M100
Performance Standards for Antimicrobial Susceptibility Testing

This document includes updated tables for the Clinical and Laboratory Standards Institute antimicrobial susceptibility testing standards M02, M07, and M11.

A CLSI supplement for global application.
Performance Standards for Antimicrobial Susceptibility Testing

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Abstract

The data in the tables are valid only if the methodologies in CLSI documents M02,1 M07,2 and M113 are followed. These standards contain information about disk diffusion (M021) and dilution (M072 and M113) test procedures for aerobic and anaerobic bacteria. Clinicians depend heavily on information from the microbiology laboratory for treating their seriously ill patients. The clinical importance of antimicrobial susceptibility test results demands that these tests be performed under optimal conditions and that laboratories have the capability to provide results for the newest antimicrobial agents. The tables presented in M100 represent the most current information for drug selection, interpretation, and quality control using the procedures standardized in M02,1 M07,2 and M113. Users should replace previously published tables with these new tables. Changes in the tables since the previous edition appear in boldface type.


The Clinical and Laboratory Standards Institute consensus process, which is the mechanism for moving a document through two or more levels of review by the health care community, is an ongoing process. Users should expect revised editions of any given document. Because rapid changes in technology may affect the procedures, methods, and protocols in a standard or guideline, users should replace outdated editions with the current editions of CLSI documents. Current editions are listed in the CLSI catalog and posted on our website at www.clsi.org.

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</table>

Abbreviations: ECV, epidemiological cutoff value; SDD, susceptible-dose–dependent; UTI, urinary tract infection.

Footnotes:

a. “New” indicates the breakpoints are listed for the first time for a specific organism or organism group in the respective Table 2.

b. “Revised” indicates previously established breakpoints for a specific organism or organism group in the respective Table 2 have changed. In some cases, unique breakpoints were added for a specific genus or species previously included within the organism or organism group breakpoints (eg, “Salmonella spp. [including S. enterica ser. Typhi]” was previously grouped with Enterobacterales).

CLSI Archived Resources

- Breakpoints that have been eliminated from M100 since 2010 have been relocated to the CLSI website. [https://clsi.org/media/pqlom3b5/_m100_archived_drugs_table.pdf](https://clsi.org/media/pqlom3b5/_m100_archived_drugs_table.pdf)
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Abbreviations: ECV, epidemiological cutoff value; QC, quality control.

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## CLSI Breakpoint Additions/Revisions Since 2010 (Continued)

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<td>New&lt;sup&gt;a&lt;/sup&gt;</td>
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### CLSI Archived Resources

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Abbreviations: ECV, epidemiological cutoff value; QC, quality control.

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Instructions for Use of Tables

These instructions apply to:

- **Tables 1A and 1B**: suggested groupings of antimicrobial agents that should be considered for testing and reporting by microbiology laboratories. These guidelines are based on antimicrobial agents approved by the US Food and Drug Administration (FDA) for clinical use in the United States. In other countries, placement of antimicrobial agents in Tables 1A and 1B should be based on available drugs approved for clinical use by relevant regulatory organizations.

- **Tables 2A through 2I**: tables for each organism group that contain:
  - Recommended testing conditions
  - Routine QC recommendations (also see Chapter 4 in M02^1 and M07^2)
  - General comments for testing the organism group and specific comments for testing particular agent/organism combinations
  - Suggested agents that should be considered for routine testing and reporting by medical microbiology laboratories, as specified in Tables 1A and 1B (test/report groups A, B, C, U)
  - Additional drugs that are appropriate for the respective organism group but would generally not warrant routine testing by a medical microbiology laboratory in the United States (test/report group O for “other”; test/report group Inv. for “investigational” [not yet FDA approved])
  - Zone diameter and minimal inhibitory concentration (MIC) breakpoints

- **Tables 1C and 2J**: tables containing specific recommendations for testing and reporting results on anaerobes and some of the information listed in the bullets above

- **Tables 3A to 3K**: tables describing tests to detect particular resistance types in specific organisms or organism groups
I. Selecting Antimicrobial Agents for Testing and Reporting

A. Appropriate Agents for Routine Testing

Selecting the most appropriate antimicrobial agents to test and report is a decision best made by each laboratory in consultation with the infectious diseases and pharmacy practitioners, the pharmacy and therapeutics and infection prevention committees of the medical staff, and the antimicrobial stewardship team. The recommendations for each organism group include agents of proven efficacy that show acceptable \textit{in vitro} test performance. Considerations in the assignment of agents to specific test/report groups include clinical efficacy, prevalence of resistance, minimizing emergence of resistance, cost, FDA clinical indications for use, and current consensus recommendations for first-choice and alternative drugs. Tests on selected agents may be useful for infection prevention purposes.

B. Equivalent Agents

Antimicrobial agents listed together in a single box are agents for which interpretive categories (susceptible, intermediate, susceptible-dose dependent, or resistant) and clinical efficacy are similar. Within each box, an “or” between agents indicates agents for which cross-resistance and cross-susceptibility are nearly complete. Results from one agent connected by an “or” can be used to predict results for the other agent (ie, equivalent agents). For example, Enterobacterales susceptible to cefotaxime can be considered susceptible to ceftriaxone. The results obtained from testing cefotaxime could be reported along with a comment that the isolate is also susceptible to ceftriaxone. For drugs connected with an “or,” combined major and very major errors are fewer than 3%, and minor errors are fewer than 10%, based on a large population of bacteria tested (see CLSI document \textit{M23} for description of error types). In addition, to qualify for an “or,” at least 100 strains with resistance to the agents in question must be tested, and a result of “resistant” must be obtained with all agents for at least 95% of the strains. “Or” is also used for comparable agents when tested against organisms for which “susceptible-only” breakpoints are provided (eg, cefotaxime or ceftriaxone with \textit{H. influenzae}). When no “or” connects agents within a box, testing of one agent cannot be used to predict results for another, owing either to discrepancies or insufficient data.

C. Test/Report Groups

1. Group A antimicrobial agents, as listed in Tables 1A, 1B, and 1C, are considered appropriate for inclusion in a routine, primary testing panel, as well as for routine reporting of results for the specific organism groups.

2. Group B includes antimicrobial agents that may warrant primary testing, but they may be reported only selectively, such as when the organism is resistant to agents of the same antimicrobial class, as in group A. Other indications for reporting the result might include a selected specimen source (eg, a third-generation cephalosporin for Enterobacterales from CSF or
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:** Includes antimicrobial agents considered appropriate for inclusion in a routine, primary testing panel, as well as for routine reporting of results for the specific organism group.

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<th>Enterococcus spp.&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>Ampicillin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ceftazidime</td>
<td>Azithromycin&lt;sup&gt;c&lt;/sup&gt; or clarithromycin&lt;sup&gt;c&lt;/sup&gt; or erythromycin&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Clindamycin&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>Tobramycin&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Penicillin&lt;sup&gt;g&lt;/sup&gt;</td>
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<tr>
<td>Enterococcus spp.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Group B:** Includes antimicrobial agents that may warrant primary testing but may be reported only selectively, such as when the organism is resistant to agents of the same antimicrobial class in Group A.<sup>l</sup>

<table>
<thead>
<tr>
<th>Amikacin&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Amikacin</th>
<th>Ceftaroline&lt;sup&gt;m&lt;/sup&gt;</th>
<th>Daptomycin&lt;sup&gt;i,n&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>Aztreonam</td>
<td>Daptomycin&lt;sup&gt;i,n&lt;/sup&gt;</td>
<td>Linezolid</td>
</tr>
<tr>
<td>Ampicillin-sulbactam</td>
<td></td>
<td></td>
<td>Tedizolid&lt;sup&gt;n&lt;/sup&gt;</td>
</tr>
<tr>
<td>Azithromycin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ceftazidime-avibactam</td>
<td></td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Cefazidime-avibactam</td>
<td>Cefepime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftolozane-tazobactam</td>
<td>Ceftazidime-avibactam</td>
<td>Linezolid</td>
<td></td>
</tr>
<tr>
<td>Imipenem-relebactam</td>
<td>Imipenem-relebactam</td>
<td>Tedizolid&lt;sup&gt;m&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Meropenem-vaborbactam</td>
<td>Ceftolozane-tazobactam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Cefuroxime</td>
<td>Doxycycline</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>Doripenem</td>
<td>Minocycline&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Tetracycline&lt;sup&gt;q&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>Doripenem</td>
<td></td>
<td>Lefamulin&lt;sup&gt;m&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cefotaxime&lt;sup&gt;b,l&lt;/sup&gt; or Ceftriaxone&lt;sup&gt;b,f&lt;/sup&gt;</td>
<td>Meropenem</td>
<td>Vancomycin&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Cefiderocol</strong></td>
<td><strong>Cefiderocol</strong></td>
<td>Rifampin&lt;sup&gt;l&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Cefotaxime&lt;sup&gt;l&lt;/sup&gt;</td>
<td>Levoflaxacin&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doripenem</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ertapenem</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Imipenem</td>
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<tr>
<td>Meropenem</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Trimethoprim-sulfamethoxazole&lt;sup&gt;b&lt;/sup&gt;</td>
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</tbody>
</table>
Table 2A. Zone Diameter and MIC Breakpoints for Enterobacterales

<table>
<thead>
<tr>
<th>Testing Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medium:</strong> Disk diffusion: MHA</td>
</tr>
<tr>
<td>Broth dilution: CAMHB; iron-depleted CAMHB for cefiderocol (see Appendix I)</td>
</tr>
<tr>
<td>Agar dilution: MHA</td>
</tr>
<tr>
<td><strong>Inoculum:</strong> Broth culture method or colony suspension, equivalent to a 0.5 McFarland standard; positive blood culture broth for select antimicrobial agents with disk diffusion (see general comment [5]).</td>
</tr>
<tr>
<td><strong>Incubation:</strong> 35°C ± 2°C; ambient air</td>
</tr>
<tr>
<td>Disk diffusion: 16-18 hours</td>
</tr>
<tr>
<td>Dilution methods: 16-20 hours</td>
</tr>
</tbody>
</table>

**Routine QC Recommendations** (see Tables 4A-1 and 5A-1 for acceptable QC ranges)

- *Escherichia coli* ATCC® 25922
- *Pseudomonas aeruginosa* ATCC® 27853 (for carbapenems)
- *Staphylococcus aureus* ATCC® 29213 (for disk diffusion) or *S. aureus* ATCC® 25923 (for dilution methods) when testing azithromycin against *Salmonella enterica* ser. Typhi or *Shigella* spp.

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.

Refer to Tables 3A, 3B, and 3C for additional testing, reporting, and QC for Enterobacterales.

**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 M02,2 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 (see the M02 Disk Diffusion Reading Guide3). 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. Strains of *Proteus* spp. may swarm into areas of inhibited growth around certain antimicrobial agents. With *Proteus* spp., ignore the thin veil of swarming growth in an otherwise obvious zone of growth inhibition. With trimethoprim and the sulfonamides, antagonists in the medium may allow some slight growth; therefore, disregard slight growth (20% or less of the lawn of growth) and measure the more obvious margin to determine the zone diameter.

2. When fecal isolates of *Salmonella* and *Shigella* spp. are tested, only amoxicillin, a fluoroquinolone, and trimethoprim-sulfamethoxazole should be reported routinely. Data regarding whether amoxicillin should be used to treat shigellosis are conflicting. When reporting ampicillin results, state that treatment of shigellosis with amoxicillin might not be comparable to ampicillin, with poorer efficacy. In addition, for extraintestinal isolates of *Salmonella* spp., a 3rd-generation cephalosporin should be tested and reported, and chloramphenicol may be tested and reported if requested. Susceptibility testing is indicated for typhoidal *Salmonella* (S. enterica ser. Typhi and S. enterica ser. Paratyphi A-C) isolated from extraintestinal and intestinal sources. Routine susceptibility testing is not indicated for nontyphoidal *Salmonella* spp. isolated from intestinal sources. In contrast, susceptibility testing is indicated for all *Shigella* isolates.

3. The dosage regimens shown in the comments column below are those needed to achieve plasma drug exposures (in adults with normal renal and hepatic functions) on which breakpoints were based. When implementing new breakpoints, it is strongly recommended that laboratories share this information with local and regional hospital acquisition and formulary committees, as well as with appropriate infection prevention committees, and the antimicrobial stewardship team.

4. An intermediate (I) with a ^ in Tables 2 indicates agents that have the potential to concentrate in the urine. The I^ is for informational use only. The decision to report I^ is best made by each laboratory based on institution-specific guidelines and in consultation with appropriate medical personnel.

5. Positive blood culture broth can be used as the inoculum for direct disk diffusion testing of select antimicrobial agents against Enterobacterales (using methods described in Table 3E-1 and applying breakpoints in Table 3E-2). For antimicrobial agents not listed in Table 3E-2 for Enterobacterales, CLSI has not yet evaluated this direct disk diffusion method.

NOTE: Information in boldface type is new or modified since the previous edition.
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 that 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:

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

The QSEs covered by M100 and its related CLSI documents are available on the CLSI website: https://clsi.org/qse

Related CLSI Reference Materialsa

EP23™ Laboratory Quality Control Based on Risk Management. 1st ed., 2011. This document provides guidance based on risk management for laboratories to develop quality control plans tailored to the particular combination of measuring system, laboratory setting, and clinical application of the test.

M02 Performance Standards for Antimicrobial Disk Susceptibility Tests. 13th ed., 2018. This standard covers the current recommended methods for disk susceptibility testing and criteria for quality control testing.

M02QG M02 Disk Diffusion Reading Guide. 1st ed., 2018. The Disk Diffusion Reading Guide provides photographic examples of the proper method for reading disk diffusion susceptibility testing results.


M11 Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria. 9th ed., 2018. This standard provides reference methods for determining minimal inhibitory concentrations of anaerobic bacteria by agar dilution and broth microdilution.

M23 Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters. 6th ed., 2018. This guideline discusses the necessary and recommended data for selecting appropriate breakpoints and quality control ranges for antimicrobial agents.

M39 Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data. 5th ed., 2022. This guideline describes methods for recording and analyzing antimicrobial susceptibility test data, consisting of cumulative and ongoing summaries of susceptibility patterns of clinically significant microorganisms.

M45 Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria. 3rd ed., 2016. 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.

M52 Verification of Commercial Microbial Identification and Antimicrobial Susceptibility Testing Systems. 1st ed., 2015. This guideline includes recommendations for verification of commercial US Food and Drug Administration–cleared microbial identification and antimicrobial susceptibility testing systems by clinical laboratory professionals to fulfill regulatory or quality assurance requirements for the use of these systems for diagnostic testing.

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