EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Comments on revised fluconazole breakpoints for *Candida* spp.

In December 2012 the revised and second version on the EUCAST rationale document for fluconazole 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 Fluconazole is also appropriate for the treatment of all forms of cryptococcosis in the consolidation and suppressive phases of treatment, (generally after initial therapy with amphteiricin B and 5-FC.) - if irrelevant to this document, take out crypto completely, and qualify in Introduction	*Cryptococcus* has been removed.
2nd paragraph: better to say "Fluconazole can be used in the prevention of Candida infections following stem cell and solid organ transplantation and in neutropenic patients."	Has been revised as suggested.
3rd paragraph: would also add in a sentence to state that susceptibility to fluconazole is not only species dependent, but that resistance rates varies with locale and patient population.	The following comment has been added: Moreover, resistance rates vary between local centres and depending on prior exposure in the individual patient.
Last paragraph: categorise the wild type as being "intermediate" in susceptibility	We have followed the terminology used in the anidulafungin RD for consistency (and which was revised according to the suggestions from the Australian NAC). This now reads as follows: "In version 2.0 of this rationale document, breakpoints for *C. glabrata* have been modified to species-specific values that categorise the wild type as intermediate in order to accommodate use of anidulafungin in some clinical situations."
2. MIC Distributions There is an unexplained asterisk next to *C. tropicalis*	The asterisk has been deleted.
Only EDEF method results should be included, and a	The data in this table have not been modified since the first version of the document. As long as the endpoints align it has

statement to that the EUCAST EDef method was used included. Data nominating this method are published on the EUCAST MIC distribution website, although the numbers are lower than this document.	been the tradition to allow inclusion of also results from other methods. Agreement between EUCAST and CLSI M27-3 has been well documented. For antifungal testing it is often a challenge to obtain sufficient data sets and hence we have not modified the MIC distribution data during this round of revision.
It looks like all the MIC distributions were truncated at the ECOFF, judging by what's published on the EUCAST MIC distribution website. It looks a little misleading to exclude values above the ECOFF. It also interferes with statistical analysis (attached, using the data from both this rationale document and the EUCAST website – EUCAST data only)	The truncated versions were used in AFST discussion of wild types and the full distributions should have been included in the rationale document. They are now restored.
Also, why were the MIC distributions for the other Candida species omitted? – there are some EUCAST data on the website for *dubliniensis*, *famata*, *guilliermondii*, *kefyr*, *lusitaniae*, and *pintolopesii*. They should probably be put in the rationale document, even though ECOFFs cannot be determined due to low numbers for most of them. We have included a statistical analysis of *C. guilliermondii* though, as total numbers and number of data sources were sufficient for this species.	We have included the dataset and ECOFF for *C. guilliermondii*, however not for the rest, due to too low number of isolates and specifically for *C. famata* due to later research questioning if this is a true pathogen or rather a mixture of misidentified *C. palmioleophila, C. guilliermondii, C. intermedia* and others (Jensen RM and Arendrup MC, JCM 2011). EUCAST normally requires more than 100 isolates from several dataset in order to set ECOFFs. We have not established breakpoints for *C. guilliermondii* but included the following motivation behind this decision in the RD: "The MICs and ECOFF for *C. guilliermondii* are 4-steps higher than those for *C. albicans.* There is insufficient clinical data to suggest if this species is a good target for fluconazole or not. Hence EUCAST has refrained from setting breakpoints for this species.
<u>3. Breakpoints prior…</u> There is no explanation of abbreviations DIN NWGA and CLSI (although most would know what they are)	Has been added.
<u>8. Clinical Breakpoints</u> Stress that the common dose (400mg/day) is for adults.	The following comment has been added: "Typically a loading dose of 800 mg day one followed by 400 mg should be used, however for severe infections, high body mass index (BMI) or infections involving *C. glabrata* the dose may be elevated to 800 mg daily."
EUCAST GC	
C. glabrata, I ≤32, R > 32mg/l should be presented following the EUCAST standard. That is defining an S breakpoint below the WT distribution.	Has been changed to *C. glabrata,* S ≤0.002, R > 32 mg/L