EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

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

Introduction

Benzylpenicillin is a penicillin that is available for parenteral use only.

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

Benzylpenicillin is used for therapy of acute meningitis, septicaemia, infective endocarditis, skin and soft tissue infections, community-acquired pneumonia and lung abscesses.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	600 mg x 4	1 g x 3-4	600 mg x 6	600 mg x 3	1 g x 4	1 g x 3-4
Maximum dose schedule	1.8 g x 6	3 g x 6	1.8 g x 6	3 g x 3	3 g x 6	3 g x 6
Available formulations	iv	iv	iv	iv	iv	iv

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
Bacteroides fragilis	0	0	0	0	0	0	0	0	0	0	1	19	42	7	0	1	3	2	0	ND
Bacteroides fragilis group	0	0	0	0	0	0	0	1	1	11	8	47	71	131	37	80	16	0	0	ND
Bacteroides thetaiotaomicron	0	0	0	0	0	0	0	0	0	0	0	0	1	14	1	1	1	7	0	ND
Clostridium butyricum	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	ND
Clostridium difficile	0	0	0	1	0	0	0	0	2	1	3	2	0	1	1	0	0	0	0	ND
Clostridium perfringens	0	0	0	12	22	23	11	6	2	0	1	0	0	0	0	0	0	0	0	0.12
Clostridium ramosum	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	ND
Clostridium septicum	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
Clostridium spp	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
Clostridium sporogenes	0	0	0	0	1	0	0	3	1	0	0	0	0	0	0	0	0	0	0	ND
Corynebacterium jeikeium	0	0	0	1	0	1	0	1	1	0	1	3	9	0	1	48	0	0	0	ND
Enterococcus avium	0	0	0	0	0	0	0	1	1	15	28	10	3	2	14	29	0	0	0	ND
Enterococcus casseliflavus	0	0	0	1	0	0	0	0	26	15	8	2	1	1	0	5	0	0	0	ND
Enterococcus faecalis	0	0	0	7	3	3	8	17	68	515	4899	4081	813	227	46	45	0	1	0	16
Enterococcus faecium	0	0	0	2	5	7	9	17	27	51	85	157	297	61	120	3026	88	127	42	16
Enterococcus gallinarum	0	0	0	0	0	1	0	0	9	32	29	5	3	4	2	26	0	0	0	8
Haemophilus influenzae	0	0	0	0	66	106	1199	6552	3528	1359	1195	370	3661	8	32	8	0	13	0	1
Haemophilus parainfluenzae	0	0	0	0	7	6	8	5	20	25	21	12	25	0	0	0	0	0	0	ND
Listeria monocytogenes	0	0	0	7	1	5	13	82	136	28	1	0	0	0	0	0	0	0	0	1
Neisseria gonorrhoeae	0	1	104	465	183	620	1818	1520	778	1023	365	76	46	424	2	1	0	0	0	ND
Neisseria meningitidis	0	0	11	144	571	765	201	127	54	3	1	0	0	0	0	0	0	0	0	0.25
Peptostreptococcus spp	0	1	0	3	2	2	5	3	0	0	0	0	0	0	0	0	0	0	0	ND
Propionibacterium acne	0	0	1	118	92	62	30	0	0	0	0	0	0	0	0	0	0	0	0	0.12
Staphylococcus aureus	0	0	85	553	547	223	199	308	891	937	794	720	2968	123	554	309	246	1	0	0.12
Staphylococcus aureus MRSA	0	0	0	0	0	0	0	0	0	0	1	2	1	1	3	19	172	0	0	0.12
Staphylococcus aureus MSSA	0	0	0	0	14	26	3	1	2	2	3	4	10	13	37	30	143	0	0	0.12

	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
Staphylococcus auricularis	0	0	0	7	9	2	7	1	2	7	3	6	5	2	5	9	0	0	0	ND
Staphylococcus capitis	0	0	0	31	19	5	12	20	13	8	11	12	14	24	28	17	0	0	0	ND
Staphylococcus coagulase negative	0	0	0	6	54	20	32	52	60	44	54	84	186	184	176	110	188	0	0	ND
Staphylococcus coagulase negative MRSE	0	0	0	0	0	2	0	0	4	0	2	4	2	20	40	80	162	0	0	ND
Staphylococcus epidermidis	0	0	3	227	143	81	140	205	351	500	669	842	1028	756	514	275	53	0	0	ND
Staphylococcus epidermidis MSSE	0	0	0	3	13	4	2	3	0	2	4	5	10	9	14	8	7	0	0	ND
Staphylococcus haemolyticus	0	0	0	14	21	7	9	16	11	13	19	20	37	65	87	343	32	0	0	ND
Staphylococcus hominis	0	0	0	38	9	5	13	27	28	32	39	42	88	83	78	26	0	0	0	ND
Staphylococcus lugdunensis	0	0	0	7	4	8	26	7	2	3	9	4	6	3	4	3	0	0	0	0.12
Staphylococcus saprophyticus	0	0	0	7	8	15	28	54	4	3	10	3	13	18	20	8	0	0	0	ND
Staphylococcus simulans	0	0	0	8	6	3	4	3	2	13	4	12	13	13	15	12	0	0	0	ND
Staphylococcus warneri	0	0	0	8	9	9	5	6	13	16	11	20	14	21	17	13	0	0	0	ND
Staphylococcus xylosis	0	0	0	4	1	1	4	0	3	3	6	6	8	9	1	2	0	0	0	ND
Streptococcus acidominimus	0	0	0	0	8	3	2	0	2	1	0	1	1	0	0	0	0	0	0	ND
Streptococcus agalactiae	0	0	8	178	1490	1332	84	4	0	1	0	0	0	0	0	0	0	0	0	0.12
Streptococcus anginosus	0	0	1	37	161	104	23	11	6	4	2	0	0	0	0	0	0	0	0	0.25
Streptococcus bovis	0	0	0	0	36	31	12	3	0	0	0	0	0	0	0	0	0	0	0	0.25
Streptococcus constellatus	0	0	0	39	263	97	38	3	1	1	1	1	2	0	2	1	0	0	0	0.25
Streptococcus dysgalactiae	0	0	0	0	183	12	2	0	1	0	0	0	1	0	0	0	0	0	0	ND
Streptococcus equinus	0	0	0	0	19	7	1	0	0	0	0	0	0	0	0	0	0	0	0	ND
Streptococcus gordonii	0	0	0	0	9	1	1	0	0	0	1	0	0	0	0	0	0	0	0	ND
Streptococcus group C	0	0	0	159	38	17	1	0	0	0	0	0	0	0	0	0	0	0	0	0.06
Streptococcus group F	0	0	0	6	19	24	6	1	0	0	0	0	0	0	0	0	0	0	0	ND
Streptococcus group G	1	59	102	24	4	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0.06
Streptococcus intermedius	0	0	0	11	31	18	7	5	5	5	2	1	2	0	0	0	0	0	0	0.25
Streptococcus milleri	0	0	0	28	55	27	16	0	2	1	0	0	0	0	1	0	0	0	0	0.12
Streptococcus mitis	0	0	0	94	190	92	106	69	35	38	25	23	19	3	1	4	0	0	0	0.25
Streptococcus mutans	0	0	0	13	21	2	3	3	1	0	1	1	0	0	0	0	0	0	0	0.25
Streptococcus oralis	0	0	6	85	218	94	80	29	24	20	19	14	16	2	0	0	0	0	0	0.25

	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
Streptococcus parasanguis	0	0	0	0	19	7	13	13	4	3	5	1	0	0	0	0	0	0	0	0.25
Streptococcus pneumoniae	108	899	5425	14387	5978	1935	1052	1164	985	981	2551	2005	172	0	0	0	0	0	0	0.06
Streptococcus pyogenes	9	180	1464	1891	60	7	2	2	0	0	0	0	0	0	0	0	0	0	0	0.06
Streptococcus salivarius	0	0	0	10	50	47	45	15	17	7	3	2	2	0	0	0	0	0	0	0.25
Streptococcus sanguis	0	0	0	30	38	35	40	25	27	9	14	5	4	1	0	0	0	0	0	0.25
Streptococcus vestibularis	0	0	0	0	2	5	2	1	3	1	0	0	0	0	0	0	0	0	0	0.25
Streptococcus viridians group	0	0	13	57	146	171	76	43	28	16	18	9	8	0	0	3	1	0	0	0

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[1] to harmonisation (mg/L) S≤ / R>

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI[2]
General breakpoint							
		0.25/16	0.25/4	0.12/1		1/4	
Species specific breakpoints:							
Enterobacteriaceae							
Pseudomonas spp.							
Acinetobacter spp.							
Staphylococcus spp.	0.12/0.12	0.25/0.25	0.25/0.25		0.064/0.125		0.12/0.12
Streptococcus spp.	0.12/0.12	0.25/16	0.25/0.25		0.12/-	0.25/1	0.12/-
Alpha haemolytic streptococci	0.12/0.12	0.25/16			0.125/2	0.25/1	0.12/2
Streptococcus pneumoniae	0.064/1	0.064/1	0.064/1		0.064/1	0.064/1	0.06/1
Enterococcus spp.					4/8	0.25/4	8/8
Haemophilus influenzae					1/4	1/1	
Moraxella catarrhalis					1/4	1/1	
Corynebacteria							1/2
Neisseria meningitidis	0.06/0.06	0.06/1	0.06/1		0.06/0.25	0.25/1	0.06/0.25
Neisseria gonorrhoeae	0.06/1	0.06/1	0.25/1		0.06/1	0.06/1	0.06/1
Pasteurella multocida	0.12/0.12						
Anaerobes, Gram-positive					0.25/1	0.25/1	0.5/1
Anaerobes, Gram-negative	1/1				β-lactamase +/-	β-lactamase +/-	0.5/1
Campylobacter spp.							
Helicobacter pylori	1/1				0.5/0.5	0.5/1	

[1]2005
[2]CLSI breakpoints converted to EUCAST terminology.

4. Pharmacokinetics

Dosage (mg)	600 x 1	2000 x 1	3000 x 1	
Bioavailability (%)	-	-	-	
Cmax (mg/L)	12	20	40	
Cmin (mg/L)	-			
Total body clearance (L/h)	28.6			
T ½ (h), mean (range)	0.75			
AUC24h (mg.h/L)	-			
Fraction unbound (%)	35-55			
Volume of distribution (L/kG)	0.2-0.7		0.2-0.7	
Comments	• Pharmacokinetics are based on single doses. • Dosing across Europe for i.v benzylpenicillin varies from 600 mg x 4 (2.4g/day) to 3g x 6 (18g/day). • Two values are given where references differ. Cells are left empty when data are not readily available.			
References	• Bush K. In: Antibiotics and Chemotherapy. 2003. Eds: Finch RG, Greendwood D, Norrby SR, Whitley RJ. Churchill Livingstone, Edinburgh, 2003: 224-258 • Bryskier, Penicillins. In Antimicrobial Agents, 2005: pp113-162, Table 8			

5. Pharmacodynamics

	Streptococcus pneumoniae	Staphylococci			
*%f*T>MIC for stasis : exp	25-35	15-20			
*%f*T>MIC for 2 log drop : exp	35-45				
*%f*T>MIC from clinical data	40				
Comments	• Cells are left empty when data are not readily available.				
References	• 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: 1-22 • MacGowan AP. Clin Microbiol Infect 2004: 52; 6-11				

6. Monte Carlo simulations and Pk/Pd Breakpoints

The following iv amoxicillin pharmacokinetics were modelled:
Volume of distribution 26±1 L
Serum half life 0.75±0.2h
Fraction unbound 37.5%

Doses modelled were those reported to be employed across Europe, namely 600 mg x 4; 600 mg x 6; 900 mg x 6; 1g x 3; 1.2g x 4; 1.2g x6; 1.5g x 4; 2.4g x 6; 3g x 3. The most common doses used were 600 mg x 4, 1.2g x 4 and 1.2g x 6.

A fT>MIC target of 30-40% was used. For a >90% target attainment rate, pharmacodynamic breakpoints range from 0.12-4 mg/L for the three most common doses.

Target Attainment Rate (%)																		
Dose	600 mg x 4		600 mg x 6		900 mg x 6		1g x 3		1.2g x 4		1.2g x 6		1.5g x 4		2.4g x 6		3g x 3	
T>MIC%	30	40	30	40	30	40	30	40	30	40	30	40	30	40	30	40	30	40
MIC(mg/L)																		
0.06	100	97	-	-	-	-	98	95	100	98	-	-	100	99	-	-	100	97
0.12	98	95	100	100	100	100	97	91	100	97	-	-	100	98	-	-	99	96
0.25	97	90	100	98	100	99	94	81	98	95	100	100	99	96	-	-	97	93
0.5	92	76	98	95	100	97	87	65	97	90	100	98	97	92	100	100	96	87
1	76	46	95	85	97	92	71	37	92	76	98	95	95	82	100	98	92	76
2	32	3	78	48	91	75	33	4	76	46	95	85	84	59	98	95	82	54
4	0	0	7	0	57	18	1	0	32	3	78	48	50	14	95	85	59	20
8	0	0	0	0	0	0	0	0	0	0	7	0	1	0	78	48	14	1

7. Clinical data

The bacteriological and clinical efficacy of benzylpenicillin has been evaluated in several trials involving patients with acute meningitis, septicaemia, infective endocarditis, skin and soft tissue infections, and community-acquired pneumonia. These trials support the efficacy of benzyl penicillin for treatment of these infections caused by wild type isolates. In particular there is convincing data supporting the use of benzylpenicillin in community-acquired pneumonia, and in skin and soft tissue infections caused by streptococci.

- Addo-Yobo E et al. Lancet 2004; 364: 1141–8
- Bonnetblanc JM, Bédane C. Am J Clin Dermatol 2003; 4: 157-63
- Whitby M, Finch R. Drugs. 1986; 31: 266-78
- Watanakunakorn C. Scand J Infect Dis Suppl 1984; 42: 110-6
- Yu VL et al. Clin Infect Dis. 2003; 37: 230-7
- MacGowan AP, J Antimicrobial Chemother 1992; 29: 239

8. Clinical breakpoints

Non-species-related breakpoints	Non-species related breakpoints have been determined using Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints. A fT>MIC target of 30-40% and a >90% target attainment rate for the most common dose of 600 mg x 3-4 results in an S breakpoint of 0.25 mg/L. The R breakpoint of 2 mg/L is based on a 2.4g x 6 dose.
Species-related breakpoints	For *Staphylococcus* spp. breakpoints are S ≤0.12 / R >0.12 mg/L. These are essentially epidemiological cut-offs. Most staphylococci are penicillinase-producers and the breakpoints will separate most penicillinase-producers from non-producers. Isolates resistant to oxacillin or cefoxitin will be resistant to benzylpenicillin. For streptococci Groups A, B, C, G breakpoints are S ≤0.25 / R >0.25 mg/L. The R breakpoint was reduced to 0.25 mg/L because isolates with MICs above the S breakpoint are very rare or not yet reported. For *S. pneumoniae* breakpoints are S ≤0.06 / R >2 mg/L. The S breakpoint was reduced to 0.06 mg/L to ensure that isolates with modified PBPs are not reported susceptible. For streptococci other than Groups A, B, C, G and *S. pneumoniae* breakpoints are S ≤0.25 / R >2 mg/L. For *Neisseria gonorrhoeae* breakpoints are S ≤0.06 / R >1 mg/L. The S breakpoint was reduced to 0.06 mg/L to ensure that isolates with a resistance mechanism are not reported susceptible. The R breakpoint was reduced to 1 mg/L to meet international consensus. For *Neisseria meningitidis* breakpoints are S ≤0.06 / R >0.25 mg/L. The breakpoint were reduced to S ≤0.06 / R >0.25 mg/L to meet international consensus. For Gram-negative and Gram-positive anaerobe breakpoints are S ≤0.25 / R >0.5 mg/L. The R breakpoint was reduced to 0.5 mg/L to ensure that beta-lactamase producing isolates were characterized as resistant.

Species without breakpoints	For most infections, breakpoints for *Enterococcus* spp. are considered inappropriate but refer to national guidelines for the treatment of endocarditis. For *H. influenzae* there was considered to be insufficient evidence to set breakpoints. Enterobacteriaceae, *Pseudomonas* spp., *Acinetobacter* spp. and *M. catarrhalis* were considered poor targets for benzylpenicillin therapy and for that reason did not receive breakpoints.
Clinical qualifications	In endocarditis caused by viridians streptococci, refer to national or international endocarditis guidelines for breakpoints.
Dosage	Dosing across Europe varies from 600 mg x 4 (2.4g/day) to 2.4g x 6 (14.4g/day). The non-species-related S and R breakpoints are based on 600 mg x 4 (2.4g/day) and 2.4g x 6 (14.4g/day) doses respectively.
Additional comment	

9. EUCAST clinical MIC breakpoints

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

10. Exceptions noted for individual national committees

None