

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.

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

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Abstract

If a bacterial pathogen's susceptibility to antimicrobial agents cannot be predicted based on the identity of the organism alone, *in vitro* antimicrobial susceptibility testing of the isolated organism may be indicated. Susceptibility testing is particularly necessary in those situations in which the etiological agent belongs to a bacterial species for which resistance to commonly used antimicrobial agents has been documented, or could arise.

A variety of laboratory techniques can be used to measure the *in vitro* susceptibility of bacteria to antimicrobial agents. Clinical and Laboratory Standards Institute document M45—*Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria* describes the standard microdilution and agar disk diffusion methods. It also includes a series of procedures designed to standardize test performance. The performance, applications, and limitations of the current CLSI-recommended methods are described.

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SAMPLE

Foreword

This document provides guidance to clinical or public health microbiology laboratories regarding the performance of standardized susceptibility testing, when needed, for infrequently isolated or fastidious bacteria that are not currently included in CLSI documents M02,¹ M07,² or M100.³ Some of the organisms included are aerobic gram-negative bacilli that are not members of the family *Enterobacteriaceae* but may be tested by the standard CLSI broth microdilution or disk diffusion methods in the same manner as the much more common *Enterobacteriaceae* isolates. Some aerobic gram-positive cocci and bacilli that are encountered periodically by clinical laboratories can also be tested reliably by the standard CLSI minimal inhibitory concentration (MIC) or disk diffusion test methods in a manner analogous to *Staphylococcus* or *Enterococcus* spp. In addition, several genera of fastidious gram-positive and gram-negative bacteria can be tested in the same manner as the streptococci, using blood-supplemented Mueller-Hinton media. For the purpose of this document, the term “fastidious” is used to describe bacteria that require media supplemented with blood or blood components and that possibly need an atmosphere other than ambient air (eg, 5% CO₂) for acceptable growth. Because the standard CLSI media, reagents, and procedures can be used to test the organisms included in this guideline, the QC procedures, strains, and acceptable zone diameter and MIC limits that have been established through previous rigorous studies can also be applied. The working group used a thorough search of the published literature in conjunction with the clinical expertise of its members to apply or adapt interpretive criteria from CLSI document M100³ to the interpretation of tests for organisms in this document. Users of the guideline should be aware that the very extensive microbiological, clinical, and pharmacodynamic databases normally used for setting breakpoints by CLSI do not exist for the collection of “orphan” organisms described in this document.

It is important for users of M45 to recognize that commercial susceptibility testing devices are not addressed in this guideline. The methods described herein are generic reference procedures that can be used for routine susceptibility testing by clinical laboratories, or that can be used by clinical laboratories to evaluate commercial devices for possible routine use. Results generated by reference methods, such as those contained in CLSI documents, may be used by regulatory authorities to evaluate the performance of commercial systems as part of the approval process. Clearance by a regulatory authority indicates that the commercial susceptibility testing device provides susceptibility results that are substantially equivalent to results generated using the reference methods for the organisms and antimicrobial agents described in the manufacturer’s approved package insert. Some laboratories could find that a commercial dilution, antibiotic gradient, colorimetric, turbidimetric, fluorometric, or other method is suitable for selective or routine use.

Overview of Changes

The changes in this document supersede the information presented in the previous edition of M45. This list includes “major” changes that appear for the first time in this edition of M45, or that were modified since publication of M45-A2. Other minor or editorial changes that were made to the general formatting are not listed here. Revisions to the document include:

Subchapter 1.2, Background (Section 2 in M45-A2)

Deleted *Plesiomonas* spp. due to reclassification as a member of *Enterobacteriaceae* (addressed in CLSI document M100³).

Modified discussion of potential bacterial agents of bioterrorism.

Resistance Mechanisms in Gram-Positive Rods (Section 2.1 in M45-A2)

Deleted section and relocated pertinent information to respective table.

Resistance in Infrequently Isolated or Fastidious Gram-Positive Cocci (Section 2.2 in M45-A2)

Deleted section and relocated pertinent information to respective table.

Infrequently Isolated Nonfastidious Gram-Negative Rods (Section 2.3 in M45-A2)

Deleted section and relocated pertinent information to respective table.

Fastidious Gram-Negative Rods (Section 2.4 in M45-A2)

Deleted section and relocated pertinent information to respective table.

***Moraxella catarrhalis* (Section 2.5 in M45-A2)**

Deleted section and relocated pertinent information to respective table.

Potential Bacterial Agents of Bioterrorism (Section 2.6 in M45-A2)

Deleted section and relocated pertinent information to respective table.

Table 1. *Abiotrophia* spp. and *Granulicatella* spp. (Formerly Known as Nutritionally Deficient or Nutritionally Variant Streptococci)

Added comment regarding combination therapy.

Table 2. *Aeroeoccus* spp.

Added new table.

Table 3. *Aeromonas* spp. (Includes Members of *Aeromonas caviae* Complex, *Aeromonas hydrophila* Complex, and *Aeromonas veronii* Complex)

Deleted *Plesiomonas* spp. due to reclassification as member of *Enterobacteriaceae* (addressed in CLSI document M100³).

Added *Pseudomonas aeruginosa* ATCC[®] 27583 as recommended QC strain for carbapenems.

Deleted zone diameter and MIC interpretive criteria for amoxicillin-clavulanate, ampicillin-sulbactam, and cefazolin.

Deleted amoxicillin-clavulanate as an agent to consider for primary testing.

Revised zone diameter and MIC interpretive criteria for cefepime.

Added dosing regimen for cefepime.

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Added zone diameter and MIC interpretive criteria for doripenem.

Revised zone diameter and MIC interpretive criteria for ertapenem, imipenem, and meropenem.

Added dosing regimen for ertapenem, imipenem, meropenem, and doripenem.

Added a note about ciprofloxacin treatment failures.

Table 4. *Bacillus* spp. (not *Bacillus anthracis*) and Related Genera

Expanded list of related genera for which this table and interpretive criteria apply to include *Brevibacillus*, *Cohnella*, *Lysinibacillus*, *Paenibacillus*, and *Sporolactobacillus*.

Added MIC interpretive criteria for meropenem.

Deleted the cephalosporin breakpoints due to ability of *Bacillus* spp. to produce potent cephalosporinases.

Table 5. *Campylobacter jejuni/coli*

Modified disk diffusion incubation conditions to 42°C for 24 hours; eliminated 36 to 37°C for 48 hours option.

Added tetracycline to the list of agents to consider for primary testing.

Added susceptible and intermediate and revised resistant disk diffusion interpretive criteria for erythromycin and ciprofloxacin.

Added susceptible, intermediate, and resistant disk diffusion interpretive criteria for tetracycline.

Added a comment regarding susceptibility of doxycycline based on tetracycline results.

Revised description of Derivation of Interpretive Criteria.

Table 6. *Corynebacterium* spp. (Including *Corynebacterium diphtheriae*) and Related Coryneform Genera

Expanded list of coryneform genera for which this table and interpretive criteria apply to include *Arthrobacter*, *Cellulosimicrobium*, and *Trueperella*.

Added comments that describe antimicrobial susceptibility data available for less common species of coryneforms and related organisms.

Revised susceptible and intermediate interpretive MIC criteria for penicillin.

Removed meningitis comment.

Revised MIC interpretive criteria for meropenem.

Deleted MIC interpretive criteria for imipenem.

Table 8. *Gemella* spp.

Added new table.

Table 9. HACEK Group: *Aggregatibacter* spp., *Cardiobacterium* spp., *Eikenella corrodens*, and *Kingella* spp.

Revised broth recommended for testing to include *Haemophilus* Test Medium and Brucella broth as alternatives for some species.

Table 10. *Helicobacter pylori*

Added note indicating that determination of metronidazole resistance under these testing conditions is not recommended because it does not reliably predict treatment failure.

Added note further emphasizing need for the use of aged blood in agar dilution testing.

Table 11. *Lactobacillus* spp.

Expanded comment indicating species that require anaerobic incubation.

Expanded comment describing species that are intrinsically vancomycin resistant and those that are vancomycin susceptible.

Deleted gentamicin interpretive criteria.

Modified comment regarding combination therapy.

Added meropenem interpretive criteria.

Added note indicating the relationship of meropenem and imipenem MICs.

Table 12. *Lactococcus* spp.

Added new table.

Table 13. *Leuconostoc* spp.

Deleted gentamicin interpretive criteria.

Modified comment regarding combination therapy.

Table 14. *Listeria monocytogenes*

Added meropenem interpretive criteria.

Revised trimethoprim-sulfamethoxazole interpretive criteria to include susceptible only.

Table 15. *Micrococcus* spp.

Added new table.

Table 16. *Moraxella catarrhalis*

Deleted interpretive criteria for cefaclor.

Table 18. *Pediococcus* spp.

Deleted gentamicin interpretive criteria.

Modified comment regarding combination therapy.

Table 19. *Rothia mucilaginosa*

Added new table.

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Table 20. *Vibrio* spp. (Including *Vibrio cholerae*)

Added *P. aeruginosa* ATCC® 27853 as recommended QC organism for carbapenems.

Added doxycycline as an agent to consider for primary testing.

Revised zone diameter and MIC interpretive criteria for cefepime.

Added dosing regimen for cefepime.

Revised zone diameter and MIC interpretive criteria for imipenem and meropenem.

Revised MIC interpretive criteria for ceftazidime.

Revised dosing regimen for ceftazidime.

Added dosing regimen for imipenem and meropenem.

Expanded comments for testing/reporting tetracyclines (including doxycycline) on *Vibrio* spp. other than *V. cholerae*.

Table 21. Potential Bacterial Agents of Bioterrorism: *Bacillus anthracis*, *Yersinia pestis*, *Burkholderia mallei*, *Burkholderia pseudomallei*, *Francisella tularensis*, and *Brucella* spp.

Added breakpoints and interpretive categories for amoxicillin and *B. anthracis*.

Revised breakpoints for penicillin and *Bacillus anthracis*.

Table 22. Summary of Testing Conditions and Quality Control Recommendations for Infrequently Isolated or Fastidious Bacteria

Deleted *Plesiomonas shigelloides* (*Plesiomonas* spp. now included with *Enterobacteriaceae* in CLSI document M100³).

Added *Aerococcus* spp., *Gemella* spp., *Lactococcus* spp., *Micrococcus* spp., and *Rothia mucilaginosa*.

Added *P. aeruginosa* ATCC® 27583 as a recommended QC strain for carbapenems when testing *Aeromonas hydrophila* complex and *Vibrio* spp. (including *V. cholerae*).

Revised temperature and incubation time for disk diffusion testing of *Campylobacter jejuni/coli*.

Table 23A. MIC: Quality Control Ranges for Nonfastidious Organisms (Unsupplemented Cation-Adjusted Mueller-Hinton Broth)

Revised QC ranges for *E. coli* ATCC® 35215 with aztreonam.

Revised QC ranges for *P. aeruginosa* ATCC® 27583 with:

- Ceftazidime
- Doripenem
- Ertapenem
- Imipenem
- Meropenem
- Tetracycline

Table 23B. MIC: Quality Control Ranges for Broth Microdilution Methods (Cation-Adjusted Mueller-Hinton Broth With Lysed Horse Blood [2.5% to 5% v/v])

Revised footnotes “a” and “b.”

Table 24A. Disk Diffusion: Quality Control Ranges for Nonfastidious Organisms (Unsupplemented Mueller-Hinton Medium)

Revised QC ranges for *P. aeruginosa* ATCC® 27583 with:

- Doripenem
- Ertapenem
- Imipenem
- Meropenem

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

Updated the footnotes.

Updated to include newer antimicrobial agents considered by the CLSI Subcommittee on Antimicrobial Susceptibility Testing, not all of which are currently referenced in M45.

These newer agents are:

- Aztreonam-avibactam
- Ceftaroline-avibactam
- Ceftazidime-avibactam
- Ceftolozane-tazobactam
- Biapenem

Glossary I (Part 2). Non- β -Lactams: Class and Subclass Designation and Generic Name

Deleted trospectinomycin.

Updated to include newer antimicrobial agents considered by the CLSI Subcommittee on Antimicrobial Susceptibility Testing, not all of which are currently referenced in M45.

These newer agents are:

- Besifloxacin
- Eravacycline
- Fidaxomicin
- Finafloxacin
- Fusidic acid
- Nitazoxanide
- Pefloxacin
- Plazomicin
- Ramoplanin
- Solithromycin
- Surtomycin
- Tedizolid
- Telithromycin
- Tinidazole
- Tizoxanide
- Ulifloxacin (prulifloxacin)

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Glossary II. Abbreviations/Routes of Administration/Drug Class for Antimicrobial Agents Listed in CLSI document M100-S25³

Deleted trospectinomycin.

Updated to include newer antimicrobial agents considered by the CLSI Subcommittee on Antimicrobial Susceptibility Testing, not all of which are currently referenced in M45.

These newer agents are:

- Aztreonam-avibactam
- Besifloxacin
- Biapenem
- Ceftaroline-avibactam
- Ceftazidime-avibactam
- Ceftolozane-tazobactam
- Eravacycline
- Fidaxomicin
- Finafloxacin
- Fusidic acid
- Metronidazole
- Nitazoxanide
- Omadacycline
- Pefloxacin
- Plazomicin
- Ramoplanin
- Solithromycin
- Surtomycin
- Tedizolid
- Tinoxanide
- Tinidazole
- Ulifloxacin (prulifloxacin)

Glossary III. List of Identical Abbreviations Used for More Than One Antimicrobial Agent in US Diagnostic Products

Added table for consistency with the current edition of CLSI document M100.³

NOTE 1: Mandates are occasionally allowed in CLSI guidelines, in cases in which the working group feels strongly that a particular action is either required or prohibited, or when a guideline addresses provisions based on regulations. In Subchapter 1.2.1, the use of the term “must” was evaluated by the working group and deemed appropriate because the use is based on a requirement.

NOTE 2: The findings and conclusions in this document are those of the authors and do not necessarily reflect the views of the organizations they represent.

Key Words

Agar dilution, antimicrobial agent, antimicrobial susceptibility, antimicrobial susceptibility testing, broth dilution, broth microdilution, disk diffusion, minimal inhibitory concentration, susceptibility testing

Subcommittee on Antimicrobial Susceptibility Testing Mission Statement

The Subcommittee on Antimicrobial Susceptibility Testing is composed of representatives from the professions, government, and industry, including microbiology laboratories, government agencies, health care providers and educators, and pharmaceutical and diagnostic microbiology industries. Using the CLSI voluntary consensus process, the subcommittee develops standards that promote accurate antimicrobial susceptibility testing and appropriate reporting.

The mission of the Subcommittee on Antimicrobial Susceptibility Testing is to:

- Develop standard reference methods for antimicrobial susceptibility tests.
- Provide quality control parameters for standard test methods.
- Establish interpretive criteria for the results of standard antimicrobial susceptibility tests.
- Provide suggestions for testing and reporting strategies that are clinically relevant and cost-effective.
- Continually refine standards and optimize detection of emerging resistance mechanisms through development of new or revised methods, interpretive criteria, and quality control parameters.
- Educate users through multimedia communication of standards and guidelines.
- Foster a dialogue with users of these methods and those who apply them.

The ultimate purpose of the subcommittee's mission is to provide useful information to enable laboratories to assist the clinician in the selection of appropriate antimicrobial therapy for patient care. The standards and guidelines are meant to be comprehensive and to include all antimicrobial agents for which the data meet established CLSI guidelines. The values that guide this mission are quality, accuracy, fairness, timeliness, teamwork, consensus, and trust.

The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system (QMS) approach in the development of standards and guidelines, which facilitates project management; defines a document structure using a template; and provides a process to identify needed documents. The QMS approach applies a core set of “quality system essentials” (QSEs), basic to any organization, to all operations in any health care service’s path of workflow (ie, operational aspects that define how a particular product or service is provided). The QSEs provide the framework for delivery of any type of product or service, serving as a manager’s guide. The QSEs are as follows:

Organization	Personnel	Process Management	Nonconforming Event Management
Customer Focus	Purchasing and Inventory	Documents and Records	Assessments
Facilities and Safety	Equipment	Information Management	Continual Improvement

M45 addresses the QSE indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

Organization	Customer Focus	Facilities and Safety	Personnel	Purchasing and Inventory	Equipment	Process Management	Documents and Records	Information Management	Nonconforming Event Management	Assessments	Continual Improvement
		M29				X M02 M07 M11 M23 VET01	M07				

Path of Workflow

A path of workflow is the description of the necessary processes to deliver the particular product or service that the organization or entity provides. A laboratory path of workflow consists of the sequential processes: preexamination, examination, and postexamination and their respective sequential subprocesses. All laboratories follow these processes to deliver the laboratory’s services, namely quality laboratory information.

M45 addresses the clinical laboratory path of workflow steps indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

Examination ordering	Preexamination			Examination			Postexamination	
	Sample collection	Sample transport	Sample receipt/processing	Examination	Results review and follow-up	Interpretation	Results reporting and archiving	Sample management
				M02 M07 M11 VET01	X M02 M07 M11 VET01 VET01S M100	X M02 M07 M11 VET01 VET01S M100	X M02 M07 M11 VET01 VET01S M100	

Related CLSI Reference Materials*

- M02** **Performance Standards for Antimicrobial Disk Susceptibility Tests. 12th ed., 2015.** This standard contains the current Clinical and Laboratory Standards Institute–recommended methods for disk susceptibility testing, criteria for quality control testing, and updated tables for interpretive zone diameters.
- M07** **Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. 10th ed., 2015.** This standard addresses reference methods for the determination of minimal inhibitory concentrations of aerobic bacteria by broth macrodilution, broth microdilution, and agar dilution.
- M11** **Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria. 8th ed., 2012.** This standard provides reference methods for the determination of minimal inhibitory concentrations of anaerobic bacteria by agar dilution and broth microdilution.
- M23** **Development of *In Vitro* Susceptibility Testing Criteria and Quality Control Parameters. 3rd ed., 2008.** This document addresses the required and recommended data needed for the selection of appropriate interpretive criteria and quality control ranges for antimicrobial agents.
- M29** **Protection of Laboratory Workers From Occupationally Acquired Infections. 4th ed., 2014.** Based on US regulations, this document provides guidance on the risk of transmission of infectious agents by aerosols, droplets, blood, and body substances in a laboratory setting; specific precautions for preventing the laboratory transmission of microbial infection from laboratory instruments and materials; and recommendations for the management of exposure to infectious agents.
- M100S** **Performance Standards for Antimicrobial Susceptibility Testing. 25th ed., 2015.** This document provides updated tables for the Clinical and Laboratory Standards Institute antimicrobial susceptibility testing standards M02-A12, M07-A10, and M11-A8.
- VET01** **Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals. 4th ed., 2013.** This document provides the currently recommended techniques for antimicrobial agent disk and dilution susceptibility testing, criteria for quality control testing, and interpretive criteria for veterinary use.
- VET01S** **Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals. 3rd ed., 2015.** This document provides updated tables for the CLSI antimicrobial susceptibility testing standard VET01.

* CLSI documents are continually reviewed and revised through the CLSI consensus process; therefore, readers should refer to the most current editions.

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