

Updates to CLSI M100



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The presenter states no conflict of interest and has no financial relationship to disclose relevant to the content of this presentation.

OUTLINE

I. General acclimation to M100 document

II. Objectives of webinar

Describe significant changes relevant to pre-existing antimicrobial susceptibility breakpoints...

Describe significant changes relevant to antimicrobial susceptibility testing methodology...

Identify (new) organism/antimicrobial combinations for which susceptibility breakpoints now exist...

as outlined in the CLSI M100-S29 document.



The Small Roman Numerals



WHAT'S IN THERE?

- Overview of changes
- Processes for establishing breakpoints, QC ranges
- CLSI reference vs. commercial methods
CLSI reference vs. FDA breakpoints
- Breakpoint additions/revisions since 2010
ECV additions/revisions since 2015

BREAKPOINT ADDITIONS FOR 2019



Investigational cefiderocol BMD for:

Enterobacteriaceae

Pseudomonas aeruginosa

Acinetobacter spp.

Stenotrophomonas maltophilia

Requires iron-depleted CAMHB

- Meropenem-vaborbactam
Enterobacteriaceae (DD, BMD)
- Azithromycin
Neisseria gonorrhoeae (MIC, S only)





Instructions for Use of Tables



INSTRUCTIONS FOR USE I

- Selecting antimicrobial agents for testing, reporting
- Breakpoint and interpretive category definitions
- Reporting results

Organisms excluded from Table 2 (CLSI M45)

Reporting concentrations (report to hundredths)

$\leq 0.125 \mu\text{g/mL}$ reported as $\leq 0.12 \mu\text{g/mL}$

- Therapy-related comments

INSTRUCTIONS FOR USE II

- Testing of repeat isolates (as little as 3-4 days)

3° cepheids	<i>Klebsiella aerogenes</i>
	<i>Citrobacter</i> spp.
	<i>Serratia</i> spp.

All agents	<i>Pseudomonas aeruginosa</i>
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Fluoroquinolones	Staphylococci
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- Supplemental (D-test), screening (vancomycin agar screen), **surrogate agent** (cefoxitin), equivalent agent (amp predict amox for *Haemophilus*) tests

Surrogate Agent Tests

Surrogate Agent	Organisms	Test Description	Results	Table Location
Cefazolin	<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 overcall resistance to cefdinir, cefpodoxime, and cefuroxime. If cefazolin tests resistant, test these drugs individually if needed for therapy.	1A, 2A
Cefoxitin	<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 overcall 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	<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
Pefloxacin	<i>Salmonella</i> spp.	Disk diffusion	Predicts reduced susceptibility to ciprofloxacin	2A
Colistin	<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



Table 1



TABLE 1A

Table 1A
Suggested Nonfastidious Groupings
M02 and M07

Table 1A. 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 Nonfastidious Organisms by Microbiology Laboratories in the United States

GROUP A PRIMARY TEST AND REPORT	<i>Enterobacteriaceae</i>	<i>Pseudomonas aeruginosa</i>	<i>Staphylococcus</i> spp.	<i>Enterococcus</i> spp. ^m
	Ampicillin ^c	Ceftazidime	Azithromycin ^b or clarithromycin ^b or erythromycin ^b	Ampicillin ⁿ Penicillin ^o
	Cefazolin ^d	Gentamicin Tobramycin	Clindamycin ^b	
	Gentamicin ^c Tobramycin ^c	Piperacillin-tazobactam	Oxacillin ^{k,t,f,g} Cefoxitin ^{k,t} (surrogate test for oxacillin)	
			Penicillin ^l	
			Trimethoprim- sulfamethoxazole	

TABLE 1A

Table 1A
Suggested Nonfastidious Groupings
M02 and M07

Table 1A. (Continued)

“Warning”: The following antimicrobial agents that are included in this document should not be routinely reported for bacteria isolated from CSF. These antimicrobial agents are not the drugs of choice and may not be effective for treating CSF infections caused by these organisms (ie, the bacteria included in Tables 2A through 2J):

- Agents administered by oral route only
- 1st- and 2nd-generation cephalosporins and cephamycins
- Clindamycin
- Macrolides
- Tetracyclines
- Fluoroquinolones

Footnotes

General

- a. Organisms that are susceptible to tetracycline are also considered susceptible to doxycycline and minocycline. However, some organisms that are intermediate or resistant to tetracycline may be susceptible to doxycycline, minocycline, or both.
- b. Not routinely reported on organisms isolated from the urinary tract.

NON-FASTIDIOUS GROUPINGS

- Group A Primary test and report
- Group B Optional primary test, report selectively
- Group C Supplemental report selectively
- Group U Supplemental for urine only

NON-FASTIDIOUS GROUPINGS

These exist for:

Enterobacteriaceae

Pseudomonas aeruginosa (no group C or group U)

Acinetobacter spp. (no group C)

Burkholderia cepacia complex (no group U)

Stenotrophomonas maltophilia (no group U)

Other non-*Enterobacteriaceae*

Staphylococcus spp.

Enterococcus spp.

CHANGES TO TABLE 1A

- Added meropenem-vaborbactam as group B testing agent for *Enterobacteriaceae*
- Clarified staphylococci that can be subject to oxacillin broth microdilution (footnote to Table)

S. aureus

S. lugdunensis

Other staphylococci

EXCEPT

epidermidis

pseudintermedius

schleiferi

TABLE 1B

Table 1B
Suggested Fastidious Groupings
M02 and M07

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> ⁱ	<i>Streptococcus pneumoniae</i> ^j	<i>Streptococcus</i> spp. β-Hemolytic Group ^g	<i>Streptococcus</i> spp. Viridans Group ^g
	Ampicillin ^{d,i}	Azithromycin ^{n,t}	Erythromycin ^{a,c}	Clindamycin ^{c,o}	Ampicillin ^{m,t} Penicillin ^{m,t}
		Ceftriaxone [†] Cefixime [†]			
		Ciprofloxacin [†] Tetracycline ^{b,t}	Penicillin ^k (oxacillin disk)	Erythromycin ^{a,o}	
			Trimethoprim- sulfamethoxazole	Penicillin ^{n,t} or ampicillin ^{n,i}	

TABLE 1B

Table 1B
Suggested Fastidious Groupings
M02 and M07

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> ^l	<i>Streptococcus pneumoniae</i> ^l	<i>Streptococcus</i> spp. β-Hemolytic Group ^o	<i>Streptococcus</i> spp. Viridans Group ^o
	Ampicillin ^{d,f}	Azithromycin ^{n,t}	Erythromycin ^{a,c}	Clindamycin ^{c,o}	Ampicillin ^{m,t} Penicillin ^{m,t}
		Ceftriaxone [†] Cefixime [†]			
		Ciprofloxacin [†]	Penicillin ^k (oxacillin disk)	Erythromycin ^{a,c,o}	
		Tetracycline ^{b,f}	Trimethoprim- sulfamethoxazole	Penicillin ^{n,t} or ampicillin ^{n,l}	

- o. **Rx:** Recommendations for intrapartum prophylaxis for group B streptococci are penicillin or ampicillin. Although cefazolin is recommended for penicillin-allergic women at low risk for anaphylaxis, those at high risk for anaphylaxis may receive clindamycin. Group B streptococci are susceptible to ampicillin, penicillin, and cefazolin, but may be resistant to erythromycin and clindamycin. When group B *Streptococcus* is isolated from a pregnant woman with severe penicillin allergy (high risk for anaphylaxis), erythromycin and clindamycin (including inducible clindamycin resistance) should be tested, and only clindamycin should be reported. See Table 3G.

FASTIDIOUS GROUPINGS

- Group A Primary test and report
- Group B Optional primary test, report selectively
- Group C Supplemental report selectively

FASTIDIOUS GROUPINGS

These exist for:

Haemophilus influenzae

Haemophilus parainfluenzae

Neisseria gonorrhoeae (no group B or no group C)

Streptococcus pneumoniae

β -hemolytic *Streptococcus*

viridans group *Streptococcus*

CHANGES TO TABLE 1B

- Added azithromycin as group A testing agent for *Neisseria gonorrhoeae*
- Susceptibility and resistance to dirithromycin (as well as azithromycin and clarithromycin) can be predicted by testing erythromycin

Streptococcus pneumoniae

β -hemolytic *Streptococcus*

viridans group *Streptococcus*

THERE'S AN ANAEROBE TABLE

Table 1C
Suggested Anaerobe Groupings
M11

Table 1C. 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 Anaerobic Organisms by Microbiology Laboratories in the United States

GROUP A PRIMARY TEST AND REPORT	Gram-Negative Anaerobes	Gram-Positive Anaerobes ^a
	Amoxicillin-clavulanate Ampicillin-sulbactam Piperacillin-tazobactam	Ampicillin ^b Penicillin ^b Amoxicillin-clavulanate Ampicillin-sulbactam Piperacillin-tazobactam
	Clindamycin	Clindamycin
	Doripenem Ertapenem Imipenem Meropenem	Doripenem Ertapenem Imipenem Meropenem
	Metronidazole	Metronidazole
GROUP C SUPPLEMENTAL REPORT SELECTIVELY	Penicillin ^b Ampicillin ^b	
	Cefotetan Cefoxitin	Cefotetan Cefoxitin
	Ceftizoxime Ceftriaxone	Ceftizoxime Ceftriaxone
	Chloramphenicol	
	Moxifloxacin	Moxifloxacin Tetracycline

“Testing may not be necessary for isolates associated with polymicrobial anaerobic infections.”
Test only isolate most likely to be resistant; *Bacteroides* spp., *Parabacteroides* spp.

CLSI M100; 29th ed.; 2019



Table 2



TABLE 2

Table 2B-1
Pseudomonas aeruginosa
M02 and M07

Table 2B-1. Zone Diameter and MIC Breakpoints for *Pseudomonas aeruginosa*

Testing Conditions Medium: Disk diffusion: MHA Broth dilution: CAMHB; For cefiderocol, special media is required for testing. See comment (13). Agar dilution: MHA Inoculum: Broth culture method or colony suspension, equivalent to a 0.5 McFarland standard Incubation: 35°C ± 2°C; ambient air Disk diffusion: 16–18 hours Dilution methods: 16–20 hours	Routine QC Recommendations (see Tables 4A-1 and 5A-1 for acceptable QC ranges) <i>Pseudomonas aeruginosa</i> ATCC® 27853 Refer to Tables 4A-2 and 5A-2 to select strains for routine QC of β-lactam combination agents. When a commercial test system is used for susceptibility testing, refer to the manufacturer's instructions for QC test recommendations and QC ranges.
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* ATCC® is a registered trademark of the American Type Culture Collection.

General Comments

- (1) For disk diffusion, test a maximum of 12 disks on a 150-mm plate and no more than 6 disks on a 100-mm plate; disks should be placed no less than 24 mm apart, center to center (see M02,¹ Subchapter 3.6). Each zone diameter should be clearly measurable; overlapping zones prevent accurate measurement. Measure the diameter of the zones of complete inhibition (as judged by the unaided eye), including the diameter of the disk. Hold the Petri plate a few inches above a black background illuminated with reflected light. The zone margin should be considered the area showing no obvious, visible growth that can be detected with the unaided eye. Ignore faint growth of tiny colonies that can be detected only with a magnifying lens at the edge of the zone of inhibited growth.
- (2) The susceptibility of *P. aeruginosa* isolated from patients with cystic fibrosis can be reliably determined by disk diffusion or dilution methods but may need extended incubation for up to 24 hours before reporting as susceptible.
- (3) *P. aeruginosa* may develop resistance during prolonged therapy with all antimicrobial agents. Therefore, isolates that are initially susceptible may become resistant within 3 to 4 days after initiation of therapy. Testing of repeat isolates may be warranted.

TABLE 2

Table 2B-1. *Pseudomonas aeruginosa* (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	I	R	S	I	R	
PENICILLINS									
O	Piperacillin	100 µg	≥ 21	15–20	≤ 14	≤ 16	32–64	≥ 128	(5) Breakpoints for piperacillin (alone or with tazobactam) are based on a piperacillin dosage regimen of at least 3 g administered every 6 h.
β-LACTAM COMBINATION AGENTS									
A	Piperacillin-tazobactam	100/10 µg	≥ 21	15–20	≤ 14	≤ 16/4	32/4–64/4	≥ 128/4	(6) Breakpoints for piperacillin (alone or with tazobactam) are based on a piperacillin dosage regimen of at least 3 g administered every 6 h.
B	Ceftazidime-avibactam	30/20 µg	≥ 21	–	≤ 20	≤ 4/4	–	≥ 16/4	(7) Breakpoints are based on a dosage regimen of 2.5 g (2 g ceftazidime + 0.5 g avibactam) administered every 8 h over 2 h.
B	Ceftolozane-tazobactam	30/10 µg	≥ 21	17–20	≤ 16	≤ 4/4	8/4	≥ 16/4	(8) Breakpoints are based on a dosage regimen of 1.5 g administered every 8 h.
O	Ticarcillin-clavulanate	75/10 µg	≥ 24	16–23	≤ 15	≤ 16/2	32/2–64/2	≥ 128/2	(9) Breakpoints for ticarcillin (alone or with clavulanate) are based on a ticarcillin dosage regimen of at least 3 g administered every 6 h.
CEPHEMS (PARENTERAL) (Including cephalosporins I, II, III, and IV. Please refer to Glossary I.)									
A	Ceftazidime	30 µg	≥ 18	15–17	≤ 14	≤ 8	16	≥ 32	(10) Breakpoints are based on a dosage regimen of 1 g administered every 6 h or 2 g administered every 8 h.
B	Cefepime	30 µg	≥ 18	15–17	≤ 14	≤ 8	16	≥ 32	(11) Breakpoints are based on a dosage regimen of 1 g administered every 8 h or 2 g administered every 12 h.

TABLE 2

Inv.	Cefiderocol	–	–	–	–	≤4	8	≥16	(12) Breakpoints are based on a dosage regimen of 2 g every 8 h administered over 3 h. (13) Testing cefiderocol requires iron-depleted CAMHB. Chelation is used for iron depletion, which also removes other cations (ie, 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.
MONOBACTAMS									
B	Aztreonam	30 µg	≥ 22	16–21	≤ 15	≤ 8	16	≥ 32	(14) Breakpoints are based on a dosage regimen of 1 g administered every 6 h or 2 g administered every 8 h.

Table 2B-1
Pseudomonas aeruginosa
M02 and M07

TABLE 2

These exist for:

Enterobacteriaceae

Pseudomonas aeruginosa

Acinetobacter spp.

Burkholderia cepacia complex

Stenotrophomonas maltophilia

Other non-*Enterobacteriaceae*

Staphylococcus spp.

Enterococcus spp.

Haemophilus influenzae

Haemophilus parainfluenzae

Neisseria gonorrhoeae

Streptococcus pneumoniae

β -hemolytic *Streptococcus*

viridans group *Streptococcus*

Neisseria meningitidis

Anaerobes

CAVEATS

Table 2B-5. Other Non-*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		
			S	I	R	S	I	R
PENICILLINS								
O	Piperacillin	—	—	—	—	≤16	32–64	≥128
β-LACTAM COMBINATION AGENTS								
B	Piperacillin-tazobactam	—	—	—	—	≤16/4	32/4–64/4	≥128/4
O	Ticarcillin-clavulanate	—	—	—	—	≤16/2	32/2–64/2	≥128/2
CEPHEMS (PARENTERAL) (Including cephalosporins I, II, III, and IV. Please refer to Glossary I.)								
A	Ceftazidime	—	—	—	—	≤8	16	≥32
B	Cefepime	—	—	—	—	≤8	16	≥32
C	Cefotaxime	—	—	—	—	≤8	16–32	≥64
C	Ceftriaxone	—	—	—	—	≤8	16–32	≥64
O	Cefoperazone	—	—	—	—	≤16	32	≥64
O	Ceftizoxime	—	—	—	—	≤8	16–32	≥64
O	Moxalactam	—	—	—	—	≤8	16–32	≥64
MONOBACTAMS								
B	Aztreonam	—	—	—	—	≤8	16	≥32
CARBAPENEMS								
B	Imipenem	—	—	—	—	≤4	8	≥16
B	Meropenem	—	—	—	—	≤4	8	≥16
AMINOGLYCOSIDES								
A	Gentamicin	—	—	—	—	≤4	8	≥16
A	Tobramycin	—	—	—	—	≤4	8	≥16
B	Amikacin	—	—	—	—	≤16	32	≥64
O	Netilmicin	—	—	—	—	≤8	16	≥32
TETRACYCLINES								
(3) Organisms that are susceptible to tetracycline are also considered susceptible to doxycycline and minocycline. However, some organisms may be susceptible to doxycycline, minocycline, or both.								
U	Tetracycline	—	—	—	—	≤4	8	≥16
O	Doxycycline	—	—	—	—	≤4	8	≥16
O	Minocycline	—	—	—	—	≤4	8	≥16
FLUOROQUINOLONES								
B	Ciprofloxacin	—	—	—	—	≤1	2	≥4
B	Levofloxacin	—	—	—	—	≤1	2	≥4



3rd Edition

M45

Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria

This guideline informs clinical, public health, and research laboratories on susceptibility testing of infrequently isolated or fastidious bacteria that are not included in CLSI documents M02, M07, or M100. Antimicrobial agent selection, test interpretation, and quality control are addressed.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.



FLUOROQUINOLONES

Organism	Method	Ciprofloxacin Previous			Ciprofloxacin New		
		S	I	R	S	I	R
<i>Enterobacteriaceae</i>	BMD	≤ 1	2	≥ 4	≤ 0.25	0.5	≥ 1
<i>P. aeruginosa</i>	BMD	≤ 1	2	≥ 4	≤ 0.5	1	≥ 2
<i>Enterobacteriaceae</i>	DD	≥ 21	16-20	≤ 15	≥ 26	22-25	≤ 21
<i>P. aeruginosa</i>	DD	≥ 21	16-20	≤ 15	≥ 25	19-24	≤ 18

Organism	Method	Levofloxacin Previous			Levofloxacin New		
		S	I	R	S	I	R
<i>Enterobacteriaceae</i>	BMD	≤ 2	4	≥ 8	≤ 0.5	1	≥ 2
<i>P. aeruginosa</i>	BMD	≤ 2	4	≥ 8	≤ 1	2	≥ 4
<i>Enterobacteriaceae</i>	DD	≥ 17	14-16	≤ 13	≥ 21	17-20	≤ 16
<i>P. aeruginosa</i>	DD	≥ 17	14-16	≤ 13	≥ 22	15-21	≤ 14

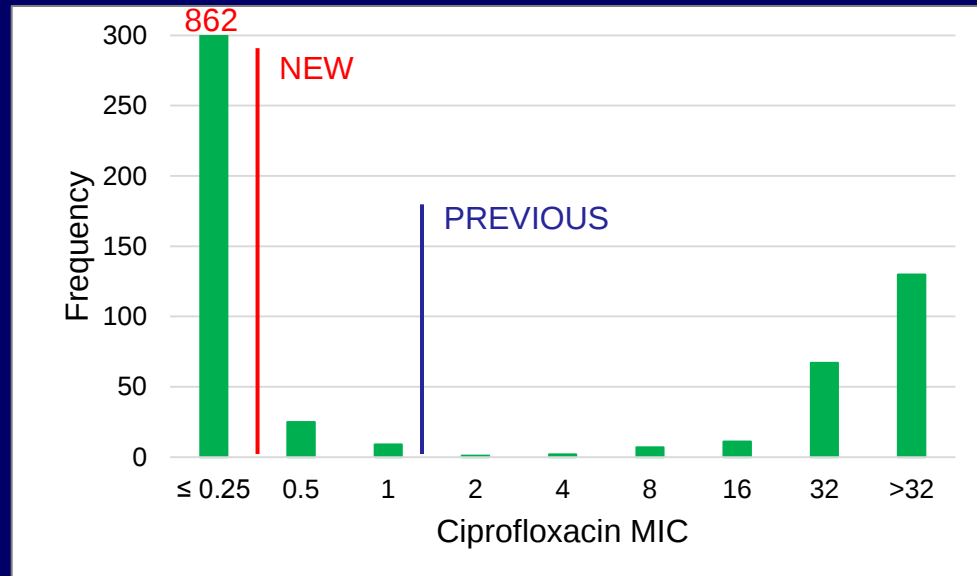
CLSI M100; 29th ed.; 2019

WISCONSIN SURVEILLANCE

Organism	n	Ciprofloxacin Previous			Ciprofloxacin New		
		%S	%I	%R	%S	%I	%R
<i>Escherichia coli</i>	1114	80.4	0.1	19.5	77.4	2.2	20.4
<i>Proteus mirabilis</i>	916	78.5	3.6	17.9	76.0	1.4	22.6
<i>Pseudomonas aeruginosa</i>	801	86.8	3.7	9.5	82.4	4.4	13.2

WISCONSIN SURVEILLANCE

Organism	n	Ciprofloxacin Previous			Ciprofloxacin New		
		%S	%I	%R	%S	%I	%R
<i>Escherichia coli</i>	1114	80.4	0.1	19.5	77.4	2.2	20.4
<i>Proteus mirabilis</i>	916	78.5	3.6	17.9	76.0	1.4	22.6
<i>Pseudomonas aeruginosa</i>	801	86.8	3.7	9.5	82.4	4.4	13.2

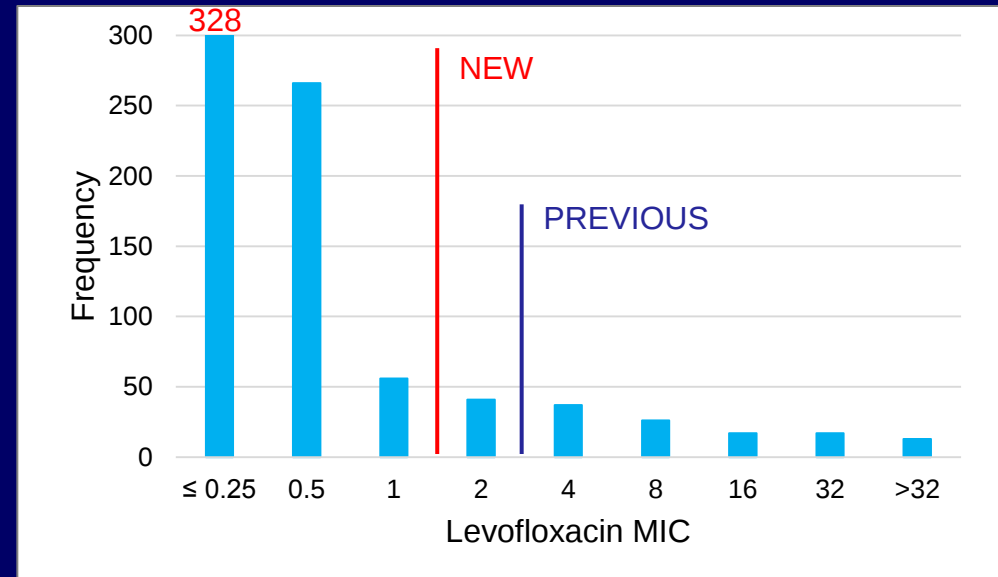
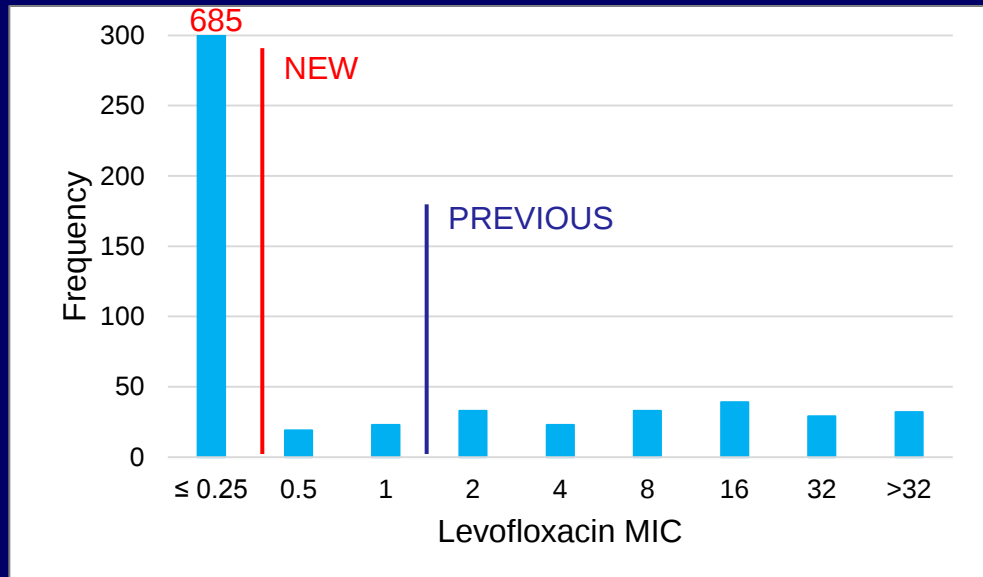


WISCONSIN SURVEILLANCE

Organism	n	Levofloxacin Previous			Levofloxacin New		
		%S	%I	%R	%S	%I	%R
<i>Escherichia coli</i>	1114	80.6	0.4	18.9	79.5	0.9	19.6
<i>Proteus mirabilis</i>	916	83.0	2.5	14.5	76.9	2.5	20.6
<i>Pseudomonas aeruginosa</i>	801	86.3	4.6	9.1	81.1	5.1	13.7

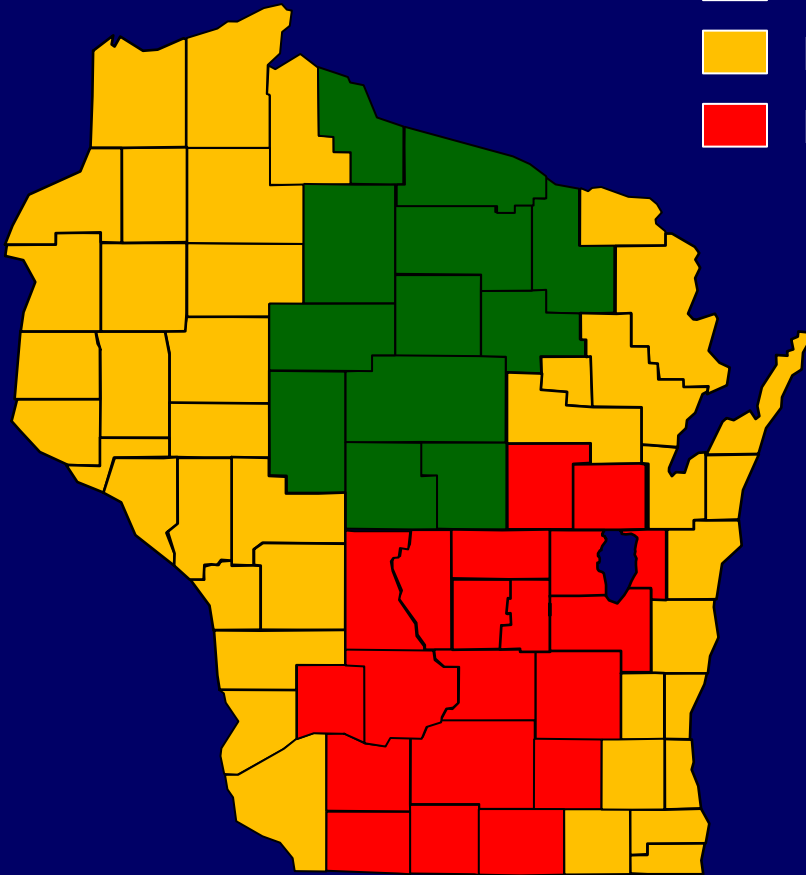
WISCONSIN SURVEILLANCE

Organism	n	Levofloxacin Previous			Levofloxacin New		
		%S	%I	%R	%S	%I	%R
<i>Escherichia coli</i>	1114	80.6	0.4	18.9	79.5	0.9	19.6
<i>Proteus mirabilis</i>	916	83.0	2.5	14.5	76.9	2.5	20.6
<i>Pseudomonas aeruginosa</i>	801	86.3	4.6	9.1	81.1	5.1	13.7

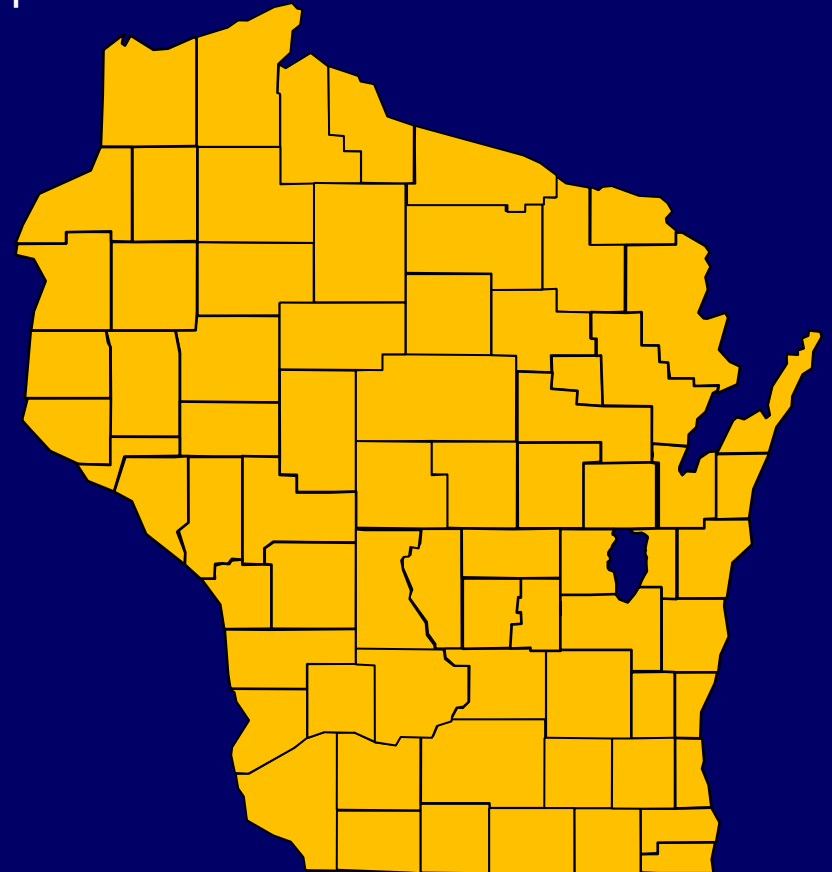


E. coli / CIPROFLOXACIN

- Percentage susceptible 5% or more greater than state mean
- Percentage susceptible $\pm 5\%$ of state mean
- Percentage susceptible 5% or more less than state mean



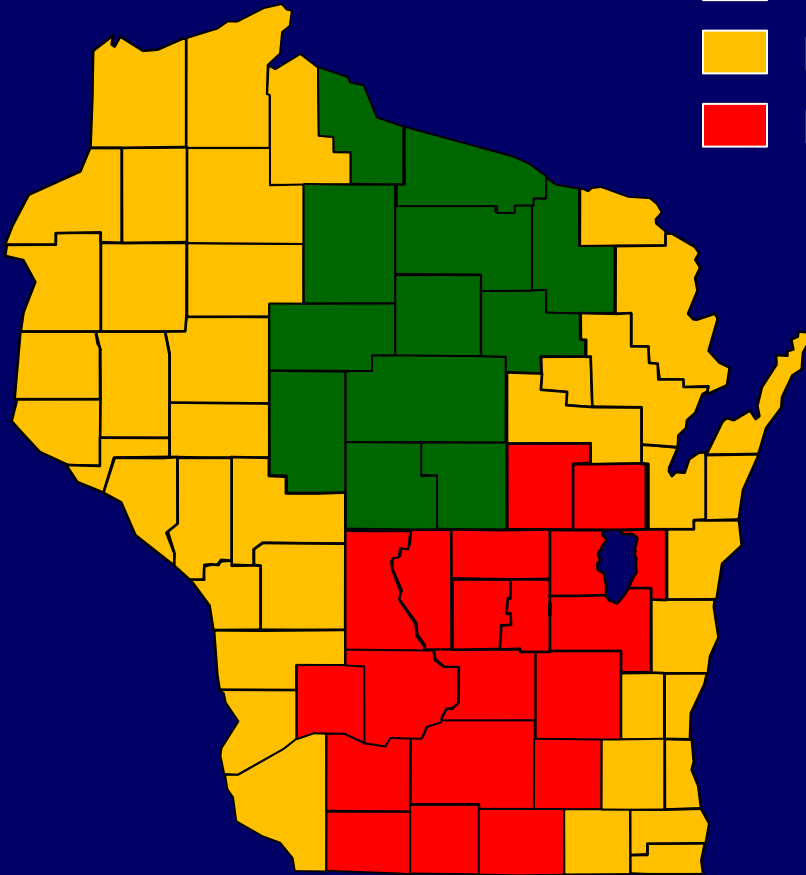
Previous
state mean 80.4%



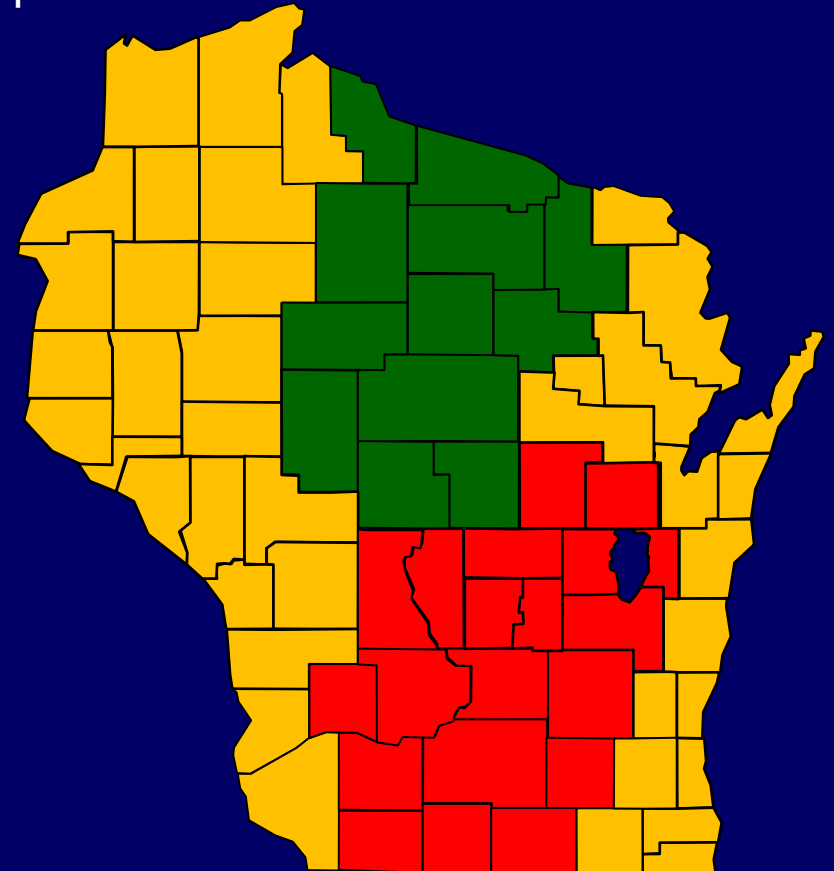
New
state mean 77.4%

E. coli / LEVOFLOXACIN

- Percentage susceptible 5% or more greater than state mean
- Percentage susceptible $\pm 5\%$ of state mean
- Percentage susceptible 5% or more less than state mean



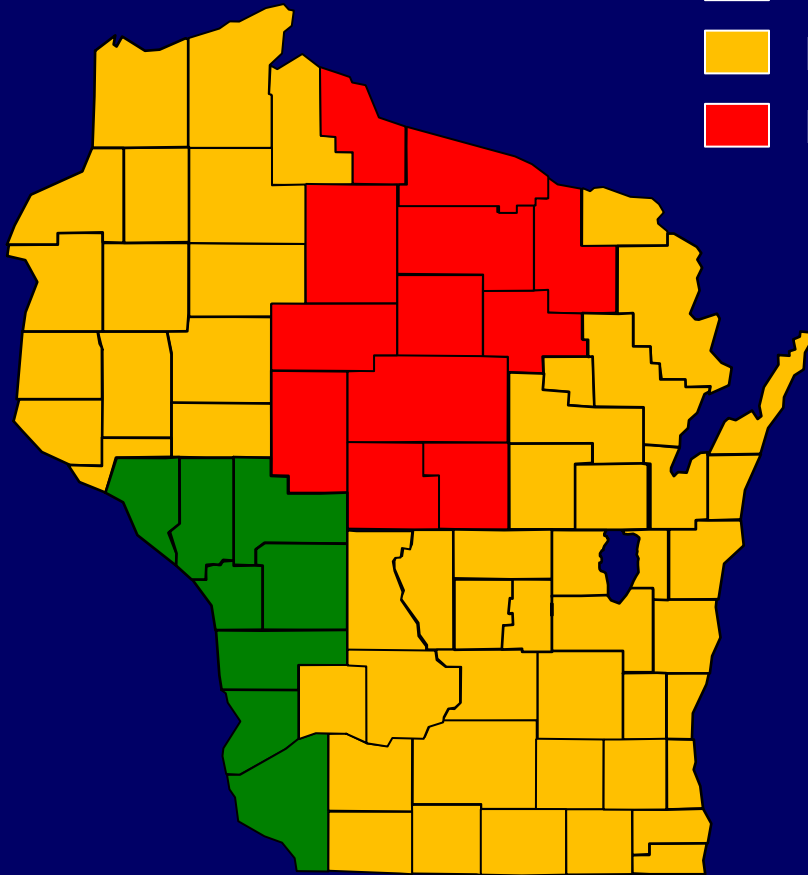
Previous
state mean 80.6%



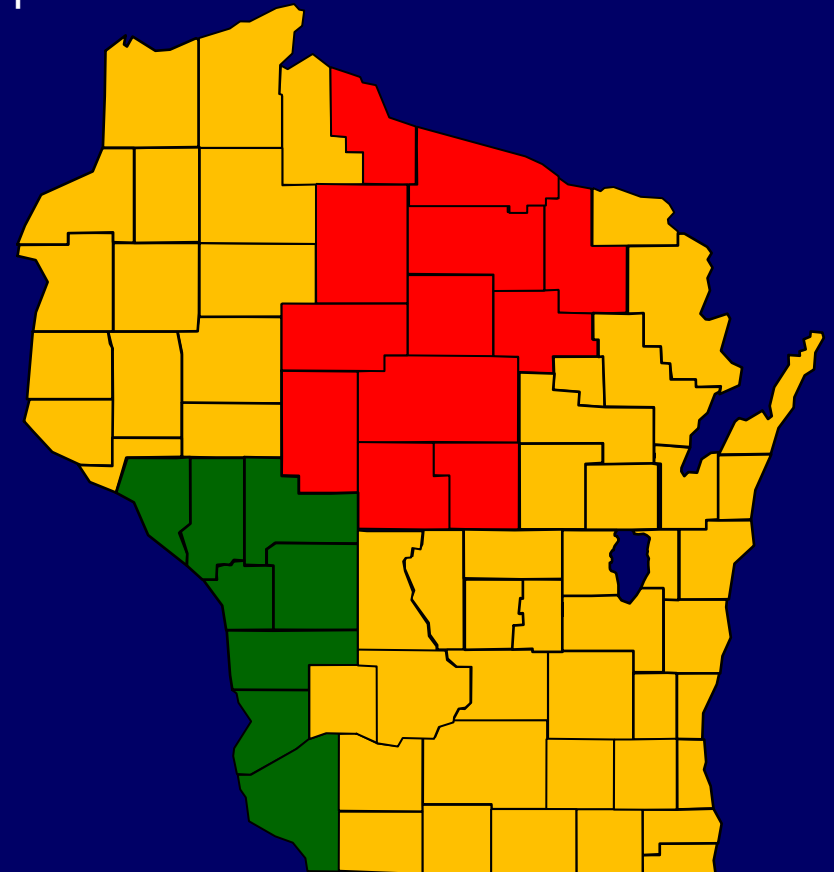
New
state mean 79.5%

P. mirabilis / CIPROFLOXACIN

- Percentage susceptible 5% or more greater than state mean
- Percentage susceptible $\pm 5\%$ of state mean
- Percentage susceptible 5% or more less than state mean



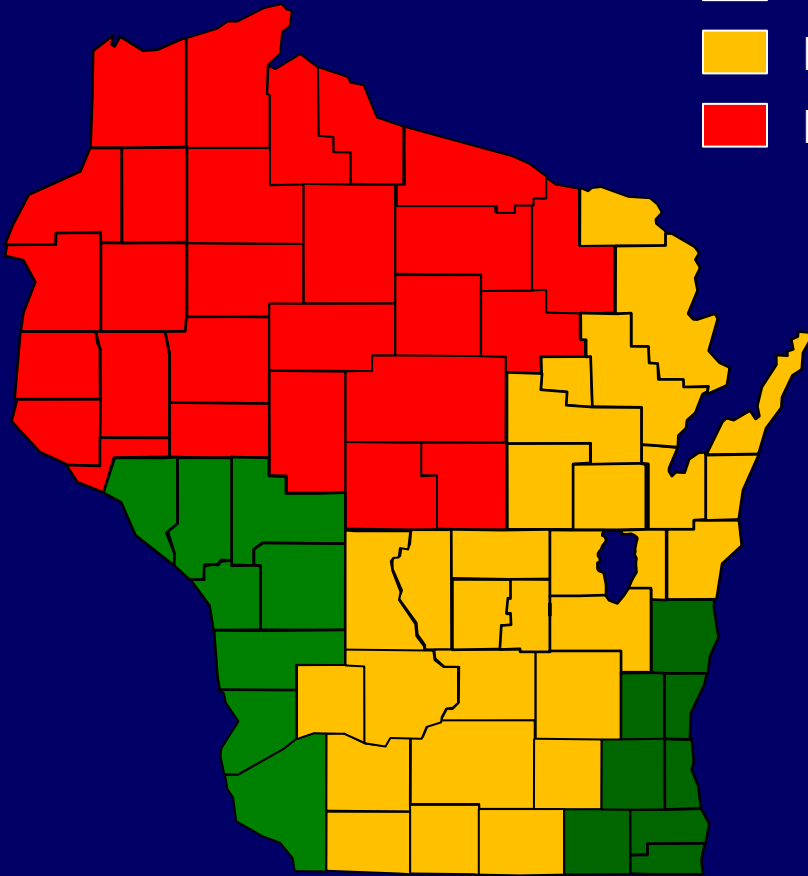
Previous
state mean 78.5%



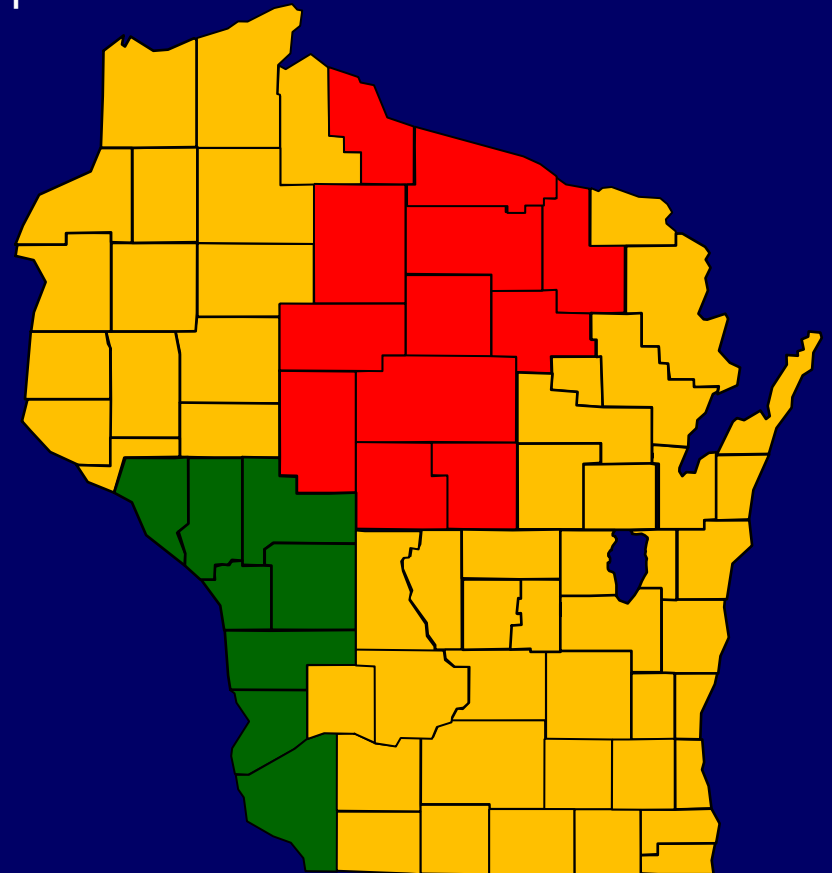
New
state mean 76.0%

P. mirabilis / LEVOFLOXACIN

- Percentage susceptible 5% or more greater than state mean
- Percentage susceptible $\pm 5\%$ of state mean
- Percentage susceptible 5% or more less than state mean



Previous
state mean 83.0%



New
state mean 76.9%

CEFTAROLINE

Organism	Method	Ceftaroline Previous			Ceftaroline New		
		S	I	R	S	SDD	R
<i>S. aureus</i> (incl. MRSA)	BMD	≤ 1	2	≥ 4	≤ 1	2-4	≥ 8
<i>S. aureus</i> (incl. MRSA)	DD	≥ 24	21-23	≤ 20	≥ 25	20-24	≤ 19

CEFTAROLINE

Organism	Method	Ceftaroline Previous			Ceftaroline New		
		S	I	R	S	SDD	R
<i>S. aureus</i> (incl. MRSA)	BMD	≤ 1	2	≥ 4	≤ 1	2-4	≥ 8
<i>S. aureus</i> (incl. MRSA)	DD	≥ 24	21-23	≤ 20	≥ 25	20-24	≤ 19

MIC	Number of Wisconsin Isolates
≤ 0.12	126
0.25	133
0.5	49
1	1
2	0
4	1
8	0

SUSCEPTIBLE DOSE DEPENDENT

- Intermediate
 - Approach attainable blood and tissue levels but have less clinical response than “susceptible”
 - Also implies clinical efficacy in sites where agents are physiologically concentrated
- Susceptible dose dependent (multiple regimens)
 - Implies that susceptibility of isolate is dependent on dosing regimen
 - Higher dose or more-frequent dosing results in higher drug exposure

REVISED LANGUAGE

- Appendix E lists doses used for establishing SDD; drug label should be consulted for recommended doses and adjustment for organ function
- SDD category may be assigned when doses well above “susceptible” breakpoint are/have:

Supported by literature
Widely used clinically
Sufficient data to justify

WISCONSIN SURVEILLANCE

Organism	n	% Cefepime Susceptible Dose Dependent (MIC 4-8 $\mu\text{g/mL}$)
<i>Escherichia coli</i>	1114	1.5
<i>Proteus mirabilis</i>	916	0.4
<i>Enterobacter cloacae</i>	277	4.7
<i>Klebsiella pneumoniae</i>	304	0.0



DAPTOMYCIN

Organism	Method	Daptomycin Previous			Daptomycin New		
		S	I	R	S	SDD	R
<i>Enterococcus</i> spp.	BMD	≤ 4			≤ 1	2-4	≥ 8

- Should not be reported for respiratory isolates
- SDD breakpoint based on dosage regimen of 8-12 mg/kg per day in adults
- Intended for serious *Enterococcus* spp. infections

OTHER TABLE 2 ADDITIONS

- Follow-up MIC testing for *Enterobacteriaceae* / ceftazidime-avibactam zone sizes of 18-20 mm (disk diffusion may overcall resistance)

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.

Mechanisms of oxacillin resistance other than *mecA* are rare and include a novel *mecA* homologue, *mecC*.³ MICs for strains with *mecC* are typically **cefoxitin resistant and oxacillin susceptible**; *mecC* resistance cannot be detected by tests directed at *mecA* or PBP2a.

STAPHYLOCOCCI AND *mecA*

- Added *S. epidermidis*-specific breakpoints

 - Oxacillin disk diffusion

 - Oxacillin broth microdilution

 - Cefoxitin disk diffusion (cefoxitin MIC not reliable)

- Noteworthy revisions

 - Oxacillin disk diffusion not reliable for *S. aureus*
and *S. lugdunensis*

 - Oxacillin MIC (0.5-2 µg/mL) may overcall resistance
in *staphylococci other than...S. aureus S. schleiferi*
S. pseudintermedius S. lugdunensis S. epidermidis

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MORE TABLE 2 ADDITIONS

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

Test/Report Group	Antimicrobial Agent	Staphylococcus spp. Indications	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm			Interpretive Categories and MIC Breakpoints, µg/mL				Comments	
			SDD	I	R	S	SDD	I	R		
CEPHEMS (PARENTERAL)											
B	Ceftaroline	S. aureus only, including MRSA	—	—	≤19	≤1	2–4	—	≥8	(18) The breakpoint for susceptible is based on a dosage regimen of 600 mg administered every 12 h. (19) The breakpoint for SDD is based on a dosage in adults of 600 mg every 8 h administered over 2 h.	
GLYCOPEPTIDES											
(20) MIC tests should be performed to determine the susceptibility of all isolates of staphylococci to vancomycin. The disk test does not differentiate vancomycin-susceptible isolates of S. aureus from vancomycin-intermediate isolates, nor does the test differentiate among vancomycin-susceptible, -intermediate, and -resistant isolates of Staphylococcus spp. other than S. aureus, all of which give similar size zones of inhibition.											
B	Vancomycin	S. aureus only	—	—	—	—	≤2	—	4–8	≥16	(21) For S. aureus, vancomycin-susceptible isolates may become vancomycin intermediate during the course of prolonged therapy. (22) Send any S. aureus for which the vancomycin is ≥8 µg/mL to a referral laboratory. See Appendix A. Also refer to Table 3F for S. aureus, Subchapter 3.12 in M07, ² and Subchapter 3.9 in M02. ¹
		Staphylococcus spp. other than S. aureus	—	—	—	—	≤4	—	8–16	≥32	See comment (19). (23) Send any Staphylococcus spp. for which the vancomycin MIC is ≥32 µg/mL to a referral laboratory. See Appendix A. See also Subchapter 3.12 in M07 ² and Subchapter 3.9 in M02. ¹
Inv.	Teicoplanin	All staphylococci	—	—	—	—	≤8	—	16	≥32	
LIPOGLYCOPEPTIDES											
C	Dalbavancin	S. aureus only, including MRSA	—	—	—	—	≤0.25	—	—	—	
C	Oritavancin	S. aureus only, including MRSA	—	—	—	—	≤0.12	—	—	—	
C	Telavancin	S. aureus only, including MRSA	—	—	—	—	≤0.12	—	—	—	

OTHER TABLE 2 DELETIONS

- Norfloxacin disk diffusion and MIC breakpoints

Enterobacteriaceae *Pseudomonas aeruginosa*
Staphylococcus spp. *Enterococcus* spp.
Non-*Enterobacteriaceae* (MIC breakpoints)

- Telrithromycin disk diffusion and MIC breakpoints

Staphylococcus spp. *Haemophilus influenzae*
Haemophilus parainfluenzae
Streptococcus pneumoniae

OTHER TABLE 2 DELETIONS

- *N. gonorrhoeae* disk diffusion and MIC breakpoints

Cefuroxime

Cefmetazole

Ceftazidime

Cefetamet

Enoxacin

Fleroxacin

Lomefloxacin

Ofloxacin

TABLE 2 CLARIFICATIONS

- Organisms susceptible to tetracycline also susceptible to doxycycline and minocycline; resistance to doxycycline and minocycline cannot be inferred by resistance to tetracycline

Haemophilus influenzae

Haemophilus parainfluenzae

Streptococcus pneumoniae

β -hemolytic *Streptococcus*

viridans group *Streptococcus*



Table 3



WHAT'S IN THERE?

- ESBL detection in *E. coli*, *K. pneumoniae*, *K. oxytoca*, *P. mirabilis*
- Carbapenemase production in *Enterobacteriaceae* and *Pseudomonas aeruginosa*

2010 breakpoints: CarbaNP, mCIM, eCIM, molecular
Current breakpoints: may not need additional tests

No longer necessary to edit carbapenem results to resistant if a carbapenemase producer is detected

WHAT ELSE IS IN THERE?

- β -lactamase detection *Staphylococcus* spp.
- Methicillin (oxacillin) resistance *Staphylococcus* spp.
- Vancomycin agar screen *Staphylococcus aureus* and *Enterococcus* spp.
- Inducible clindamycin resistance
- High-level mupirocin resistance *S. aureus*
- High-level aminoglycoside resist *Enterococcus* spp.



Table 4



TABLE 4

Table 4A-1
Nonfastidious Disk Diffusion QC Excluding β -Lactam Combination Agents
M02

E. coli ATCC 25922
P. aeruginosa ATCC 27853
S. aureus ATCC 25923

Table 4B
Fastidious Disk Diffusion QC
M02

H. influenzae ATCC 49247
H. influenzae ATCC 49766
N. gonorrhoeae ATCC 49226
S. pneumoniae ATCC 49619

Table 4A-2
Nonfastidious Disk Diffusion QC for β -Lactam Combination Agents
M02

Same as left; add:

E. coli ATCC 35218
K. pneumoniae ATCC 700603
E. coli NCTC 13353
K. pneumoniae ATCC BAA-1705
K. pneumoniae ATCC BAA-2814
A. baumannii NCTC 13304

DISK DIFFUSION QC RANGES

- Noteworthy additions

ATCC 25922 and ATCC 27853 range for tebipenem
ATCC 49226 ranges for azithromycin, gepotidacin
Acinetobacter baumannii NCTC 13304 as QC strain
Caveat for imipenem-relebactam (one manufacturer)

- Noteworthy deletions

Ranges for methicillin
Ranges for mezlocillin
Ranges for norfloxacin

DISK DIFFUSION QC ADDED RANGES

<i>E. coli</i> ATCC 25922	cefepime-zidebactam imipenem-relebactam
<i>P. aeruginosa</i> ATCC 27853	cefepime-zidebactam imipenem-relebactam
<i>K. pneumoniae</i> ATCC 700603	cefepime; cefepime-zidebactam imipenem; imipenem-relebactam
<i>E. coli</i> NCTC 13353	cefepime; cefepime-zidebactam
<i>K. pneumoniae</i> ATCC BAA-1705	imipenem; imipenem-relebactam
<i>K. pneumoniae</i> ATCC BAA-2814	imipenem; imipenem-relebactam
<i>A. baumannii</i> NCTC 13304	cefepime; cefepime-zidebactam

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Table 5



TABLE 5

Table 5A-1
Nonfastidious MIC QC Excluding β -Lactam Combination Agents
M07

E. coli ATCC 25922
P. aeruginosa ATCC 27853
S. aureus ATCC 29213
E. faecalis ATCC 29212

Table 5B
Fastidious MIC QC Broth Dilution
M07

H. influenzae ATCC 49247
H. influenzae ATCC 49766
N. gonorrhoeae ATCC 49226 (agar dilution)
S. pneumoniae ATCC 49619

Table 5A-2
Nonfastidious MIC QC for β -Lactam Combination Agents
M07

Same as left; add:

E. coli ATCC 35218
K. pneumoniae ATCC 700603
E. coli NCTC 13353
K. pneumoniae ATCC BAA-1705
K. pneumoniae ATCC BAA-2814
A. baumannii NCTC 13304

MORE TABLE 5

Table 5D
Anaerobe MIC QC
Agar Dilution
M11

Table 5E
Anaerobe MIC QC
Broth Microdilution
M11

B. fragilis ATCC 25285

B. thetaiotaomicron ATCC 29741

C. difficile ATCC 700057

E. lenta ATCC 43055

MIC QC RANGES

- Noteworthy additions

ATCC 27853 range for meropenem
QC ranges established for tebipenem

- Noteworthy revisions

ATCC 27853 range for ciprofloxacin
ATCC 35218 and NCTC 13353 for cefepime

- Noteworthy deletions

Ranges for methicillin, norfloxacin
Ranges for mezlocillin (including anaerobe agar dilution)

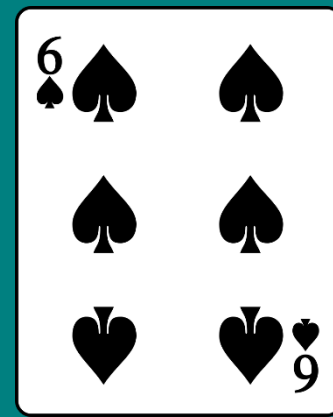
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MIC QC ADDED RANGES

<i>E. coli</i> ATCC 25922	meropenem-nacubactam; nacubactam
<i>P. aeruginosa</i> ATCC 27853	meropenem-nacubactam; nacubactam
<i>E. coli</i> ATCC 35218	cefpodoxime
<i>K. pneumoniae</i> ATCC 700603	cefpodoxime
<i>E. coli</i> NCTC 13353	cefpodoxime
<i>K. pneumoniae</i> ATCC BAA-2814	meropenem-nacubactam; nacubactam

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Tables 6-8

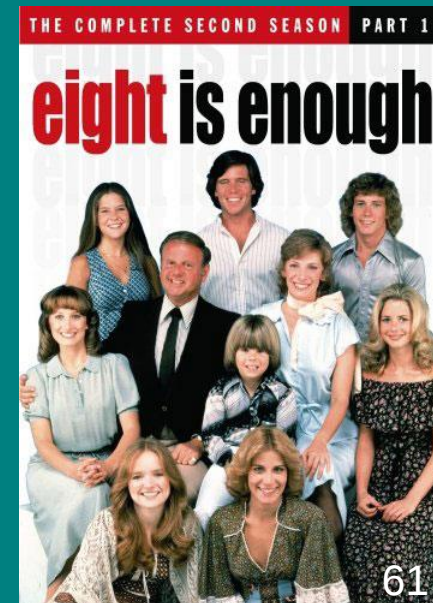
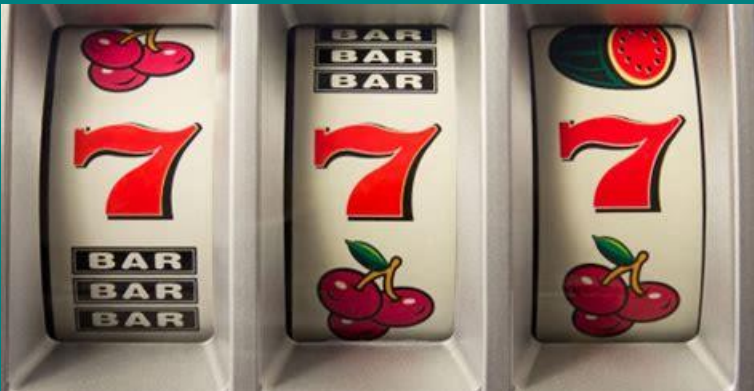


TABLE 6 PREPARING STOCK SOLNS

- Added solvent and diluent information for:

Nacubactam

Tebipenem

Zidebactam

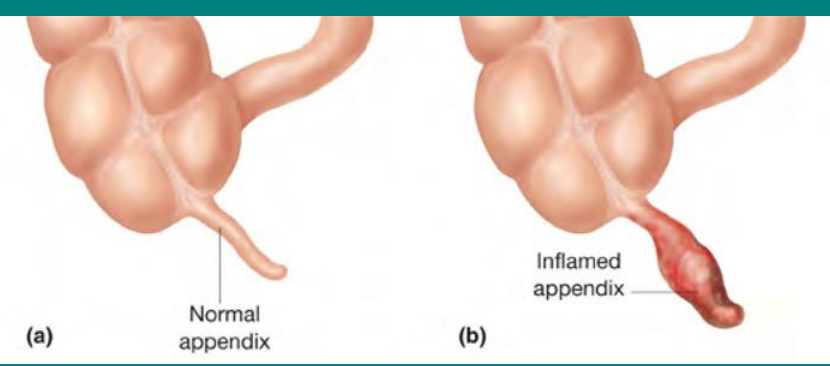
- Prep instructions for meropenem/nacubactam

- Deleted solvent and diluent information for:

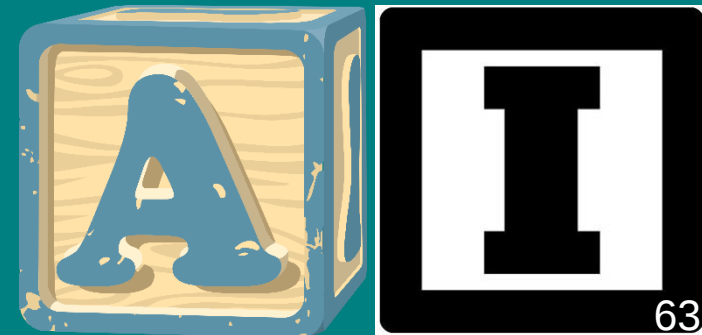
Methicillin

Mezlocillin

Norfloxacin



Appendices



APPENDIX A; SUGGESTED CONFIRM

Appendix A. (Continued)				
Organism or Organism Group	Resistance Phenotype Detected ^a	Occurrence and Significance of Resistance and Actions to Take Following Confirmation of Results ^a		
		Category I	Category II	Category III
		Not reported or only rarely reported to date	Uncommon in most institutions	May be common but generally considered of epidemiological concern
<i>Stenotrophomonas maltophilia</i>	Trimethoprim-sulfamethoxazole – I or R		X	
<i>Haemophilus influenzae</i>	Carbapenem – NS	X		
	Ceftaroline – NS			
	Extended-spectrum cephalosporin ^c – NS			
<i>Neisseria gonorrhoeae</i>	Fluoroquinolone – NS			
	Amoxicillin-clavulanate – R		X	
	Ampicillin – R and β -lactamase negative			
<i>Neisseria meningitidis</i>	Azithromycin – NS		X	
	Extended-spectrum cephalosporin ^c – NS		X	
	Fluoroquinolone – I or R			X
<i>Enterococcus</i> spp.	Ampicillin or penicillin – R	X		
	Extended-spectrum cephalosporin ^c – NS			
	Meropenem – NS			
<i>Enterococcus</i> spp.	Ampicillin or penicillin – I		X	
	Azithromycin – NS			
	Chloramphenicol – I or R			
<i>Enterococcus</i> spp.	Fluoroquinolone – I or R			
	Minocycline – NS			
	Rifampin – I or R			
<i>Enterococcus</i> spp.	Dalbavancin – NS	X		
	Oritavancin – NS			
	Telavancin – NS			
<i>Enterococcus</i> spp.	Daptomycin – NS		X	
	Linezolid – R			
	Tedizolid – NS			
<i>Enterococcus</i> spp.	High-level aminoglycoside – R			X
	Vancomycin – R			

APPENDIX B; INTRINSIC RESISTANT

Appendix B. (Continued)

B1. Enterobacteriaceae

Antimicrobial Agent Organism	Ampicillin	Amoxicillin-clavulanate	Ampicillin-sulbactam	Piperacillin	Ticarcillin	Cephalosporins I: Cefazolin, Cephalothin	Cephameycins: Cefoxitin, 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> , <i>Citrobacter amalonaticus</i> group^a	R				R									
<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>Hafnia alvei</i>	R	R	R			R	R							
<i>Klebsiella</i> (formerly <i>Enterobacter</i>) <i>aerogenes</i>	R	R	R			R	R							
<i>Klebsiella pneumoniae</i> , <i>Klebsiella oxytoca</i>, <i>Klebsiella</i> <i>variicola</i>	R				R									
<i>Morganella morganii</i>	R	R				R		R	°		R	R	R	
<i>Proteus mirabilis</i>	There is no intrinsic resistance to penicillins and cephalosporins in this organism.								°	R	R	R	R	
<i>Proteus penneri</i>	R					R		R	°	R	R	R	R	
<i>Proteus vulgaris</i>	R					R		R	°	R	R	R	R	
<i>Providencia rettgeri</i>	R	R				R			°	R	R	R	R	
<i>Providencia stuartii</i>	R	R				R			°	R	R	R	R	^d
<i>Raoultella</i> spp.^e	R				R									

APPENDIX B; INTRINSIC RESISTANT

B2. Non-Enterobacteriaceae

Antimicrobial Agent Organism	Ampicillin, Amoxicillin	Piperacillin	Ticarcillin	Ampicillin-sulbactam	Amoxicillin-clavulanate	Piperacillin-tazobactam	Cefotaxime	Ceftriaxone	Ceftazidime	Cefepime	Aztreonam	Imipenem	Meropenem	Ertapenem	Polymyxin B Colistin	Aminoglycosides	Tetracyclines/ Tigecycline	Trimethoprim	Trimethoprim- sulfamethoxazole	Chloramphenicol	Fosfomycin
<i>Acinetobacter baumannii</i> / <i>Acinetobacter calcoaceticus</i> complex	R				R						R			R				R		R	R
<i>Burkholderia cepacia</i> complex^a	R	R	R	R	R	^a	^a	^a		^a	^a	^a		R	R	^a		^a			R
<i>Pseudomonas aeruginosa</i>	R			R	R		R	R						R			R	R	R	R	
<i>Stenotrophomonas maltophilia</i>	R	R	R	R	R	R	R	R			R	R	R	R		R	^b	R			R

Abbreviation: R, resistant.

**** a insufficient *in vitro* / *in vivo* correlation**

**Additional tables for *Staphylococcus* spp., *Enterococcus* spp., *Bacteroides* spp.;
select *Clostridium* spp., *Fusobacterium* spp.**

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APPENDIX C; QC STRAINS

Appendix C. (Continued)

QC Strains	Organism Characteristics	Disk Diffusion Tests	MIC Tests	Other Tests	Comments
<i>Escherichia coli</i> ATCC® 25922	• β -lactamase negative	• Nonfastidious gram-negative bacteria • <i>Neisseria meningitidis</i>	• Nonfastidious gram-negative bacteria • <i>N. meningitidis</i>		
<i>E. coli</i> ATCC® 35218 ^{a,b,1,2}	• TEM-1	• β -lactam combination agents	• β -lactam combination agents		
<i>E. coli</i> NCTC 13353 ^{a,b,3}	• CTX-M-15 (ESBL)	• β -lactam combination agents	• β -lactam combination agents		
<i>Haemophilus influenzae</i> ATCC® 10211					• Assess each batch/lot of HTM for growth capabilities.
<i>H. influenzae</i> ATCC® 49247	• BLNAR	• <i>H. influenzae</i> • <i>Haemophilus parainfluenzae</i>	• <i>H. influenzae</i> • <i>H. parainfluenzae</i>		
<i>H. influenzae</i> ATCC® 49766	• Ampicillin susceptible	• <i>H. influenzae</i> • <i>H. parainfluenzae</i>	• <i>H. influenzae</i> • <i>H. parainfluenzae</i>		• More reproducible than <i>H. influenzae</i> ATCC® 49247 with selected β -lactam agents
<i>Klebsiella pneumoniae</i> ATCC® 700603 ^{a,b}	• SHV-18 (ESBL) ^{1,2} • OXA-2 • Mutations in OMPK35 and OMPK37	• β -lactam combination agents	• β -lactam combination agents	• ESBL tests	
<i>K. pneumoniae</i> ATCC® BAA-1705 ^{TM,a,b}	• KPC-2 (carbapenemase) • TEM • SHV	• β -lactam combination agents	• β -lactam combination agents	• Carbapenemase tests	
<i>K. pneumoniae</i> ATCC® BAA-1706 TM	• Resistant to carbapenems by noncarbapenemase mechanism			• Carbapenemase tests	
<i>K. pneumoniae</i> ATCC® BAA-2146 TM	• NDM			• Carbapenemase tests	

APPENDIX D; N ANTIBIOGRAM

Appendix D. Cumulative Antimicrobial Susceptibility Report for Anaerobic Organisms¹

NOTE: Isolates collected from selected US hospitals from 1 January 2013 to 31 December 2016.^a

Six US laboratories
Agar dilution

D1. *Bacteroides* spp. and *Parabacteroides* spp.

Anaerobic Organisms	Number of Strains	Ampicillin-sulbactam		Number of Strains	Piperacillin-tazobactam		Number of Strains	Cefoxitin		Number of Strains	Ertapenem		Number of Strains	Imipenem		Number of Strains	Meropenem	
Percent susceptible (% S) and percent resistant (% R) ^c		%S	%R		%S	%R		%S	%R		%S	%R		%S	%R		%S	%R
Breakpoints, µg/mL		≤ 8/4	≥ 32/16		≤ 16/4	≥ 128/4		≤ 16	≥ 64		≤ 4	≥ 16		≤ 4	≥ 16		≤ 4	≥ 16
<i>B. fragilis</i>	129	84	2	1030	96	1	830	100	0	133	82	14	189	97	1	1505	93	5
<i>B. thetaiotaomicron</i>	76	82	5	252	87	0	258	13	54	—	—	—	70	100	0	328	99	0
<i>B. ovatus</i>	30	80	3	206	94	0	177	20	34	19 ^b	84 ^b	16 ^b	49	100	0	236	95	1
<i>B. vulgatus</i>	20 ^b	45 ^b	15 ^b	168	92	0	153	73	14	—	—	—	35	97	0	171	96	4
<i>B. uniformis</i>	19 ^b	84 ^b	0 ^b	78	96	0	72	85	10	—	—	—	19 ^b	100 ^b	0 ^b	93	100	0
<i>Parabacteroides distasonis</i>	27 ^b	59 ^b	19 ^b	92	95	1	82	29	43	—	—	—	26 ^b	100 ^b	0	119	97	2

APPENDIX D; N ANTIBIOGRAM

D2. Anaerobic Organisms Other Than *Bacteroides* spp. and *Parabacteroides* spp.

Anaerobic Organisms	Number of Strains	Ampicillin-sulbactam		Number of Strains	Piperacillin-tazobactam		Number of Strains	Imipenem		Number of Strains	Meropenem		Number of Strains	Penicillin	
Percent susceptible (% S) and percent resistant (% R) ^b		%S	%R		%S	%R		%S	%R		%S	%R		%S	%R
Breakpoints, µg/mL		≤ 8/4	≥ 32/16		≤ 32/4	≥ 128/4		≤ 4	≥ 16		≤ 4	≥ 16		≤ 0.5	≥ 2
<i>Prevotella</i> spp.	29 ^c	97 ^c	3 ^c	63	100	0	29 ^c	100	0	92	98	0	63	100	0
<i>Fusobacterium</i> spp.	20 ^c	100 ^c	0 ^c	55	96	2	75	95	4	20 ^c	100 ^c	0 ^c	— ^d	— ^d	— ^d
Anaerobic gram-positive cocci ^e	— ^d	— ^d	— ^d	1853	99	1	134	99	0	1647	100	0	1647	100	0
<i>Cutibacterium</i> (formerly <i>Propionibacterium</i>) <i>acnes</i> ^f	— ^d	— ^d	— ^d	18 ^c	100 ^c	0 ^c	17 ^c	94 ^c	0 ^d	— ^d	— ^d	— ^d	— ^d	— ^d	— ^d
<i>Clostridium perfringens</i>	15 ^c	100 ^c	0	410	100	0	23 ^c	100 ^c	0 ^c	417	100	0	402	90	4
<i>Clostridioides</i> (formerly <i>Clostridium</i>) <i>difficile</i> ^g	76	99	0	542	93	0	480	69	4	609	99	0	533	6	37
Other <i>Clostridium</i> spp.	— ^d	— ^d	— ^d	439	94	1	71	99	0	390	100	0	390	69	13

APPENDIX E; S and SDD DOSING

Appendix E. Dosage Regimens Used to Establish Susceptible or Susceptible-Dose Dependent Breakpoints

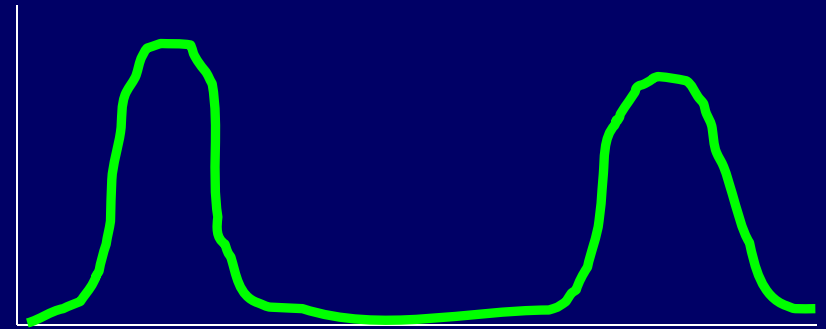
The evolving science of pharmacokinetics-pharmacodynamics has become increasingly important in recent years in determining minimal inhibitory concentration (MIC) breakpoints. Recently approved susceptible or susceptible-dose dependent (SDD) breakpoints for a number of agents have been based on a specific dosage regimen(s); these dosage regimens are listed in the table below. Proper application of the breakpoints necessitates drug exposure at the site of infection that corresponds to or exceeds the expected systemic drug exposure at the dose listed in adult patients with normal renal function. This information should be shared with pharmacists, infectious diseases staff, and others making dosing recommendations for the institution.

Antimicrobial Agent	Breakpoints and Interpretive Categories			
	Susceptible		SDD	
	MIC	Dose	MIC	Dose
Table 2A. Enterobacteriaceae				
Azithromycin (<i>Salmonella</i> Typhi)	≤ 16 µg/mL	500 mg administered daily	N/A	
Aztreonam	≤ 4 µg/mL	1 g administered every 8 h	N/A	
Cefazolin	≤ 2 µg/mL	2 g administered every 8 h	N/A	
Ceftaroline	≤ 0.5 µg/mL	600 mg administered every 12 h	N/A	
Cefepime	≤ 2 µg/mL	1 g administered every 12 h	4 µg/mL	1 g administered every 8 h or 2 g administered every 12 h
			8 µg/mL	2 g administered every 8 h
			or zone diameter: 19–24 mm	(Because it is not possible to correlate specific zone diameters with specific MICs, an isolate with a zone diameter in the SDD range should be treated as if it might be an MIC of 8 µg/mL.)

Big susceptible dose dependent Q & A in Appendix F

EPIDEMIOLOGICAL CUTOFF VALUE

- MIC values that separate bacterial populations into those that have (don't have) resistance mechanisms strictly on basis of phenotype
- Strictly *in vitro*; no clinical correlation
- Wild type below ECV
Non-wild type above ECV (presumed resistant)



ECV DETERMINATION

- Only within same species
- Use a CLSI reference method for testing
- ≥ 100 unique strains; ≥ 3 laboratories
- Must be “on-scale”; lowest concentration tested cannot be the mode
- Data can be augmented with molecular profiles

APPENDIX G; ECV

Table G1. ECVs for *Enterobacteriaceae*

Antimicrobial Agent	Disk Content	Zone Diameter ECV, mm		MIC ECV, µg/mL		Comments
		WT	NWT	WT	NWT	
Azithromycin ¹⁻⁶	15 µg	≥ 16	≤ 15	≤ 8	≥ 16	For use with <i>Shigella flexneri</i> . See Table 2A for azithromycin and <i>Salmonella</i> spp.
	–	–	–	≤ 16	≥ 32	For use with <i>Shigella sonnei</i> .
Colistin	–	–	–	≤ 2	≥ 4	For use with <i>Klebsiella</i> (formerly <i>Enterobacter</i>) <i>aerogenes</i> , <i>Enterobacter cloacae</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , and <i>Raoultella ornithinolytica</i> . The only approved method for testing colistin is MIC by broth microdilution. Disk diffusion and gradient diffusion methods should not be used. The MICs obtained from testing colistin predict MICs for polymyxin B.

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

Table G2. ECVs for Specific Anaerobic Species

Antimicrobial Agent	MIC ECV, µg/mL		Comments
	WT	NWT	
Vancomycin	≤ 2	≥ 4	For use with <i>Cutibacterium</i> (formerly <i>Propionibacterium</i>) <i>acnes</i> ¹⁻⁴ and <i>Clostridioides</i> (formerly <i>Clostridium</i>) <i>difficile</i> . ^{5,7}

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

APPENDIX H; MOLECULAR ASSAYS

- Strategies for reporting methicillin (oxacillin) results when using molecular/phenotypic AST methods for *S. aureus*
- Strategies for reporting vancomycin results when using molecular/phenotypic AST methods for *Enterococcus* spp.
- Reporting results from ESBL and carbapenemase molecular tests for *Enterobacteriaceae*

GLOSSARIES

Glossary I

Glossary I (Part 1). β -Lactams: Class and Subclass Designations and Generic Name

In the late 1990s, several authorities were consulted to construct the glossary. The intention was to include all agents that appeared in M100, along with related agents available for human use. Since that time, agents have been added to the glossary as they were introduced to CLSI, and they do not need to be FDA cleared to be included. It cannot be assumed that the list is exhaustive, and it should be noted that some agents are no longer available for human use.

Antimicrobial Class	Antimicrobial Subclass(es)		Agent(s) Included; Generic Name(s)
Penicillins	Penicillinase-labile penicillins ^a	Penicillin	Penicillin
		Aminopenicillins	Amoxicillin Ampicillin
		Carboxypenicillins	Carbenicillin Ticarcillin
		Ureidopenicillins	Azlocillin
	Penicillinase-stable penicillins ^b		Piperacillin
			Cloxacillin Dicloxacillin
	Aminopenicillin		Nafcillin Oxacillin Medillinam

Additions

meropenem-nacubactam
tebipenem
imipenem-relebactam

Deletions

methicillin
mezlocillin
norfloxacin

Glossary II

Glossary II. Antimicrobial Agent Abbreviation(s), Route(s) of Administration, and Drug Class

In the late 1990s, several authorities were consulted to construct the glossary. The intention was to include all agents that appeared in M100, along with related agents available for human use. Since that time, agents have been added to the glossary as they were introduced to CLSI, and they do not need to be FDA cleared to be included. It cannot be assumed that the list is exhaustive, and it should be noted that some agents are no longer available for human use.

Antimicrobial Agent	Abbreviation(s) ^a	Route(s) of Administration ^b				Drug Class or Subclass
		PO	IM	IV	Topical	
Amikacin	AN, AK, Ak, AMI, AMK		X	X		Aminoglycoside
Amikacin-fosfomycin	AKF	X ^c				Aminoglycoside-fosfomycin



Thank you for your attention.
Have a good 2019.