30 August 2023

To: Recipients of M100-Ed33

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Vice President, Standards and Quality

Subject: Combined corrections

This notice is intended to inform users of corrections made to CLSI document M100, *Performance Standards for Antimicrobial Susceptibility Testing*, 33rd ed. The corrections are described below and shown as stricken and/or highlighted text in the table excerpts.

Corrections: 30 August 2023

Antimicrobial Agent Test and Report Tiers and Additional Considerations for Agents Listed in Tables 1

Tier	Definition	Test	Report[a]	Additional Testing and Reporting Considerations
1	Antimicrobial agents that are appropriate for routine, primary testing and reporting	Routine	Routine	
2	Antimicrobial agents that are appropriate for routine, primary testing but may be reported following cascade reporting rules established at each institution	Routine	Cascade[b]	• Report following cascade reporting rules due to resistance to agent(s) in Tier 1. • May be reported routinely based on institution-specific guidelines.
3	Antimicrobial agents that are appropriate for routine, primary testing in institutions that serve patients at high-risk for MDROs but should only be reported following cascade reporting rules established at each institution[c][b]	Routine or by request	Cascade[b]	Test routinely based on institution-specific guidelines or by clinician request and report following cascade reporting rules due to resistance to agent(s) in Tiers 1 and 2.

Footnotes

a. Antimicrobial agents should be reported selectively, as appropriate (eg, because it is effective in treating uncomplicated UTIs only, nitrofurantoin would be reported only on isolates from urine). Refer to section D for definition of cascade reporting.

b. Identification of patients at high risk for MDROs will likely be communicated by infection preventionists. For examples of criteria used to identify patients at high risk for MDROs, see https://www.cdc.gov/hai/organisms/ESBL.html and https://www.cdc.gov/mrsa/community/index.html

Table 1A. Enterobacterales (not including *Salmonella/Shigella*)[a]

Tier 1: Antimicrobial agents that are appropriate for routine, primary testing and reporting	Tier 2: Antimicrobial agents that are appropriate for routine, primary testing but may be reported following cascade reporting rules established at each institution	Tier 3: Antimicrobial agents that are appropriate for routine, primary testing in institutions that serve patients at high risk for MDROs but should only be reported following cascade reporting rules established at each institution	Tier 4: Antimicrobial agents that may warrant testing and reporting by clinician request if antimicrobial agents in other tiers are not optimal because of various factors
Ampicillin			
Cefazolin	Cefuroxime		
Cefotaxime or ceftriaxone[b]	Cefepime[c]		
	Ertapenem Imipenem Meropenem	Cefiderocol	
		Ceftazidime-avibactam	
		Imipenem-relebactam	
		Meropenem-vaborbactam	
Amoxicillin-clavulanate Ampicillin-sulbactam			
Piperacillin-tazobactam			
Gentamicin	Tobramycin	Plazomicin	
	Amikacin		
Ciprofloxacin Levofloxacin			
Trimethoprim-sulfamethoxazole			
	Cefotetan Cefoxitin		
	Tetracycline[d]		
			Aztreonam
			Ceftaroline[b]
			Ceftazidime[b]
			Ceftolozane-tazobactam
Urine Only			
Cefazolin (surrogate for uncomplicated UTI)[e]			
Nitrofurantoin			
		Fosfomycin[f] (*Escherichia coli*)	

Abbreviations: MDRO, multidrug-resistant organism; UTI, urinary tract infection.

Footnotes

b. *Citrobacter freundii* complex, *Enterobacter cloacae* complex, *Hafnia alvei*, *Klebsiella* (formerly *Enterobacter) aerogenes*, *Morganella morganii*, *Providencia* spp., *Serratia marcescens*, and *Yersinia enterocolitica* may test susceptible to ceftriaxone, cefotaxime, ceftazidime, and ceftaroline, but these agents may be ineffective against these genera within a few days after initiation of therapy due to derepression of inducible AmpC ß-lactamase. The risk of AmpC derepression during therapy is moderate to high with *C. freundii* complex, *E. cloacae complex*, and *K. aerogenes* and appears to be less frequent with *M. morganii*, *Providencia* spp., and *S. marcescens*.[1] Therefore, isolates that are initially susceptible may become resistant. Testing subsequent isolates may be warranted if clinically indicated.

c. Cefepime should be considered a Tier 1 agent for testing and/or reporting of *C. freundii* complex, *E. cloacae* complex, *H. alvei*, *K. aerogenes*, *M. morganii*, *Providencia* spp., *S. marcescens*, and *Y. enterocolitica* (see footnote b).[1]

Reference for Table 1A

[1] Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections, version 3.0. Infectious Diseases Society of America; 2023. Accessed 12 July 2023. https://www.idsociety.org/practice-guideline/amr-guidance/

Table 1H. *Staphylococcus* spp.

Tier 1: Antimicrobial agents that are appropriate for routine, primary testing and reporting	Tier 2: Antimicrobial agents that are appropriate for routine, primary testing but may be reported following cascade reporting rules established at each institution	Tier 3: Antimicrobial agents that are appropriate for routine, primary testing in institutions that serve patients at high risk for MDROs but should only be reported following cascade reporting rules established at each institution	Tier 4: Antimicrobial agents that may warrant testing and reporting by clinician request if antimicrobial agents in other tiers are not optimal because of various factors
Azithromycin or clarithromycin or erythromycin[a]			
Clindamycin[a]			
Oxacillin[b,c,d,e] Cefoxitin[b,c,d] (surrogate for oxacillin)		Ceftaroline[f]	
Doxycycline Minocycline[a] Tetracycline[g]			
Trimethoprim-sulfamethoxazole			
Vancomycin[h]			
	Penicillin [b,i]		
	Daptomycin[h,j]		
	Linezolid	Tedizolid[f]	
		Rifampin[b,k]	
		Lefamulin[a,f]	
			Ciprofloxacin or levofloxacin Moxifloxacin
			Dalbavancin[f,h]
			Oritavancin[f,h]
			Telavancin[f,h]
			Gentamicin[l]
Urine Only			
Nitrofurantoin			

Footnotes

h. MIC testing only; disk diffusion test is unreliable.

k. *Rx*: Rifampin should not be used alone for antimicrobial therapy.

Table 2A. Zone Diameter and MIC Breakpoints for Enterobacterales

CEPHEMS (PARENTERAL) (Including cephalosporins I, II, III, and IV. Please refer to Glossary I.)

(23) WARNING: For *Salmonella* spp. and *Shigella* spp., first- and second-generation cephalosporins and cephamycins may appear active *in vitro* but are not effective clinically and should not be reported as susceptible.

(24) Following evaluation of PK/PD properties, limited clinical data, and MIC distributions, revised breakpoints for cephalosporins (cefazolin, cefotaxime, ceftazidime, ceftizoxime, and ceftriaxone) and aztreonam were first published in January 2010 (M100-S20) and are listed in this table. Cefuroxime (parenteral) was also evaluated; however, no change in breakpoints was necessary for the dosage indicated below. When using current breakpoints, routine ESBL testing is not necessary before reporting results. However, **in consultation with the antimicrobial stewardship team and other relevant institutional stakeholders, laboratories may decide to perform phenotypic or genotypic testing for ESBLs, and the results may be used to guide therapeutic management or** for epidemiological or infection prevention purposes. **Limitations of phenotypic and genotypic methods must be considered (see Table 3A introductory text).**[4]

Breakpoints for drugs with limited availability in many countries (eg, moxalactam, cefonicid, cefamandole, and cefoperazone) were not evaluated. If considering use of these drugs for *E. coli*, ***K. pneumoniae*** **and** ***K. oxytoca*****,** or *Proteus* spp., ESBL testing should be performed (see Table 3A). If isolates test ESBL positive, the results for moxalactam, cefonicid, cefamandole, and cefoperazone should be reported as resistant.

(25) Some Enterobacterales may develop resistance during therapy with third-generation cephalosporins as a result of derepression of AmpC ß-lactamase. This derepression is most commonly seen with *Citrobacter freundii* complex, *Enterobacter cloacae* complex, and *Klebsiella* (formerly *Enterobacter*) *aerogenes*. Isolates that are initially susceptible may become resistant within **a few days** after initiation of therapy. Testing **subsequent** isolates may be warranted **if clinically indicated. The approach to reporting AST results for these organisms should be determined in consultation with the antimicrobial stewardship team and other relevant institutional stakeholders. See Table 1A, footnotes b and c.**[4]

References for Table 2A

[4] **Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections, version 3.0. Infectious Diseases Society of America; 2023. Accessed 12 July 2023. https://www.idsociety.org/practice-guideline/amr-guidance/**

Table 2A. Zone Diameter and MIC Breakpoints for Enterobacterales

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	
CEPHEMS (PARENTERAL) (Including cephalosporins I, II, III, and IV. Please refer to Glossary I.) (Continued)										
Cefotetan*	30 µg	≥16	-	13-15^	≤12	≤16	-	32^	≥64	

Symbol: ***, designation for "Other" agents that are not included in Tables 1 but have established clinical breakpoints.**

Table 2A. Zone Diameter and MIC Breakpoints for Enterobacterales

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	
QUINOLONES AND FLUOROQUINOLONES for *Salmonella* spp. (Please refer to Glossary I.)										
Ofloxacin*	-	-	-	-	-	≤0.12	-	0.25-1^	≥2	

Symbol: ***, designation for "Other" agents that are not included in Tables 1 but have established clinical breakpoints.**

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

Institutional treatment guidelines, infection prevention procedures, or epidemiological investigations may necessitate identification of carbapenemase-producing Enterobacterales and *P. aeruginosa*.[1]

Reference for Introduction to Tables 3B and 3C

[1] Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections, version 3.0. Infectious Diseases Society of America; 2023. Accessed 12 July 2023. https://www.idsociety.org/practice-guideline/amr-guidance/

Table 3E-2. Zone Diameter Disk Diffusion Breakpoints for Enterobacterales Direct From Blood Culture (Tobramycin direct disk diffusion breakpoints removed because they were not evaluated with the 2023 standard disk diffusion revisions.)

Antimicrobial Agent	Disk Content	Read Times, hours	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm				Comments
			S	SDD	I	R	
~~AMINOGLYCOSIDES~~							
~~Tobramycin~~	~~10 µg~~	~~8-10~~	~~≥15~~	~~-~~	~~13-14~~	~~≤12~~	
		~~16-18~~	~~≥15~~	~~-~~	~~13-14~~	~~≤12~~	

Abbreviations: I, intermediate; MIC, minimal inhibitory concentration; R, resistant; S, susceptible; SDD, susceptible-dose dependent.

Table 3E-3. Zone Diameter Disk Diffusion Breakpoints for *Pseudomonas aeruginosa* Direct From Blood Culture (Tobramycin direct disk diffusion breakpoints removed because they were not evaluated with the 2023 standard disk diffusion revisions.)

Antimicrobial Agent	Disk Content	Read Times, hours	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm				Comments
			S	SDD	I	R	
~~AMINOGLYCOSIDES~~							
~~Tobramycin~~	~~10 µg~~	~~8-10~~	~~≥ 15~~	~~-~~	~~13-14~~	~~≤12~~	
		~~16-18~~	~~≥ 15~~	~~-~~	~~13-14~~	~~≤12~~	

Abbreviations: I, intermediate; R, resistant; S, susceptible; SDD, susceptible-dose dependent.

Correction: 21 March 2023

Table of Contents

Overview of Changes

Tables 1. Antimicrobial Agents That Should Be Considered for Testing and Reporting by Microbiology Laboratories	
Table 1A. Enterobacterales (not including ~~inducible AmpC producers and~~ *Salmonella/Shigella*) (new table)	Added: • Antimicrobial agents for Enterobacterales (not including ~~inducible AmpC producers and~~ *Salmonella/Shigella*) (pp. 26-27)

Table 1A. Enterobacterales (not including ~~inducible AmpC producers and~~ *Salmonella/Shigella*)

Tier 1: Antimicrobial agents that are appropriate for routine, primary testing and reporting	Tier 2: Antimicrobial agents that are appropriate for routine, primary testing but may be reported following cascade reporting rules established at each institution	Tier 3: Antimicrobial agents that are appropriate for routine, primary testing in institutions that serve patients at high risk for MDROs but should only be reported following cascade reporting rules established at each institution	Tier 4: Antimicrobial agents that may warrant testing and reporting by clinician request if antimicrobial agents in other tiers are not optimal because of various factors

If you require any additional clarification regarding these corrections, please contact CLSI Customer Service (customerservice@clsi.org).

We appreciate your commitment to CLSI and regret any inconvenience.