



EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Cefotaxime

Rationale for the EUCAST clinical breakpoints, version 1.0

26th September 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. Cefotaxime: Rationale for the clinical breakpoints, version 1.0, 2010. <http://www.eucast.org>.

Introduction

The cephalosporins are a large group of compounds with a 6-membered dihydrothiazine ring fused to a beta-lactam ring. They are derivatives of 7-aminocephalosporanic acid with various modifications to several ring positions resulting in differences in activity, beta-lactamase stability, and pharmacokinetic properties.

Cefotaxime is a 3rd generation cephalosporin with potent antimicrobial activity and is more stable to beta-lactamases than most earlier cephalosporins. It is bactericidal at concentrations close to the MIC. Cefotaxime is available only for parenteral administration.

Cefotaxime is used for therapy of septicaemia, meningitis, post-operative sepsis, nosocomial pneumonia, community acquired pneumonia, and complicated skin- and soft tissue infections caused by Enterobacteriaceae, *Staphylococcus* spp. (methicillin susceptible), *Streptococcus* spp. (including *S. pneumoniae*) and *Haemophilus influenzae*. Cefotaxime is not considered to have useful activity against *Enterococcus* spp., *Acinetobacter* spp., *Pseudomonas aeruginosa* or Gram-negative anaerobic bacteria.

Cefotaxime resistance in *S. pneumoniae* may be conferred by alterations in penicillin-binding proteins. In *Enterobacteriaceae* resistance to cefotaxime may be conferred by several mechanisms alone or in combination, including the production of some beta-lactamases (ESBLs, AmpC and others), porin loss and alterations in efflux pumps.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	2 g x 3	1 g x 3	1 g x 3 - 4	2 g x 3	1 g x 3	1 g x 3
Maximum dose schedule	3 g x 4	3 g x 4	2 g x 6	2 g x 3	2-3 g x 3-4	3 g x 3
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
<i>Acinetobacter baumannii</i>	0	0	0	0	1	2	0	26	6	14	25	107	437	458	187	224	48	164	5	ND
<i>Acinetobacter calcoaceticus</i>	0	0	0	0	0	0	0	0	0	1	0	0	3	1	0	1	0	0	0	ND
<i>Acinetobacter lwoffii</i>	0	0	0	0	0	0	0	31	23	45	64	38	65	35	9	7	0	0	15	ND
<i>Acinetobacter</i> spp	0	0	0	0	0	0	0	33	35	61	88	92	146	116	52	25	3	0	22	ND
<i>Burkholderia cepacia</i>	0	0	0	0	0	0	0	0	0	7	4	5	9	5	4	6	0	1	0	ND
<i>Citrobacter freundii</i>	0	0	0	0	1	3	42	5	5	2	3	4	3	18	18	5	1	0	0	0.5
<i>Citrobacter</i> spp	0	0	0	0	17	35	19	11	10	9	2	4	3	4	4	3	0	0	0	0.5
<i>Enterobacter aerogenes</i>	0	0	0	0	7	28	33	9	3	3	4	2	8	15	8	9	6	11	0	0.5
<i>Enterobacter cloacae</i>	0	0	1	6	19	64	213	189	129	44	26	19	35	53	90	59	56	58	12	0.5
<i>Enterobacter</i> spp	0	0	0	1	19	47	79	45	29	22	7	10	4	20	11	4	0	5	0	0.5
<i>Escherichia coli</i>	0	5	40	282	1656	4953	2591	485	194	100	59	56	44	58	83	134	26	35	28	0.25
<i>Haemophilus influenzae</i>	44	362	3497	6087	2512	823	139	32	7	4	0	1	0	0	0	0	0	0	0	0.064
<i>Klebsiella oxytoca</i>	0	1	7	55	155	80	19	22	9	12	13	14	9	4	11	11	0	1	0	0.125
<i>Klebsiella pneumoniae</i>	0	2	12	99	523	745	271	84	65	18	27	34	54	43	46	68	105	199	20	0.125
<i>Klebsiella</i> spp	0	5	21	86	103	73	34	13	16	11	4	1	2	1	0	1	1	0	0	0.125
<i>Moraxella catarrhalis</i>	0	0	0	27	107	477	429	268	902	517	9	1	0	0	0	0	0	0	0	0.25
<i>Morganella morganii</i>	0	8	27	35	24	18	12	8	6	2	7	10	4	2	2	0	0	1	0	ND
<i>Neisseria gonorrhoeae</i>	45	223	169	194	217	103	82	31	4	0	0	0	0	0	0	0	0	0	0	0.016
<i>Neisseria meningitidis</i>	352	436	179	62	12	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0.016
<i>Proteus mirabilis</i>	0	1	107	212	71	11	2	3	3	13	1	1	2	1	2	4	1	1	0	0.064
<i>Proteus vulgaris</i>	0	0	14	22	27	23	20	11	3	0	0	0	4	2	1	0	0	4	0	0.125
<i>Pseudomonas aeruginosa</i>	0	0	0	0	2	3	2	2	10	13	21	93	412	419	274	155	79	14	0	32
<i>Salmonella</i> spp	0	0	0	0	3	436	10648	1281	184	16	2	6	7	35	11	0	0	0	0	0.5
<i>Serratia marcescens</i>	0	0	0	0	0	3	51	35	34	44	12	19	33	25	24	9	1	48	0	1
<i>Serratia</i> spp	0	0	0	0	1	7	42	43	43	26	13	5	20	35	7	6	1	1	0	1
<i>Staphylococcus aureus</i>	0	0	2	0	1	3	18	103	383	2174	2383	400	92	25	242	10	6	15	0	4

	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 capitis</i>	0	0	0	0	0	0	6	20	42	51	11	9	7	1	6	0	0	0	0	2
<i>Staphylococcus coagulase negative</i>	0	0	0	1	1	2	17	57	98	76	57	63	46	13	14	41	1	3	0	2
<i>Staphylococcus epidermidis</i>	0	0	0	0	0	5	28	114	204	113	137	408	363	51	59	1	0	0	0	2
<i>Staphylococcus hominis</i>	0	0	0	0	0	0	3	8	16	60	55	115	58	14	16	0	0	0	0	ND
<i>Staphylococcus saprophyticus</i>	0	0	0	0	0	0	0	0	0	3	12	6	0	0	0	0	0	0	0	ND
<i>Staphylococcus warneri</i>	0	0	0	0	0	0	0	6	23	14	4	4	2	0	0	0	0	0	0	ND
<i>Stenotrophomonas maltophilia</i>	0	0	0	0	0	0	1	0	0	2	11	13	8	24	18	10	21	49	0	ND
<i>Streptococcus agalactiae</i>	0	0	0	16	556	398	57	8	0	0	0	0	0	0	0	2	0	0	0	0.125
<i>Streptococcus anginosus</i>	0	0	0	0	4	10	26	4	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus</i> group G	0	1	9	151	10	21	0	1	0	0	0	0	0	0	0	0	0	0	0	0.125
<i>Streptococcus oralis</i>	0	1	8	17	46	59	30	19	7	2	3	2	2	0	0	0	0	0	0	ND
<i>Streptococcus pneumoniae</i>	157	551	3535	5790	1108	449	328	240	339	211	74	13	2	3	0	0	0	0	0	0.064
<i>Streptococcus pyogenes</i>	1	21	402	218	27	22	1	0	0	0	0	0	0	0	0	0	0	0	0	0.064
<i>Streptococcus viridans</i> group	1	3	16	39	113	111	155	129	58	24	15	6	9	6	1	1	0	1	1	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	CLSI²
General breakpoint							
		4/32	4/16	2/8	1/4	8/8	
Species specific breakpoints:							
Enterobacteriaceae	1/1	4/32			1/4	0.5/1	8/32
<i>Pseudomonas</i> spp.	1/1						8/32
<i>Acinetobacter</i> spp.	1/1						8/32
<i>Staphylococcus</i> spp.	1/1				2/8		8/32
<i>Streptococcus</i> spp.	1/1	0.5/16				0.12/2	0.5/- (beta-haem) 1/2 (viridians)
<i>Streptococcus pneumoniae</i>	1/1	0.5/2	0.5/1		0.5/2	0.12/1	0.5/1 (meningitis) 0.5/2 (other)
<i>Enterococcus</i> spp.							2/4
<i>Haemophilus influenzae</i>	1/1	all S			0.12/2	0.12/1	2/-
<i>Moraxella catarrhalis</i>	1/1	all S			0.12/2	0.12/1	2/-
Corynebacteria							1/4
<i>Neisseria meningitidis</i>	1/1	0.25/-	0.5/1		0.25/-	0.06/1	0.12/-
<i>Neisseria gonorrhoeae</i>	1/1		0.25/-		0.25/-	0.06/1	0.5/-
<i>Pasteurella multocida</i>						0.12/1	
Anaerobes, Gram-positive		4/32					16/16
Anaerobes, Gram-negative		4/32					16/16
<i>Campylobacter</i> spp.		4/32					
<i>Helicobacter pylori</i>							

¹2005

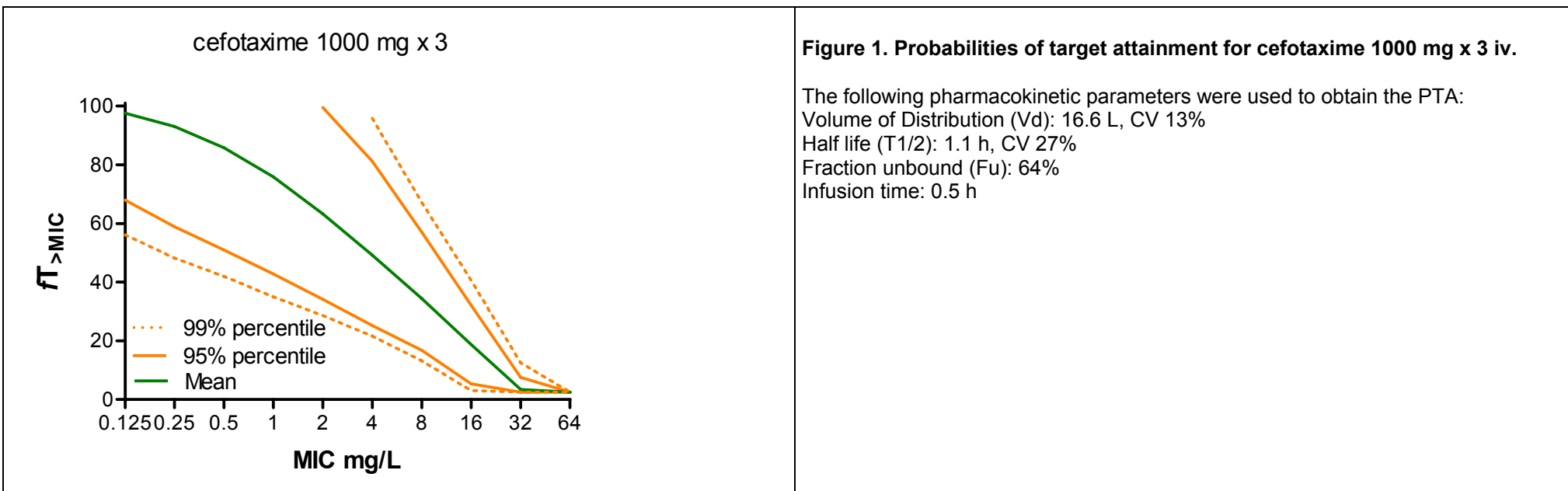
²CLSI breakpoints converted to EUCAST terminology.

4. Pharmacokinetics				
Dosage (mg)	1000 x 3 iv			
Cmax (mg/L)	25-80			
Cmin (mg/L)				
Total body clearance (L/h)				
T ½ (h), mean (range)	1-1.2			
AUC24h (mg.h/L)	40- 70			
Fraction unbound (%)	60-97			
Volume of distribution (L/kg)	0.2-0.3			
Comments	<ul style="list-style-type: none"> • Two values are given where references differ. Cells are left empty when data are not readily available. • The metabolite desacetylcefotaxime has 10% antimicrobial activity of the parent compound and has a half life of 2-4 hours. • Peak serum concentrations are achieved in 30-60 min. 			
References	<ul style="list-style-type: none"> • Bryskier A. In Antimicrobial Agents 2005. ASM; 174 • Finch R. In Antibiotic and Chemotherapy 1997. Churchill-Livingstone; 235-6 • Kemmerich et al., J Antimicrob Chemother 1983; 83: 429 • Standiford et al., Rev Inf Dis 1982; 4 Suppl: S585 			

5. Pharmacodynamics				
	<i>Enterobacteriaceae</i>	<i>Streptococcus pneumoniae</i>	<i>S. aureus</i>	
%fT>MIC for bacteriostasis	36-40	36-40	20-28	
%fT>MIC for 2 log reduction				
%fT>MIC from clinical data				
Comments	<ul style="list-style-type: none"> • %fT>MIC is the dominant pharmacodynamic index. 			
References	<ul style="list-style-type: none"> • Craig. Diagn Microbiol Infect Dis 1995; 22: 89 			

6. Monte Carlo simulations and Pk/Pd breakpoints

Probabilities of target attainment (PTA) for cefotaxime 1000 mg x 3 iv are shown in figure 1.



7. Clinical data

Clinical trials have shown the efficacy of cefotaxime treatment of patients with septicaemia, meningitis, post-operative sepsis, nosocomial pneumonia, community acquired pneumonia, and complicated skin and soft tissue infections caused by microorganisms categorized as wild type.

8. Clinical breakpoints

Non-species-related breakpoints	<p>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.</p> <p>A 2 log drop in viable Gram-negative organisms in animal model infections requires 40-50% $fT > MIC$. The 95% confidence interval of the 1 g dose administered by bolus intravenous injection results in an S/I breakpoint of 1 mg/L. The I/R breakpoint of 2 mg/L is based on a 2g dose. These breakpoints render wild type Enterobacteriaceae, <i>Staphylococcus</i> spp., <i>Streptococcus</i> spp. (including <i>S. pneumoniae</i>), <i>Haemophilus influenzae</i> and <i>Neisseria</i> spp. susceptible.</p>
Species-related breakpoints	<p>For Enterobacteriaceae and <i>Moraxella catarrhalis</i> the breakpoints are S \leq1 mg/L / R $>$2 mg/L.</p> <p>For <i>Streptococcus pneumoniae</i> the breakpoints are S \leq0.5 mg/L / R $>$2 mg/L. The S/I breakpoint was reduced to 0.5 mg/L because high dose therapy is necessary for isolates with reduced susceptibility.</p> <p>For <i>Haemophilus influenzae</i>, <i>Neisseria gonorrhoeae</i> and <i>Neisseria meningitidis</i> breakpoints were reduced to S \leq0.12 mg/L / R $>$0.12 mg/L and for streptococci other than <i>S. pneumoniae</i> and Groups A, B, C and G to S \leq0.5 mg/L / R $>$0.5 mg/L as isolates with reduced susceptibility are rare or have not been reported and clinical outcome is uncertain.</p>
Species without breakpoints	<p>For <i>Staphylococcus</i> spp. susceptibility to cefotaxime is inferred from the cefoxitin susceptibility.</p> <p>For group A, B, C and G streptococci susceptibility to cefotaxime is inferred from the benzylpenicillin susceptibility.</p> <p><i>Pseudomonas aeruginosa</i>, <i>Acinetobacter</i> spp., <i>Enterococcus</i> spp., and anaerobes were considered poor targets for cefotaxime therapy and for that reason did not receive breakpoints.</p>
Clinical qualifications	
Dosage	<p>Breakpoints apply to a daily intravenous dose of 1 g x 3 and a high dose of at least 2 g x 3.</p> <p>For central nervous system infections a high dose is required (Tunkel AR, Scheld WM. Acute meningitis. In: Principles and Practice of Infectious Diseases. Mandell, Bennett, Dolin eds. Elsevier Churchill Livingstone 6th Edn 2004, pp 1083-1126).</p>
Additional comment	

9. EUCAST clinical MIC breakpoints

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

10. Exceptions noted for individual national committees

None