EUCAST Technical Note on Voriconazole and Aspergillus spp.

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Abstract

The European Committee on Antimicrobial Susceptibility Testing Subcommittee on Antifungal Susceptibility Testing (EUCAST-AFST) has determined breakpoints for voriconazole against Aspergillus spp. This Technical Note is based on the EUCAST rationale document for voriconazole (available on the EUCAST website: http://www.eucast.org). Voriconazole breakpoints are based on epidemiological cut-off values, pharmacokinetic/pharmacodynamic data and clinical experience. Breakpoints will be reviewed regularly or when new data emerge.

Keywords: Breakpoints, EUCAST Technical Note, itraconazole, amphotericin, posaconazole, Aspergillus, susceptibility testing

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The European Committee on Antimicrobial Susceptibility Testing-Subcommittee on Antifungal Susceptibility Testing (EUCAST-AFST) has determined breakpoints for voriconazole against Aspergillus spp. This Technical Note is based on the EUCAST rationale document (available at: http://www.eucast.org). The rationale documents include more detail and published references related to the selection of EUCAST-AFST breakpoints.

Voriconazole is a second-generation triazole agent with broad-spectrum antifungal activity [1]. Voriconazole is approved for treatment of a variety of fungal infections including invasive aspergillosis. Breakpoints for Candida have previously been established [2]. Voriconazole is available as an intravenous formulation, an oral tablet and oral suspension. The dosage that is currently licenced for adults receiving intravenous therapy is 6 mg/kg intravenously, twice daily for two dosages, followed by 4 mg/kg/day intravenously, twice daily. The recommended oral regimen for adults is 400 mg twice daily for two dosages followed by 200 mg twice daily. The oral dosage can be increased to 300 mg twice daily if clinically indicated. For children, a loading dose of 9 mg/kg twice daily is recommended, followed by a maintenance dosage of 8 mg/kg twice daily [3,4]. Therapeutic drug monitoring is increasingly advocated in both children and adults, although there is no regulatory requirement for this to be performed. Trough concentrations of <1 mg/L have been associated with a lower probability of clinical response and higher mortality in adults and children, respectively, and is commonly found despite standard dosing [5,6].

The pharmacokinetics of voriconazole are well characterized. In adults, the pharmacokinetics are highly variable but are classical non-linear pharmacokinetics [7]. In children, there is still considerable pharmacokinetic variability, but (pseudo)-linear pharmacokinetics are observed. The point of transition between seemingly linear pharmacokinetic behaviour and classical non-linear pharmacokinetic occurs somewhere in adolescence, and is difficult to predict on an individual basis. The pharmacodynamics of voriconazole against Aspergillus have been difficult to estimate. Most recently, a dynamic in vitro model of the human alveolus suggested that area under the curve : MIC and trough : MIC ratios of 32.1 and 1, respectively, are associated with near-maximal antifungal activity [8]. These estimates are broadly concordant with estimates obtained from other preclinical models that have used CLSI methodology [9]; it should be noted, however, that MICs determined using EUCAST methodology are usually one-dilution higher compared with CLSI methodology.

The EUCAST breakpoints are based on a compilation of microbiological, pharmacokinetic/pharmacodynamic data, and clinical experience. Epidemiological cut-off values were determined from MIC values obtained from multiple European laboratories, and are summarized in Table 1. Monte Carlo simulation using a population pharmacokinetic model fitted to human adult pharmacokinetic data [7] suggests that pharmacodynamic targets associated with successful outcomes in preclinical models can only be achieved for a suitably high proportion of patients infected with an isolate with an MIC ≤ 1 mg/L. The proportion of patients infected with an isolate
with an MIC 2 mg/L that have an area under the curve: MIC > 32.1 is 67.5%, which then quickly drops to unacceptably low levels for MICs of 4 mg/L and higher [8]. Data from multiple clinical trials suggest that Aspergillus is a good target for voriconazole [10,11]. Unfortunately, however, there are no specific MIC data (determined using EUCAST methodology) that enable a relationship between MIC and clinical outcome to be established. Consequently, the AFST subcommittee has defined breakpoints in the following way: susceptibility ≤ 1, resistance >2 mg/L, providing adequate drug exposure has been confirmed with therapeutic drug monitoring. Isolates with an MIC of 2 mg/L are classified as ‘intermediate’ to indicate that dosage escalation may be required to achieve the necessary drug exposure to maximize the probability of a successful outcome. Furthermore, most isolates with a CYP51A mutation have an MIC using EUCAST methodology >1 mg/L. Therefore, if voriconazole therapy is contemplated for isolates with an MIC of 2 mg/L, the possibility of an underlying resistance mechanism should be considered; this can be further investigated by testing against other triazoles and/or referral to a specialized laboratory for further genotypic and phenotypic characterization. If phenotypic resistance is confirmed or if an underlying molecular mechanism of resistance is identified, then voriconazole should not be used if there are suitable therapeutic alternatives.

EUCAST breakpoints only apply to licensed regimens. The breakpoints will be reviewed when more data are available for Aspergillus species that were not assigned breakpoints during the present review, when there are clinical data for isolates with MIC values outside the wild-type distribution or when there are further data related to optimal drug exposures.

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TABLE 1. Epidemiological cut-off values and breakpoints for voriconazole against various Aspergillus species

<table>
<thead>
<tr>
<th>Species</th>
<th>Epidemiological cut-off value (mg/L)</th>
<th>Breakpoints* (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. fumigatus</td>
<td>1</td>
<td>S ≤ 1; R &gt;2</td>
</tr>
<tr>
<td>A. flavus</td>
<td>2</td>
<td>IE</td>
</tr>
<tr>
<td>A. nidulans</td>
<td>1</td>
<td>IE</td>
</tr>
<tr>
<td>A. niger</td>
<td>1</td>
<td>IE</td>
</tr>
<tr>
<td>A. terreus</td>
<td>2</td>
<td>IE</td>
</tr>
</tbody>
</table>

*To simplify the EUCAST tables, the intermediate category is not listed, but is readily interpreted from the value between the susceptibility (S) and the resistance (R) breakpoint. For example, for MIC breakpoints listed as S ≤ 1 and R >2 mg/L, the intermediate category is 2 mg/L.

**Provided adequate drug exposure has been confirmed using therapeutic drug monitoring.

There is insufficient evidence (IE) to set non-species-related breakpoints.

Transparency Declaration

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Appendix

Member of EUCAST-AFST

EUCAST-AFST: MC Arendrup (Chairman, Denmark), WW Hope (Secretary), C Lass-Flörl, Steering Committee (Austria), M Cuenca-Estrella, Steering Committee (Spain), S Arikan-Akdagli (Turkey), F Barchiesi (Italy), J Bille (Switzerland), E Chryssanthou (Sweden), P Gaustad (Norway), A Groll (Germany), H Järv (Estonia), N Klimko (Turkey), K Lagrou (Belgium), O Lortholary (France), C Moore (UK), A Velegraki (Greece), P Verweij (the Netherlands).

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