EUCAST Technical Note on Candida and micafungin, anidulafungin and fluconazole

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Summary

The European Committee on Antimicrobial Susceptibility Testing Subcommittee on Antifungal Susceptibility Testing has determined breakpoints for micafungin and revised breakpoints for anidulafungin and fluconazole for Candida spp. This Technical Note is based on the corresponding rationale documents (http://www.eucast.org). The micafungin breakpoints are based on PK data, animal PK/PD data, microbiological data and clinical experience. The anidulafungin breakpoints for C. parapsilosis and fluconazole breakpoints for C. glabrata have been modified to species-specific values that categorise the wild-type as intermediate to accommodate use of these compounds in some clinical situations.

Key words: EUCAST breakpoints, Candida, susceptibility testing, MIC, microdilution.

The EUCAST-AFST (European Committee on Antimicrobial Susceptibility Testing Subcommittee on AntifungalSusceptibility Testing) has determined breakpoints for micafungin and Candida and has revised breakpoints for anidulafungin and fluconazole for Candida spp. This Technical Note is based on the EUCAST micafungin, anidulafungin and fluconazole rationale documents (available on the EUCAST website: http://www.eucast.org). The rationale documents include more detail and published references related to the selection of EUCAST-AFST breakpoints.

Micafungin is an echinocandin antifungal agent active against the majority of Candida species. It is licensed for treatment of invasive candidiasis, and prophylaxis of Candida infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells μl⁻¹) for 10 or more days (adults and children, including neonates). Micafungin is also licensed for treatment of oesophageal candidiasis in adult patients for whom intravenous therapy is appropriate. The epidemiological cut-off values (ECOFFs, Table 1) were established using minimum inhibitory concentration (MIC) distributions from many sources. Clinical studies have suggested that micafungin is efficacious in treatment of oesophageal candidiasis in adults and candidaemia in adults and children. For oesophageal candidiasis, micafungin and fluconazole were equally efficacious in a study of 523 patients, the majority of whom had C. albicans infection.1 Success rates for treatment of candidaemia with micafungin have been similar to those for liposomal amphotericin B and caspofungin and across the various Candida species.2–4 Breakthrough infections in patients with
invasive candidiasis receiving micafungin have been reported. In one study summarising 12 cases, half of these involved *C. parapsilosis*, which harbours a naturally occurring alteration in the FKS1 target gene, and the other half involved *C. glabrata*, *C. tropicalis*, *C. albicans*, *C. dubliniensis* or an unspecified yeast (6/9 available isolates with a hot spot target gene mutation). The main conclusion was that *C. parapsilosis*, which harbours a naturally occurring alteration in the target gene, was over-represented in breakthrough cases, but these cases were not associated with acquired resistance. The majority of other cases involved isolates with acquired resistance and hot spot Fksp alterations. Pharmacodynamic data and preclinical to clinical bridging studies for *C. albicans* and *C. glabrata* suggest that wild-type isolates are covered by standard dosing with success rate estimates of 89.2% and 96.3% respectively. A notable drop in predicted response rates is predicted for isolates with elevated MICs.

### Table 1

<table>
<thead>
<tr>
<th>Species</th>
<th>Micafungin</th>
<th>Anidulafungin</th>
<th>Fluconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ECOFF</td>
<td>S≤ 2</td>
<td>R&gt; 4</td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>0.016</td>
<td>0.016</td>
<td>0.016</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>0.25</td>
<td>IE3</td>
<td>IE3</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>2</td>
<td>0.002</td>
<td>2</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>0.06</td>
<td>IE3</td>
<td>IE3</td>
</tr>
</tbody>
</table>

1. There is insufficient evidence (IE) to set non-species-related breakpoints.
2. 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 ≤ 2 and R > 4, the intermediate category is 4 (technically >2–4). For MIC breakpoints listed as S ≤ 0.002 and R > 4, the intermediate category includes the entire wild-type population, and for breakpoints listed as S ≤ 0.016 and R > 0.016, there is no intermediate category. There is insufficient clinical evidence to set breakpoints for other species than those listed.
3. The MIC values are in general higher than those for *C. albicans*. Whether this translates into a poorer clinical response remains unknown. There is IE to set breakpoints for these species.
4. “–” 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.

EUCAST breakpoints were established for anidulafungin and *Candida* species in 2012. At that time a conservative approach was adopted, categorising *C. parapsilosis* as a poor target for anidulafungin. *C. parapsilosis* harbours an intrinsic alteration in the target gene, which is the likely mechanism for the higher MICs than with other *Candida* species. In a clinical trial the outcome for anidulafungin with *C. parapsilosis* was not statistically different from other species (23 patients: 64% success for anidulafungin vs. 83% for fluconazole, *P* = 0.37). The PK/PD target is lower for *C. parapsilosis* than for other *Candida* species. This may be due to *C. parapsilosis* being less virulent than *C. albicans* and *C. glabrata*. Echinocandins are generally not recommended as first-line agents for serious infections caused by *C. parapsilosis*. However, echinocandins can be used if the patient is clinically stable and/or has responded to initial echinocandin therapy, and/or if the use of other agents is not appropriate. Therefore, the clinical breakpoints have been revised to categorise the entire wild-type population of *C. parapsilosis* as intermediate (Table 1).

EUCAST breakpoints for fluconazole and *Candida* species were established in 2007. A significant number of infections involve *C. glabrata*, which exhibits fluconazole MICs of 2–32 mg l⁻¹ when without resistance mechanisms. Any reasonable susceptibility breakpoint based on PK data would divide wild-type *C. glabrata*, obviating reproducible susceptibility testing. Therefore, EUCAST-AFST at that time refrained from
giving *C. glabrata* breakpoints for fluconazole. As there are, however, few agents suitable for the treatment of urinary tract infections and mucosal infections managed in the primary health care setting, fluconazole may be a suitable choice provided the infecting strain has no acquired resistance mechanisms. In such cases where fluconazole is the only available antifungal agent for treating *C. glabrata* infections, the use of fluconazole at higher dosage may be required. Therefore, the clinical breakpoints have been revised to categorise the entire wild-type population of *C. glabrata* as intermediate (Table 1), thereby facilitating discrimination between wild-type and isolates with elevated MICs and acquired resistance mechanisms.

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**Disclosures**

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