

Benzylpenicillin: Rationale for EUCAST Clinical Breakpoints

Current version	2.0	September 2023
Previous versions	1.0	22/11/2010

Introduction

Benzylpenicillin is active against wild type staphylococci, streptococci (including *Streptococcus pneumoniae*), *Neisseria meningitidis* and *Neisseria gonorrhoeae*, and has some useful activity against many Gram-positive anaerobic bacteria. 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* and some other streptococci.

This version is extracted from version 1.0, and will be format for future updates. Previous versions are available on request.

Dosages related to clinical breakpoints

Standard dosage: 0.6 g (1 MU) x 4 iv

High dosage: 1.2 g (2 MU) x 6 iv

MIC distributions and epidemiological cut-off (ECOFF) values

MIC distributions and ECOFFs can be found at <https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=init>

Pharmacokinetics

PK parameter	Pharmacological studies		Efficacy studies	
	Rumble et al. 1986	Visser et al. 1993		
Dosage	0.6 g iv	7.2 g/24 h continuous infusion		
C _{max} (mg/L)				
C _{ss} (mg/L) (mean, SD, range)		13.7 (10.6, 5.2-53.6)		
Total body clearance (L/h) mean, (SD)	32.6 (7.4)	24 (6)		
T ½ (h), mean (SD)	0.90			
AUC ₀₋₁₂ (mg.h/L)				
AUC ₀₋₂₄ (mg.h/L)				
AUC _{0-∞} (mg.h/L)				
Fraction unbound (%)(range)		55 (13-70)		
Volume of distribution _{ss} (L)	12 (V _c)	26		

* Values expressed as median and [interquartile range]

Pharmacodynamics

Index	<i>S. pneumoniae</i>	<i>S. aureus</i>			
	Range	Range			
f%T>MIC for bacteriostasis	25-35	15-20			
f%T>MIC for 2-log ₁₀ kill	35-45				
f%T>MIC from clinical data	40				

Monte Carlo simulations

A simulation was carried out in Pmetrics. The following assumptions were made: a 1 compartment model, CL 24L/h, V 26L, 25% CV on each parameter, fraction unbound 55% (fixed) (based on Visser et al. 1993)

Dosage	0.6 g x 4	1.2 g x 4	1.2 g x 6	2.4 g x 6	3 g x 3	3 g x 4	3 g x 6
f%T>MIC	40	40	40	40	40	40	40
0.06	97.1	98.3	100	100	99.3	99.1	100
0.125	93.3	97.1	100	100	98.3	98.8	100
0.25	81.9	93.0	100	100	97.0	97.6	100
0.5	61.0	81.9	99.8	100	93.7	94.5	100
1	26.8	61.0	99.5	99.8	84.9	86.1	99.9
2	6.6	26.8	95.0	99.5	65.6	68.4	99.8
4	0.9	6.6	49.6	95.0	32.8	38.8	97.9
8	0.1	0.1	8.1	49.6	8.6	10.5	72.0

Clinical studies

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 benzylpenicillin for treatment of these infections caused by wild type isolates. In particular, there are convincing data supporting the use of benzylpenicillin in community-acquired pneumonia, and in skin and soft tissue infections caused by streptococci.

The summary of product characteristics can be found at <https://www.medicines.org.uk/emc/product/3828/smpc/print>

Clinical breakpoints

The clinical breakpoints for benzylpenicillin can be found in the most recent version of the Breakpoint tables: https://www.eucast.org/clinical_breakpoints

References

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