EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Comments on proposed itraconazole breakpoints for *Aspergillus* spp.

In October 2011 the EUCAST rationale document for itraconazole and *Aspergillus* 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 Data are insufficient (esp no PK-PD) and the disconnect between MICs and free drug levels (99.8% protein bound) needs explanation. The data quality is clearly inferior to that of posaconazole. Some good quality PK/PD animal model data would be helpful I believe, or at least some clinical MIC versus outcome data. The BPs proposed for itraconazole might be correct, but we don't feel confident about that, based on the limited data. Tentative BPs, largely defined by ECVs, could be set, but with a caveat that they might be modified when better PD data become available.	Itraconazole is in Europe mainly used for chronic forms of aspergillosis and considerable evidence is available that patients fail therapy when the isolates are resistant in vitro (non-wild type). Although some patients may fail therapy despite being infected with wild type isolates simply due to insufficient drug levels it is, however, helpful to identify those infected with a non-wild type isolate. One of the issues that concerned the EUCAST AFST was that the posaconazole MICs for wild type versus cyp51a mutant isolates are often not very well separated, in contrast to the situation with itraconazole, which is nicely illustrated in the paper by Verweij et al (Drug Resistance Updates, 2009; 12:141–147) and many others. Basically, this means that within the posaconazole wild type MIC distribution (i.e. below the ECOFF) we may have mutants with a truly different susceptibility than the wild type isolates and for which the MIC_{50} is not the representative MIC. On the other hand, for itraconazole this is not the case, and isolates with posaconazole but not itraconazole resistance are not yet described to our knowledge. Hence, for two reasons (the difficulty in separating isolates with posaconazole resistance from wild type and the fact that itraconazole testing is not only a good predictor for resistance but also associated with clinical response) it is be helpful to provide a rationale document for itraconazole even though breakpoints are based mainly on the ECOFF because the PK/PD data are not optimal. A comment regarding potential updates when more data are available has been included (under additional comments). The distinction between clinical breakpoints and ECOFFs is a matter of frequent questions and confusion, although they are clearly defined (ECOFFs being the upper MIC values defining the wild type distributions and clinical breakpoints being the MIC values indicating likely clinical response This problem applies to antimicrobial agents in general and not just antifungals. The EUCAST Steering Committee notes that clinical breakpoints are based on whatever information is available when the breakpoint is set. Ideally we will have extensive MIC distributions, good Pk/Pd data and clear data relating MIC to outcome. We know that the ideal is rarely achieved and breakpoints are set based on various amounts of data, sometimes only with MIC distributions and some clinical data showing that infections caused by wild type isolates are treatable. The breakpoints are still breakpoints for clinical use and it is confusing to call some of them ECOFFs. The rationale document indicates what data were used to set the breakpoint and both the breakpoint and rationale document may change if additional data become available.

Arendrup and Lass-Floerl, EUCAST AFST Change the ECOFF for *A. terreus* from 1 to 0.5. This is in agreement with the data set and an isolate with a M217I mutation (equivalent to the azole resistance mutation in *A. fumigatus*) has just been detected for which repeated testing yielded MICs of 1-2 mg/L (personal communication). It is unknown if this isolate, which is non-wild type, would respond to treatment	An ECOFF of 0.5 mg/L better describes the wild type distribution and the ECOFF has been lowered accordingly.

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