

EUCAST Technical note on Amphotericin B

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Abstract

The European Committee on Antimicrobial Susceptibility Testing-Subcommittee on Antifungal Susceptibility Testing (EUCAST-AFST) has determined breakpoints for amphotericin B for *Candida* spp. This Technical Note is based on the EUCAST amphotericin B rationale document (available on the EUCAST website: <http://www.eucast.org>). Species-specific breakpoints for *C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis* and *C. tropicalis* are S: MIC \leq 1 mg/L, R: MIC > 1 mg/L. There are insufficient data to set breakpoints for other species. The breakpoints are based upon pharmacokinetic data, epidemiological cut-off values and clinical experience. Breakpoints will be reviewed regularly.

Keywords: Amphotericin B, breakpoints, EUCAST technical note, susceptibility testing

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Introduction

Amphotericin B is a polyene antifungal agent that is active against yeasts and moulds. In Europe, it is available in four different parental formulations, including amphotericin B deoxycholate and three lipid formulations. The active compound is identical but the pharmacokinetics and toxicity profiles vary from formulation to formulation. The licensed indications for each formulation are as follows: amphotericin B deoxycholate (AMB-DC), serious infections due to amphotericin B-susceptible fungi; amphotericin B lipid complex (ABLC), first-line treatment of systemic *Candida* infections; amphotericin B colloidal dispersion (ABCD), serious infections due to amphotericin-susceptible fungi, where amphotericin B deoxycholate is contraindicated or has failed; liposomal amphotericin B (L-amphotericin B), treatment of invasive fungal infections due to amphotericin B-susceptible fungi, and treatment of suspected fungal infection in neutropenic patients with persistent fever despite antibacterial treatment for 5–7 days.

The European Committee on Antimicrobial Susceptibility Testing-Subcommittee on Antifungal Susceptibility Testing (EUCAST-AFST) has determined breakpoints of amphotericin B for *Candida* spp. This Technical Note is based on the EUCAST amphotericin B rationale document (available on the EUCAST website: <http://www.eucast.org>). The rationale document includes more detail and published references related to the selection of EUCAST-AFST breakpoints (<http://www.srga.org/eucastwt/MICTAB/EUCAST%20clinical%20MIC%20breakpoints%20-%20antimicrobials%20for%20Candida%20infections.htm>).

The breakpoints are based upon the following dosages administered intravenously: amphotericin B, 0.6–1 mg/kg/day; liposomal amphotericin, 3 mg/kg/day; amphotericin B lipid complex (ABLC) and amphotericin B colloidal dispersion (ABCD), 3–5 mg/kg/day. Breakpoints were established using MIC values from multiple laboratories. Wild-type isolates of each of the five common species (*C. albicans*,

TABLE 1. EUCAST MIC breakpoints for amphotericin B

| Species | Species-related breakpoints (mg/L) | |
|------------------------|------------------------------------|-------|
| <i>C. albicans</i> | S ≤ 1 | R > 1 |
| <i>C. glabrata</i> | S ≤ 1 | R > 1 |
| <i>C. parapsilosis</i> | S ≤ 1 | R > 1 |
| <i>C. tropicalis</i> | S ≤ 1 | R > 1 |
| <i>C. krusei</i> | S ≤ 1 | R > 1 |

The clinical response of infection due to *Candida* species as a whole was similar to that of infections caused by *C. albicans*, *C. parapsilosis* and *C. tropicalis*. However, there were only 12 cases available for analysis, which is too few to allow any recommendation to be made. Therefore, there is insufficient evidence to set clinical breakpoints for other species of *Candida*.

C. glabrata, *C. krusei*, *C. parapsilosis* and *C. tropicalis*) exhibit MICs ≤ 1 mg/L.

The EUCAST breakpoints (Table 1) are based on pharmacokinetic [1–7] and microbiological data and clinical experience [8–15]. For most studies clinical outcome data were not specified for the individual *Candida* species. Combining the studies that provided such data [8,12,14], failure rates were as follows. For L-amphotericin B the overall failure rate was 9% (16/174) and for individual species: *C. albicans* 11% (7/73), *C. tropicalis* 4% (2/45), *C. parapsilosis* 10% (3/29), *C. glabrata* 20% (3/15) and *C. krusei* 20% (1/5). For amphotericin B deoxycholate the overall failure rate was 38% (44/115) and for individual species: *C. albicans* 8% and *C. krusei* 3%. These data indicate that the five commonest species are good targets for all amphotericin B formulations. There are too few data to enable any definitive recommendation to be made for species other than those addressed in this document. None of the clinical studies estimated MICs using EUCAST methodology so a direct correlation between *in vitro* MICs and clinical outcome is currently not possible. Furthermore, there is no clinical experience with isolates with acquired resistance mechanisms; hence the breakpoints are based upon epidemiological cut-off values.

Transparency Declaration

The authors do not have any potential conflicts of interests related particularly to this paper. Otherwise, MCA has received research grants and acted as speaker for Astellas, Gilead, MSD and Pfizer, and been a consultant for Gilead, MSD and Pcovery. JLRT has received grant support from Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme, Pfizer, Schering Plough, Soria Melguizo SA, the European Union, the Spanish Agency for International Cooperation, the Spanish Ministry of Culture and Education, The Spanish Health Research Fund, The Instituto de Salud Carlos III, The Ramon Areces Foundation and The Mutua Madrileña Foun-

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