EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Comments on revised anidulafungin breakpoints for *Candida* spp.

In December 2012 the revised and second version of the EUCAST rationale document for anidulafungin and *Candida* spp. was released for consultation. Comments received and responses from the EUCAST Antifungal Susceptibility Testing Subcommittee (EUCAST AFST) are listed below:

Comment	EUCAST AFST response
Australian Society for Antimicrobials, National AST Committee	
Introduction First sentence is strictly speaking not technically correct – also has activity against *Aspergillus,* some other yeasts	The phrase has been harmonised with the statement in the micafungin RD and now reads: "Anidulafungin is an echinocandin antifungal agent active against the majority of *Candida* species."
Introduction, paragraph 2, 2nd sentence: Better written as "Anidulofungin susceptibility has so far been investigated in patients with candidaemia but only a small number of patients with deep-seated organ infection and abscesses"	Revised as suggested.
Introduction, paragraph 3, 3rd sentence: "target enzyme", not "target enzyme gene" (the gene is not the target) & "known to confer *reduced susceptibility*" not "known to confer resistance" because 'resistance' can only be defined using clinical breakpoints	Corrected as suggested. No change. Anidulafungin BPs are defined for other species (which in this context are *C. albicans, C. glabrata, C. krusei, C. tropicalis*), and the alterations been associated with MIC elevations above these BPs.
Introduction, paragraph 3, 4th sentence: Although obvious, we suggest adding ""before reporting anidulofungin susceptibility" to the end of the sentence	No change. Even before the final species identification is available an MIC value may be helpful.
Introduction, paragraph 6: Might be clearer if written as "In version 2.0 of this rationale document, breakpoints for *C. parapsilosis* have been modified to species-specific values that categorise the wild type as	Revised as suggested.

intermediate…"	
2. MIC distributions We question the wisdom of merging the Etest data for the tabulation of MIC distributions with the EUCAST EDEF data. From Arendrup et al. (AAC 2010; 54:426-439) it appears that the Etest usually reads a little higher than the EUCAST EDEF method – see attached brief spreadsheet analysis (on "Xtab" sheet). The Etest also tends to read higher in the publication of Pfaller et al., JCM 2010; 48:1592-1599. We favour the use of EUCAST EDEF data only, as this is the reference method, and the only data that should be used for estimating ECOFFs.	The MIC data set is unchanged from the previous version. Basically we agree that data set with only EUCAST values are in general preferable, and that small differences may occur. However for *C. albicans* several EUCAST dataset were truncated and hence we chose to include some Etest values as they appeared to align within a dilution step with those for EUCAST (as also found in your comparison). When sufficient data are available we will revise the table.
2. MIC distributions It doesn't seem that ECOFFs were calculated statistically. We would recommend statistical analysis after removing the Etest data. We can provide the spreadsheet tool that does the calculation (examples of output attached)	When the breakpoints for the other species are re-evaluated we will appreciate this. However, the purpose with this update was to reclassify *C. parapsilosis* as intermediate.
3. Breakpoints prior We are not exactly clear when CLSI's M27-S4 will be published, but I imagine it will be very soon (it has been approved for publication), so maybe it would be better to list the new breakpoints from that in section 3.	The M27-S4 has just been released, and the species specific BPs revised accordingly.
5. Pharmacodynamics Of course there *are* animal model data on PK-PD: Andes et al. AAC 2010; 54: 2497. That article uses MICs as measured by the CLSI method. In theory at least, the target fAUC/MIC ratios published in that article could be adjusted using the comparative MICs. While the attached spreadsheet attempts to make the comparison, it is using the published Arendrup et al. data rather than the raw data. The raw data may provide more accurate comparative data and would be worth examining. Once that had been done the target fAUC/MIC can be adjusted to the EUCAST method and provide some PK-PD cutoff	The EUCAST AFST feels slightly uncomfortable about such an approach. At the current time, the pharmacodynamics of anidulafungin have only been determined using CLSI methodology. The most commonly employed way of identifying pharmacodynamic targets is directly from a PK-PD model-differences in MICs can significantly affect these values. Further in vivo pharmacodynamic studies that estimate the MIC using EUCAST methodology and enable a "EUCAST specific" pharmacodynamic target are required. We have specified this in the RD.

values after Monte Carol simulation	
7. Clinical data, paragraph 4, 3rd sentence Using comparative MIC output that might be generated following the recommendation in the previous comment, it might well be possible to make the translation	See comment to 5., above
8. Clinical Breakpoint, Dosage Specify that this is the adult dosage – might add a sentence saying that dosing is not adequately studied in children and no recommendations can be made.	Revised suggested. The sentence now reads: "Breakpoints apply to an iv dose of 200 mg on day 1, then 100 mg/day in adults (dosing is not adequately studied in children and no recommendations can be made)."
EUCAST GC	
C. parapsilosis, I ≤4, R > 4mg/L should be presented following the EUCAST standard. That is defining an S breakpoint below the WT distribution.	Has been changed to *C. parapsilosis,* S ≤0.002, R > 4 mg/L
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Suggest to order the species alphabetically in the MIC distribution and ECOFF table	Revised as suggested