This document includes epidemiological cutoff values and quality control tables developed according to criteria provided in the Clinical and Laboratory Standards Institute guideline M57.

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Abstract

Clinical and Laboratory Standards Institute document M59—Epidemiological Cutoff Values for Antifungal Susceptibility Testing includes epidemiological cutoff values (ECVs) and quality control tables developed following the guidelines described in CLSI document M57.¹

These ECVs are valid only when developed following guidelines described in CLSI document M57¹ and when minimal inhibitory concentrations/minimal effective concentrations are generated according to the CLSI reference broth dilution methods described in CLSI documents M27² and M38³.

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Foreword

With the development of standard methodologies for testing susceptibility of fungal species to several antifungal agents, minimal inhibitory concentration (MIC)/minimal effective concentration (MEC) distributions are available to determine epidemiological cutoff values (ECVs) for Candida spp., Cryptococcus spp., and Aspergillus spp. for antifungal agents. The ECVs provided as supplemental information in this document were established using the guidelines published in CLSI document M57. The ECV is the MIC or MEC value that defines the upper limit of the wild-type (WT) distribution and is useful for distinguishing between WT isolates without intrinsic or acquired resistance mechanisms and non-wild-type isolates harboring intrinsic or acquired resistance mechanisms. Users of CLSI documents M27, M60, M38, and M61 should be aware that ECVs do not classify isolates as treatable (susceptible) or nontreatable (resistant) as breakpoints do. In lieu of breakpoints, ECVs alone can be useful to clinicians when deciding whether to treat a patient with a certain agent (see CLSI document M57); however, they do not predict therapeutic response. For ECVs to be clinically useful, the MIC or MEC should be determined by following the broth microdilution procedure for yeasts (see CLSI document M27) or the broth microdilution procedure for filamentous fungi (see CLSI document M38).

Overview of Changes

This document replaces the previous edition of the approved document, M59, 1st ed., published in 2016. Several changes were made in this edition, including:

- **Table 1. Epidemiological Cutoff Values for In Vitro Susceptibility Testing of Candida spp. With No Breakpoints:**
  - Title revised as: “Epidemiological Cutoff Values for In Vitro Susceptibility Testing of Various Candida spp. With No Breakpoints”
  - Added ECVs for posaconazole and fluconazole and various Candida spp.
  - *Deleted* footnote (*) and renumbered all subsequent footnotes
  - Added a footnote (**) regarding the need to validate other susceptibility testing methods against the reference broth microdilution method (see CLSI document M27) before reporting ECVs
  - Added a footnote (§) regarding the species included with ECVs for C. parapsilosis complex
  - Added a footnote (¶) regarding the timeframe for adopting posaconazole ECVs

- **Table 2. Epidemiological Cutoff Values for In Vitro Susceptibility Testing of Cryptococcus spp. With No Breakpoints:**
  - Title revised as: “Epidemiological Cutoff Values for In Vitro Susceptibility Testing of Various Cryptococcus spp. With No Breakpoints”
  - New table with footnotes and references added with ECVs for various Cryptococcus spp.
  - Subsequent tables renumbered

- **Table 3 (formerly Table 2). Epidemiological Cutoff Values for In Vitro Susceptibility Testing of Aspergillus spp. With No Breakpoints:**
  - Title revised as: “Epidemiological Cutoff Values for In Vitro Susceptibility Testing of Various Aspergillus spp. With No Breakpoints”
Deleted footnote (*) and renumbered all subsequent footnotes

Added a footnote (‡) regarding the need to validate other susceptibility testing methods against the reference broth microdilution method (see CLSI document M38\(^\text{3}\)) before reporting ECVs

Table 4 (formerly Table 3). Epidemiological Cutoff Values for \textit{In Vitro} Susceptibility Testing of \textit{Candida} spp. With Breakpoints:

- Added ECVs for fluconazole and voriconazole for various \textit{Candida} spp.
- Revised footnote (*) to remove redundant information
- Added a footnote (§) regarding the need to validate other susceptibility testing methods against the reference broth microdilution method (see CLSI document M27\(^\text{2}\)) before reporting ECVs
- Added a footnote (¶) regarding the timeframe for adopting posaconazole and voriconazole ECVs
- Added a footnote (#) regarding the species included with ECVs for \textit{C. parapsilosis} complex

Glossary. Antifungal Agent Abbreviation(s), Route(s) of Administration, and Drug Class:

- Added footnote (‡) regarding the availability of IV itraconazole in the United States

Request for antifungal susceptibility testing data from fungal pathogens needed for the development of ECVs to be included in future editions of M59:

The Working Group on Antifungal Epidemiological Cutoff Values is requesting submission of raw antifungal susceptibility testing data for yeasts and filamentous fungi using the protocols provided in the most current editions of CLSI documents M27, \textit{Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts}, and M38, \textit{Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi}. This request is only for reference broth microdilution and should not include data generated using commercially available panels. Because the data will be combined with data from other laboratories, even a small amount of data is useful, especially for the more infrequently identified species. All species should be identified using a molecular assay or matrix-assisted laser desorption/ionization time-of-flight mass spectrometry.

A standardized worksheet for data submission is available on the CLSI website at http://clsi.org/standards/micro/sub-antifungal/. This worksheet can also be requested by contacting CLSI at standard@clsi.org. Completed worksheets can be submitted to CLSI directly at standard@clsi.org.

NOTE: The content of this document is supported by the CLSI consensus process and does not necessarily reflect the views of any single individual or organization.

Key Words

Epidemiological cutoff value, minimal effective concentration, minimal inhibitory concentration, non-wild-type, wild-type
Table 1. Epidemiologic Cutoff Values for *In Vitro* Susceptibility Testing of Various *Candida* spp. With No Breakpoints

<table>
<thead>
<tr>
<th>Antifungal Agent</th>
<th>Species</th>
<th>ECV, µg/mL&lt;sup&gt;*+†‡&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td><em>C. albicans</em></td>
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</tr>
<tr>
<td></td>
<td><em>C. glabrata</em></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td><em>C. krusei</em></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td><em>C. parapsilosis</em>&lt;sup&gt;§&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td><em>C. tropicalis</em></td>
<td>2</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td><em>C. dubliniensis</em></td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td><em>C. lusitaniae</em></td>
<td>1</td>
</tr>
<tr>
<td>Fluconazole&lt;sup&gt;¶&lt;/sup&gt;</td>
<td><em>C. dubliniensis</em></td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td><em>C. guilliermondii</em></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td><em>C. lusitaniae</em></td>
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<td>Itraconazole</td>
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<tr>
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<tr>
<td></td>
<td><em>C. lusitaniae</em></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><em>C. tropicalis</em></td>
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</tr>
<tr>
<td>Micafungin</td>
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<tr>
<td></td>
<td><em>C. lusitaniae</em></td>
<td>0.5</td>
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<tr>
<td>Posaconazole&lt;sup&gt;#&lt;/sup&gt;</td>
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<td></td>
<td><em>C. glabrata</em></td>
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<tr>
<td></td>
<td><em>C. guilliermondii</em></td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td><em>C. krusei</em></td>
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</tr>
<tr>
<td></td>
<td><em>C. lusitaniae</em></td>
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<td><em>C. parapsilosis</em>&lt;sup&gt;§&lt;/sup&gt;</td>
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<td><em>C. tropicalis</em></td>
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</tr>
<tr>
<td>Voriconazole&lt;sup&gt;¶&lt;/sup&gt;</td>
<td><em>C. glabrata</em></td>
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</tbody>
</table>

<sup>*The ECVs in M59 were established using broth microdilution as outlined in CLSI document M27. If another methodology is used for susceptibility testing, this method must be validated against broth microdilution before using the ECVs, just as validation of other methods must be performed before using breakpoints established using broth microdilution.</sup>

<sup>† ECVs capture ≥97.5% of the statistically modeled population. ECVs may overlook potentially resistant isolates (NWT).</sup>

<sup>‡ If the 24-hour growth control shows insufficient growth, incubate for an additional 24 hours.</sup>

<sup>§ The ECV established for posaconazole and amphotericin B are for the *C. parapsilosis* species complex, which may include isolates of *C. orthopsilosis* and *C. metapsilosis.*</sup>

<sup>¶ Fluconazole, posaconazole, and voriconazole ECVs were adopted by the Subcommittee on Antifungal Susceptibility Tests during an electronic vote held in February 2017.</sup>

Abbreviations: ECV, epidemiological cutoff value; NWT, non-wild-type.

**NOTE:** Information in bold is new or modified since the previous edition.
Table 1. (Continued)

References for Table 1


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
- Personnel
- Process Management
- Nonconforming Event Management
- CUSTOMER FOCUS
- Purchasing and Inventory
- Equipment
- Documents and Records
- Information Management
- Assessments
- Continual Improvement

M59 covers 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.

<table>
<thead>
<tr>
<th>Organization</th>
<th>Customer Focus</th>
<th>Facilities and Safety</th>
<th>Personnel</th>
<th>Purchasing and Inventory</th>
<th>Equipment</th>
<th>Process Management</th>
<th>Documents and Records</th>
<th>Information Management</th>
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</table>

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 their services, namely quality laboratory information.

M59 covers the medical laboratory path of workflow processes indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section.

<table>
<thead>
<tr>
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<th>Examination</th>
<th>Postexamination</th>
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<tr>
<td>Examination ordering</td>
<td>Sample collection</td>
<td>Sample transport</td>
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<tr>
<td>Sample receipt and processing</td>
<td>Examination</td>
<td>Result review and follow-up</td>
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Related CLSI Reference Materials*

**M27**  

**M38**  
Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi. 3rd ed., 2017. This standard includes antifungal agent selection, preparation of antifungal stock solutions and dilutions for testing, test procedure implementation and interpretation, and quality control requirements for susceptibility testing of filamentous fungi (moulds) that cause invasive and cutaneous fungal infections.

**M57**  
Principles and Procedures for the Development of Epidemiological Cutoff Values for Antifungal Susceptibility Testing. 1st ed., 2016. This guideline includes the criteria for developing and using epidemiological cutoff values for guiding clinical decisions when testing fungal species and antifungal agent combinations for which there are no breakpoints.

**M60**  
Performance Standards for Antifungal Susceptibility Testing of Yeasts. 1st ed., 2017. This document includes updated minimal inhibitory concentration, zone diameter, and quality control tables for the Clinical and Laboratory Standards Institute antifungal susceptibility testing documents M27 and M44.

**M61**  

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