EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Voriconazole and A*spergillus* spp.	Rationale for the EUCAST clinical breakpoints, version 1.0	20 May 2012

Foreword

EUCAST
The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is organised by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the European Centre for Disease Prevention and Control (ECDC), and the active national antimicrobial breakpoint committees in Europe. EUCAST was established by ESCMID in 1997, was restructured in 2001-2002 and has been in operation in its current form since 2002. The current remit of EUCAST is to harmonise clinical breakpoints for existing drugs in Europe, to determine clinical breakpoints for new drugs, to set epidemiological (microbiological) breakpoints, to revise breakpoints as required, to harmonise methodology for antimicrobial susceptibility testing, to develop a website with MIC and zone diameter distributions of antimicrobial agents for a wide range of organisms and to liaise with European governmental agencies and European networks involved with antimicrobial resistance and resistance surveillance.

Information on EUCAST and EUCAST breakpoints is available on the EUCAST website at http://www.EUCAST.org.

EUCAST rationale documents
EUCAST rationale documents summarise the information on which the EUCAST clinical breakpoints are based.

Availability of EUCAST document
All EUCAST documents are freely available from the EUCAST website at http://www.EUCAST.org.

Citation of EUCAST documents
This rationale document should be cited as: “European Committee on Antimicrobial Susceptibility Testing. Voriconazole: Rationale for the clinical breakpoints, version 1.0, 2012. http://www.eucast.org.

Introduction

Voriconazole is a triazole antifungal agent with broad spectrum in vitro activity against *Aspergillus* spp., and other medically important fungal pathogens. The drug is approved for the following indications:

- Treatment of invasive aspergillosis.
- Treatment of candidaemia in non-neutropenic patients
- Treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*).
- Treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.

The European Committee on Antimicrobial susceptibility Testing - Subcommittee on Antifungal Susceptibility Testing (EUCAST-AFST) has determined breakpoints for voriconazole against *Aspergillus* spp. These breakpoints will be revised after two years.

The mould species most frequently causing human infections include *Aspergillus fumigatus, Aspergillus flavus, Aspergillus terreus* and *Aspergillus niger*. The in vitro activity of voriconazole against these species of *Aspergillus* is reasonably uniform, but acquired resistance has been reported, even among isolates obtained from triazole naive patients (hence routine susceptibility testing is of utmost importance). *A. fumigatus* is a species complex including rarer sibling species that may exhibit differences in their susceptibility to antifungal agents.

1. Dosage

Most common regimen	iv therapy: 6 mg/kg two dosages every 12 h followed by 4 mg/kg every 12 h. oral therapy: 400 mg orally every 12 h for two dosages followed by 200 mg every 12 h.
Available formulations	iv infusion, oral tablet, oral solution

2. MIC distributions and epidemiological cut-off (ECOFF) values (mg/L)

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Aspergillus flavus	0	0	0	0	2	4	8	25	46	149	42	4	1	2	0	0	0	0	0	2
Aspergillus fumigatus	0	0	0	0	3	9	85	405	906	288	67	54	44	30	54	0	0	0	0	1
Aspergillus nidulans	0	0	0	3	2	5	18	42	24	6	1	0	1	5	0	0	0	0	0	1
Aspergillus niger	0	0	0	1	1	2	4	13	68	84	35	1	0	1	0	0	0	0	0	2
Aspergillus terreus	0	0	0	0	1	2	2	18	52	154	67	9	1	0	0	0	0	0	0	2
Aspergillus versicolor	0	0	0	0	0	0	2	6	7	7	3	0	1	1	0	0	0	0	0	ND
Aspergillus sydowii	0	0	0	0	1	1	4	11	17	21	0	0	0	0	0	0	0	0	0	ND

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple sources and time periods. The distributions are used to define the epidemiological cut-offs (ECOFF) and give an indication of the MICs for organisms with acquired or mutational resistance mechanisms. They should not be used to infer resistance rates. When there is insufficient evidence no epidemiological cut-off has been determined (ND).

3. Breakpoints prior to harmonisation (mg/L) S≤ / R>		
	European breakpoints	**CLSI**
General breakpoints:		
	NA	NA
Species specific breakpoints:		
	NA	NA

NA = Not available

4. Pharmacokinetics

	Oral therapy	Intravenous therapy
Dosage (mg)	400 mg every 12 h for two dosages and then 200 mg every 12 h.	6 mg/kg every 12 h for two dosages and then 4 mg/kg every 12 h.
Absorption lag (h); Mean (CV %)	1.12 (105.42)	N/A
Bioavailability; Mean (CV %)	0.86 (15.12)	N/A
Vmax (mg/h); Mean (CV %)	37.67 (29.71)	37.67 (29.71)
Km (mg/L); Mean (CV %)	2.07 (53.62)	2.07 (53.62)
Volume (L); Mean (CV %)	149.11 (116.35)	149.11 (116.35)
$AUC_{0\text{-}12}$ (mg.h/L) total drug; Mean (CV %)	17.99 (119.90)	45.24 (168.19)
Fraction unbound (%)	40	40
Comments	• Vmax is the maximum rate of enzyme activity and provides an indication of the maximum rate of voriconazole metabolism (mg/h). • Km is the serum voriconazole concentration at which enzyme activity is half-maximum. • Voriconazole exhibits Michaelis-Menten (or non-linear) pharmacokinetics, meaning that dosage escalation may lead to a disproportionate increase in systemic drug exposure (AUC).	
References	• Hope. Antimicrob Agents Chemother 2011: 56: 526-31. • Similar population Pk models have been fitted to paediatric datasets. See, for example, Neely et al. Clin Infect Dis 2010: 50; 27-36 and Karlsson et al. Antimicrob Agents Chemother 2009: 53; 935-44.	

5. Pharmacodynamics				
Total drug AUC:MIC ratio associated with near maximum effect in a dynamic in vitro model of invasive pulmonary aspergillosis.	32.1			
Trough (Cmin) concentration associated with an approximately 70% response rate in adult patients.	1 mg/L			
Comments	• The AUC may be the dynamic variable that best links drug exposure with the observed outcome, but this has not been formally demonstrated for *Aspergillus* spp. • Preclinical data suggests that *A. fumigatus* isolates with higher MICs may be treated with higher voriconazole exposures. • A total drug AUC:MIC ratio of 30 and a trough concentration:MIC ratio of 1 results in suppression of galactomannan concentrations in a dynamic in vitro model of the human alveolus. • A trough concentration of >1 mg/L has been associated with a higher probability of a successful outcome in a cohort of patients most of whom had invasive aspergillosis (Pascual et al) and in the paediatric setting (Neely et al). • A trough concentration:MIC ratio of 2-5 (CLSI MIC method) is associated with a higher probability of a successful clinical outcome, but clinical outcomes from both *Candida* and *Aspergillus* were considered to derive this endpoint (Troke et al). There are no comparable data using EUCAST MIC methodology.			
References	• Jeans AR et al. J Infect Dis 2012: in press. • Pascual et al. Clin Infect Dis 2008: 46: 201-211. • Troke et al. Antimicrob Agents Chemother 2011: 55: 4782-8. • Neely et al. Clin Infect Dis 2010: 50: 27-36.			

6. Monte Carlo simulations and Pk/Pd breakpoints

Voriconazole may be used intravenously or orally. The Phase III clinical trial of Herbrecht et al required initial use of iv voriconazole. The drug exposure (AUC_{0-12}) associated with iv therapy is significantly higher than achieved with oral therapy for patients receiving a standard regimen.

A population Pk model fitted to data from healthy volunteers (n=21) and patients (n=43) receiving both iv and oral voriconazole was used to estimate the AUC at the end of the first week of therapy following the currently licensed iv regimen (6 mg/kg every 12 h for two dosages followed by 4 mg/kg every 12 h). A Pd target from the work of Jeans et al was used (AUC:MIC ratio 32.1[1]), which corresponds to a trough concentration:MIC ratio of approximately 1. The proportion of 5,000 simulated patients that attain this Pd target as a function of MIC are as follows:

MIC (mg/L)	% target attainment
0.03	99.98
0.06	99.98
0.125	99.98
0.25	99.98
0.5	99.94
1	92.78
2	67.50
4	32.18
8	10.64
16	2.38
32	0.02

References:
Herbrecht et al. New Eng J Med 2002: 347: 408-15.
Hope. Antimicrob Agents Chemother 2011: 56: 526-31.
Jeans AR et al. J Infect Dis 2012: in press.

[1]The AUC used to calculate the Pd target here is AUC_{0-24} at the end of the first week, and is therefore different from the AUC_{0-12} that is cited in the Pk section, above.

7. Clinical data

Aspergillosis

Voriconazole is a first-line agent for the treatment of invasive aspergillosis. Use of the currently licensed regimen with at least 1 week of iv dosing results in better clinical responses and overall mortality at the end of 12 weeks compared with amphotericin B deoxycholate (Herbrecht et al). Voriconazole is the drug of choice for treatment of aspergillosis of the central nervous system (Schwartz et al).

References:
Herbrecht et al. New Eng J Med 2002: 347: 408-15.
Schwartz et al. Blood 2005: 106: 2641-5.

Acquired Resistance

The frequency of voriconazole resistance is largely undefined, as many centres do not routinely test the susceptibility of their *Aspergillus* isolates. Resistance has currently been reported in Belgium, Canada, China, Denmark, France, Norway, Spain, Sweden, The Netherlands, UK and the USA. Most commonly the resistance is linked to point mutations in the target gene *cyp51A*. However, at some centres a significant proportion of the isolates with elevated voriconazole MICs lack these mutations, suggesting that other mechanisms may be significant. Importantly, *A. fumigatus* isolates with acquired resistance mechanisms have been increasingly found in the environment, probably due to agricultural azole pesticide use, and are also found in azole-naive patients failing therapy. The EUCAST voriconazole MICs for such isolates vary with the underlying mechanism, but are >1 mg/L for the most commonly identified mutants (alterations at G54, G138, M220, and the environmental phenotype TR-L98H).

Correlation of in vitro voriconazole MIC data with clinical outcome has not been done as such data sets are not available for EUCAST MIC methods. If the MIC suggests the isolate may not belong to the wild-type population, voriconazole should not be used.

References:
Denning et al. Antimicrob Agents Chemother 1997; 41: 1364-8.
Howard et al. Emerg Infect Dis 2009; 15: 1068-76.
Snelders et al. PLoS Med 2008; 5: e219.
Arendrup et al. PLoS One 2010; 5: e10080.
Snelders et al. Appl Environ Microbiol 2009; 75: 4053-7.
van der Linden et al. Clin Inf Dis 2009; 48: 1111-13.
Mortensen et al. Antimicrob Agents Chemother. 2010; 54: 4545-9.
Howard et al. Med Mycol 2011; 49 Suppl 1: S90-5.
Mortensen et al. J Clin Microbiol 2011 49: 2243-51.
Mellado E et al. Antimicrob Agents Chemother. 2007; 51: 1897-904.
Mellado E et al. Antimicrob Agents Chemother. 2005; 49: 2536-8.
Mellado E et al. Antimicrob Agents Chemother. 2004; 48: 2747-50.
Diaz-Guerra TM et al. Antimicrob Agents Chemother. 2003; 47: 1120-4. Erratum in Antimicrob Agents Chemother 2004; 48: 1071.

8. Clinical breakpoints

Non-species-related breakpoints	There is insufficient evidence to set non-species-related breakpoints.
Species-related breakpoints	Breakpoints were based on PK data, microbiological data and patient outcomes from clinical trials. Clinical information suggests that the wild type population of *A. fumigatus* is susceptible to voriconazole. No clinical studies have so far presented outcome data for a significant number of cases involving the other species. While there is inadequate clinical information on outcome for wild type populations of *A. flavus, A. nidulans, A. terreus*, the MIC distributions are similar to those obtained for *A. fumigatus.* *Aspergillus fumigatus* S ≤1, R >2 mg/L Provided adequate drug exposure as been confirmed using therapeutic drug monitoring (TDM)[1] [1]Increasing data suggest that therapeutic drug monitoring is an important adjunct for the optimal clinical use of voriconazole. Most accept that a trough concentration of >1 mg/L is a reasonable target. This was originally based on the MIC_{90} of medically important fungal pathogens, but several recent studies suggest that patients who attain this target have better clinical outcomes and survival. Isolates with a higher MIC require proportionally higher drug exposure to achieve the same effect. While there are no clinical data available that have specifically used EUCAST MIC methodology, preclinical models suggest that a trough:MIC ratio value of >1 is a potential target for therapeutic drug monitoring for treatment of non-wild-type isolates (e.g. MIC 2 mg/L). If the MIC is used in this manner to individualise dosing, the MIC should be repeated to ensure robust estimates are obtained. References: Troke et al. Antimicrob Agents Chemother 2011; 55: 4782-8. Jeans AR et al. J Infect Dis 2012; in press. Neely et al. Clin Infect Dis 2010; 50: 27-36. Pascual et al. Clin Infect Dis 2008; 46: 201-211. Andes et al. Antimicrob Agents Chemother 2009; 53: 2223-4. Hope et al. Curr Opin Infect Dis 2008 ; 21: 580-6.
Species without breakpoints	There is inadequate clinical information on the clinical outcome for patients infected with wild type isolates of non-*fumigatus Aspergillus* species. If the voriconazole exposure-response relationships for these organisms are similar to those for *A. fumigatus*, the breakpoints for *A. fumigatus* could be applied to these species. Until these data are available, EUCAST has refrained from setting breakpoints for these species.

Clinical qualifications	The EUCAST AFST considers voriconazole appropriate therapy for the following *Aspergillus* infections when caused by wild type isolates • Primary treatment of invasive aspergillosis including *Aspergillus* infections of the central nervous system • Treatment of chronic pulmonary aspergillosis
Dosage	The EUCAST breakpoints apply to licensed dosing of voriconazole. Loading dose: iv 6 mg/kg every 12 h for two dosages, followed by 4 mg/kg every 12 h. Orally, 400 mg every 12 h for two dosages followed by 200 mg every 12 h. Dosage escalation may be considered if clinically indicated, and may be guided by therapeutic drug monitoring.
Additional comment	Voriconazole therapeutic drug monitoring is highly recommended to ensure optimal drug exposure. Voriconazole exhibits (pseudo)linear pharmacokinetics in younger children and transitions in adolescence to classical non-linear pharmacokinetics. The probability of elevated liver function tests and central nervous system toxicity is higher with higher drug exposures.

9. EUCAST clinical MIC breakpoints

All EUCAST breakpoints can be found at **http://www.eucast.org**

10. Exceptions noted for individual national committees

None