EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Amphotericin B	Rationale for the EUCAST clinical breakpoints, version 1.0	19th November 2010

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. Amphotericin B: Rationale for the clinical breakpoints, version 1.0, 2010. http://www.eucast.org.

Introduction

Amphotericin B is a polyene antifungal agent active against yeasts and moulds. It is available in four different formulations including amphotericin B deoxycholate and three lipid formulations. The active compound is identical but the pharmacokinetics and toxicity profiles are different from formulation to formulation.
The formulations are licensed as follows:

Amphotericin B deoxycholate
Serious infections due to amphotericin B susceptible fungi.

Amphotericin B lipid complex (ABLC)
First line treatment of systemic *Candida* infections.

Amphotericin B colloidal dispersion (ABCD)
Serious infections due to amphotericin susceptible fungi, where amphotericin B deoxycholate is contraindicated or has failed.

Lipsomal amphotericin B (L-amphotericin B)
Treatment of invasive fungal infections due to amphotericin B susceptible fungi. Treatment of suspected fungal infection in neutropenic patients with persistent fever despite antibacterial treatment for 5-7 days.

1a. Dosage	Amphotericin B deoxycholate								
	Denmark	**Spain**	**Sweden**	**Switzerland**	**Turkey**	**Austria**	**Norway**	**France**	**The Netherlands**
Minimum dose (mg/kg/day)	0.7-1	0.3	0.3	NA	0.5	0.5	0.5	NA	0.5
Most common dose (mg/kg/d)	0.7-1	0.7-1	0.7	0.5-1	1-1.2	1-1.5	0.75	0.5-1	1
1st day dose (mg/kg/day)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
2nd day dose (mg/kg/day)	0.5	0.5	0.5	NA	NA	NA	0.5	NA	0.5
Maximum dose (mg/kg/d)	1-1.5	1	1	1.5	1.5	1.5	1	1	1.5
Loading dose	1 mg/kg	NA	NA	0.25 mg/kg	NA	NA	NA	NA	NA
Available formulations	iv	iv	iv, oral 10 mg tablet	iv	iv	iv	iv	iv, oral 250 mg tablets 10% oral suspension	iv

NA = Not applicable

1b. Dosage	Liposomal amphotericin B								
	Denmark	**Spain**	**Sweden**	**Switzerland**	**Turkey**	**Austria**	**Norway**	**France**	**The Netherlands**
Minimum dose (mg/kg/day)	3	1	1	1	1	1	1	NA	3
Most common dose (mg/kg/d)	3	3	3	3	3-5	3-5	3	3	3
1st day dose (mg/kg/day)	1	1	3	1	1	1	1	1	1
2nd day dose (mg/kg/day)	1	1	3	3	1	1	1	1	3
Maximum dose (mg/kg/d)	5, 7 and 10	5, 7 and 10	3	5-6	5	5	5	10	5
Loading dose	NA	NA	NA	NA	NA	NA	NA	NA	NA
Available formulations	iv	iv	iv	iv	iv	iv	iv	iv	iv

NA = Not applicable

1c. Dosage	Amphotericin B lipid complex								
	Denmark	**Spain**	**Sweden**	**Switzerland**	**Turkey**	**Austria**	**Norway**	**France**	**The Netherlands**
Minimum dose (mg/kg/day)	5	3	NA		3	3	5	NA	3
Most common dose (mg/kg/d)	5	5	5		5	3-5	5	5	3-5.5
1st day dose (mg/kg/day)	5	5	5		5	5	NA	NA	3-5.5
2nd day dose (mg/kg/day)	5	5	5		NA	NA	NA	NA	3-5.5
Maximum dose (mg/kg/d)	Rarely used	5	5		5	5	5	5	5.5
Loading dose	NA	NA	NA		NA	NA	NA	NA	NA
Available formulations	iv	iv	iv	NA	iv	iv	iv	iv	iv

NA = Not applicable

1d. Dosage	Amphotericin B colloidal dispersion								
	Denmark	**Spain**	**Sweden**	**Switzerland**	**Turkey**	**Austria**	**Norway**	**France**	**The Netherlands**
Minimum dose (mg/kg/day)						3			3
Most common dose (mg/kg/d)						3-5			3
1st day dose (mg/kg/day)						3-5			1
2nd day dose (mg/kg/day)						3-5			3
Maximum dose (mg/kg/d)						5			4
Loading dose						NA			NA
Available formulations	NA	NA	NA	NA	NA	iv	NA	NA	iv

NA = Not applicable

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
Candida albicans	0	0	0	1	230	683	668	470	238	39	0	0	0	0	0	0	0	0	0	1
Candida glabrata	0	0	0	0	19	94	264	284	153	26	5	0	0	0	0	0	0	0	0	1
Candida krusei	0	0	0	0	1	3	11	67	105	49	3	0	0	0	0	0	0	0	0	1
Candida parapsilosis	0	0	0	0	27	115	287	216	101	20	4	0	0	0	0	0	0	0	0	1
Candida tropicalis	0	0	0	0	6	92	170	86	66	20	8	0	1	0	0	0	0	0	0	1

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[1]

NA = Not available
[1]No breakpoint has been established for amphotericin B, but, according to the text in CLSI M27-A3, *Candida* isolates with MIC ≤1 mg/L should be regarded as susceptible.

4. Pharmacokinetics

	Amphotericin B deoxycholate	Amphotericin B lipid complex	Liposomal amphotericin B[2]	Amphotericin B colloidal dispersion
Dosage (mg/kg/day)	0.6	2	0.6	3
Cmax (mg/L)	1.4	2-3	22.9	Approximately 2-2.5
Cmin (mg/L)				
Total body clearance/F (L/h)				
Terminal T ½ (h)	127	393	152	29
AUC_{0-24}h (mg.h/L)	13.9	19.2 (dosage 5 mg/kg/day)	171	Approximately 45
Fraction unbound[1] (%)	<5	<5	<5	<5
Volume of central compartment, Vc (L/kg)	0.136		Approximately 0.05-0.1	0.089
Comments	• [1]The binding of amphotericin B is extremely complex and poorly understood • [2]Pharmacokinetics may vary with dosages >7.5 mg/kg • Cells are left empty when data are not readily available			
References	• Bekersky et al. *AAC* 2002; 46: 828-833 • Bekersky et al. *AAC* 2002; 46; 834-840 • Walsh et al. *AAC* 2001; 45: 3487-3496 • Gubbins et al. *AAC* 2009; 53: 3664-3674 • Adedoyin et al. *AAC* 1997; 41: 2201-2208 • Adedoyin et al. *AAC* 2000; 44: 2900-2902 • Amantea et al. *Chemotherapy* 1999; 45(Suppl 1): 48-53			

5. Pharmacodynamics				
*f*AUC/MIC for stasis				
*f*AUC/MIC for 2 log reduction				
*f*AUC/MIC from clinical data				
Comments	• Not available for EUCAST methodology. • Cells are left empty when data are not readily available.			
References				

6. Monte Carlo simulations and Pk/Pd breakpoints

Not available.

7. Clinical data

Clinical data was collated from the following clinical trials:

- Walsh et al. *NEJM,* 1999, 340:764-771
  L-amphotericin B, 3mg/kg/d with 343 patients, mean treatment duration of 10.4 days. Showed a treatment success rate of 50.1%.
  Amphotericin B deoxycholate, 0.6 mg/kg/d with 344 patients, mean treatment duration of 10.3 days. Showed a treatment success rate of 49.4%.
- Wingard et al. *CID* 2000, 31: 1155-1163
  L-amphotericin B, 3mg/kg/d with 85 patients, mean treatment duration of 8.6 days. Showed a treatment success rate of 40%.
- Walsh et al. *NEJM* 2004,351: 1391-1402
  L-amphotericin B, 3mg/kg/d with 539 patients, mean treatment duration of 12 days. Showed a treatment success rate of 33.7%.
- Walsh et al. *NEJM* 2002, 346: 225-234
  L-amphotericin B, 3mg/kg/d with 422 patients, mean treatment duration of 12 days. Showed a treatment success rate of 30.6%.
- Kuse et al. *Lancet* 2007, 369: 1519-1527
  L-amphotericin B, 3mg/kg/d with 190 patients, mean treatment duration of 15 days. Showed a treatment success of 89%
- Queiroz-Telles et al. *PIDJ* 2008,27: 820-826
  L-amphotericin B, 10 mg/kg/d with 50 patients, mean treatment duration of 14.5 days. Showed a treatment success rate of 76%.
- Fleming et al. *Leukemia and Lymphoma* 2001,40: 511-520
  ABLC, 5mg/kg/d with 70 patients (proven infections and empirical treatment), mean treatment duration of 12.4 days. Showed a treatment success rate of 63%.
- Noskin et al. *BMT* 1999, 23: 697-703
  ABCD, 4 mg/kg/d with 220 patients (proven and suspected infection), mean treatment duration of 23 days. Showed a treatment success rate of 52%.

For most of the studies above clinical outcome data was not specified for the individual *Candida* species. Combining the studies that provided such data (Walsh, 2004; Kuse, 2007, Fleming, 2001) failure rates were as follows: For L-amphotericin B the overall failure rate was 9% (16/174) and for individual species: *C. albicans* 11% (7/73), *C. tropicalis* 4% (2/45), *C.* parapsilosis 10% (3/29), *C. glabrata* 20% (3/15) and *C. krusei* 20% (1/5). For amphotericin B deoxycholate the overall failure rate was 38% (44/115) and for individual species: *C. albicans* 8% and *C. krusei* 3%. These data indicate that the species are good targets for amphotericin B formulations.

These studies did not include MICs by the EUCAST method so a correlation of in vitro MICs with clinical outcome has not been possible.

8. Clinical breakpoints	
Non-species-related breakpoints	There is insufficient evidence to set non-species-related breakpoints.
Species-related breakpoints	Breakpoints were based on pharmacokinetic data, microbiological data and clinical experience. *C. albicans,* S ≤1, R >1 mg/L *C. glabrata,* S ≤1, R >1 mg/L *C. parapsilosis* S ≤1, R >1 mg/L *C. tropicalis,* S ≤1, R >1 mg/L *C. krusei,* S ≤1, R >1 mg/L
Species without breakpoints	The clinical response of infection due to *Candida* species as a whole was similar to that of infections caused by *C. albicans, C. parapsilosis* and *C. tropicalis.* However, there were only 12 cases available for analysis which is too few to allow any recommendation to be made. Therefore, there is insufficient evidence (IE) to set clinical breakpoints for other species of *Candida*.
Clinical qualifications	The EUCAST-AFST considers amphotericin B preparations to be appropriate therapy for invasive candidiasis.
Dosage	The EUCAST breakpoints apply to licensed dosing of amphotericin B deoxycholate, liposomal amphotericin B, amphotericin B lipid complex and amphotericin B colloidal dispersion.
Additional comment	The EUCAST-AFST will review breakpoints for amphotericin B when more data available for *Candida* species which were not assigned breakpoints during the present review and when there are clinical data for *Candida* isolates with MIC values outside the wild type distribution.

9. EUCAST clinical MIC breakpoints

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

10. Exceptions noted for individual national committees

None