



EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Mupirocin

Rationale for the EUCAST clinical breakpoints, version 1.0

6th July 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. Mupirocin: Rationale for the clinical breakpoints, version 1.0, 2010. <http://www.eucast.org>.

Introduction

Mupirocin (pseudomonic acid A) is a fermentation product of *Pseudomonas fluorescens*. It has in vitro activity against staphylococci, aerobic streptococci, *Enterococcus faecium* (not *Enterococcus faecalis*), *Neisseria* spp. and *Haemophilus influenzae*.

Mupirocin is slowly bactericidal and inhibits protein synthesis by irreversible binding to isoleucyl t-RNA synthetase. Resistance may be mediated by two mechanisms. Mutation of the chromosomal *mupA* gene confers a low-level resistance (MIC 8-256 mg/L). A plasmid-mediated version of the *mupA* gene confers high level resistance (MIC >256 mg/L).

Mupirocin is mainly used for nasal decolonization of *Staphylococcus aureus*, particularly MRSA, as part of decolonization regimens. Mupirocin may also be used for topical treatment of uncomplicated skin infections such as impetigo, although prolonged use is associated with selection of resistance. EUCAST breakpoints are related particularly to nasal decolonization of *S. aureus*.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	Nasal application 3x daily for 5 d	Nasal application 3x daily for 5 d	Nasal application 3x daily for 5 d		Nasal application 3x daily for 5-10 d	Nasal application 3x daily for 5 d
Maximum dose schedule						
Available formulations	Topical	Topical	Topical		Topical	Topical

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

	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
<i>Staphylococcus aureus</i>	0	0	0	4	13	473	3704	3758	490	77	48	44	81	190	86	34	55	24	428	1
<i>Staphylococcus aureus</i> MRSA	0	0	0	0	0	10	20	95	14	10	6	0	14	15	11	0	0	0	32	1
<i>Staphylococcus aureus</i> MSSA	0	0	0	0	0	5	17	74	6	0	0	0	0	0	0	0	0	0	0	1
<i>Staphylococcus coagulase negative</i> MRSCN	0	0	0	0	0	0	16	49	21	5	1	1	1	1	8	0	0	3	36	ND
<i>Staphylococcus lugdunensis</i>	0	0	0	0	6	25	60	3	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus agalactiae</i>	0	0	0	0	0	6	25	55	402	514	35	11	5	8	2	2	3	3	0	ND
<i>Streptococcus pyogenes</i>	0	0	0	0	35	870	1327	303	139	26	11	11	8	0	5	2	25	2	7	0.5

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_{>}							
	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
General breakpoints							
		2/2					
Species-related breakpoints							
Enterobacteriaceae							
<i>Pseudomonas</i> spp.							
<i>Acinetobacter</i> spp.							
<i>Staphylococcus</i> spp.	4/256	2/2	4/256		4/4 <i>S. aureus</i>	4/256	256/256
<i>Streptococcus</i> spp.							
<i>Streptococcus pneumoniae</i>							
<i>Enterococcus</i> spp.							
<i>Haemophilus influenzae</i>							
<i>Moraxella catarrhalis</i>							
Corynebacteria							
<i>Neisseria meningitidis</i>							
<i>Neisseria gonorrhoeae</i>							
<i>Pasteurella multocida</i>							
Anaerobes, Gram-positive							
Anaerobes, Gram-negative							
<i>Campylobacter</i> spp.							
<i>Helicobacter pylori</i>							

4. Pharmacokinetics				
Dosage (mg)				
Cmax (mg/L)				
Cmin (mg/L)				
Total body clearance (L/h)				
T ½ (h), mean (range)				
AUC24h (mg.h/L)				
Fraction unbound (%)				
Volume of distribution (L/kg)				
Comments	<ul style="list-style-type: none"> No pharmacokinetics available for topical use 			
References				

5. Pharmacodynamics				
fAUC/MIC for bacteriostasis				
fAUC/MIC for 2 log reduction				
fAUC/MIC from clinical data				
Comments	<ul style="list-style-type: none"> No pharmacodynamics available for topical use 			
References				

6. Monte Carlo simulations and Pk/Pd breakpoints

No data.

7. Clinical data

Clinical studies indicate that topical mupirocin treatment is effective in nasal decolonization of wild type *Staphylococcus aureus* (Perl et al, N Eng J Med 2002; 346: 1871-7; Konvalinka et al, J Hosp Infect 2006; 64: 162-8; Doebbeling et al, Clin Infect Dis 1993; 17: 466-74; Hansen et al, Infection 2007; 35: 260-4).

Low-level resistant isolates are initially cleared as effectively as wild type isolates but recolonization, probably due to endogenous relapse, is very common (Walker et al, Infect Control Hosp Epidemiol 2003; 24: 342-6; Harbarth et al, Antimicrob Agents Chemother 1999; 43: 1412-16).

Clearance rates for high-level resistant isolates are low.

There is no evidence on outcome for isolates with MICs above the wild type (ECOFF 1 mg/L) but without a recognised resistance mechanism (MIC \leq 4 mg/L).

8. Clinical breakpoints

Non-species-related breakpoints	There is insufficient evidence to set non-species-related breakpoints.
Species-related breakpoints	Breakpoints were based on microbiological data (ECOFFs) and clinical experience. For <i>Staphylococcus aureus</i> the breakpoints are 1/256 mg/L. Wild type isolates will be reported susceptible, low-level resistant isolates intermediate and high-level resistant isolates resistant. Isolates with MICs above the wild type (ECOFF 1 mg/L) but without a recognised resistance mechanism (MIC \leq 4 mg/L) will be reported intermediate.
Species without breakpoints	Organisms other than <i>S. aureus</i> are not targets for mupirocin topical nasal therapy and for that reason did not receive breakpoints.
Clinical qualifications	Topical nasal treatment with mupirocin is used as part of a decontamination regimen.
Dosage	Breakpoints apply to topical nasal administration x 3/day.
Additional comment	

9. Mupirocin - EUCAST clinical MIC breakpoints

These can be found at <http://www.eucast.org>

10. Exceptions noted for individual national committees

None