsigereda Tekle[i], Patricia J. Simner[i,j], Romney M. Humphries[a]

- All platforms performed okay against BMD but still had higher error rates (especially VME) than recommended
- Could be a function of the population of isolates tested or where the BP is in relation to the WT distribution
- Our isolates had lower error rates when compared using BMD than disk

Solution – Send to a Lab Doing M07 Reference Testing

Pros

- Get your isolates tested as opposed to getting isolates that may be different from what you see in your area
- Can work for rare testing that you don't intend on bringing in-house

Cons

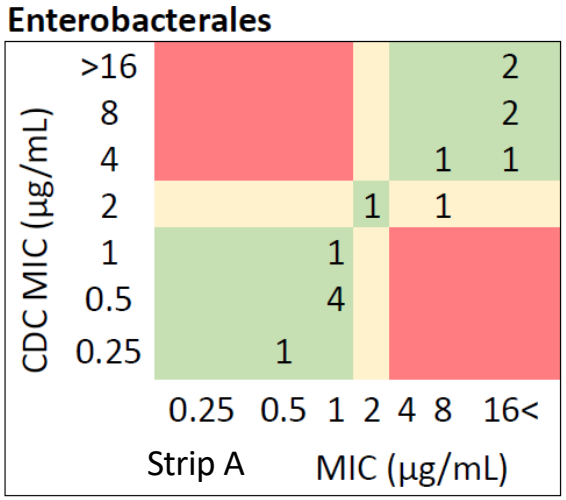
- Hard to determine when referral labs are doing M07 reference testing
- "Phone a friend" labs may not have the bandwidth for testing

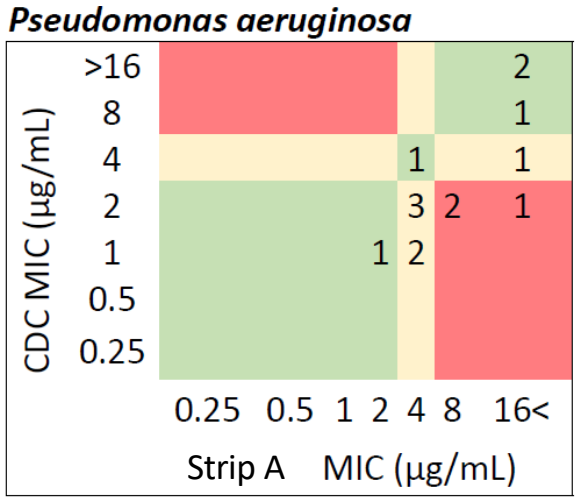
Imipenem-Relebactam: a second case study

- Limited commercial panels contain imipenem-relebactam
- Diffusion gradient strips and disks are available
- Strips may be preferred over disks because of the ability to report an MIC

Performance of gradient strips vs CDC-FDA AR Bank isolates – Imipenem-Relebactam

- Strip A performs well against Enterobacterales but has a concerning number of mE and MEs when tested for *Pseudomonas aeruginosa*





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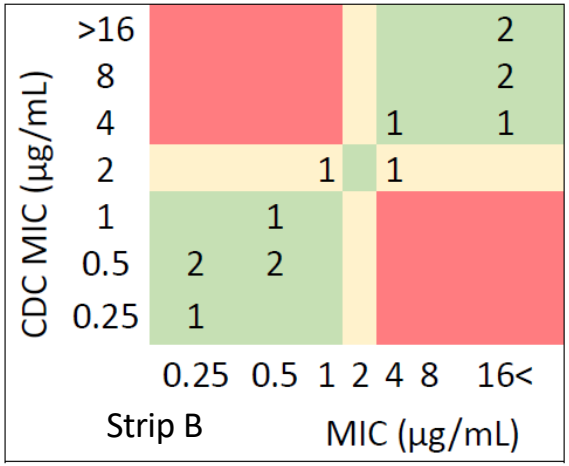
https://www.cdc.gov/drugresistance/resistance-bank/index.html

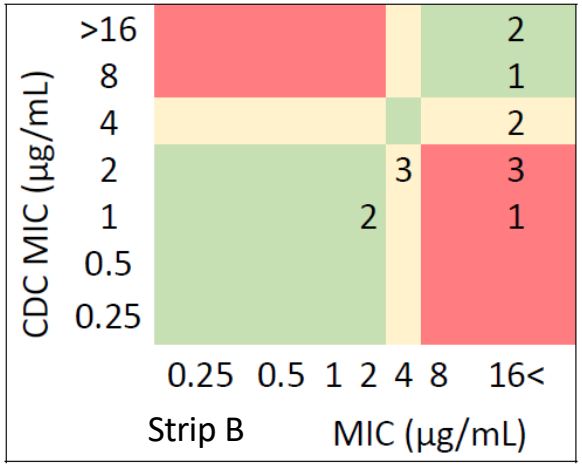
Performance of gradient strips against CDC-FDA AR Bank isolates - Imipenem-Relebactam

- Similar to Strip A, Strip B performs well against Enterobacterales but has high numbers of errors when tested against *Pseudomonas*

Enterobacterales



Pseudomonas aeruginosa



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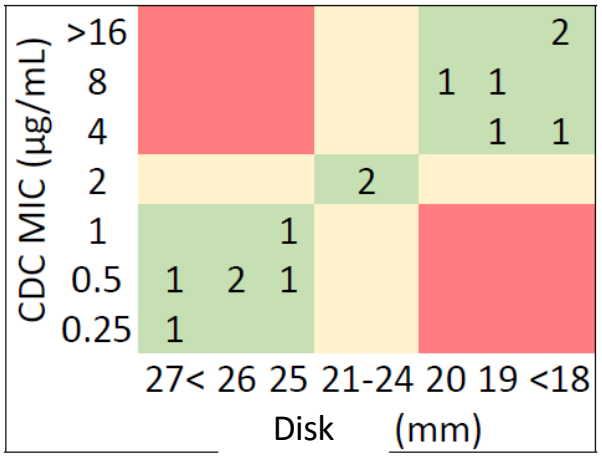
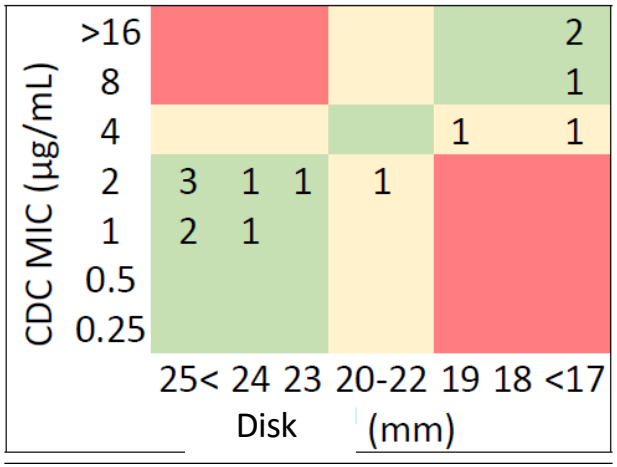
Performance of disk against CDC-FDA AR Bank isolates - Imipenem-Relebactam

- Disk also performs well against Enterobacterales with fewer and less severe errors against *Pseudomonas*

Enterobacterales



Pseudomonas aeruginosa



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Performance Summary - Imipenem-Relebactam

- Based on our evaluation we adopted the disk diffusion methodology for testing imipenem-relebactam
- Although a higher than desired amount of mE we considered two things
  - These were “more resistant” errors
  - Nearly all isolates tested were near the BPs

Enterobacterales	Categorical Agreement	Minor Error
Strip A	92.9%	7.1%
Strip B	85.7%	14.3%
Disk	100.0%	--

P. aeruginosa	Categorical Agreement	Minor Error	Major Error
Strip A	21.4%	42.9%	33.3%
Strip B	21.4%	35.7%	44.4%
Disk	78.6%	21.4%	--

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Solution – Isolate Banks

Pros

- Clinical labs do not need to prepare M07 reference BMD panels.
- Clinical labs are using a defined reference method for their comparisons.

Cons

- Not all phenotypes are stable – how to confirm when discrepancies occur?
  - -70C storage required for CDC-FDA AR Bank…issue for smaller labs!
- No standardized way to set the referral MIC (single replicate vs multiple replicates; median vs exact MIC)
- Can you get enough isolates?

Challenges for the clinical laboratory

- M07 reference testing is often not readily available
- Labs use whatever methods they have available to them in order to move forward
  - Especially true in labs without dedicated microbiology directors
- Isolate banks can be useful if methodology is transparent
- Better information is needed from referral laboratories as to the methods available for testing


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