CLINICAL AND LABORATORY STANDARDS INSTITUTE®

2nd Edition

M59

Epidemiological Cutoff Values for Antifungal Susceptibility Testing

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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Epidemiological Cutoff Values for Antifungal Susceptibility Testing

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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 M57[1] and when minimal inhibitory concentrations/minimal effective concentrations are generated according to the CLSI reference broth dilution methods described in CLSI documents M27[2] and M38.[3]

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Contents

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.[1] 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,[2] M60,[4] M38,[3] and M61[5] 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[1]); 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[2]) or the broth microdilution procedure for filamentous fungi (see CLSI document M38[3]).

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[2]) 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[3]) before reporting ECVs

- **Table 4 (formerly Table 3). Epidemiological Cutoff Values for *In Vitro* Susceptibility Testing of *Candida* spp. With Breakpoints:**
  - Added ECVs for fluconazole and voriconazole for various *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[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 *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, *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts*, and M38, *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

Terminology

A Note on Terminology

CLSI, as a global leader in standardization, is firmly committed to achieving global harmonization whenever possible. Harmonization is a process of recognizing, understanding, and explaining differences while taking steps to achieve worldwide uniformity. CLSI recognizes that medical conventions in the global metrological community have evolved differently in different countries and regions and that legally required use of terms, regional usage, and different consensus timelines are all important considerations in the harmonization process. CLSI recognizes its important role in these efforts, and its consensus process focuses on harmonization of terms to facilitate the global application of standards and guidelines.

NOTE: Mandates are generally reserved for CLSI standards but are occasionally allowed in CLSI supplements. In CLSI supplements, use of the term "must" is either 1) based on a requirement or 2) indicative of a necessary step to ensure patient safety or proper fulfillment of a procedure. The working group evaluated use of the term "must" and deemed it appropriate.

Abbreviations and Acronyms

DNA	deoxyribonucleic acid
ECV	epidemiological cutoff value
MEC	minimal effective concentration
MIC	minimal inhibitory concentration
NWT	non-wild-type
WT	wild-type

Table 1. Epidemiological Cutoff Values for *In Vitro* Susceptibility Testing of Various *Candida* spp. With No Breakpoints[1-6]

Antifungal Agent	Species	ECV, µg/mL[*,†,‡]
Amphotericin B	*C. albicans*	2
	C. glabrata	2
	C. krusei	2
	C. parapsilosis[§]	2
	C. tropicalis	2
Anidulafungin	*C. dubliniensis*	0.12
	C. lusitaniae	1
Fluconazole[¶]	***C. dubliniensis***	**0.5**
	C. guilliermondii	**8**
	C. lusitaniae	**1**
Itraconazole	*C. glabrata*	4
	C. krusei	1
	C. lusitaniae	1
	C. tropicalis	0.5
Micafungin	*C. dubliniensis*	0.12
	C. lusitaniae	0.5
Posaconazole[#]	***C. albicans***	**0.06**
	C. glabrata	**1**
	C. guilliermondii	**0.5**
	C. krusei	**0.5**
	C. lusitaniae	**0.06**
	C. parapsilosis[§]	**0.25**
	C. tropicalis	**0.12**
Voriconazole[¶]	***C. glabrata***	**0.25**

[*] The ECVs in M59 were established using broth microdilution as outlined in CLSI document M27.[1] 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.

[†] ECVs capture ≥97.5% of the statistically modeled population. ECVs may overlook potentially resistant isolates (NWT).

[‡] If the 24-hour growth control shows insufficient growth, incubate for an additional 24 hours.

[§] 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.*

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

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

NOTE: Information in bold is new or modified since the previous edition.