

What's New in the 2019 CLSI Standards for Antimicrobial Susceptibility Testing (AST)?

February 20 & 21, 2019

Moderator

Janet A Hindler, MCLS MT(ASCP) F(AAM)
Consultant, Clinical Microbiology
Los Angeles, CA

Presenters

Romney M. Humphries, PhD, D(ABMM)
Chief Scientific Officer, Accelerate Diagnostics
Professor, Pathology, University of Arizona
Tucson, AZ

Audrey Schuetz, MD, MPH, D(ABMM)
Associate Professor of Laboratory Medicine and
Pathology
Division of Clinical Microbiology
Mayo Clinic College of Medicine and Science
Rochester, MN

Speaker Disclosures

Romney M. Humphries, PhD D(ABMM)

Employment: Accelerate Diagnostics

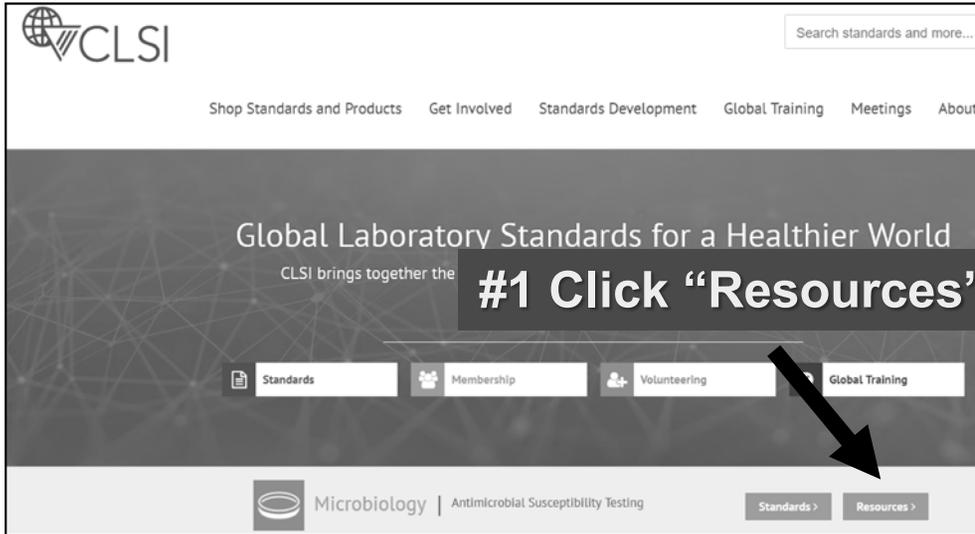
Audrey Schuetz, MD, MPH, D(ABMM)

Employment: Mayo Clinic Laboratories

Klaris Diagnostics - Scientific Advisory Board

Objectives for Today' s Talk!

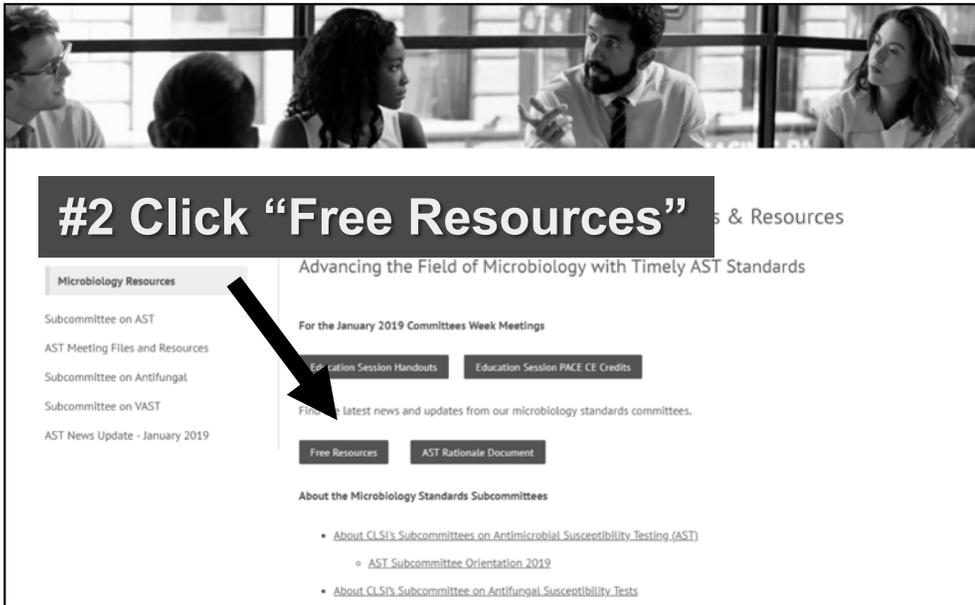
- ◆ **Identify the major changes found in the updated editions of CLSI documents M100.**
- ◆ **Design a strategy for implementing the new standards into laboratory practices.**
- ◆ **Develop a communication strategy for informing clinical staff of significant AST and reporting changes.**



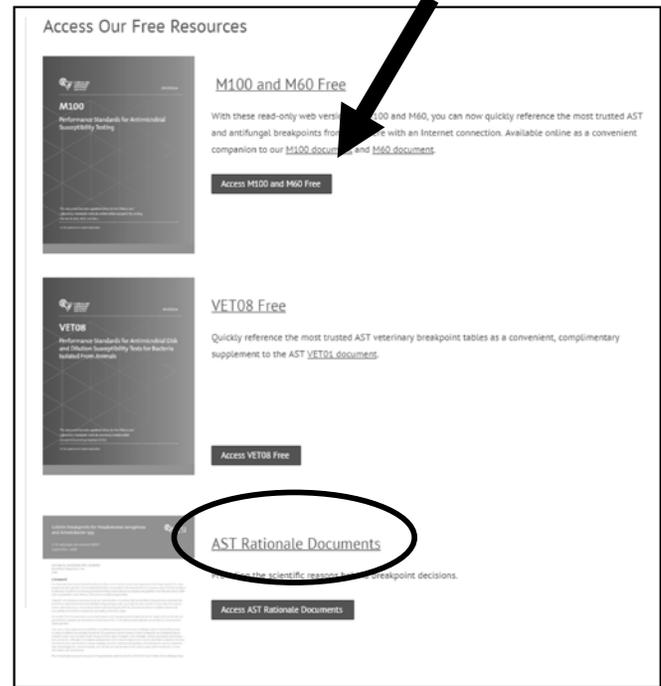
#1 Click “Resources”

www.clsi.org

#3 Click “Access M100 and M60 Free”



#2 Click “Free Resources”



Access M100 Free (on screen use only)

**From Main page
"Resources"**

www.clsi.org

Advancing the Field of Microbiology with Timely AST Standards

For the January 2019 Committees Week Meetings

[Education Session Handouts](#) [Education Session PACE CE Credits](#)

Find the latest news and updates from our microbiology standards committees.

[Free Resources](#) [AST Rationale Document](#)

About the Microbiology Standards Subcommittees

- [About CLSI's Subcommittees on Antimicrobial Susceptibility Testing \(AST\)](#)
 - [AST Subcommittee Orientation 2019](#)
- [About CLSI's Subcommittee on Antifungal Susceptibility Tests](#)
- [About CLSI's Subcommittee on Veterinary Antimicrobial Susceptibility Testing \(VAST\)](#)

View Meeting Files and Resources

- Meeting Presentation Minutes
 - [AST Meeting Minutes](#)
 - [Antifungal Meeting Minutes](#)
 - [VAST Meeting Minutes](#)
- M100 Resources
 - [CLSI Archived Breakpoints](#)
 - [CLSI Archived Methods](#)
- Other Tools Used for Decisions
 - [Range Finder](#)
 - [ECOFF Finder](#)
 - [Epidemiological Cutoff Value \(ECV\) Raw Data Submission](#)

View Educational Resources

- Newsletters
 - [Sign-up to receive the next AST News Update](#)
 - [January 2019 AST News Update \(English\)](#)
 - [Archived Newsletters](#)
- Webinars
 - [Upcoming Microbiology Webinars](#)
 - [On-Demand Archived Microbiology Webinars](#)
- Other
 - [Statisticians Summary](#)
 - [CLSI and AST](#)
 - [FDA Makes Up-to-Date Susceptibility Test Interpretive Criteria \(Breakpoint\) Resources Available Online](#)

**Orientation to
CLSI AST SC
Meetings**



**Meeting
Minutes**



**Archived
Breakpoints /
Methods**



**News
Updates**



Webinars



CLSI AST Subcommittee Outreach Working Group (ORWG)

- ◆ **Educate you about AST practices and recommendations**
- ◆ **Provide resources to help you understand and implement CLSI AST recommendations**
 - **Outreach Working Group Educational Newsletter twice/year**
 - **Webinars**
 - **Annual Update of new standards (this webinar!!)**
 - **Pre-meeting Workshops and Educational Sessions twice/year at CLSI meetings**
 - **Partnerships with other organizations (e.g., APHL, ASM, CAP)**
 - **Assist you in learning how to “volunteer”**
 - **...and more!**



CLSI Subcommittee on Antimicrobial Susceptibility Testing

CLSI AST News Update

Janet A. Hindler, MCLS, MT(A)
Audrey N. Schuetz, MD, MP

The CLSI Outreach Working Group (ORWG) is providing this Newsletter to highlight some recent issues related to antimicrobial susceptibility testing and reporting. We are listing links to some new educational materials and reminding you where you can find information about the CLSI AST Subcommittee proceedings.

CLSI AST Subcommittee Partnerships

Representatives with expertise in antimicrobials from the following organizations attend and participate in CLSI AST Subcommittee meetings and aid in dissemination of information regarding CLSI decisions and AST issues.

American College of Clinical Pharmacy Infectious Diseases Practice and Research Network (ACCP INFDP RN)

American Society for Microbiology (ASM)

Association of Public Health Laboratories (APHL)

ASTM International

College of American Pathologists (CAP)

European Committee on Antimicrobial Susceptibility Testing (EUCAST)

Infectious Diseases Society of America (IDSA)

Pediatric Infectious Diseases Society (PIDS)

Society for Healthcare Epidemiology of America (SHEA)

Society of Infectious Diseases Pharmacists (SIDP)

Susceptibility Testing Manufacturers Association (STMA)

What does the CLSI AST Subcommittee do?

The first edition of the CLSI AST News Update (Vol 1, Issue 1, Spring 2016) described details about the organization and operation of the CLSI AST Subcommittee.

- Access that newsletter [here](#).
- To learn more about upcoming or past meetings, click [here](#).
- CLSI posts meeting minutes and summaries for public access [here](#).
- If you are planning on attending a CLSI AST Subcommittee meeting, check out the Orientation presentation [here](#).

Interested in becoming a CLSI volunteer? Learn more [here](#).

Please remember that CLSI's AST Subcommittee welcomes suggestions from you about any aspect of CLSI documents, materials, or this Newsletter.

Inside This Issue

Featured Article:

Applying Fluoroquinolone Pharmacokinetics, Pharmacodynamics, and Updated Clinical Breakpoints for Gram-Negative Pathogens to Determine Optimal Dosing

Case Study:

Digging Deeper into Understanding Cefazolin Reporting for Enterobacteriaceae

Practical Tips:

#1 When Should Antifungal Susceptibility Testing be Performed for *Candida* species Isolated from Clinical Specimens?

#2 Differences in Disk Content Recommended by CLSI and EUCAST for Disk Diffusion Testing

Hot Topic:

The Cefazolin Inoculum Effect for MSSA

Quality Corner:

Antimicrobial Susceptibility Testing Quality Control of β -lactam/ β -lactamase Inhibitor Combination Agents in Clinical Development

Inside This Issue:

Featured Article:

Applying Fluoroquinolone Pharmacokinetics, Pharmacodynamics, and Updated Clinical Breakpoints for Gram-Negative Pathogens to Determine Optimal Dosing 4

Case Study:

Digging Deeper into Understanding Cefazolin Reporting for Enterobacteriaceae 9

Practical Tips:

#1 When Should Antifungal Susceptibility Testing be Performed for *Candida* species Isolated from Clinical Specimens? 12

#2 Differences in Disk Content

Recommended by CLSI and EUCAST for Disk Diffusion Testing 17

Hot Topic:

The Cefazolin Inoculum Effect for MSSA 18

Quality Corner:

Antimicrobial Susceptibility Testing Quality Control of β -lactam/ β -lactamase Inhibitor Combination Agents in Clinical Development 20

www.clsi.org

New!

January 2019

Translations: Spanish; Chinese

New!

CLSI AST Standards January 2019

◆ **M100 29th edition Tables (2019)¹**

to be used with....

◆ **M02 13th ed Disk Diffusion Method (2018)²**

◆ **M07 11th ed MIC Method (2018)²**

◆ **M11 9th ed Anaerobe MIC Method (2018)**

¹ **M100 updated at least yearly**

² **M02, M07 updated every 3 years**



New!

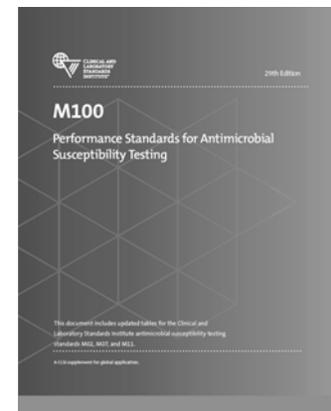
Major Changes 2019 M100 29th ed

◆ New Breakpoints

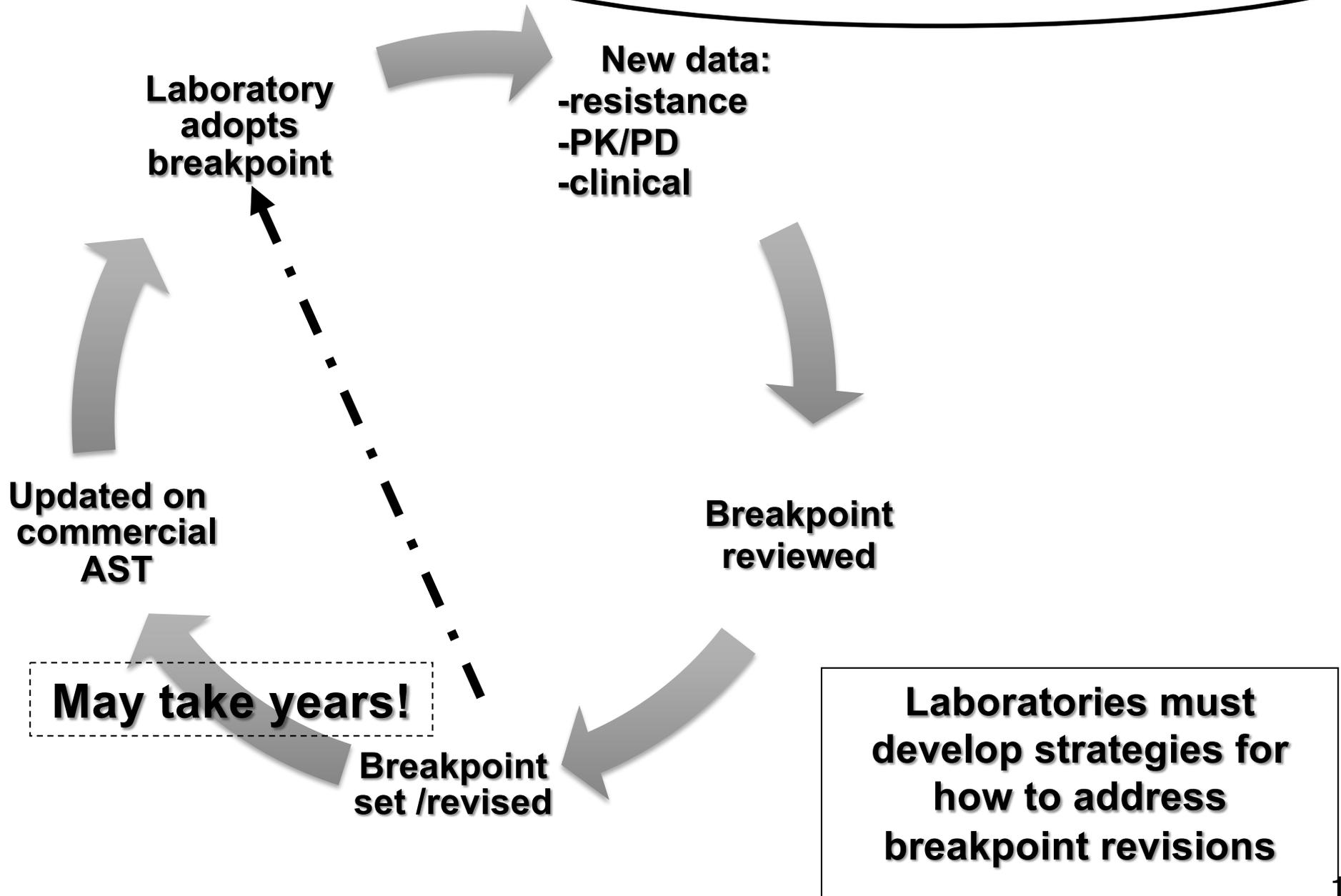
- Meropenem-vaborbactam (*Enterobacteriaceae*)
- Azithromycin (*Neisseria gonorrhoeae*)
- Cefiderocol [tentative (investigational) BPs]

◆ Revised breakpoints

- Ciprofloxacin / Levofloxacin (*Enterobacteriaceae* & *P. aeruginosa*)
- Daptomycin (*Enterococcus* spp.)
- Ceftaroline (*Staphylococcus aureus*)



The Breakpoint "Cycle"



CLSI Rationale Documents



- ◆ **Available on CLSI website**
- ◆ **Provide information supporting a breakpoint addition / revision and includes data presented during CLSI AST meetings:**
 - **PK/PD**
 - **Microbiological distributions**
 - **Clinical outcome**
- ◆ **Share with your stakeholders**

See our January 2019 and Winter 2018 News Updates to learn more about PK/PD!

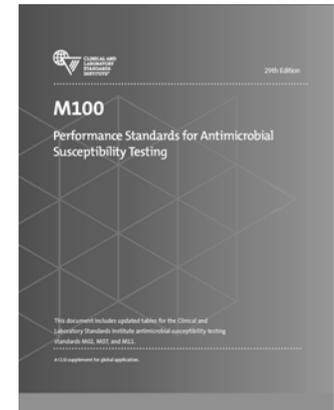
New!

Major Changes 2019 M100 29th ed (cont)

◆ Updated guidance

- Disk diffusion testing for ceftazidime-avibactam
- Fosfomycin testing
- Use of colistin MIC to predict polymyxin B MIC
- Coagulase-negative *Staphylococcus* spp.
- Intrinsic resistance
- Testing/reporting β -lactam combination agents
(Table 1A)

◆ Added molecular tables



Overview of Changes

M100, 29th ed. replaces the previous edition of the supplement, M100, 28th ed., published in 2018. The major changes in M100, 29th ed., are listed below. Other minor or editorial changes were made to the general formatting and to some of the table footnotes and comments. Changes to the tables since the previous edition appear in boldface type. The following are additions or changes unless otherwise noted as a “*deletion.*”

- **General:**

- Terminology:
 - o Coagulase-negative staphylococci (CoNS) designation removed in Surrogate Agent Tests table (for ceftoxitin testing only), in Tables 1A, 2C, and 3E, and in direct references to these tables and replaced with language to reflect species-dependent testing recommendation
 - o CoNS designation retained in all other locations for this edition of M100

- **CLSI Breakpoint Additions/Revisions Since 2010:**

- Added:
 - o Cefiderocol investigational minimal inhibitory concentration (MIC) breakpoints for *Enterobacteriaceae* (p. xxix), *Pseudomonas aeruginosa* (p. xxx), *Acinetobacter* spp. (p. xxx), and *Stenotrophomonas maltophilia* (p. xxx)
 - o Meropenem-vaborbactam disk diffusion and MIC breakpoints for *Enterobacteriaceae* (p. xxix)
 - o Azithromycin susceptible-only MIC breakpoint for *Neisseria gonorrhoeae* (p. xxxi)
- Revised:
 - o Ciprofloxacin disk diffusion and MIC breakpoints for *Enterobacteriaceae* (p. xx)
 - o Levofloxacin disk diffusion and MIC breakpoints for *Enterobacteriaceae* (p. xx)
 - o Ceftriaxone disk diffusion and MIC breakpoints for *Staphylococcus aureus* (p. xx)
 - o Daptomycin MIC breakpoints for *Enterococcus* spp. (p. xxx)

- **CLSI Epidemiological Cutoff Value Additions/Revisions Since 2015:**

- Deleted azithromycin epidemiological cutoff value (ECV) for *N. gonorrhoeae* (now)

- **CLSI Archived Resources:**

- Updated the Web address for the archived table of breakpoints eliminated from M100

M100, 29th ed.

Overview of Changes

CLSI Antimicrobial Susceptibility Testing (AST) Recommendations - 2019 M100 29th edition- Implementation Checklist

NA, not applicable

Have	Will Obtain	NA	Document
New CLSI Documents for AST			
			M100 29th ed. 2019. Performance standards for antimicrobial susceptibility testing.
Other CLSI Documents for AST of bacteria			
			M02 13th ed. 2018. Performance standards for antimicrobial disk susceptibility tests.
			M07 11th ed. 2018. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically.
			M11-A9. 2018. Methods for antimicrobial susceptibility testing of anaerobic bacteria.
			M39-A4. 2014. Analysis and presentation of cumulative antimicrobial susceptibility test data.
			M45 3rd ed. 2015. Methods for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria.
			M52 1st ed. 2015. Verification of Commercial Microbial Identification and Antimicrobial Susceptibility Testing Systems.
			CLSI AST News Update. Biannual publication that provides an update of CLSI AST Subcommittee activities and highlights contemporary AST and reporting issues. Newsletter and other CLSI resources can be accessed here: https://clsi.org/education/microbiology/

M100 29th ed. pp. xiv-xxvi.

Checklist provided with this webinar!

Reminder

CLSI Breakpoint Additions / Revisions Since 2010

CLSI Breakpoint Additions/Revisions Since 2010		
Antimicrobial Agent	Date of Addition/Revision* (M100 edition)	Comments
Enterobacteriaceae		
Azithromycin – <i>S. Typhi</i> only	January 2015 (M100-S25)	
Aztreonam	January 2010 (M100-S20)	
Cefazolin	January 2010 (M100-S20)	Breakpoints were revised twice since 2010.
	January 2011 (M100-S21)	
	January 2014 (M100-S24) January 2016 (M100S, 26th ed.)	Breakpoints were added to predict results for cefazolin when cefazolin is used for therapy of uncomplicated UTIs.
Cefepime	January 2014 (M100-S24)	
Cefiderocol	January 2019 (M100, 29th ed.)	NPBP
Cefotaxime	January 2010 (M100-S20)	
Ceftaroline	January 2013 (M100-S23)	NPBP
Ceftazidime	January 2010 (M100-S20)	
Ceftazidime-avibactam	January 2018 (M100, 28th ed.)	NPBP
Ceftizoxime	January 2010 (M100-S20)	
Ceftolozane-tazobactam	January 2016 (M100S, 26th ed.)	NPBP Disk diffusion breakpoints were added.
	January 2018 (M100, 28th ed.)	
Ceftriaxone	January 2010 (M100-S20)	
Ciprofloxacin	January 2019 (M100, 29th ed.)	Disk diffusion and MIC breakpoints were revised.
Ciprofloxacin – <i>Salmonella</i> spp. (including <i>S. Typhi</i>)	January 2012 (M100-S22)	Body site-specific breakpoint recommendations were removed in 2013.
Doripenem	June 2010 (M100-S20-U)	NPBP
Ertapenem	June 2010 (M100-S20-U)	Breakpoints were revised twice since 2010.
	January 2012 (M100-S22)	
Imipenem	June 2010 (M100-S20-U)	
Levofloxacin	January 2019 (M100, 29th ed.)	Disk diffusion and MIC breakpoints were revised.
Levofloxacin – <i>Salmonella</i> spp. (including <i>S. Typhi</i>)	January 2013 (M100-S23)	
Meropenem	June 2010 (M100-S20-U)	
Meropenem-vaborbactam	January 2019 (M100, 29th ed.)	NPBP
Ofloxacin – <i>Salmonella</i> spp. (including <i>S. Typhi</i>)	June 2013 (M100-S23)	
Pefloxacin – <i>Salmonella</i> spp. (including <i>S. Typhi</i>)	January 2015 (M100-S25)	Surrogate test for ciprofloxacin was added.

M100 29th ed. pp. xxix – xxxii.

Reminder

“Rounding out” MIC ($\mu\text{g}/\text{mL}$) Values

Actual two-fold concentration ($\mu\text{g}/\text{ml}$)	Report as: ¹
128	128
64	64
32	32
16	16
8	8
4	4
2	2
1	1
0.5	0.5
0.25	0.25

Actual two-fold concentration ($\mu\text{g}/\text{ml}$)	Report as: ¹
0.125	0.12
0.0625	0.06
0.03125	0.03
0.015625	0.016
0.0078125	0.008
0.0039063	0.004
0.0019531	0.002

¹ interpret MIC using this value

Gram-negative Rods

New!

Meropenem-vaborbactam

- ◆ **Class: β -lactam combination agent**
- ◆ **Trade Name: VABOMERE®**
- ◆ **Indications: cUTI (complicated UTI)**

Organism Group	MIC ($\mu\text{g/ml}$)			Zone (mm)		
	S	I	R	S	I	R
<i>Enterobacteriaceae</i>	$\leq 4/8$	8/8	$\geq 16/8$	≥ 18	15-17	≤ 14

M100 29th ed. Table 2A. p. 33.

Meropenem-vaborbactam

- ◆ **Vaborbactam - novel β -lactamase inhibitor that binds and inhibits KPCs**
- ◆ **Most requests will be for CRE (e.g., KPCs)**
 - **Active against most serine carbapenemases**
- ◆ **Not active against:**
 - **NDM or other MBL carbapenemase producers**
 - **OXA carbapenemases (e.g. OXA-48-like group)**
 - **Non Enterobacteriaceae (*P. aeruginosa*)**

Meropenem-vaborbactam Testing Methods¹

Disk Diffusion (Vendor)	Gradient Diffusion (Vendor)	Broth Microdilution (Vendor)	Automated US AST Systems (Vendor)
Yes (Hardy [MAST]; Oxoid)	Yes (Liofilchem MTS)	Yes (Sensititre; Thermo-Fisher)	Yes (BD Phoenix)

¹ Other commercial tests forthcoming 2019; check with your reps!

Isolates for verification:

- Laboratory Specialists, Inc. (<http://www.labspec.org/>)
- CDC FDA AR Bank - pending

New!

Ceftazidime-Avibactam Disk Diffusion Rule

Table 2A. Enterobacteriaceae

Table 2A. Enterobacteriaceae (Continued)											
Test/Report Group	Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm				Interpretive Categories and MIC Breakpoints, µg/mL				Comments
			S	SDD	I	R	S	SDD	I	R	
PENICILLINS											
A	Ampicillin	10 µg	≥17	-	14-16	≤13	≤8	-	16	≥32	(4) Results of ampicillin testing can be used to predict results for amoxicillin. See general comment (2).
O	Piperacillin	100 µg	≥21	-	18-20	≤17	≤16	-	32-64	≥128	
O	Mecillinam	10 µg	≥15	-	12-14	≤11	≤8	-	16	≥32	(5) For testing and reporting of <i>E. coli</i> urinary tract isolates only.
β-LACTAM COMBINATION AGENTS											
B	Amoxicillin-clavulanate	20/10 µg	≥18	-	14-17	≤13	≤8/4	-	16/8	≥32/16	
B	Ampicillin-sulbactam	10/10 µg	≥15	-	12-14	≤11	≤8/4	-	16/8	≥32/16	
B	Ceftolozane-tazobactam	30/10 µg	≥21	-	18-20	≤17	≤2/4	-	4/4	≥8/4	(6) Breakpoints are based on a dosage regimen of 1.5 g administered every 8 h.
B	Ceftazidime-avibactam	30/20 µg	≥21	-	-	≤20	≤8/4	-	-	≥16/4	(7) Breakpoints are based on a dosage regimen of 2.5 g (2 g ceftazidime + 0.5 g avibactam) every 8 h administered over 2 h. (8) Disk diffusion may overcall

Agent	Zone (mm)			
	S	SDD	I	R
Ceftazidime-avibactam	≥21	-	-	≤20

(8) Disk diffusion may overcall resistance for isolates with zones of 18–20 mm; confirmatory MIC testing is indicated.

M100 29th ed. Table 2A. P 33.

Ceftazidime-avibactam Resistance

◆ Resistance may be due to:

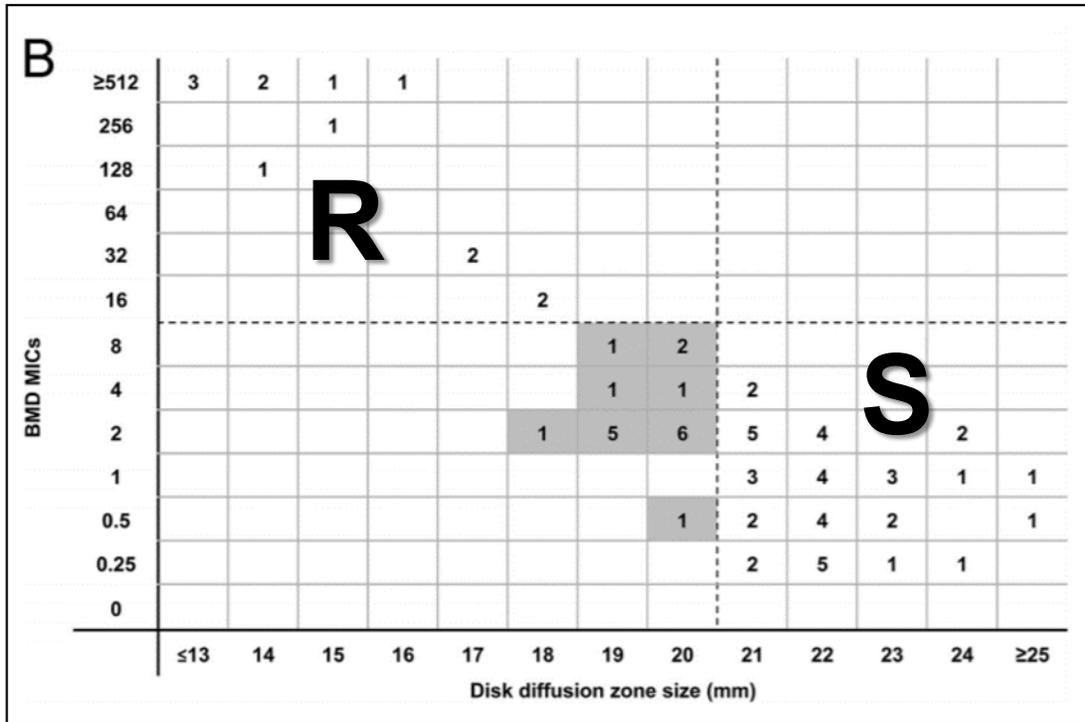
- Presence of MBL (metallo-beta-lactamase)
 - e.g., IMP, VIM, NDM
 - May be present with KPC in same strain
 - Usually still travel-associated in US
- Mutation to KPC gene
 - Patients with prior therapy with ceftazidime-avibactam
 - Meropenem-S / ceftazidime-avibactam-R
 - treatment with meropenem reverts to meropenem-R
- Hyperexpression of KPC + porin loss

◆ Outcomes better with ceftazidime-avibactam-"S" versus colistin-"S" CRE!

Hemarajata and Humphries 2019 JAC In press.
Barnes et al. 2017. Mbio 8: 528.
Nelson et al. 2017. AAC 61:989.
Van Duin et al. 2018. CID 66:163-171.

F
r
e
q
u
e
n
c
y

Ceftazidime-Avibactam Zone (mm) vs. MIC – 74 CRE



Shields et al. 2018. J Clin Microbiol. 56:e01093-17.

No. CRE Isolates	Range of MICs (µg/mL)	No. (%) "R" Isolates	No. (%) Category Agree	No. Major Errors (false S)	No. Very Major Errors (false R)
74	0.25-512	13 (18)	56 (76)	18	0

New! β -Lactam Combination Agents

Table 1A. Suggested Agents to Test/Report

Table 1A. Suggested Groupings of Antimicrobial Agents Approved by the US Food and Drug Administration (FDA) Should Be Considered for Testing and Reporting on Nonfastidious Organisms by Microbiology Laboratory

GROUP A PRIMARY TEST AND REPORT	<i>Enterobacteriaceae</i>	<i>Pseudomonas aeruginosa</i>
	Ampicillin ^c	Ceftazidime
	Cefazolin ^d	Gentamicin Tobramycin
	Gentamicin ^c Tobramycin ^c	Piperacillin-tazobactam
GROUP B SECONDARY TEST ONLY	Amikacin ^e	Amikacin
	Amoxicillin-clavulanate	Aztreonam
	Ampicillin-sulbactam	Cefepime
	Ceftazidime-avibactam	Ceftazidime-avibactam
	Ceftolozane-tazobactam	Ceftolozane-tazobactam
	Piperacillin-tazobactam	Ciprofloxacin Levofloxacin

Old

Amoxicillin-clavulanate
Ampicillin-sulbactam
Ceftazidime-avibactam
Ceftolozane-tazobactam
Piperacillin-tazobactam

Ceftazidime-avibactam
Ceftolozane-tazobactam

M100 28th ed. Table 1A. p. 16.

Table 1A. Suggested Groupings of Antimicrobial Agents Approved by the US Food and Drug Administration (FDA) Should Be Considered for Testing and Reporting on Nonfastidious Organisms by Microbiology Laboratory

GROUP A PRIMARY TEST AND REPORT	<i>Enterobacteriaceae</i>	<i>Pseudomonas aeruginosa</i>
	Ampicillin ^c	Ceftazidime
	Cefazolin ^d	Gentamicin Tobramycin
	Gentamicin ^c Tobramycin ^c	Piperacillin-tazobactam
GROUP B SECONDARY TEST ONLY	Amikacin ^e	Amikacin
	Amoxicillin-clavulanate	Aztreonam
	Ampicillin-sulbactam	Cefepime
	Ceftazidime-avibactam	Ceftazidime-avibactam
	Ceftolozane-tazobactam	Ceftolozane-tazobactam
	Meropenem-vaborbactam Piperacillin-tazobactam	Ciprofloxacin

Current

Amoxicillin-clavulanate
Ampicillin-sulbactam
Ceftazidime-avibactam
Ceftolozane-tazobactam
Meropenem-vaborbactam
Piperacillin-tazobactam

Ceftazidime-avibactam
Ceftolozane-tazobactam

M100 29th ed. Table 1A. p. 18.

Newer Antimicrobial Agents Active Against Carbapenemase-producing CRE

Agent	Class A Serine (KPC)	Class B MBL (NDM, IMP, VIM)
Ceftazidime-avibactam	yes	no
Meropenem-vaborbactam	yes	no
Plazomicin	yes	yes*
Not FDA cleared; in clinical trials:		
Imipenem-relebactam	yes	no
Cefiderocol	yes	yes
Aztreonam-avibactam	yes	yes

*some NDM are resistant

also refer to....

Clinical Microbiology
NEWSLETTER

CMN
Stay Current...
Stay Informed.

CMN
Vol. 40, No. 18
September 15, 2018
www.cmnewsletter.com

New and Novel Agents Targeting Resistant Gram-Negative Bacteria: A Review for the Clinical Microbiologist

IN THIS ISSUE
147 New and Novel Abstract

Stephanie Mitchell, Ph.D., D(ABMM)¹ and Ramsey M. Humphries, Ph.D., D(ABMM),² ¹Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania, ²Accurate Diagnostics, Tucson, Arizona

New!

Cefiderocol

- ◆ **Class: Siderophore cephalosporin**
- ◆ **Indications: not yet FDA approved; anticipated 2019 for cUTI**
- ◆ **Inv. Breakpoint = agent is investigational and has not yet been approved by the FDA for use in US**

Organism Group	MIC (µg/ml)*		
	S	I	R
<i>Enterobacteriaceae</i>	≤4	8	≥16
<i>P. aeruginosa</i>	≤4	8	≥16
<i>Acinetobacter</i> spp.	≤4	8	≥16
<i>Stenotrophomonas maltophilia</i>	≤4	8	≥16

* Disk breakpoints for 2020

Cefiderocol

- ◆ **Sidero- (iron); -phore (bearing)**
- ◆ **Novel agent which chelates iron**
- ◆ **Enters bacterial cells through active iron transport system – “Trojan horse”**
 - **Binds to penicillin-binding proteins (PBP3) and disrupts cell wall synthesis**
- ◆ **Active against wide range of MDR GNB**
 - **CRE (including KPCs, majority of MBLs)**
 - **Carbapenem-resistant *P. aeruginosa* & *A. baumannii***
 - ***Stenotrophomonas maltophilia***

Cefiderocol Testing

- ◆ **Use iron-depleted media**
- ◆ **No currently available commercial test method; in development**

“Testing cefiderocol requires iron-depleted CAMHB. Chelation is used for iron depletion, which also removes other cations (i.e., calcium, magnesium, and zinc). Following this process, cations are added back to concentrations of calcium 20-25 mg/L, magnesium 10-12.5 mg/L, and zinc 0.5-1.0 mg/L.”

Revised

Enterobacteriaceae

Pseudomonas aeruginosa

Fluoroquinolones

Antimicrobial	Obsolete^{1,2} MIC (µg/mL)			Current^{2,3} MIC (µg/mL)		
	S	I	R	S	I	R
<i>Enterobacteriaceae</i>						
Ciprofloxacin	≤1	2	≥4	≤0.25	0.5	≥1
Levofloxacin	≤2	4	≥8	≤0.5	1	≥2
<i>P. aeruginosa</i>						
Ciprofloxacin	≤1	2	≥4	≤0.5	1	≥2
Levofloxacin	≤2	4	≥8	≤1	2	≥4

¹ M100 28th ed

² Corresponding disk diffusion ranges also new

³ M100 29th ed

Enterobacteriaceae

Pseudomonas aeruginosa

Fluoroquinolones

- ◆ Updated for *Enterobacteriaceae* other than *Salmonella* spp. and *P. aeruginosa*
- ◆ For critically ill patients, low probability of treatment success for:
 - *Enterobacteriaceae*: ciprofloxacin MIC >0.25 µg/ml; levofloxacin >0.5 µg/mL
 - *P. aeruginosa*: ciprofloxacin MIC >0.5 µg/ml; levofloxacin >1 µg/ml
- ◆ These breakpoints are to protect the *sickest* patients!
- ◆ FDA has not recognized current CLSI breakpoints

See: CLSI News Update January 2019 for story on cipro PK/PD
CLSI website for rationale document on this breakpoint.

The Story!

Fluoroquinolone Use

Pros

IV and oral

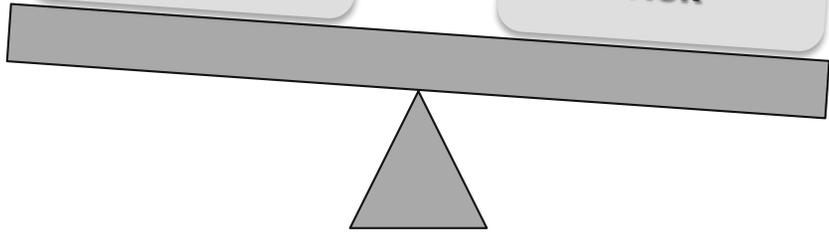
broad spectrum

Cons

Associated with emerging resistance

High rate of adverse events

High C. diff risk



Current IDSA guidance:
- ASP target for restriction / audit

FDA guidance:
- Not for sinusitis, UTI or bronchitis

Kabbani et al. 2018. CID 67:134-6.
Pepin et al. 2005. CID 41:1254.
Barlam et al. 2016. CID 62:e51-77.

Fluoroquinolones - Testing and Reporting Options for Laboratories Utilizing Commercial AST Systems

Test / Report Strategy	Approach*	Advantage	Disadvantage
Option 1: all isolates	Reflex testing: if cipro MIC ≤ 1 or levo MIC ≤ 2 → perform agar gradient strip or disk diffusion	Updated breakpoints consistently provided	Manual & labor-intensive; most (~80%) isolates will qualify for this testing
Option 2: select isolates	Reflex testing (<i>option 1 approach</i>) on sterile site isolates or select patient populations (eg, immune compromised)	Updated breakpoints provided for most clinically relevant situations	Different breakpoints for different clinical situations may be confusing for clinicians
Option 3: validate new breakpoints	Validate updated breakpoints for all sources	Updated breakpoints consistently provided	Validation required
Option 4: delay adoption of new breakpoints	Utilize report comments to warn clinicians of possible undertreatment despite susceptible results	Lowest labor for the laboratory	Report comments not consistently read

* For all reflex options, may opt to suppress result and only test on request

Specimen: Blood

Diagnosis: Pneumonia

E. coli

**OPTION 1 Example:
Preliminary
Report**

Setting: Lab using reflex testing

	<u>MIC (µg/ml)</u>
ampicillin	32 R
amp-sulbactam	8/4 S
ceftriaxone	0.5 S
ciprofloxacin	≤1 S
gentamicin	≤1 S
piper-tazobactam	≤4/4 S

- 1. If ciprofloxacin MIC ≤1 µg/ml or levofloxacin MIC ≤2 µg/ml, withhold result.**
- 2. Perform reflex testing by disk diffusion or agar gradient diffusion.**
- 3. Report MIC & interpretive category using revised (current) breakpoints.**

Clinician may wish to use ciprofloxacin as oral option when discharging patient.

Specimen: Blood
Diagnosis: Pneumonia

**OPTION 1 Example:
Final Report**

E. coli

Setting: Lab using reflex testing

	<u>MIC (µg/ml)</u>
ampicillin	32 R
amp-sulbactam	8/4 S
ceftriaxone	0.5 S
ciprofloxacin	0.25 S
gentamicin	≤1 S
piper-tazobactam	≤4/4 S

Specimen: Blood

Diagnosis: Pneumonia

**OPTION 4 Example:
Final Report**

E. coli

**Setting: Lab using commercial
automated device**

	<u>MIC (µg/ml)</u>
ampicillin	8 S
amp-sulbactam	8/4 S
ceftriaxone	0.5 S
ciprofloxacin	call lab
gentamicin	≤1 S
piper-tazobactam	≤4/4 S

**Result comment:
“Ciprofloxacin susceptibility
results are available upon
request only. If therapy with
ciprofloxacin is indicated,
contact the Microbiology
Laboratory at X-XXXX for
further testing.”**

Updated

Fosfomycin Disk Diffusion

Table 2A. *Enterobacteriaceae*

Table 2A. <i>Enterobacteriaceae</i> (Continued)											
Test/Report Group	Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm				Interpretive Categories and MIC Breakpoints, µg/mL				Comments
			S	SDD	I	R	S	SDD	I	R	
FOSFOMYCINS											
U	Fosfomycin	200 µg	≥ 16	–	13–15	≤ 12	≤ 64	–	128	≥ 256	<p>(49) Disk diffusion and MIC breakpoints apply only to <i>E. coli</i> urinary tract isolates and should not be extrapolated to other species of <i>Enterobacteriaceae</i>.</p> <p>(50) The 200-µg fosfomycin disk contains 50 µg of glucose-6-phosphate.</p> <p>(51) The only approved MIC method for testing is agar dilution using agar media supplemented with 25 µg/mL of glucose-6-phosphate. Broth dilution MIC testing should not be performed.</p>
NITROFURANS											

(49) Disk diffusion and MIC breakpoints apply only to *E. coli* urinary tract isolates and should not be extrapolated to other species of *Enterobacteriaceae*.

(51) The only approved MIC method for testing is agar dilution using agar media supplemented with 25 µg/mL of glucose-6-phosphate. Broth dilution MIC testing should not be performed.

**M100 29th ed.
Table 2A. p 40.**

Fosfomycin

~~Acinetobacter~~

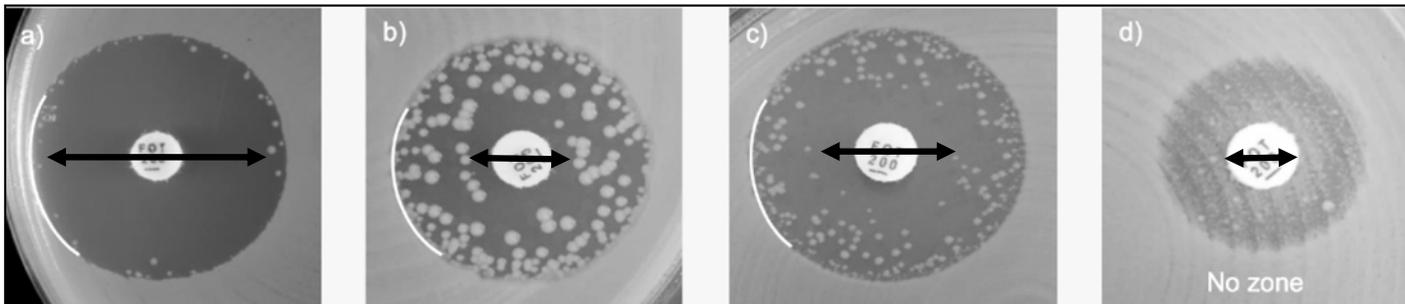
- ◆ Oral “sachet” formulation
- ◆ Clinical trials underway for IV formulation
- ◆ Excellent activity vs. MDR gram-negative infections
 - Only FDA cleared for *E. coli* and *E. faecalis*
 - CLSI breakpoints only for these two organisms



asm.org blogs...
(many others!)

Fosfomycin: AST Considerations (EUCAST vs CLSI)

EUCAST	CLSI
<p>Use disk diffusion only for <i>E. coli</i> Use agar dilution MIC for other organisms</p> <p>Ignore colonies in zone for <i>E. coli</i> (except panel D) Why? Mutation frequency for fosfomycin is low (1:10⁴) → more cells in 0.5 McFarland used for disk diffusion vs. agar dilution.</p>	<p>Use disk diffusion and agar dilution only for <i>E. coli</i> urine isolates</p> <p>Do not ignore colonies in the zone; no data to suggest they are clinically insignificant.</p>



Photos from eucast.org; arrows (↔) reflect CLSI recommendations

Colistin is Surrogate for Polymyxin B

New!

Surrogate Agent Tests				
Surrogate Agent	Organisms	Test Description	Results	Table Location
Cefazolin	<ul style="list-style-type: none"> <i>E. coli</i> <i>Klebsiella pneumoniae</i> <i>P. mirabilis</i> 	Broth microdilution or disk diffusion	When used for therapy of uncomplicated UTIs, predicts results for the following oral antimicrobial agents: cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime, cephalexin, and loracarbef Cefazolin as a surrogate may overall resistance to cefdinir, cefpodoxime, and cefuroxime. If cefazolin tests resistant, test these drugs individually if needed for therapy.	1A, 2A
Cefoxitin	<ul style="list-style-type: none"> <i>S. aureus</i> <i>S. lugdunensis</i> <i>S. epidermidis</i> Other <i>Staphylococcus</i> spp. (excluding <i>S. pseudintermedius</i> and <i>S. schleiferi</i>) 	Broth microdilution (<i>S. aureus</i> and <i>S. lugdunensis</i> only) or disk diffusion	Predicts results for <i>mecA</i> -mediated oxacillin resistance NOTE: For <i>Staphylococcus</i> spp. other than <i>S. aureus</i> , <i>S. lugdunensis</i> , <i>S. epidermidis</i> , <i>S. pseudintermedius</i> , and <i>S. schleiferi</i> , oxacillin MIC breakpoints may overall resistance. Isolates for which the oxacillin MICs are 0.5-2 µg/mL have been shown to be <i>mecA</i> positive and <i>mecA</i> negative. Isolates from serious infections with MICs in this range may be tested for <i>mecA</i> or for PBP2a	1A, 2C
Oxacillin	<ul style="list-style-type: none"> <i>S. pneumoniae</i> 	Disk diffusion	Predicts penicillin susceptibility if oxacillin zone is ≥ 20 mm. If oxacillin zone is ≤ 19 mm, penicillin MIC must be done.	1B, 2G
Polysporin	<i>Salmonella</i> spp.	Disk diffusion	Predicts reduced susceptibility to streptomycin	2A
Colistin	<i>Enterobacteriaceae</i>	Broth microdilution	MICs obtained from testing colistin predict	2B-1, 2B-2

MICs obtained from testing colistin predict MICs for polymyxin B.

Colistin	<ul style="list-style-type: none"> <i>Enterobacteriaceae</i> <i>P. aeruginosa</i>* <i>A. baumannii</i> complex 	Broth microdilution	MICs obtained from testing colistin predict MICs for polymyxin B.	2B-1, 2B-2, Appendix G
-----------------	---	----------------------------	--	-------------------------------

M100 29th ed. Instructions for Use. p. 12.

Organism Group	Colistin MIC (µg/mL)			Polymyxin B MIC (µg/mL)			Colistin ECV (µg/mL)	
	S	I	R	S	I	R	WT	NWT
<i>A. baumannii</i> complex	≤2	-	≥4	≤2	-	≥4	-	-
<i>P. aeruginosa</i>*	≤2	-	≥4	≤2	4	≥8	-	-
<i>Enterobacteriaceae</i>*	-	-	-	-	-	-	≤2	≥4

Polymyxin B vs. Colistin

Colistin / Polymyxin B

- ◆ Resistance mechanisms are the same
- ◆ Differences between colistin and polymyxin B MICs most likely due to technical variability, not true differences

Polymyxin B

- ◆ Testing options are limited
 - Disk diffusion and agar gradient diffusion methods are not accepted by CLSI; additionally, EUCAST does not accept agar dilution
- ◆ Used preferentially for treatment in some institutions
- ◆ Note: colistin outcomes are poor! Best to use alt. agent if possible

Data supporting new recommendation:

Sader et al. 2015. Diagn Microbiol Infect Dis. 83:379.

Chew et al. 2017. J Clin Microbiol. 55:2609.

Specimen: BAL
Diagnosis: Pneumonia

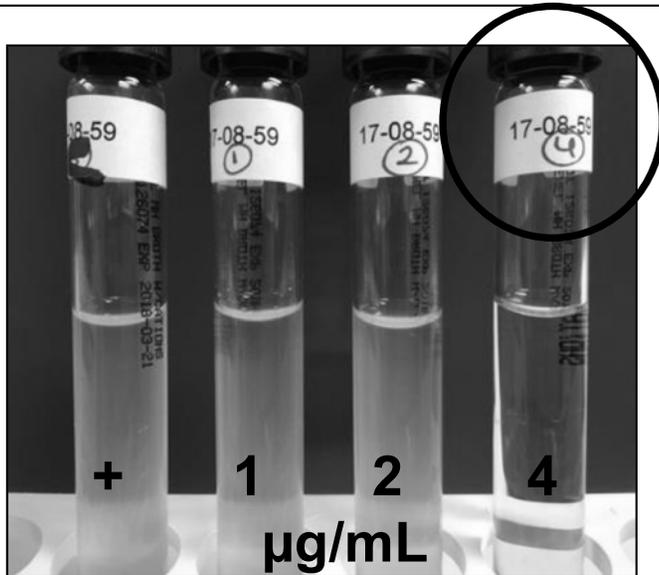
**Final Report with
Optional Comment
(example)**

Pseudomonas aeruginosa

	<u>MIC (µg/ml)</u>
amikacin	>32 R
cefepime	>32 R
ciprofloxacin	>4 R
colistin	1.0 S*
gentamicin	>16 R
meropenem	>8 R
piper-tazobactam	>128/4 R
tobramycin	>16 R

***“A colistin MIC of 1 µg/ml (S) predicts a polymyxin MIC of 1 µg/ml (S). Polymyxin B reported per Dr. Jones request.”**

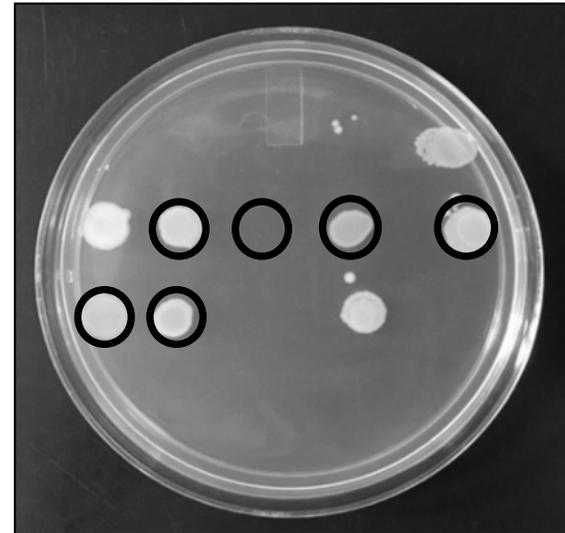
Colistin Broth Disk Elution



Add 0, 1, 2, or 4 colistin disks / 10 ml CAMHB

Simner et al. 2019. J Clin Microbiol. 57:e01163-18.

Colistin Agar Screen



**MHA + 2 µg/ml colistin
10 µl spot
Growth = MIC >2 µg/ml and “R”**

The screenshot shows the CDC & FDA Antibiotic Resistance Isolate Bank website. The header includes the CDC logo and the text 'Centers for Disease Control and Prevention CDC 24/7 Saving Lives, Protecting People™'. Below the header, there is a navigation menu with options like 'AR Isolate Bank Home', 'About the Bank', 'All Isolate Panels', 'Isolate Search', and 'Contact Us'. The main content area features the 'ARISOLATEBANK' logo and a section titled 'Isolates with New or Novel Antibiotic Resistance'. A 'Check for Isolates' button is visible at the bottom right of the main content area.

Check to obtain isolates with *mcr* to validate colistin assays.

Updated

Introduction to Tables 3B and 3C. Tests for Carbapenemases in *Enterobacteriaceae* and *Pseudomonas aeruginosa*

“After implementing the current breakpoints, these additional tests* may not need to be performed other than for epidemiological or infection control purposes (i.e., it is no longer necessary to edit results for the carbapenems to resistant if a carbapenemase producer is detected).”

***CarbaNP test, mCIM, eCIM, and/or a molecular assay**

M100 29th ed. Table 3. p. 108.

Specimen: Blood
Diagnosis: Acute Peritonitis
Enterobacter cloacae

	<u>MIC (µg/ml)</u>
amikacin	8 S
cefepime	>16 R
ceftriaxone	>8 R
ciprofloxacin	>2 R
ertapenem	>4 R
gentamicin	>8 R
imipenem	1 S
meropenem	2 I
piper-tazobactam	>128/4 R
tobramycin	>8 R
trimeth-sulfa	>4/76 R

**Molecular Method:
OXA carbapenemase
detected**

**Do not edit
carbapenems to “R”!**

Gram-Positive Cocci

Daptomycin - FDA-approved Indications for Treatment¹

Indication	Dose
Complicated skin and skin structure infections (cSSSI) in adults and pediatrics due to MSSA and MRSA, <i>Streptococcus pyogenes</i>, <i>Streptococcus agalactiae</i>, <i>Streptococcus dysgalactiae</i> subsp. <i>equisimilis</i>, and <i>Enterococcus faecalis</i> (VSE only)	4 mg/kg/day
<i>S. aureus</i> bloodstream infections (MSSA and MRSA) including right-sided infective endocarditis in adults	6 mg/kg/day
<i>S. aureus</i> bloodstream infections in pediatrics	6 mg/kg/day

Daptomycin Prescribing Information.

Revised

Enterococcus spp. Daptomycin

Organism Group	Obsolete ¹ MIC (µg/mL)			Current ² MIC (µg/mL)				Notes
	S ³	I	R	S	I	SDD	R	
Enterococcus spp.	≤4	-	-	≤1	-	2-4	≥8	Breakpoints are based on a dosage regimen of 6 mg/kg/day in adults SDD category is based on a dosage regimen of 8-12 mg/kg in adults and is intended for serious infections due to <i>Enterococcus</i> spp. Consultation with an infectious diseases' specialist is recommended.

¹ M100 28th ed

² M100 29th ed

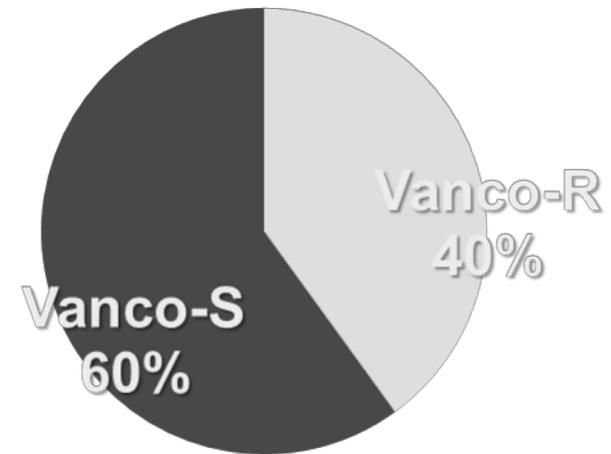
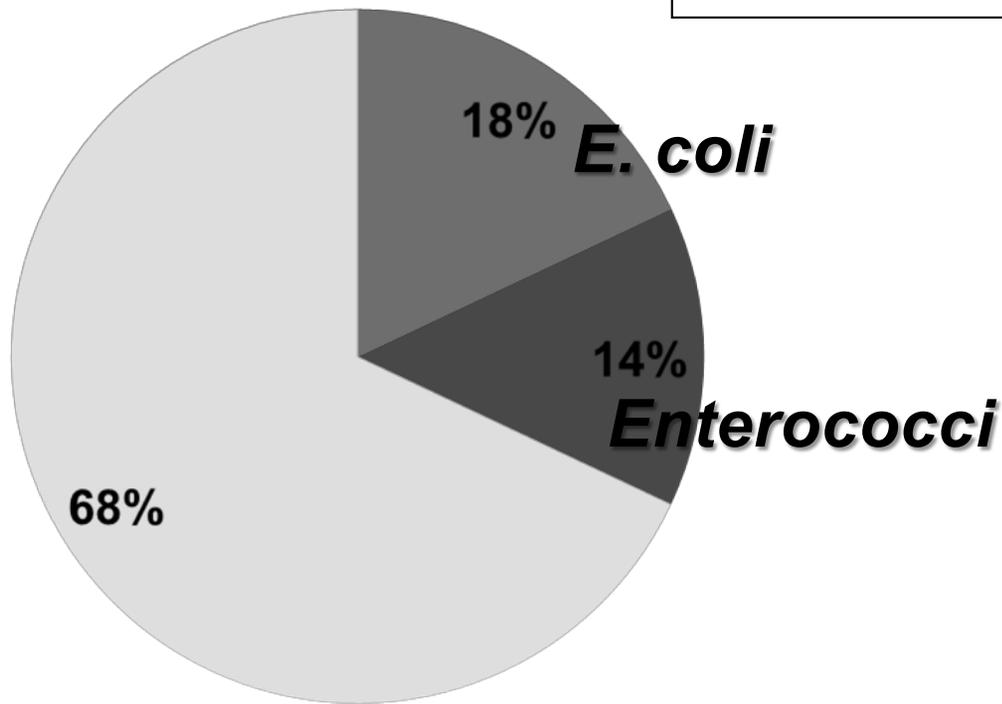
³ Previously, if MIC >4 µg/mL (obsolete breakpoints), report as “nonsusceptible”. Very few isolates with MIC >4 µg/ml at time of original breakpoint approval.

NOTE: no disk breakpoints for daptomycin, as disk diffusion is not a valid method for daptomycin

The Story!

Why did daptomycin breakpoints change for *Enterococcus* spp.?

**UCLA 2017
Blood Isolates**



Enterococci

***Enterococcus* species**

Typical AST Profiles

Antimicrobial	<i>Enterococcus faecium</i>	<i>Enterococcus faecalis</i>
Aminoglycosides Cephems Clindamycin Trimethoprim-sulfa	Intrinsic Resistance	Intrinsic Resistance
Ampicillin	Usually R	Usually S
Quinupristin-dalfopristin*	Usually S	Intrinsic Resistance
Vancomycin	Often R	Usually S
High-level aminoglycosides	Often R	Often S

*** Quinupristin-dalfopristin infrequently used due to side effects (muscle pain)**

Specimen: Blood
Diagnosis: Endocarditis

Final Report with
Optional Comment

Enterococcus faecalis

	<u>MIC (µg/ml)</u>
ampicillin	2 S
vancomycin	≤0.5 S
gentamicin synergy	S
streptomycin synergy	S

“Serious enterococcal infections need combination therapy with ampicillin or vancomycin plus an aminoglycoside. Synergy occurs only when both drugs in the combination are “S””

**Specimen: Blood
Diagnosis: Endocarditis**

Enterococcus faecium

	<u>MIC ($\mu\text{g/ml}$)</u>
ampicillin	>32 R
daptomycin	≤ 1 S
linezolid	1 S
quinupris/dalfopris	≤ 0.5 S
vancomycin	>32 R
gent synergy	R
strep synergy	R

**Few treatment options for
VRE bloodstream infections...**

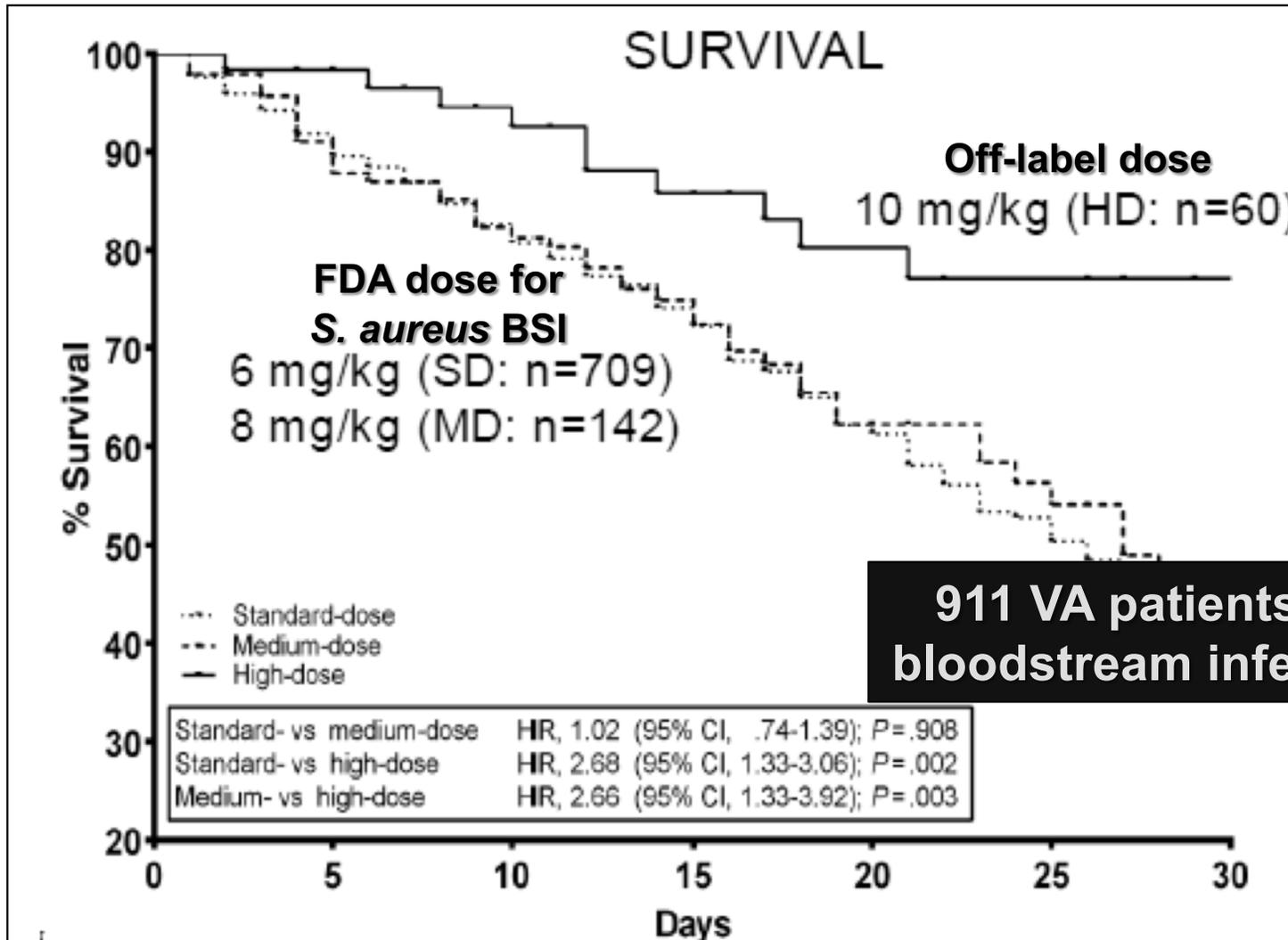
Bacteriocidal
- Daptomycin

Bacteriostatic
- Linezolid*
- Tigecycline

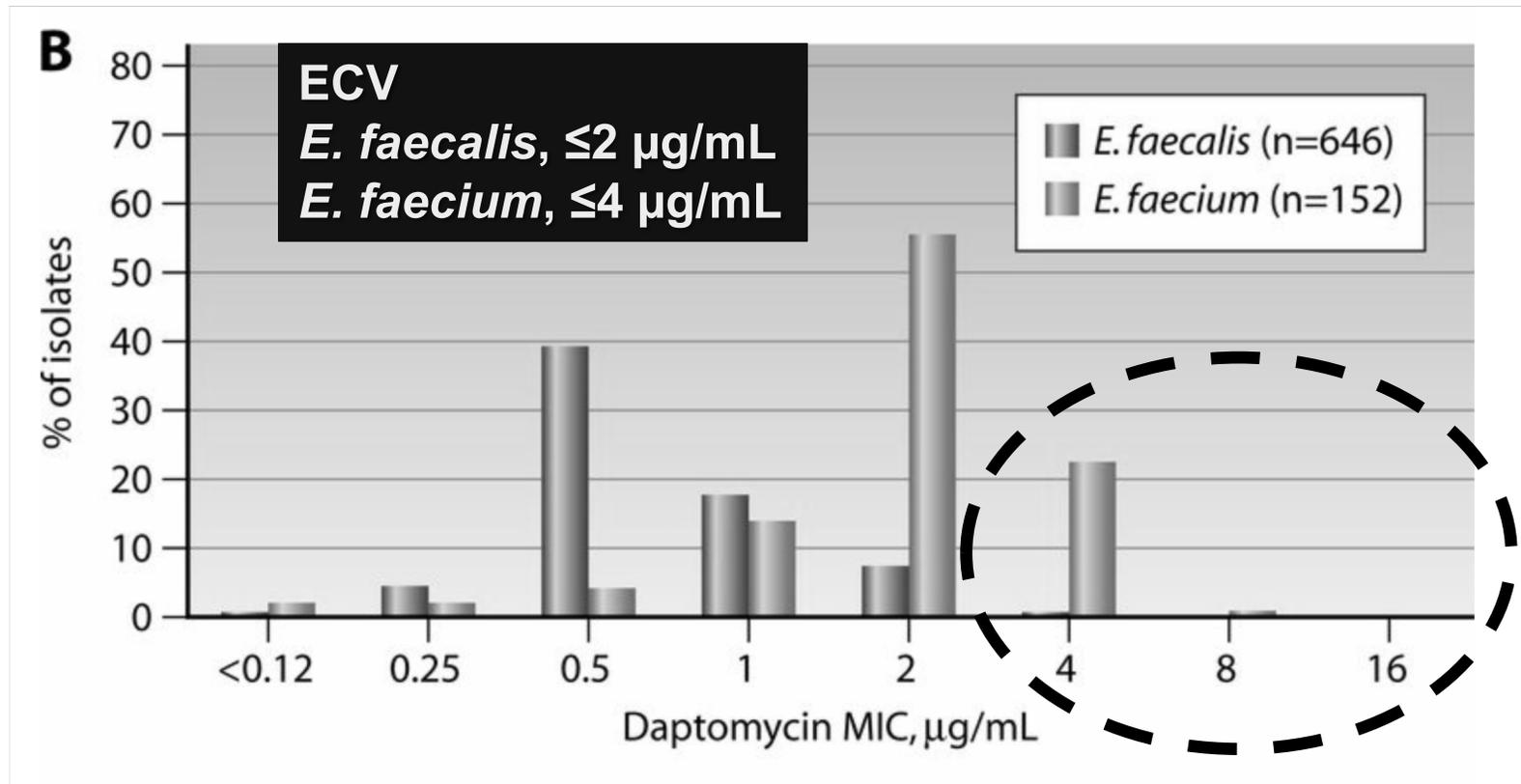
*FDA indication for use

**“VRE isolated. Please check infection control policies.
Infectious Diseases consult suggested.”**

Daptomycin outcomes for VRE infections depend on dose....



Enterococcus spp. Daptomycin MIC Distributions



Humphries, Pollett, Sakoulas 2013. Clin Micro Rev. 4:759; Chuang et al. 2017. Clin Infect Dis. 64:1026; Casapao et al. 2013. Antimicrob Ag Chemother. 57:4190; Shukla et al. 2016. Clin Infect Dis. 62:1514; Moise et al. 2015. Clin Ther. 37:1443; Chong et al. 2016. Clin Ther. 38:2468.

Increasing reports of treatment failures with *E. faecium* MIC $\geq 4 \mu\text{g/mL}$

***Enterococcus* spp.**

SDD Daptomycin Breakpoint

- ◆ **FIRST TIME CLSI lists non-FDA approved (“off-label”) dose used for SDD, because:**
 - Many prescribe doses of 8-12 mg/kg/day to treat serious VRE infections
 - IDSA has commentary on use of high-dose daptomycin for ampicillin-R, vancomycin-R enterococcal infections
 - Safety data reviewed by CLSI demonstrated low risk of adverse events with higher dose
 - “Best practices” breakpoint to address urgent clinical need

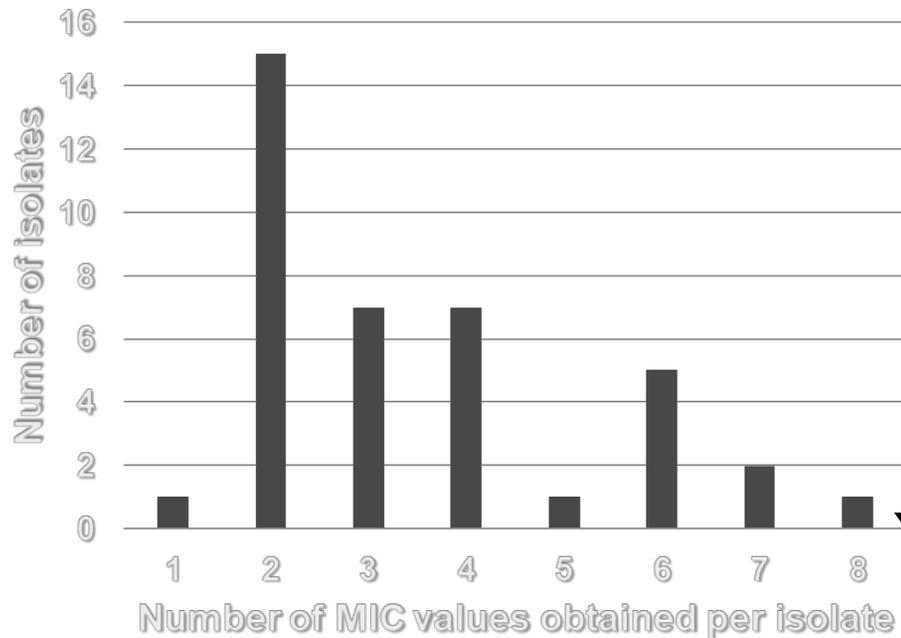
Daptomycin MIC (µg/mL)			
S	I	SDD	R
≤1	-	2 – 4	≥8

***Enterococcus* spp. - Daptomycin Continuing AST Challenges**

- ◆ **Breakpoints bisect the wild-type MIC distribution for *E. faecium*; results for a single isolate may show different category results:**
 - S or SDD** **SDD or R** **S or R! (next slide)**
- ◆ **FDA may not recognize current CLSI breakpoints**
 - **No commercial AST system adoption**
- ◆ **Data predominantly for *E. faecium***
- ◆ **CLSI reviewed these issues in January 2019 and changed breakpoint again in light of this!**

***Enterococcus faecium* - Daptomycin AST Challenges**

Daptomycin MICs - *E. faecium*



- ◆ **40 *E. faecium* isolates**
- ◆ **Tested by BMD at 3 labs**
- ◆ **N = 3 replicate MICs per lab**
 - Same media
 - Same inoculum
 - (9 results/isolate)
- ◆ **30% of MICs for frankly “R” isolates (MIC ≥ 8 $\mu\text{g/mL}$) called “S” (MIC ≤ 1 $\mu\text{g/mL}$)**

Isolate #32:

- MICs ranged from 0.25 to 32 $\mu\text{g/mL}$
- Recovered from daptomycin treatment failure case

Campeau et al. 2018. AAC 62:745.

Enterococcus spp. - Daptomycin

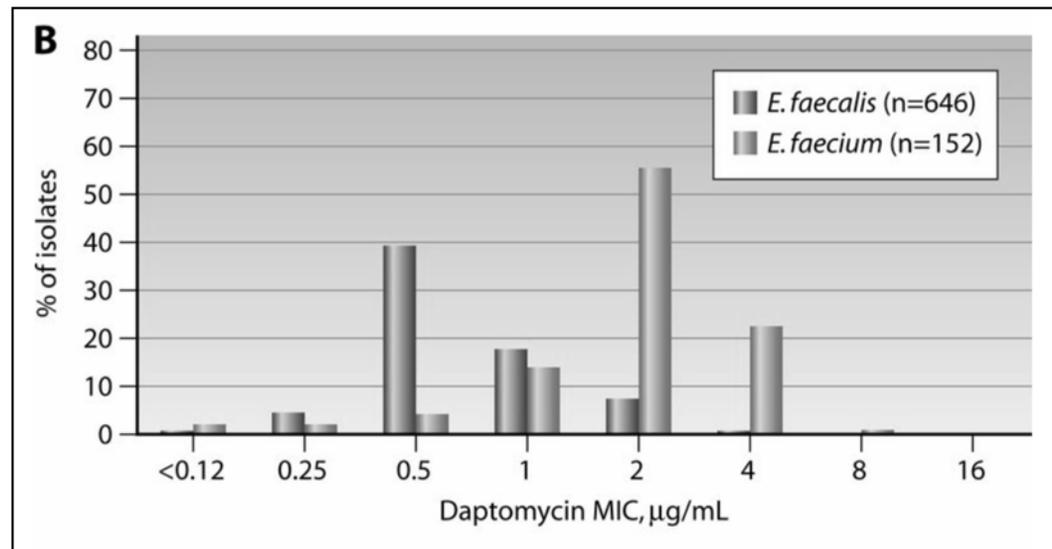
New SDD Breakpoint (again!) in 2020!

Organism	MIC ($\mu\text{g}/\text{mL}$)			
	S	I	SDD	R
<i>Enterococcus spp.</i>	≤ 1	-	2 – 4*	≥ 8

Organism	MIC ($\mu\text{g}/\text{mL}$)			
	S	I	SDD	R
<i>E. faecium</i>	-	-	$\leq 4^*$	≥ 8
Other Enterococci	≤ 2	4	-	≥ 8

* SDD is for doses >6 mg/kg/day
M100 29th ed. Table 2D. p. 70. 2019.

* SDD is for doses >6 mg/kg/day
M100 30th ed. Table 2D. 2020.



Strategies for addressing daptomycin breakpoint revision...

1. **Current CLSI breakpoints not yet recognized by FDA and applies an off-label dose.**
2. **FDA clearance not possible for commercial automated AST systems.**
3. **Discuss changes with ASP, ID, pharmacy etc.**
 - **Challenge of treating VR *E. faecium* infections**
 - **Data supports high dose daptomycin for optimal outcomes (8-12 mg/kg/day)**
4. **Wait until 2020 to make major changes**
5. **For now consider:**
 - a) **Continue to report with obsolete breakpoints and add comment to report regarding need for high dose of 8-12 mg/kg/day for *E. faecium***
 - b) **If MIC ≥ 8 $\mu\text{g/mL}$, report as “R”; suppress result if MIC ≤ 4 $\mu\text{g/mL}$ and add comment regarding need for 8-12 mg/kg/day for *E. faecium***

Remember! Daptomycin should be reserved for serious infections – consider reporting MIC for *Enterococcus* spp. isolated from blood / heart tissue only!

Specimen: Blood
Diagnosis: Urosepsis
Enterococcus faecium

	<u>MIC (µg/ml)</u>
ampicillin	>32 R
daptomycin	call lab
linezolid	1 S
quinupris/dalfopris	≤0.5 S
vancomycin	>32 R
gent synergy	R
strep synergy	R

**“If daptomycin is a consideration for this *E. faecium*,
high dose (8-12 mg/kg/day) should be considered.
Infectious Diseases consult suggested.”**

Ceftaroline - FDA-approved Indications for Treatment

Indication	Dose
Acute bacterial skin and skin structure infections ¹	600 mg q 12h
Community-acquired bacterial pneumonia ²	600 mg q 12h

- 1** *Staphylococcus aureus* (including MSSA and MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *E. coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.
- 2** *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (MSSA only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *E. coli*.

Ceftaroline use in serious MRSA infections....

- ◆ **Good efficacy, few adverse events, including in patients not responding to vancomycin**
- ◆ **Several recent studies:**
 - **Cosimi RA et al. 2017. Op Forum ID: 4:ofx084.**
 - **Britt et al. 2017. Drugs. 77:1345.**
 - **White et al. 2017. Am J Health Syst Pharm. 74:201.**
- ◆ **\$200 per dose vs. \$4 per dose for vancomycin**

Revised *Staphylococcus aureus* Ceftaroline

Organism Group	Obsolete ^{1,2} MIC (µg/mL)			Current ^{2,3} MIC (µg/mL)			
	S	I	R	S	I	SDD	R
<i>S. aureus</i> only, including MRSA	≤1	2	≥4	≤1	-	2-4	≥8

¹ M100 28th ed

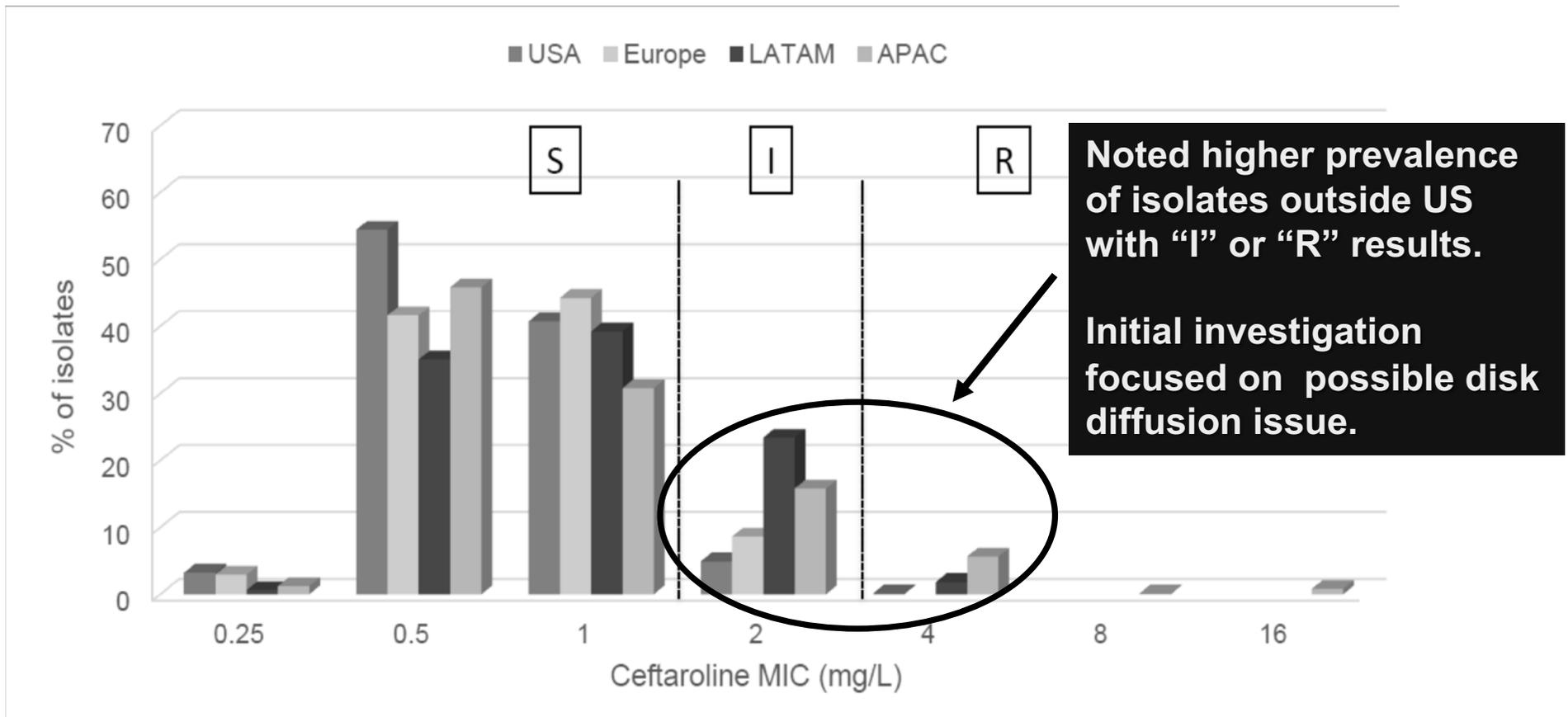
² Corresponding disk diffusion ranges also new

³ M100 29th ed

Breakpoint	Dose	Reference
Obsolete	“S” based on 600 mg q 12h	FDA drug label
Current	“S” based on 600 mg q 12h	FDA drug label
	“SDD” based on 600 mg q8 h over 2 h	Outside US (off-label US)

The Story!

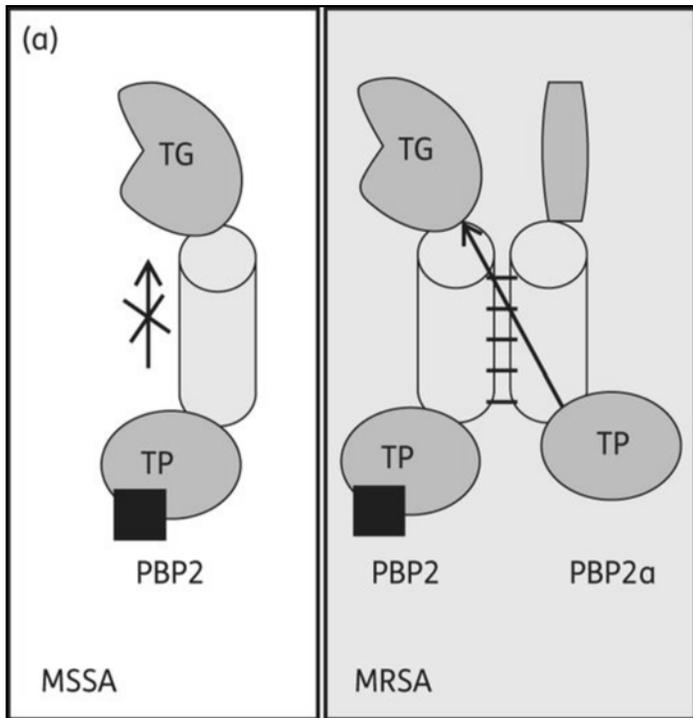
Why did ceftaroline breakpoints change for *Staphylococcus aureus*?



LATAM, Latin America; APAC, Asia Pacific

MSSA vs. MRSA

Penicillin-binding Proteins (PBPs)

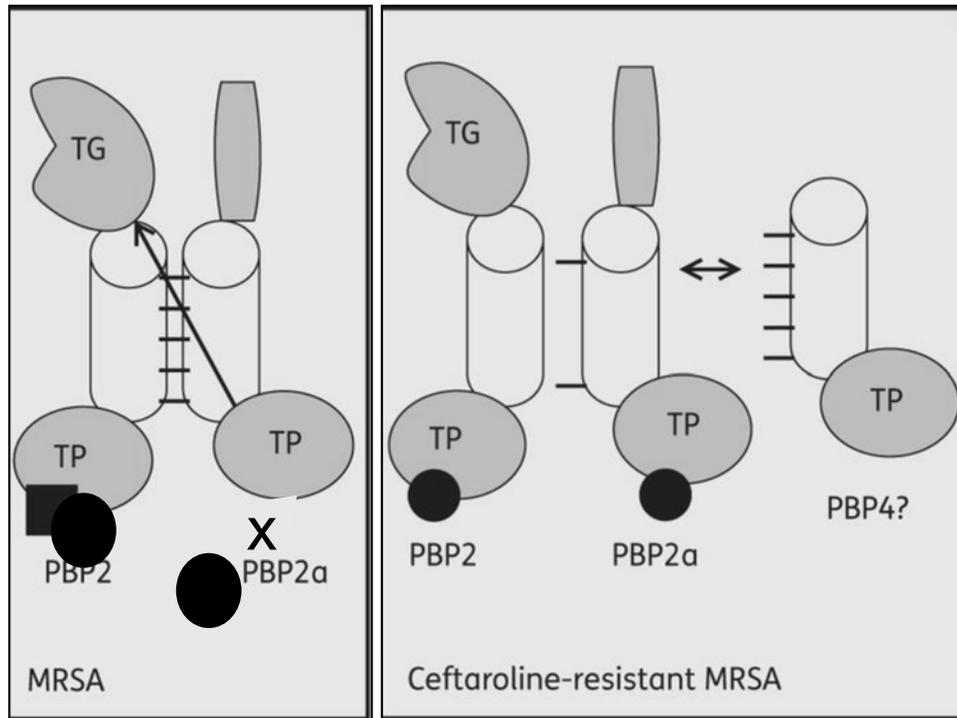


- ◆ PBP2 = peptidoglycan synthesis
 - 2 active domains:
 - transpeptidase (TP)
 - transglycosylase (TG)
- ◆ PBP2a
 - TP but no TG

Agent	MSSA	MRSA
Oxacillin	Binds PBP2 TP = cell dies	Binds PBP2, not PBP2a TP = cell lives
Ceftaroline	Binds PBP2 TP = cell dies	Binds PBP2 and PBP2a TP = cell dies

Ceftaroline-R MRSA

Two Mechanisms



- 1. Mutation to PBP2a TP**
 - Neither OX or CFT bind
- 2. Mutation outside PBP2a TP**
 - can't supplement PBP2 activity, but PBP4 does

Mutation	Mechanism	Ceftaroline MIC (µg/mL)	Treat with ceftaroline?
PBP2a TP	Can't bind ceftaroline	4 - > 8	No
PBP2a, not TP	Can't interact with PBP2 PBP4 takes up role	0.5 – 2.0	Yes, at high dose

Strategies for addressing ceftaroline breakpoint revision...

- 1. Current CLSI breakpoint not yet recognized by FDA – and applies an off-label dose.**
- 2. FDA clearance not possible for commercial automated AST systems.**
- 3. Discuss changes with ASP, ID, pharmacy etc. to see if a ceftaroline breakpoint update is needed**
 - Typically do not see isolates with MIC >1 µg/mL in the US / Europe**
 - Some may be reluctant to use higher dose because not FDA cleared**
- 4. Option:**
 - Continue to report with obsolete breakpoints, and add a comment to the patient report if ceftaroline MIC is 2-4 µg/ml (“I” or “R”, respectively by old breakpoint) such as “ID consult suggested”**

Specimen: BAL
Diagnosis: Pneumonia

Staphylococcus aureus

	<u>MIC (µg/ml)</u>
ceftaroline	2 I*
clindamycin	>4 R
erythromycin	>4 R
oxacillin	>4 R
vancomycin	≤0.5 S

**“Ceftaroline reported per Dr. Jones request.
Infectious Diseases consult suggested to
discuss ceftaroline results”**

Susceptible Dose Dependent (SDD) Modifications to Definition

- ◆ Both daptomycin and ceftaroline new SDD breakpoints are based on FDA off-label doses of antimicrobial
- ◆ Previous definition indicates when MIC is SDD, “consideration should be given to the “maximum approved dosage regimen” ...consult the drug label”
- ◆ Revised definition refers to “maximum, literature-supported dosage regimens”

• **susceptible-dose dependent (SDD)** – a category defined by a breakpoint that implies that susceptibility of an isolate depends on the dosing regimen that is used in the patient. To achieve levels that are likely to be clinically effective against isolates for which the susceptibility testing results (either minimal inhibitory concentrations [MICs] or zone diameters) are in the SDD category, it is necessary to use a dosing regimen (ie, higher doses, more frequent doses, or both) that results in higher drug exposure than that achieved with the dose that was used to establish the susceptible breakpoint. Consideration should be given to the maximum, literature-supported dosage regimens, because higher exposure gives the highest probability of adequate coverage of an SDD isolate. **Appendix E lists the doses used when establishing SDD categories.** The drug label should be consulted for **recommended doses and adjustment for organ function**; **NOTE:** The concept of SDD has been included within the intermediate category definition for antimicrobial agents. However, this is often overlooked or not understood by clinicians and microbiologists when an intermediate result is reported. The SDD category may be assigned when doses well above those used to calculate the susceptible breakpoint are **supported by the literature, widely used clinically, and/or approved** and for which sufficient data to justify the designation exist and have been reviewed. When the intermediate category is used, its definition remains unchanged. See Appendix F for additional information.

M100 29th ed. p 4.

***Staphylococcus* species
(not *Staphylococcus aureus*!) ***

***most are coagulase-negative staphylococci (CoNS)**

Further Complexity with CoNS

Detection of oxacillin resistance in staphylococci is achieved by using specific methods as listed in Table 2C and further described in Table 3E.

Organism	Acceptable Methods				
	Cefoxitin MIC	Cefoxitin disk diffusion	Oxacillin MIC	Oxacillin disk diffusion	Oxacillin salt agar
<i>S. aureus</i>	Yes	Yes	Yes	No	Yes
<i>S. lugdunensis</i>	Yes	Yes	Yes	No	No
<i>S. epidermidis</i>	No	Yes	Yes	Yes	No
<i>S. pseudintermedius</i>	No	No	Yes	Yes	No
<i>S. schleiferi</i>	No	No	Yes	Yes	No
Other <i>Staphylococcus</i> spp. (not listed above)	No	Yes	Yes*	No	No

* For other *Staphylococcus* spp. with oxacillin MICs between 0.5–2 µg/mL, see comment (17) for recommendations on testing for *mecA* or for PBP2a.

- Added oxacillin disk option for *S. epidermidis*
- Changed language for CoNS, to “other *Staphylococcus* spp.”

M100 29th ed. Table 2C. p 59.

New!

Table 2C. *Staphylococcus* spp.

Table 2C. *Staphylococcus* spp. (Continued)

Test/Report Group	Antimicrobial Agent	<i>Staphylococcus</i> spp. Indications	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm				Interpretive Categories and MIC Breakpoints, µg/mL				Comments
				S	SDD	I	R	S	SDD	I	R	
PENICILLINASE-STABLE PENICILLINS (Continued)												
A	Oxacillin	<i>S. epidermidis</i>	1 µg oxacillin	≥18 (oxacillin)	-	-	≤17 (oxacillin)	≤0.25 (oxacillin)	-	-	≥0.5 (oxacillin)	See general comments (5) and (6) and comments (8), (11), and (12). (15) Cefoxitin MIC testing is not reliable for detecting <i>mecA</i> -mediated resistance in <i>S. epidermidis</i> .
		<i>S. pseudintermedius</i> and <i>S. schleiferi</i>	1 µg oxacillin	≥18	-	-	≤17	≤0.25	-	-	≥0.5	(16) Neither cefoxitin MIC nor cefoxitin disk tests are reliable for detecting <i>mecA</i> -mediated resistance in <i>S. pseudintermedius</i> and <i>S. schleiferi</i> .

New! Column to indicate which species BP applies to

M100 29th ed. Table 2C. p 59.

Table 2C. *Staphylococcus* spp. (Continued)

Test/Report Group	Antimicrobial Agent		Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm				Interpretive Categories and MIC Breakpoints, µg/mL				Comments	
			S	SDD	I	R	S	SDD	I	R		
PENICILLINASE-STABLE PENICILLINS (Continued)												
A	Oxacillin	(For <i>S. pseudintermedius</i> and <i>S. schleiferi</i>)	1 µg oxacillin	≥18	-	-	≤17	≤0.25	-	-	≥0.5	or cefoxitin disk tests are reliable for detecting <i>mecA</i> -mediated resistance in <i>S. pseudintermedius</i> and <i>S. schleiferi</i> .

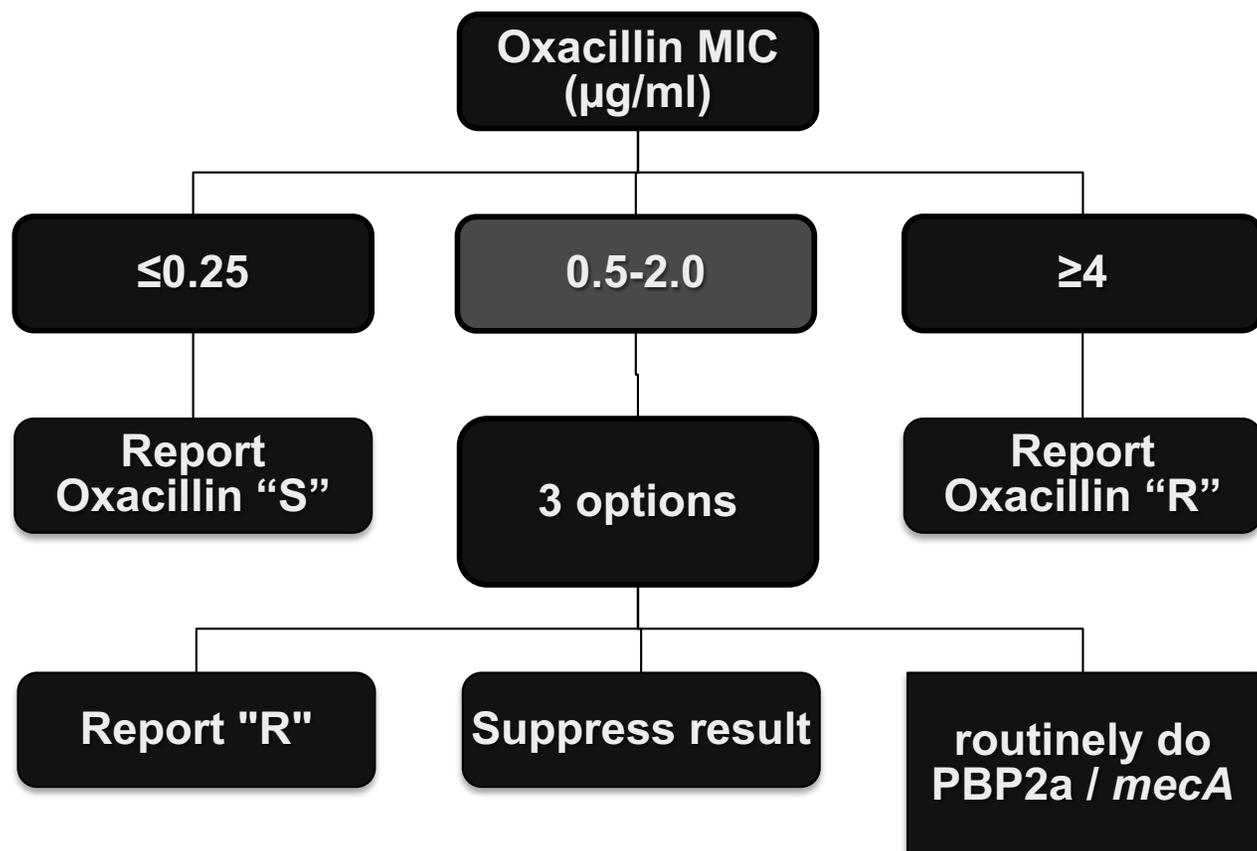
Old! Species indicated in brackets

M100 28th ed. Table 2C. p 58.

What if my lab doesn't identify non-S. aureus to species?

- ◆ **Confirm need for AST: sterile site, true infection**
- ◆ **Confirm need for oxacillin results**
 - Many physicians will not use oxacillin to treat due to concern of heteroresistance
- ◆ **Rule out *S. lugdunensis***
 - PYR + , ODC +
 - If *S. lugdunensis* → use *S. aureus* breakpoints
- ◆ **Perform oxacillin MIC on automated system**

“Oxacillin”- Other *Staphylococcus* spp. No MALDI Strategy



- ~ 8% of CoNS isolates have MIC 0.5-2.0 µg/mL (UCLA = 16 per year)
- AST strategy is facility specific

Neisseria gonorrhoeae

Neisseria gonorrhoeae

CDC treatment recommendations:

Uncomplicated gonococcal infections of the cervix, urethra, and rectum

- **Ceftriaxone 250 mg IM + azithromycin 1 gm PO**

<https://www.cdc.gov/std/tg2015/gonorrhea.htm>



United Kingdom –*N. gonorrhoeae* with high-level resistance to azithromycin and resistance to ceftriaxone acquired abroad

Multidrug-resistant gonorrhea detected n Australia



New!

Neisseria gonorrhoeae

Azithromycin

Organism Group	MIC ($\mu\text{g}/\text{mL}$)		
	S	I	R
<i>N. gonorrhoeae</i>	≤ 1	-	-

“This breakpoint presumes that azithromycin (1 gm single dose) is used in an approved regimen that includes an additional antimicrobial agent (i.e., ceftriaxone 250mg IM single dose).”

***Deleted* disk diffusion and MIC breakpoints for:**

**Cefuroxime
Cefmetazole
Ceftazidime
Cefetamet
Enoxacin
Fleroxacin
Lomefloxacin
Ofloxacin**

Azithromycin

◆ **After oral administration, azithromycin enters tissues and achieves high concentration**

- **~70-fold higher in cervical tissue vs. blood**
- **~100-fold higher in tonsil vs. blood**
- **~800-fold higher in PMNs vs. serum**

Kong et al. 2017. PLoS One. 12:e174372.

Kong et al. 2015. J Antimicrob Chem. 70:1290.

Obsolete

Neisseria gonorrhoeae **Azithromycin ECV**

- ◆ CLSI published ECV for *N. gonorrhoeae* and azithromycin in 2017

Table G2. ECVs for *Neisseria gonorrhoeae*

Antimicrobial Agent	MIC ECV, $\mu\text{g/mL}$		Comments
	WT	NWT	
Azithromycin ¹⁻³	≤ 1	≥ 2	For use with <i>N. gonorrhoeae</i> .

Abbreviations: ECV, epidemiological cutoff value; MIC, minimal inhibitory concentration; NWT, non-wild-type; WT, wild-type.

- ◆ ***Why was a breakpoint needed?***
 - Could not obtain FDA-clearance for commercial ASTs with an ECV
 - Cause of confusion for surveillance

New!

Neisseria gonorrhoeae **Azithromycin**

Organism Group	MIC ($\mu\text{g}/\text{mL}$)		
	S	I	R
<i>N. gonorrhoeae</i>	≤ 1	-	-

- ◆ “S” supported by clinical data from 1980s, 1990s when azithromycin used as monotherapy for gonorrhea
- ◆ Only 1 treatment failure documented due to isolate with MIC ($\mu\text{g}/\text{mL}$): ceftriaxone = 0.25, azithromycin = 1
- ◆ Few data for isolates with azithromycin MIC $>1 \mu\text{g}/\text{mL}$

Strategies for addressing azithromycin breakpoint addition for *N. gonorrhoeae*...

Table 1B. Suggested Groupings of Antimicrobial Agents Approved by the US Food and Drug Administration for Clinical Use That Should Be Considered for Testing and Reporting on Fastidious Organisms by Microbiology Laboratories in the United States

GROUP A PRIMARY TEST AND REPORT	<i>Haemophilus influenzae</i> ^d and <i>Haemophilus parainfluenzae</i>	<i>Neisseria gonorrhoeae</i> ^j	<i>Streptococcus pneumoniae</i> ^l	<i>Streptococcus</i> spp. β-Hemolytic Group ^p	<i>Streptococcus</i> spp. Viridans Group ^p
	Ampicillin ^{d,†}	Azithromycin ^{*,†}	Erythromycin ^{a,°}	Clindamycin ^{°,°}	Ampicillin ^{m,†}
	Ceftriaxone [†]				
	Cefixime [†]				
	Ciprofloxacin [†]		Penicillin ^k (oxacillin disk)	Erythromycin ^{a,°}	
	Tetracycline ^{b,†}		Trimethoprim- sulfamethoxazole	Penicillin ^{n,†} or ampicillin ^{n,†}	
	Ampicillin-sulbactam		Cefepime [*]	Cefepime or cefotaxime or	Cefepime Cefotaxime
			Cefotaxime ^{k,*}		

* MIC testing only; disk diffusion test unreliable.

† Routine testing is not necessary (see footnotes i and n).

- i. Culture and susceptibility testing of *N. gonorrhoeae* should be considered in cases of treatment failure. Antimicrobial agents recommended for testing include, at a minimum, the agents listed in group A. The most current guidelines for treatment and testing are available from the Centers for Disease Control and Prevention at <https://www.cdc.gov/std/gonorrhea/stdfact-gonorrhea.htm>.

Anaerobes

New!

Anaerobes Nomenclature Changes

Table 1C (What to Test and Report)	Table 2J (Breakpoints)
<p>Old: <i>Bacteroides fragilis</i> grp.</p> <p>Now: Gram-negative anaerobes</p>	<p>Old: <i>Bacteroides fragilis</i> grp.</p> <p>Now: <i>Bacteroides</i> spp. <i>Parabacteroides</i> spp.</p>

“*B. fragilis* group” is outdated taxonomically

M100 29th ed.

Intrinsic Resistance

New!

Intrinsic “R” Tables (Appendices B)

Appendix B. (Continued)
B1. Enterobacteriaceae

Antimicrobial Agent	Ampicillin	Amoxicillin-clavulanate	Ampicillin-sulbactam	Piperacillin	Ticarcillin	Cephalosporins I: Cefazolin, Cephalothin	Cephalosporins: Cefotaxim, Cefotetan	Cephalosporin II: Cefuroxime	Imipenem	Tetracyclines	Tigecycline	Nitrofurantoin	Polymyxin B Colistin	Aminoglycosides
<i>Citrobacter freundii</i>	R	R	R			R	R	R						
<i>Citrobacter koseri</i>	R				R									
Citrobacter amalonaticus group*														
<i>Enterobacter cloacae</i> complex ^b	R	R	R			R	R							
<i>Escherichia coli</i>	There is no intrinsic resistance to β -lactams in this organism.													
<i>Escherichia hermannii</i>	R				R									
<i>Haflnia alvei</i>	R	R	R			R	R							
<i>Klebsiella</i> (formerly <i>Enterobacter</i>) <i>aerogenes</i>	R				R									
<i>Klebsiella pneumoniae</i> , <i>Klebsiella oxytoca</i> , <i>Klebsiella variicola</i>	R													
<i>Morganella morganii</i>	R	R				R		R ^c		R	R	R	R	
<i>Morganella morganii</i>	There is no intrinsic resistance to penicillins and cephalosporins in this organism.													
<i>Proteus mirabilis</i>								R ^c		R	R	R	R	
<i>Proteus penneri</i>	R							R ^c		R	R	R	R	
<i>Proteus vulgaris</i>	R					R		R ^c		R	R	R	R	
<i>Providencia rettgeri</i>	R	R				R		R ^c		R	R	R	R	
<i>Providencia stuartii</i>	R							R ^c		R	R	R	R	
<i>Raoultella</i> spp. ^d	R				R									d

- ◆ ***Citrobacter amalonaticus* group includes *C. amalonaticus*, *C. farmeri*, and *C. sedlakii***
- ◆ ***Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Klebsiella variicola* grouped together**
- ◆ ***Raoultella* spp. includes *R. ornithinolytica*, *R. terrigena*, and *R. planticola***

◆ ***Burkholderia cepacia* complex**

- “R” genes are complex
- “There is insufficient clinical evidence to confirm whether strains that test susceptible *in vitro*, despite the presence of resistance mechanisms, will respond *in vivo*. Therefore, intrinsic resistance to the footnoted antibiotics (listed as resistant in previous editions of M100) cannot be confirmed.”

M100 29th ed. pp. 218-224.

Genotypic vs Phenotypic Detection of Antimicrobial Resistance

Relocated Appendix H. Using Molecular Assays for Resistance Detection

- ◆ **Practical approach for testing and reporting results when using molecular techniques for detecting antimicrobial resistance.**
- ◆ **Encourages understanding for detecting “resistance” determinants and testing phenotypic “susceptibility.”**
 - **Detecting a resistance marker does not always predict therapeutic failure of antimicrobial agents; gene may be nonfunctional or expressed at clinically insignificant levels.**
 - **The absence of a genetic marker does not necessarily indicate susceptibility.**
- ◆ **Suggests ways to resolve discrepancies between genotype and phenotype.**

Appendix H. Using Molecular Assays for Resistance Detection

- ◆ **Table H1.**
Strategies for Reporting Methicillin (Oxacillin) Results When Using Molecular and Phenotypic AST Methods for *Staphylococcus aureus*
- ◆ **Table H2.**
Strategies for Reporting Vancomycin Results When Using Molecular and Phenotypic AST Methods for *Enterococcus* spp.
- ◆ **Table H3.**
Reporting Results from Extended-Spectrum β -Lactamase and Carbapenemase Molecular Tests for *Enterobacteriaceae*

Previously posted on CLSI website

Table H3. Reporting Results from Extended-Spectrum β -Lactamase Resistance and Carbapenemase Molecular Tests for *Enterobacteriaceae*

Appendix H. (Continued)

Table H3. Reporting Results From Extended-Spectrum β -Lactamase Resistance and Carbapenemase Molecular Tests for *Enterobacteriaceae*

Indication	Target(s)	Method	Specimen Type	Results		Suggestions for Resolution	Report as:	Comments ^a
				Molecular Target Results	Observed Phenotype (if tested)			
Detection of ESBL resistance in <i>Enterobacteriaceae</i> (in an isolate susceptible to all carbapenems)	ESBL type <i>CTX-M</i> , <i>SHV</i> , <i>TEM</i>	NAAT, microarray	Colony, blood culture	Detection of any ESBL target	R to all 3rd- and 4th-generation cephalosporins tested (eg, ceftriaxone R, cefotaxime R, ceftazidime R, cefepime R)	N/A	Report phenotypic results as found (if available); consider reporting presence of molecular target per institutional protocol.	1–12
				Detection of any ESBL target	S to all 3rd- and 4th-generation cephalosporins tested (eg, ceftriaxone S, cefotaxime S, ceftazidime S, cefepime S)	Repeat molecular and phenotypic tests. If blood culture, check for mixed culture. If mixed, test isolates individually and report phenotypic results as found.	If the discrepancy is not resolved, repeat AST should be performed using a reference method, and the conflicting genotypic and phenotypic testing results should both be reported.	1–12
				Detection of <i>CTX-M</i> ESBL target	Variable resistance to 3rd- and 4th-generation cephalosporins (eg, ceftriaxone R, cefotaxime R, ceftazidime R or S, cefepime R or S)	Expected phenotype for some <i>CTX-M</i> strains. Check cefepime using a reference method if S.	Report phenotypic results as found, including reference cefepime result; consider reporting presence of molecular target per institutional protocol.	1–12
				Detection of <i>TEM</i> or <i>SHV</i> ESBL target	Variable resistance to 3rd- and 4th-generation cephalosporins (eg, ceftriaxone R or S, cefotaxime R or S, ceftazidime R or S, cefepime R or S).	Expected phenotype for some <i>TEM/SHV</i> strains. Check cefepime using a reference method if S.	Report phenotypic results as found, including reference cefepime result; consider reporting presence of molecular target per institutional protocol.	1–12

Specimen: Blood
Diagnosis: Urosepsis

E. coli

MIC (µg/ml)

ampicillin	R
ceftriaxone	0.5 S
ceftazidime	0.5 S
ciprofloxacin	1 R
ertapenem	≤0.25 S
gentamicin	1 S

Molecular assay:

- ***E. coli* detected**
- **CTX-M detected**

How to resolve AST (phenotype) vs. genotype discrepancies?

◆ IF:

- **ESBL target detected (e.g. CTX-M)**
- **S to all 3rd and 4th gen cephalosporins tested**

◆ Then:

- **Repeat molecular and phenotypic tests**
- **Check for mixed culture**
- **If confirmed, no mix:**
 - **Perform reference MIC method**
 - **Report BOTH results to physician**

Why? Risk of “R” emerging during therapy; gene might not be expressed in AST.

Quality Control

Update - Quality Control

- ◆ **Very few additions / deletions / changes in 2019**
- ◆ **β -lactam combination agents (Tables 4A-2 and 5A-2); added QC ranges for:**
 - **Several agents not yet FDA cleared**
 - **Several agents that can be used for “integrity check” of β -lactamase producing QC strains**
- ◆ **Added QC ranges for *Neisseria gonorrhoeae* ATCC 49226 and azithromycin**
- ◆ **Some reformatting / rewording Troubleshooting Guides (Tables 4D and 5G)**

Reminder

Table 5A-2. MIC QC Ranges for Nonfastidious Organisms and β -lactam Combination Agents

Table 5A-2. (Continued)

Antimicrobial Agent	QC Organisms and Characteristics									
	<i>Escherichia coli</i> ATCC [®] 25922	<i>Pseudomonas aeruginosa</i> ATCC [®] 27853	<i>Staphylococcus aureus</i> ATCC [®] 29213	<i>Enterococcus faecalis</i> ATCC [®] 29212	<i>Escherichia coli</i> ATCC [®] 35218 ^{b,c}	<i>Klebsiella pneumoniae</i> ATCC 700603 ^{b,c}	<i>Escherichia coli</i> NCTC 13353 ^{b,c}	<i>Klebsiella pneumoniae</i> ATCC [®] BAA-1705 ^{b,c}	<i>Klebsiella pneumoniae</i> ATCC [®] BAA-2614 ^{b,c}	<i>A. baumannii</i> NCTC 13304 ^{b,c}
	β -lactamase negative	Inducible Amp C	Weak β -lactamase <i>mecA</i> negative		TEM-1	SHV-18 OXA-2 Mutations in OmpK35 and OmpK37	CTX-M-15	KPC-2 TEM SHV	KPC-3 SHV-11 TEM-1	OXA-27
	MIC QC Ranges, μ g/mL									
Meropenem-vaborbactam ^d	0.008/8–0.06/8	0.12/8–1/8	0.03/8–0.12/8	–	0.008/8–0.06/8	0.016/8–0.06/8	–	0.008/8–0.06/8	0.12/8–0.5/8	–
Nacubactam ^e	0.5–4	64–256	–	–	–	–	–	–	0.5–4	–
Piperacillin	1–4	1–8	1–4	1–4	> 64	–	–	–	–	–
Piperacillin-tazobactam ^d	1/4–4/4	1/4–8/4	0.25/4–2/4	1/4–4/4	0.5/4–2/4	8/4–32/4	–	–	–	–
Ticarcillin	4–16	8–32	2–8	16–64	> 128	> 256	–	–	–	–
Ticarcillin-clavulanate ^d	4/2–16/2	8/2–32/2	0.5/2–2/2	16/2–64/2	8/2–32/2	32/2–128/2	–	–	–	–

^d Unsupplemented Mueller-Hinton medium (cation-adjusted if broth). See Table 5A-1 for QC ranges for combination agents from other drug classes. Abbreviations: ATCC[®], American Type Culture Collection; MIC, minimal inhibitory concentration; NCTC, National Collection of Type Cultures; QC, quality control; R, resistant; S, susceptible.

QC strain selection codes: QC strain is recommended for routine QC. Test one of these agents by a disk diffusion or MIC method to confirm the integrity of the respective QC strain.^{b,c}

Footnotes

- ATCC[®] is a registered trademark of the American Type Culture Collection. Per ATCC[®] convention, in conjunction with the registered ATCC[®] name.
- Careful attention to organism maintenance (eg, minimal subcultures) and storage (eg, –60°C) is required. Spontaneous loss of the plasmid encoding the β -lactamase has been documented. If stored strains may lose their resistance characteristics and QC results may be outside the acceptable range.
- To confirm the integrity of the QC strain, test one of the single β -lactam agents highlighted in Table 5A-2. The QC strain is first subcultured from a frozen or lyophilized stock culture. In-range results for the combination agents. It is not necessary to check the QC strain again with a single agent unless the QC strain is found to be outside the acceptable range. Recommendations for handling QC strains as described in M02¹ and M07² are followed. If the range listed for the particular antimicrobial agent and the MIC result obtained for the QC strain are outside the acceptable range, the QC strain is not reliable for QC of β -lactam combination agents (eg, ampicillin panel concentrations 1–16 [I], ≥ 32 [R]; MIC of >16 μ g/ml [R] would be acceptable for *K. pneumoniae* ATCC[®] 700603).

Volume 3, Issue 2 Spring 2018

CLSI

CLSI AST News Update

Janet A. H. Audrey N.

The CLSI Outreach Working Group (ORWG) is providing this Newsletter to highlight some recent issues related to antimicrobial susceptibility testing and reporting. We are listing links to some new educational materials and reminding you where you can find information about the CLSI AST Subcommittee proceedings.

Upcoming Webinar:
Preparation, Presentation, and Promotion of Cumulative Antibiograms To Support Antimicrobial Stewardship Programs

Spring 2018

Inside This Issue:

Featured Article: Part 1

New β -lactam combination agents for the treatment of Gram-negative bacterial infections: what the clinical microbiologist needs to know! 4

Featured Article: Part 2

Why all the fuss over quality control of β -lactam combination agents? 8

M100 29th ed. Table 5A-2 pp. 174-176.

β-lactam Combination Agents Recommended QC Strains

QC Strain	Piperacillin-tazobactam	Ceftazidime-avibactam	Ceftolozane-tazobactam	Meropenem-vaborbactam
<i>E. coli</i> ATCC 25922¹	x	x	x	x
<i>P. aeruginosa</i> ATCC 27853¹	x	x	x	x
<i>E. coli</i> ATCC 35218²	x			
<i>K. pneumoniae</i> ATCC 700603²	x	x	x³	
<i>K. pneumoniae</i> ATCC 1705²				x
<i>K. pneumoniae</i> ATCC BAA-2814				x

¹ Select one of these – most similar to clinical isolate(s) tested

² ■ Test one of these with green highlights

³ Typo in Table 4A-2 (green omitted) OOPS!

β-lactam Combination Agents Recommended QC Strains

QC Strain	Piperacillin-tazobactam	Ceftazidime-avibactam	Ceftolozane-tazobactam	Meropenem-vaborbactam
<i>E. coli</i> ATCC 25922 ¹	x	x	x	x
<i>P. aeruginosa</i> ATCC 27853 ¹				x
<i>E. coli</i> ATCC 35218 ²				
<i>K. pneumoniae</i> ATCC 700603 ²	x		x	
<i>K. pneumoniae</i> ATCC 1705 ²				x
<i>K. pneumoniae</i> ATCC BAA-2814				x

Streamlined
QC???

¹ Test one of these – most similar to clinical isolate(s) tested

² ■ Test one of these with green highlights

³ Typo in Table 4A-2 (green omitted) OOPS!

Some Additional Topics Currently Under Evaluation by CLSI AST Subcommittee

- ◆ **Breakpoints under review (changes and additions)**
 - **Azithromycin and *Shigella* spp.**
 - **Aminoglycosides**
 - **Amoxicillin-clavulanate**
 - **Several for Nonfermenters**
- ◆ **Methods**
 - **Colistin testing options**
 - **Further evaluation of other *Staphylococcus* spp. and oxacillin resistance**
 - **Direct disk diffusion testing from blood**
 - ***Streptococcus pneumoniae* test media**
 - **Harmonization of disk content selection and QC parameter protocols with EUCAST**

Some Additional Topics Currently Under Evaluation by CLSI AST Subcommittee (cont)

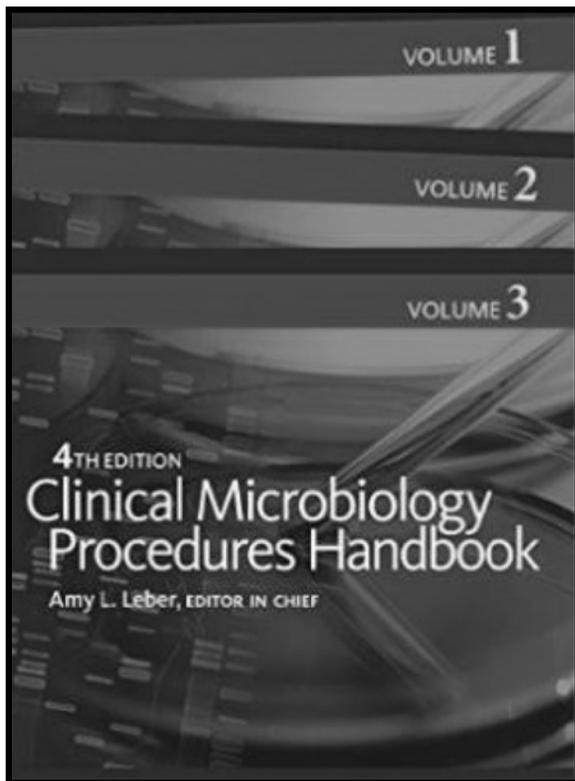
◆ Formatting

- **Reorganization of Staphylococcus tables**

◆ Other

- **Continued monitoring of QC ranges**
- **Streamlined QC**
- **Availability of tests for new drugs**
- **AST of *Burkholderia cepacia***
- **AST and changing organism nomenclature**
- **Dealing with RUO ASTs**
- **New edition of M39 (antibiograms)**

Additional Resources



CDC MASTER Program Multilevel Antimicrobial Susceptibility Testing Educational Resource FREE!

The screenshot shows the CDC Laboratory Training website. The main heading is 'Methods of Antimicrobial Susceptibility Testing Educational Resource (MASTER) eLearning Curriculum'. Below the heading is a large image of a petri dish with bacterial colonies. To the left of the main content is a sidebar with navigation links: 'CDC Laboratory Training', 'External Training Links', 'FAQs', 'Continuing Education Units (CEU)', and 'Contact Us'. Below these links is an email subscription form with the text 'Get Email Updates' and a 'Submit' button. To the right of the main heading is a 'Curriculum Description' section with a sub-heading 'Antimicrobial Susceptibility Testing Methods (AST)' and a sub-heading 'Antimicrobial Susceptibility CLSI Standards'. A black box on the right side of the screenshot contains the text 'Courses: 1. Methods 2. CLSI Standards'.

Courses:
1. Methods
2. CLSI Standards

Use Google!

FDA-Recognized Antimicrobial Susceptibility Test Interpretive Criteria

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

Looking for FDA-Recognized Susceptibility Test Interpretive Criteria?

[Antibacterial Susceptibility Test Interpretive Criteria](#)

[Antifungal Susceptibility Test Interpretive Criteria](#)

Thank You!

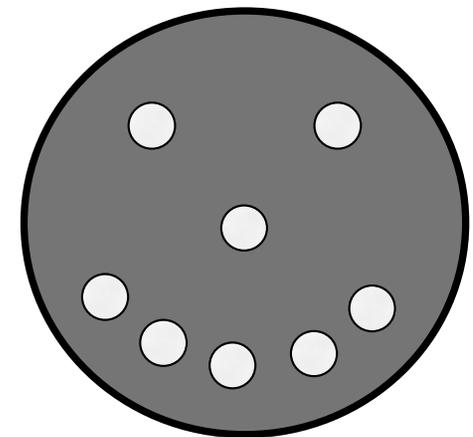
....for listening today...

And thanks to:

CLSI Staff

CLSI AST Outreach Working Group

CLSI Subcommittee on AST



The following summary slides will not be discussed and are presented for participant's review.

Summary (1)

- ◆ **CLSI updates AST tables (M100) each January.**
- ◆ **CLSI updates documents that describe how to perform reference disk diffusion (M02) and reference MIC (M07) tests every 3 years. (most recent update 2018).**
- ◆ **Changes to CLSI documents are summarized in the front of each document.**
- ◆ **Information listed in boldface type is new or modified since the previous edition of M100.**
- ◆ **Recent breakpoint addition/revision dates are listed in the front of M100 29th ed (pages xxix-xxxii).**

Summary (2)

- ◆ **CLSI AST Outreach Working Group (ORWG) provides educational materials to help you better understand AST and reporting recommendations.**
- ◆ **The ORWG News Updates can be found here:**
 - **<https://clsi.org/meetings/microbiology/>**
 - **A free version of M100 is available on the CLSI website!**
- ◆ **Breakpoints are revised when new information is presented to suggest breakpoints are no longer reliable. Such data include that related to antimicrobial resistance, PK/PD and/or clinical outcomes.**
- ◆ **“Rationale” documents that describe the data / information used to revise breakpoints are now listed on the CLSI website.**

Summary (3)

- ◆ **An MIC result of 0.125 µg/ml should be rounded out to 0.12 µg/ml for interpretation.**
- ◆ **Meropenem-vaborbactam is active against Enterobacteriaceae that produce serine carbapenemases, but not those that produce MBLs.**
- ◆ **Cefiderocol has broad spectrum activity against many GNR including MDR.**
- ◆ **Investigational breakpoints are listed for cefiderocol in M100; cefiderocol is not yet FDA approved for clinical use.**
- ◆ **Ceftazidime-avibactam disk diffusion may overcall resistance for isolates with zones of 18–20 mm. An MIC test should be performed for confirmation of resistance when this zone size is encountered.**

Summary (4)

- ◆ **Newer β -lactam inhibitor combination agents have unique activities against GNR. Results with one cannot be used to predict results from another.**
- ◆ **Fosfomycin disk diffusion and MIC breakpoints apply only to *E. coli* urinary tract isolates and should not be extrapolated to other species of Enterobacteriaceae.**
- ◆ **Any colonies observed within a fosfomycin zone of inhibition should not be ignored when measuring zones.**
- ◆ **MICs obtained from testing colistin predict MICs for polymyxin B; colistin serves as a surrogate agent for polymyxin B.**
- ◆ **Broth disk elution or agar dilution (single 2 μ g/ml plate) may represent a practical approach for colistin testing for some laboratories.**

Summary (5)

- ◆ **Results of “S” or “I” should not be edited to “R” when a carbapenemase is detected in a GNR using current CLSI carbapenem breakpoints.**
- ◆ **Revised breakpoints for both daptomycin / *Enterococcus* spp. and ceftaroline / *S. aureus* now include an SDD and no “I” interpretive category.**
 - **Higher doses (currently off label) are suggested for isolates with SDD**
 - **For daptomycin / *Enterococcus* spp. this mainly pertains to VR *E faecium* where there are few therapeutic options due to MDR nature of these isolates**
 - **For ceftaroline / *S. aureus*, this relates to higher doses widely used outside the USA**

Summary (6)

- ◆ **Several species of CoNS now have specific cefoxitin and/or oxacillin breakpoints in M100. Staphylococci that do not fit one of the species highlighted in M100 are now referred to as “Other *Staphylococcus* spp.” and not “CoNS”.**
- ◆ **The oxacillin disk diffusion test can be used reliably for detection of oxacillin / methicillin resistance in *S. epidermidis*, *S. pseudintermedius*, and *S. schleiferi*.**
- ◆ **Current CDC recommendations for treating gonorrhoeae include ceftriaxone + azithromycin.**
- ◆ **Although azithromycin nonsusceptible *N. gonorrhoeae* are uncommon, addition of azithromycin breakpoints will help address the significant public health concern of antimicrobial resistance among *N. gonorrhoeae*.**

Summary (7)

- ◆ The term “*Bacteroides* spp.” is no longer used in M100.
- ◆ Guidance is now available in M100 to foster understanding of molecular assays for resistance markers and strategies for addressing any discrepancies obtained when performing both genotypic assays and phenotypic ASTs on an isolate.
- ◆ QC of β -lactam combination agents requires inclusion of a β -lactamase producing strain.
- ◆ Check references from this webinar; local pharmaceutical reps; diagnostic manufacturers for up to date information on availability of tests for newer antimicrobial agents.

Summary (8)

- ◆ **CLSI AST ORWG welcomes suggestions for how we can improve communicating AST issues to you!**

The End!