CLINICAL AND LABORATORY STANDARDS INSTITUTE®

1st Edition

M57

Principles and Procedures for the Development of Epidemiological Cutoff Values for Antifungal Susceptibility Testing

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.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

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Principles and Procedures for the Development of Epidemiological Cutoff Values for Antifungal Susceptibility Testing

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Abstract

Clinical and Laboratory Standards Institute guideline M57—*Principles and Procedures for the Development of Epidemiological Cutoff Values for Antifungal Susceptibility Testing* presents criteria for determining epidemiological cutoff values (ECVs) for yeasts and filamentous fungi. Data collection, ECV development, and indications for their use are discussed. This guideline provides an analysis of the criteria that determine whether an isolate has a wild-type or non-wild-type minimal inhibitory concentration/minimal effective concentration value and discusses how ECVs can be used for fungal species and antifungal agent combinations for which there are no breakpoints.

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Foreword

Breakpoints are the most reliable tool for predicting whether a given antimicrobial agent will be active against an infecting isolate. Breakpoints are developed using pharmacokinetic/pharmacodynamic analysis, clinical trial outcome data, standard distributions of minimal inhibitory concentration (MIC) values as obtained by a reference method, and postmarketing susceptibility data. Quite often, for many fungal species and antifungal agent combinations, the only available data are the distribution of MIC/minimal effective concentration (MEC) values. MIC/MEC distributions are used to determine the epidemiological cutoff value (ECV) that defines the upper limit of the wild-type (WT) distribution. Although MIC/MEC distributions are not sufficient for breakpoint development, these cutoff values can be useful for distinguishing between WT isolates (ie, those having no acquired resistance mechanisms) and non-wild-type (NWT) isolates (ie, those having presumptive acquired resistance mechanisms). In this regard, ECVs distinguish between organisms with and without phenotypically expressed resistance mechanisms for a fungal species and an antifungal agent in a defined test system. Moreover, within a species, it is the highest MIC/MEC of an organism lacking phenotypically expressed resistance. ECVs can be considered in the absence of formal breakpoints.

As a result, the Subcommittee on Antifungal Susceptibility Tests determined a document was needed that:

- Defines how to develop an ECV
- Distinguishes between ECVs and breakpoints
- Lists, in a supplement, ECVs for available fungal species and antifungal agent combinations
- Provides guidance on the use of ECVs for the interpretation of MIC/MEC values for fungal species and antifungal agent combinations for which there are no breakpoints
- Provides epidemiologists with ECVs that are useful for performing surveillance testing locally, regionally, or globally to evaluate any changes in MIC patterns over time

This guideline defines the protocol for ECV development. It provides assistance to clinicians and laboratory directors for fungal species and antifungal agent combinations for which there are no breakpoints or the data needed to develop them. Additionally, M57 provides information for developing and interpreting ECVs so clinical guidance is available on the potential response to therapy of a fungal species and antifungal agent combination when only MIC/MEC values are available. This information can assist clinicians and laboratory directors in making an informed decision when an NWT organism has been isolated that may not respond to an antifungal agent as predicted from the species identification alone.

NOTE: The findings and conclusions in this guideline are those of the authors and are supported by the CLSI consensus process, and do not necessarily reflect the views of the organizations the authors represent.

Request for antifungal susceptibility testing data from fungal pathogens needed for the development of ECVs to be included in future editions of M59[1]:

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,[2] *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts* and M38,[3] *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.

Key Words

Acquired resistance, epidemiological cutoff value, minimal effective concentration, minimal inhibitory concentration, non-wild-type, wild-type

Principles and Procedures for the Development of Epidemiological Cutoff Values for Antifungal Susceptibility Testing

Chapter 1: Introduction

This chapter includes:

- Guideline scope and applicable exclusions
- Background information pertinent to the guideline content
- "Note on Terminology" that highlights particular use and/or variation in use of terms and/or definitions
- Terms and definitions used in the guideline
- Abbreviations and acronyms used in the guideline

1.1 Scope

This guideline specifies requirements and recommendations for developing and using epidemiological cutoff values (ECVs) in antifungal susceptibility testing.

The guideline's intended users are developers of ECVs for antifungal agents, laboratory directors who provide assistance to clinicians on interpreting antifungal minimal inhibitory concentration (MIC)/minimal effective concentration (MEC) values, and clinicians who interpret MIC/MEC values for the application of proper antifungal therapy and surveillance of emerging resistance.

This guideline:

- Is not intended to provide an equivalent to breakpoint development
- Does not discuss breakpoint development
- Is not intended to provide a replacement for breakpoints

1.2 Terminology

1.2.1 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.

In many countries, epidemiological cutoff values (ECVs) are often referred to as epidemiological cutoffs or "ECOFFs." The terms are equivalent. In order to be consistent with other CLSI documents, including CLSI document M100S,[4] the abbreviation "ECV" is used throughout this guideline.

NOTE: Mandates are generally reserved for CLSI standards, but are occasionally allowed in CLSI guidelines. In CLSI guidelines, 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.

1.2.2 Definitions

dataset – a set of minimal inhibitory or minimal effective concentration data generated in a single laboratory.

epidemiological cutoff value (ECV) – the minimal inhibitory concentration (MIC)/minimal effective concentration value that separates fungal populations into those with and without acquired and/or mutational resistance based on their phenotypes (MICs); **NOTE:** Often referred to as the "epidemiological cutoff" or "ECOFF."

minimal effective concentration (MEC) – the lowest concentration of an antifungal agent that leads to the growth of small, rounded, compact hyphal forms as compared to the hyphal growth seen in the growth control well; **NOTE:** This terminology is currently only used with respect to testing of filamentous fungi against echinocandin antifungal agents.

minimal inhibitory concentration (MIC) – the lowest concentration of an antimicrobial agent that prevents visible growth of a microorganism in an agar or broth dilution susceptibility test.

non-wild-type (NWT) – describes isolates with presumed or known mechanisms of acquired resistance and reduced susceptibility for the antifungal agent being evaluated.

pooled dataset – minimal inhibitory concentration/minimal effective concentration susceptibility values collected according to reference method criteria and combined from multiple laboratories.

wild-type (WT) – describes isolates with no mechanisms of acquired resistance or reduced susceptibility for the antifungal agent being evaluated.

wild-type distribution – the distribution of minimal inhibitory concentration/minimal effective concentration values of a given species with a given antifungal agent when there are no known mutational resistance mechanisms present in any species representatives.

1.2.3 Abbreviations and Acronyms

ECV	epidemiological cutoff value
MEC	minimal effective concentration
MIC	minimal inhibitory concentration
NWT	non-wild-type
QC	quality control
WT	wild-type
WT-MIC/MEC	wild-type-minimal inhibitory concentration/minimal effective concentration

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

M57 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 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
						X M27 M27S M38 M59					

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.

M57 does not cover any of the medical laboratory path of workflow steps. For a description of the documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

Preexamination				**Examination**			**Postexamination**	
Examination ordering	Sample collection	Sample transport	Sample receipt and processing	Examination	Results review and follow-up	Interpretation	Results reporting and archiving	Sample management
				M27 M27S M38	M27 M27S M38 M59 M100S	M27 M27S M38 M59 M100S	M27 M27S M38 M59 M100S	M27 M27S M38

Related CLSI Reference Materials*

M27 **Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts. 3rd ed., 2008.** This document addresses the selection and preparation of antifungal agents; implementation and interpretation of test procedures; and quality control requirements for susceptibility testing of yeasts that cause invasive fungal infections.

M27S **Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts. 4th ed., 2012.** This document provides updated tables for the CLSI antimicrobial susceptibility testing standard M27-A3.

M38 **Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi. 2nd ed., 2008.** This document addresses the selection of antifungal agents, preparation of antifungal stock solutions and dilutions for testing implementation and interpretation of test procedures, and quality control requirements for susceptibility testing of filamentous fungi (moulds) that cause invasive and cutaneous fungal infections.

M59 **Epidemiological Cutoff Values for Antifungal Susceptibility Testing. 1st ed., 2016.** This document includes the epidemiological cutoff value and quality control tables developed according to criteria provided in the Clinical and Laboratory Standards Institute guideline M57.

M100S **Performance Standards for Antimicrobial Susceptibility Testing. 26th ed., 2016.** This document provides updated tables for the Clinical and Laboratory Standards Institute antimicrobial susceptibility testing standards M02-A12, M07-A10, and M11-A8.

* 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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