



EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Phenoxymethylpenicillin

Rationale for the EUCAST clinical breakpoints, version 1.0

22nd 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. Phenoxymethylpenicillin: Rationale for the clinical breakpoints, version 1.0, 2010. <http://www.eucast.org>.

Introduction

Phenoxymethylpenicillin is a penicillin available for oral use.

Phenoxymethylpenicillin is active against wild type staphylococci, streptococci (including *Streptococcus pneumoniae*) and *Neisseria* spp. It is poorly active against *Enterococcus* spp., *Haemophilus influenzae* and many Gram-positive anaerobic bacteria. Phenoxymethylpenicillin has no clinically useful activity against *Pseudomonas* spp., *Acinetobacter* spp. or Enterobacteriaceae. Due to the production of beta-lactamases, resistance to phenoxymethylpenicillin is common in many organisms. Resistance to phenoxymethylpenicillin may also be conferred by changes in penicillin binding proteins (PBPs).

Phenoxymethylpenicillin is used for therapy of upper respiratory tract infections caused by Gram-positive bacteria, i.e. tonsillitis, pharyngitis, otitis media, sinusitis and streptococcal skin infection. It is also relevant for treatment of erythema migrans (borreliosis) and prophylaxis in splenectomy and rheumatic fever.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	500 mg x 4	-	500 mg x 3	1 MIU ¹ x 3	600 mg x 3-4	500 mg - 1 g x 3
Maximum dose schedule	1 g x 4	-	1 g x 4	1.5 MIU ¹ x 3	1 g x 4	1 g x 3
Available formulations	Oral	-	Oral	Oral	Oral	Oral

¹MIU = Mega international Unit

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
<i>Clostridium difficile</i>	0	0	0	0	0	0	0	0	0	17	159	165	45	6	5	0	1	3	0	ND
<i>Enterococcus faecalis</i>	0	0	0	0	0	0	0	0	0	4	16	7	0	0	0	0	0	0	0	ND
<i>Enterococcus faecium</i>	0	0	0	0	0	0	0	0	0	2	3	4	1	0	0	0	4	2	0	ND
<i>Haemophilus influenzae</i>	0	0	0	0	0	2	0	9	39	129	294	124	46	44	23	10	5	53	0	8
<i>Moraxella catarrhalis</i>	0	0	0	2	1	6	17	29	13	34	52	20	41	38	5	0	0	1	0	ND
<i>Neisseria meningitidis</i>	0	0	0	8	11	13	107	226	140	39	9	0	0	0	0	0	0	0	0	ND
<i>Pasteurella multocida</i>	0	0	0	0	0	2	5	13	1	1	0	0	0	0	0	0	0	0	0	ND
<i>Staphylococcus aureus</i>	0	0	1	338	309	96	234	539	613	460	206	77	37	23	10	4	4	16	0	ND
<i>Staphylococcus coagulase negative</i>	0	0	0	6	5	4	6	4	7	1	2	1	2	0	1	0	1	0	0	ND
<i>Staphylococcus saprophyticus</i>	0	0	0	0	5	10	3	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus agalactiae</i>	0	0	0	5	12	3	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus pneumoniae</i>	0	41	327	594	103	24	20	27	30	16	16	3	0	0	0	0	0	0	0	ND
<i>Streptococcus pyogenes</i>	0	0	40	73	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus viridians</i> group	0	0	0	0	0	7	6	8	3	0	0	1	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 prior¹ to harmonisation (mg/L) S ≤ R >							
	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
General breakpoint							
						0.25/4	
Species specific breakpoints:							
Enterobacteriaceae							
<i>Pseudomonas</i> spp.							
<i>Acinetobacter</i> spp.							
<i>Staphylococcus</i> spp.					0.06/0.125		
<i>Streptococcus</i> spp.						0.25/1	
Alpha haemolytic streptococci							
<i>Streptococcus pneumoniae</i>					0.06/1	0.06/1	
<i>Enterococcus</i> spp.							
<i>Haemophilus influenzae</i>					0.5/4	0.5/4	
<i>Moraxella catarrhalis</i>					0.5/4	0.5/4	
Corynebacteria							
<i>Neisseria meningitidis</i>						1/1 (prophylactic)	
<i>Neisseria gonorrhoeae</i>						0.06/1	
<i>Pasteurella multocida</i>						0.5/0.5	
Anaerobes, Gram-positive							
Anaerobes, Gram-negative							
<i>Campylobacter</i> spp.							
<i>Helicobacter pylori</i>							

¹2005

4. Pharmacokinetics					
Dosage (mg)	500 x 1	1000 x 1			
Bioavailability (%)	60	60			
Cmax (mg/L)	3-5	15.0 ± 4.3			
Cmin (mg/L) 6 hr	-	-			
Total body clearance (L/g/h)					
T ½ (h), mean (range)	0.5	0.5			
AUC24h (mg.h/L)					
Fraction unbound (%)	20-50	20-50			
Volume of distribution (L/kg)	0.2	0.2			
Comments	<ul style="list-style-type: none"> • Pharmacokinetics are based on single doses. • Two values are given where references differ. Cells are left empty when data are not readily available. 				
References	<ul style="list-style-type: none"> • Josefsson K, Bergan T, <i>Chemotherapy</i> 1982; 28: 241-6 				

5. Pharmacodynamics

	<i>Streptococcus pneumoniae</i>				
%T>MIC for stasis : exp	25 – 35				
%T>MIC for 2 log drop : exp	35 – 45				
%T>MIC from clinical data					
Comments	<ul style="list-style-type: none"> • Cells are left empty when data are not readily available. • Beta-lactam antibiotics are bactericidal. The effect is dependent on the time during which the free concentration in serum is above the MIC value for the bacterium. 				
References	<ul style="list-style-type: none"> • Gerber AU et al. J Infect Disease 1986 : 153 ; 90-97 • Craig WA et al. 33rd ICAAC, 1993; Abstract 86 • Craig WA. In Antimicrobial Pharmacodynamics Theory and Clinical Practice. Eds. C Nightingale, TT Murakawa, PG Ambrose, Marcel Dekker Inc, Basel, 2002: pp 1-22 • MacGowan AP. Clin Microbiol Infect 2004: 52; 6-11 				

6. Monte Carlo simulations and PK/PD Breakpoints

Not available.

7. Clinical data

Several clinical studies suggest that phenoxymethylpenicillin is effective in upper respiratory tract infections such as sore throat, tonsillitis, acute sinusitis and otitis media caused by *S. pyogenes* and wild type *S. pneumoniae*. Erythema migrans can also be treated with phenoxymethylpenicillin.

- Bisno AL *Clin Infect Dis* 2002; 35: 113-25
- Balle V *Int J Pediatr Otorhinolaryngol* 1998; 45: 77-82
- Fredlund H *Scand J Infect Dis* 1987; 19: 459-66
- Bennet L *Scand J Infect Dis* 2003; 35: 129-31

8. Clinical breakpoints

Non-species-related breakpoints	There is insufficient evidence to set non-species-related breakpoints.
Species-related breakpoints	None.
Species without breakpoints	<p>The susceptibility of streptococci Groups A, B, C and G and <i>S. pneumoniae</i> to phenoxymethylpenicillin is inferred from the susceptibility to benzylpenicillin.</p> <p>Enterobacteriaceae, <i>Pseudomonas</i> spp., <i>Acinetobacter</i> spp., streptococci other than Groups A, B, C and G and <i>S. pneumoniae</i>, <i>Enterococcus</i> spp., <i>H. influenzae</i>, <i>M. catarrhalis</i>, <i>Neisseria</i> spp. and anaerobes were considered to be poor or inappropriate targets for phenoxymethylpenicillin and for that reason did not receive breakpoints.</p>
Clinical qualifications	Treatment is limited to pharyngotonsillitis, acute sinusitis, acute otitis media, community-acquired pneumonia, erythema migrans and streptococcal skin infection.
Dosage	Breakpoints apply to oral doses of 500 mg - 1 g x 3-4.
Additional comment	

9. EUCAST clinical MIC breakpoints

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

10. Exceptions noted for individual national committees

None