



# EUCAST

EUROPEAN COMMITTEE  
ON ANTIMICROBIAL  
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

**Cefuroxime iv**

**Rationale for the EUCAST clinical breakpoints, version 1.0**

26<sup>th</sup> 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. Cefuroxime: 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.

Cefuroxime is a 2<sup>nd</sup> generation cephalosporin with moderate antimicrobial activity and moderate resistance to hydrolysis by beta-lactamases. It is bactericidal at concentrations close to the MIC. Cefuroxime is available for parenteral administration and, in the form of cefuroxime axetil (see cefuroxime axetil rationale document), for oral use.

Cefuroxime is used for intravenous for therapy of complicated urinary tract infections with or without septicaemia, community acquired pneumonia, and complicated skin and soft tissue infections caused by *Staphylococcus* spp., *Streptococcus* spp. (including *S. pneumoniae*), *Haemophilus influenzae* and Enterobacteriaceae, especially *Escherichia coli*. Cefuroxime is only marginally active against many Enterobacteriaceae and is not considered to have useful activity against *Pseudomonas* spp., *Stenotrophomonas maltophilia*, *Acinetobacter* spp., *Enterococcus* spp. or anaerobic bacteria.

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

## 1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	0.75g x 3	0.75g x 3	0.75g x 3	1.5g x 3	0.75-1.5g x 3	0.75-1.5g x 3
Maximum dose schedule	1.5g x 3	1.5g x 3	1.5g x 3	1.5g x 3	1.5g x 3	1.5g x 3
Available formulations <sup>1</sup>	iv	iv	iv	iv	iv	iv

<sup>1</sup>See cefuroxime axetil rationale document for oral use

## 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	0	0	1	0	0	2	13	21	97	311	2841	27	14	14	0	ND
<i>Acinetobacter lwoffii</i>	0	0	0	0	0	0	3	2	35	32	75	110	122	96	165	21	12	0	16	ND
<i>Acinetobacter</i> spp	0	0	0	0	0	2	11	7	19	38	150	256	415	724	7313	25	7	15	0	ND
<i>Citrobacter freundii</i>	0	0	0	0	0	0	1	0	43	43	410	624	199	79	399	30	223	12	31	8
<i>Citrobacter koseri</i>	0	0	0	0	0	0	1	0	2	7	66	316	66	26	40	0	0	0	0	8
<i>Citrobacter</i> spp	0	0	0	0	0	0	1	7	30	64	390	1027	312	164	506	39	85	15	40	8
<i>Clostridium difficile</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	401	0	ND
<i>Enterobacter aerogenes</i>	0	0	0	0	0	0	0	3	11	43	368	642	284	128	756	28	171	55	47	8
<i>Enterobacter agglomerans</i>	0	0	0	0	0	0	0	0	2	19	60	81	9	2	3	5	1	0	0	ND
<i>Enterobacter cloacae</i>	0	0	0	0	0	0	4	2	31	107	252	1056	2693	1414	2855	175	864	425	84	16
<i>Enterobacter dissolvens</i>	0	0	0	0	0	0	0	0	0	3	3	26	39	5	2	0	3	0	0	ND
<i>Enterobacter</i> spp	0	0	0	0	0	0	4	10	30	148	569	1369	2057	1171	3688	48	247	24	89	16
<i>Escherichia coli</i>	0	0	1	1	1	5	93	228	1954	6571	27444	60621	18911	4177	3771	263	260	98	73	8
<i>Haemophilus influenzae</i>	0	0	1	0	23	129	1096	4623	35400	31470	9949	9864	1376	256	77	15	0	0	256	2
<i>Haemophilus parainfluenzae</i>	0	0	0	0	0	14	175	220	265	110	39	23	1	1	2	0	0	0	0	1
<i>Klebsiella oxytoca</i>	0	0	0	0	0	0	5	20	242	1102	1639	1060	340	158	519	37	139	48	83	8
<i>Klebsiella pneumoniae</i>	0	0	0	0	0	8	68	193	1211	5875	15222	9068	3263	2101	4833	227	181	119	91	8
<i>Klebsiella</i> spp	0	0	0	0	1	0	6	13	51	200	467	180	47	44	34	14	7	4	0	8
<i>Legionella pneumophila</i>	0	0	0	0	0	0	0	2	10	26	34	21	7	0	0	0	0	0	0	ND
<i>Moraxella catarrhalis</i>	0	0	0	1	2	18	168	839	3586	5997	3913	659	175	23	0	0	0	0	0	4
<i>Morganella morganii</i>	0	0	0	0	3	0	2	2	5	21	29	32	70	202	887	162	78	20	8	ND
<i>Neisseria gonorrhoeae</i>	0	4	53	59	142	226	171	87	87	24	6	0	3	0	0	0	0	0	0	0.12
<i>Neisseria meningitidis</i>	0	0	4	3	39	80	131	15	6	2	0	0	0	0	1	0	0	0	0	0.12
<i>Proteus mirabilis</i>	0	0	0	0	0	0	24	140	1587	5530	3645	642	172	72	317	25	210	10	120	4
<i>Proteus vulgaris</i>	0	0	0	0	0	0	0	0	9	29	27	29	33	40	294	33	219	74	0	ND
<i>Providencia rettgeri</i>	0	0	0	0	0	0	27	11	9	8	5	2	2	4	10	0	0	0	0	ND

	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>Providencia stuartii</i>	0	0	0	0	0	0	3	1	9	14	21	21	22	33	63	0	0	0	0	ND
<i>Salmonella enteritidis</i>	0	0	0	0	0	0	0	1	0	2	12	294	234	12	0	0	0	0	0	16
<i>Salmonella</i> spp	0	0	0	0	0	0	1	5	6	25	330	2508	1554	161	29	0	0	0	0	16
<i>Salmonella typhi</i>	0	0	0	0	0	0	0	1	0	1	68	202	44	4	3	0	0	0	0	16
<i>Salmonella typhimurium</i>	0	0	0	0	0	0	0	0	1	3	17	88	57	7	16	0	0	0	0	16
<i>Serratia liquefaciens</i>	0	0	0	0	0	0	0	0	0	4	5	7	5	33	85	12	1	0	0	ND
<i>Shigella flexneri</i>	0	0	0	0	0	0	1	0	0	39	201	82	9	1	0	0	0	0	0	8
<i>Shigella sonnei</i>	0	0	0	0	0	0	1	0	1	6	144	254	17	0	2	0	0	0	0	8
<i>Staphylococcus aureus</i>	0	0	0	2	3	2	55	363	1265	7253	1443	234	125	890	247	1	0	8	0	4
<i>Staphylococcus capitis</i>	0	0	0	0	0	0	23	37	53	13	8	6	1	1	7	0	0	0	0	ND
<i>Staphylococcus</i>	0	0	0	0	0	5	69	51	48	63	64	55	37	7	25	0	0	2	0	ND
<i>Staphylococcus hominis</i>	0	0	0	0	0	0	7	17	65	81	86	40	15	3	21	0	0	0	0	ND
<i>Streptococcus agalactiae</i>	0	0	0	0	30	7	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus pneumoniae</i>	0	12	1166	4430	10166	5458	1420	1430	1115	841	672	2299	3165	545	8	2	0	0	0	0.12

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).

<b>3. Breakpoints prior<sup>1</sup> to harmonisation (mg/L) S<sub>≤</sub> / R<sub>&gt;</sub></b>							
	<b>BSAC</b>	<b>CA-SFM</b>	<b>CRG</b>	<b>DIN</b>	<b>NWGA</b>	<b>SRGA</b>	<b>CLSI<sup>2</sup></b>
<b>General breakpoint</b>							
		4/32	4/16	2/8	1/4	8/8	
<b>Species specific breakpoints:</b>							
Enterobacteriaceae	8/8	8/32			0.5/8	0.5/1	8/32
<i>Pseudomonas</i> spp.							
<i>Acinetobacter</i> spp.	8/8						
<i>Staphylococcus</i> spp.	1/1				2/8	Cefoxitin	8/32
<i>Streptococcus</i> spp.	1/1					0.12/2	
<i>Streptococcus pneumoniae</i>	1/1	0.5/2			0.5/4	0.12/0.25	0.5/1
<i>Enterococcus</i> spp.							
<i>Haemophilus influenzae</i>	1/1				2/4	2/2	4/8
<i>Moraxella catarrhalis</i>	1/1				2/4	2/2	4/8
Corynebacteria							
<i>Neisseria meningitidis</i>						0.25/1	
<i>Neisseria gonorrhoeae</i>	1/1		0.25/1			0.06/1	1/2
<i>Pasteurella multocida</i>							
Anaerobes, Gram-positive							
Anaerobes, Gram-negative							
<i>Campylobacter</i> spp.							
<i>Helicobacter pylori</i>							

<sup>1</sup>2005

<sup>2</sup>CLSI breakpoints converted to EUCAST terminology.

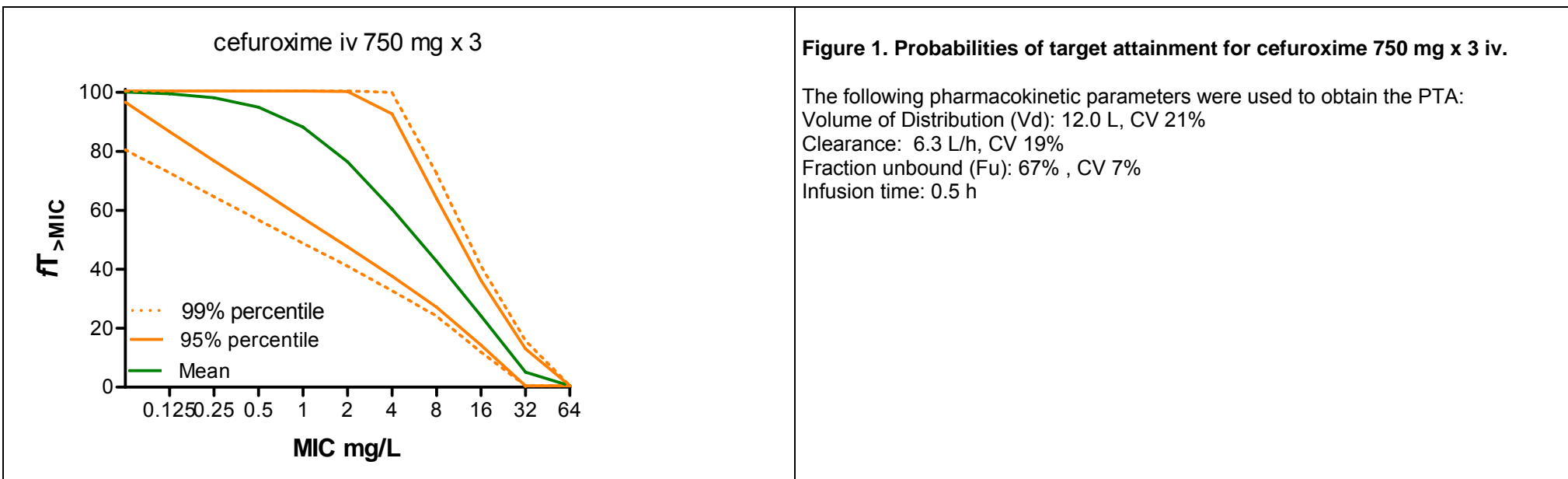
<b>4. Pharmacokinetics</b>				
Dosage (mg)	750 x 3 iv	1500 x 3 iv		
Cmax (mg/L)	75	200		
Cmin (mg/L)				
Total body clearance (L/h)				
T ½ (h), mean (range)	1.1-1.4	1-1.4		
AUC24h (mg.h/L)				
Fraction unbound (%)	60-70	60-70		
Volume of distribution (L/kg)				
Comments	<ul style="list-style-type: none"> <li>• Two values are given where references differ. Cells are left empty when data are not readily available.</li> <li>• No active metabolites. &gt;90% renal excretion.</li> </ul>			
References	<ul style="list-style-type: none"> <li>• Bryskier A. In Antimicrobial Agents 2005. ASM; 174</li> <li>• Finch R. In Antibiotic and Chemotherapy 1997. Churchill-Livingstone; 229-231</li> <li>• Smith and LeFrock. Ther Drug Mon 1983; 5:149-60</li> </ul>			

## 5. Pharmacodynamics

	Enterobacteriaceae	<i>Streptococcus pneumoniae</i>	<i>Staphylococcus aureus</i>	
%fT>MIC for bacteriostasis	35-40	35-40	20-30	
%fT>MIC for 2 log reduction				
%fT>MIC from clinical data				
Comments	<ul style="list-style-type: none"> <li>• %fT&gt;MIC is the dominant pharmacodynamic index.</li> <li>• Values based on general characteristics of cephalosporins.</li> </ul>			
References	<ul style="list-style-type: none"> <li>• Craig. Diagn Microbiol Infect Dis 22; 89: 1995</li> </ul>			

## 6. Monte Carlo simulations and Pk/Pd breakpoints

Probabilities of target attainment (PTA) for cefuroxime 750 mg x 3 iv are shown in figure 1.



## **7. Clinical data**

Clinical trials have shown the efficacy of cefuroxime treatment of patients with complicated urinary tract infections with or without septicaemia, 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% <math>fT &gt; MIC</math>. The 95% confidence interval of the 750mg dose administered by bolus intravenous injection results in an S/I breakpoint of 4 mg/L. The I/R breakpoint of 8 mg/L is based on a 1.5g dose. These breakpoints render wild type <i>Staphylococcus</i> spp., <i>Streptococcus</i> spp. (including <i>S. pneumoniae</i>) and <i>Haemophilus influenzae</i> susceptible. Enterobacteriaceae are borderline susceptible/intermediate.</p>
Species-related breakpoints	<p>For Enterobacteriaceae the breakpoints are S <math>\leq 8</math> mg/L / R <math>&gt; 8</math> mg/L. The S/I breakpoint was increased from 4 to 8 mg/L to avoid splitting the wild type MIC distributions. Consequently the breakpoints relate to high dose therapy (1.5 g x 3) and apply to <i>E. coli</i>, <i>Klebsiella</i> spp. and <i>P. mirabilis</i> only as activity is marginal and other species are frequently less susceptible.</p> <p>For <i>Staphylococcus</i> spp. susceptibility to cefuroxime is inferred from the cefoxitin susceptibility.</p> <p>For group A, B, C and G streptococci susceptibility to cefuroxime is inferred from the benzylpenicillin susceptibility.</p> <p>For <i>Streptococcus pneumoniae</i> the breakpoints are S <math>\leq 0.5</math> mg/L / R <math>&gt; 1</math> mg/L. The S/I breakpoint was reduced from 4 to 0.5 mg/L because high dose therapy is necessary for isolates with reduced susceptibility and the I/R breakpoint was reduced from 8 to 1 mg/L because outcome of infections caused by isolates with MICs <math>&gt; 1</math> mg/L is uncertain.</p> <p>For <i>Haemophilus influenzae</i>, and <i>Moraxella catarrhalis</i> the breakpoints are S <math>\leq 1</math> mg/L / R <math>&gt; 2</math> mg/L. Breakpoints were reduced to S <math>\leq 1</math> mg/L / R <math>&gt; 2</math> mg/L so that wild type isolates are reported susceptible. Outcome of infections caused by isolates with MICs <math>&gt; 2</math> mg/L is uncertain.</p> <p>For streptococci other than <i>S. pneumoniae</i> and Groups A, B, C and G the breakpoints are S <math>\leq 0.5</math> mg/L / R <math>&gt; 0.5</math> mg/L. Breakpoints were reduced to S <math>\leq 0.5</math> mg/L / R <math>&gt; 0.5</math> mg/L as isolates with reduced susceptibility are rare or have not been reported and clinical outcome is uncertain.</p>
Species without breakpoints	<p><i>Pseudomonas aeruginosa</i>, <i>Acinetobacter</i> spp., <i>Enterococcus</i> spp., <i>Neisseria</i> spp. and anaerobes were considered poor targets for cefuroxime therapy and for that reason did not receive breakpoints.</p>
Clinical qualifications	<p>For Enterobacteriaceae the breakpoints relate to high dose therapy (1.5g x 3).</p>
Dosage	<p>Breakpoints apply to a daily intravenous dose of 750 mg x 3 and a high dose of at least 1.5 g x 3.</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

**The DIN Committee (Germany)** is not convinced that there is sufficient evidence that dosing cefuroxime at 750mg x 3 per day will be sufficient to treat infections with Enterobacteriaceae in pharmacokinetically difficult to reach compartments. It therefore has set the breakpoints at 1/8 g/L to categorize Enterobacteriaceae as "intermediate" and to ensure high dose therapy in appropriate cases.

**The NWGA (Norway)** wishes to lodge the following exception to the EUCAST cefuroxime breakpoint for Enterobacteriaceae: EUCAST cefuroxime breakpoints for Enterobacteriaceae relate to a dosage of 1.5 g x 3 and to *E. coli* and *Klebsiella* spp only. The current and well-established Norwegian SPC recommends a cefuroxime dosage of 0.75 g x 3 - 1.5 g x 3 for septicemia, pulmonary infections, pyelonephritis and other systemic infections caused by cefuroxime-susceptible microorganisms. The NWGA is convinced that there is not sufficient evidence that dosing cefuroxime at 750mg x 3 per day is sufficient to treat infections with Enterobacteriaceae outside the urinary tract. Therefore the categorization should indicate that only the high dose of 1.5 g x 3 should be used for treating systemic infections but allow the lower dosage to be used for urinary tract infections. Thus, NWGA has set the breakpoints at 0.5/8 mg/L in order to categorize wild type *E. coli* and *Klebsiella* spp. as "intermediate" and thereby ensure high dose therapy in systemic infections, as indicated by the breakpoints set by EUCAST.