European Committee on Antimicrobial Susceptibility Testing

Antifungal Agents

Breakpoint tables for interpretation of MICs

Version 9.0, valid from 2018-02-12

Content	Page
Notes	1
Changes	2
Candida spp.	3
Aspergillus spp.	4

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Notes

1. The EUCAST tables of clinical breakpoints for antifungal agents contain clinical MIC breakpoints determined over the period 2007-2018.

2. Numbered footnotes relating to MIC breakpoints are listed in a column on the right of the spreadsheet rather than below the table.

3. Highlighted names of antifungal agents link to EUCAST rationale documents. Highlighted MIC breakpoints link to EUCAST MIC distributions.

4. One version of the document is released as an unprotected Excel file to enable users to alter the list of agents to suit the range of agents tested locally and to present breakpoints in the format used locally. The content of single cells cannot be changed.
Hide lines by right-clicking on the line number and choosing "hide".
Hide columns by right-clicking on the column letter and choosing "hide".
If you wish to add the intermediate columns for MICs and/or zone diameters right-click on the column letter and choose "insert". The intermediate values are inferred from the

5. In order to simplify the EUCAST tables, the intermediate category is not listed. It is readily interpreted as the values between the S and the R breakpoint. For example, for MIC breakpoints listed as S ≤ 1 mg/L and R > 8 mg/L, the intermediate category is 2-8 (technically >1-8) mg/L.

"-" indicates that susceptibility testing is not recommended as the species is a poor target for therapy with the drug. Isolates may be reported as R without prior testing.

"IE" indicates that there is insufficient evidence that the species in question is a good target for therapy with the drug. An MIC with a comment but without an accompanying S, I or R categorisation may be reported.

NA = Not Applicable

IP = In Preparation

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Table	**Changes (cells containing a change, a deletion or an addition) from v. 8.1 are marked yellow.** **New or changed comments are underlined. Removed comments are shown in strikethrough font style.**
***Candida* spp.**	• New breakpoints for *C. dubliniensis* . • Voriconazole breakpoints revised for *C. albicans* , *C. parapsilosis* and *C. tropicalis* . • Comment 5 revised. • Comment 6 new.

Candida spp.

EUCAST Antifungal Clinical Breakpoint Table v. 9.0 valid from 2018-02-12

MIC method (EUCAST standardised broth microdilution method)
Medium: RPMI1640-2% glucose, MOPS buffer
Inoculum: Final $0.5x10^5$ – $2.5x10^5$ cfu/mL
Incubation: 18-24h
Reading: Spectrophotometric, complete (>90%) inhibition for amphotericin B but 50% growth inhibition for other compounds
Quality control: *C. parapsilosis* ATCC 22019 or *C. krusei* ATCC 6258

Antifungal agent	MIC breakpoint (mg/L)															
	C. albicans		*C. dubliniensis*		*C. glabrata*		*C. krusei*		*C. parapsilosis*		*C. tropicalis*		*C. guilliermondii*		Non-species related breakpoints[1]	
	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >
Amphotericin B	1	1	IE	IE	1	1	1	1	1	1	1	1	IE	IE	IE	IE
Anidulafungin	0.032	0.032	IE	IE	0.064	0.064	0.064	0.064	0.002	4	0.064	0.064	IE[2]	IE[2]	IE	IE
Caspofungin	Note[3]	Note[3]	IE	IE	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	IE[2]	IE[2]	IE	IE
Fluconazole	2	4	IE	IE	0.002	32	-	-	2	4	2	4	IE[2]	IE[2]	2	4
Isavuconazole	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE
Itraconazole	0.064	0.064	0.064	0.064	IE[2]	IE[2]	IE[2]	IE[2]	0.125	0.125	0.125	0.125	IE[2]	IE[2]	IE	IE
Micafungin	0.016	0.016	IE	IE	0.032	0.032	IE[4]	IE[4]	0.002	2	IE[4]	IE[4]	IE[4]	IE[4]	IE	IE
Posaconazole	0.064	0.064	0.064	0.064	IE[2]	IE[2]	IE[2]	IE[2]	0.064	0.064	0.064	0.064	IE[2]	IE[2]	IE	IE
Voriconazole[6]	0.064[5]	0.25[5]	0.064	0.25	IE	IE	IE	IE	0.125[5]	0.25[5]	0.125[5]	0.25[5]	IE[2]	IE[2]	IE	IE

Notes

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.

2. The ECOFFs for these species are in general higher than for *C. albicans.*

3. Isolates that are susceptible to anidulafungin as well as micafungin should be considered susceptible to caspofungin, until caspofungin breakpoints have been established. Similarly, *C. parapsilosis* isolates intermediate to anidulafungin and micafungin can be regarded intermediate to caspofungin. EUCAST breakpoints have not yet been established for caspofungin, due to significant inter-laboratory variation in MIC ranges for caspofungin.

4. MICs for *C. tropicalis* are 1-2 two-fold dilution steps higher than for *C. albicans* and *C. glabrata*. In the clinical study successful outcome was numerically slightly lower for *C. tropicalis* than for *C. albicans* at both dosages (100 and 150 mg daily). However, the difference was not significant and whether it translates into a relevant clinical difference is unknown. MICs for *C. krusei* are approximately three two-fold dilution steps higher than those for *C. albicans* and, similarly, those for *C. guilliermondii* are approximately eight two-fold dilutions higher. In addition, only a small number of cases involved these species in the clinical trials. This means there is insufficient evidence to indicate whether the wild-type population of these pathogens can be considered susceptible to micafungin.

5. Strains with MIC values above the S/I breakpoint are rare or not yet reported. The identification and antifungal susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant. A clinical response of 76% was achieved in infections caused by the species listed below when MICs were lower than or equal to the epidemiological cut-offs. Therefore, wild type populations of *C. albicans, C. dubliniensis, C. parapsilosis* and *C. tropicalis* are considered susceptible.

6. For *Candida* the intermediate category is introduced to acknowledge that the increased exposure obtained by iv dosing is sufficient (potentially confirmed by TDM).
There is not enough information available for the response to voriconazole of infections caused by Candida isolates with higher MICs.

Aspergillus spp.

EUCAST Antifungal Clinical Breakpoint Table v. 9.0 valid from 2018-02-12

MIC method (EUCAST standardised broth microdilution method)
Medium: RPMI1640-2% glucose, MOPS as buffer
Inoculum: Final 1x10(5) – 2.5x10(5) cfu/mL
Incubation: 48h
Reading: Visual, complete inhibition for amphotericin B and azoles (MIC), aberrant growth endpoint for echinocandins (MEC).
Quality control: *A. fumigatus* ATCC 204305, *A. flavus* ATCC 204304, *A. fumigatus* F 6919, *A. flavus* CM 1813, *C. parapsilosis* ATCC 22019 (read after 18-24 h) or *C. krusei* ATCC 6258 (read after 18-24 h).

Antifungal agent	MIC breakpoint (mg/L)											
	A. flavus		*A. fumigatus*		*A. nidulans*		*A. niger*		*A. terreus*		Non-species related breakpoints[1]	
	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >
Amphotericin B	IE[2]	IE[2]	1	2	Note[3]	Note[3]	1	2	-	-	IE	IE
Anidulafungin	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE
Caspofungin	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE
Fluconazole	-	-	-	-	-	-	-	-	-	-	-	-
Isavuconazole	IE[2]	IE[2]	1	1	0.25	0.25	IE[2]	IE[2]	1	1	IE	IE
Itraconazole[4]	1	2	1	2	1	2	IE[2,5]	IE[2,5]	1	2	IE[5]	IE[5]
Micafungin	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE
Posaconazole[4]	IE[2]	IE[2]	0.125[6]	0.25[6]	IE[2]	IE[2]	IE[2]	IE[2]	0.125[6]	0.25[6]	IE	IE
Voriconazole[4]	IE[2]	IE[2]	1	2	IE	IE	IE[2]	IE[2]	IE[2]	IE[2]	IE	IE

Notes

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.

2. The ECOFFs for these species are in general one step higher than for *A. fumigatus* .

3. There are too few MIC data to establish ECOFFs and hence to suggest any breakpoints.

4. Monitoring of azole trough concentrations in patients treated for fungal infection is recommended.

5. The MIC values for isolates of *A. niger* and *A. versicolor* are in general higher than those for *A. fumigatus* . Whether this translates into a poorer clinical response is unknown.

6. Provided adequate drug exposure has been confirmed using therapeutic drug monitoring (TDM). There remains some uncertainty regarding cut-off values for posaconazole concentrations that separate patients with a high probability of clinical success from those with a low probability of clinical success. In some circumstances (e.g. patients with persistent and profound neutropenia, large lesions, or those with other features associated with a poor clinical outcome) a relatively high trough concentration should be sought. Preclinical and clinical data suggest this value should be >1 mg/L at steady state. For other patient groups a lower trough concentration may be acceptable. For prophylaxis a target concentration of >0.7 mg/L has been suggested.