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EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Ceftazidime	Rationale for the EUCAST clinical breakpoints, version 1.0	26 th September 2010
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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.

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

Ceftazidime is used for therapy of Enterobacteriaceae and *Pseudomonas* spp. infections including septicaemia and severe urinary and wound infections in immunocompromised patients, nosocomial pneumonia and respiratory tract infections in cystic fibrosis patients. Ceftazidime is not considered to have useful activity against *Staphylococcus* spp., *Enterococcus* spp. or Gram-negative anaerobic bacteria.

Ceftazidime resistance in Enterobacteriaceae and *Pseudomonas* spp. 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.



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1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	2g x 3	1g x 3	1g x 3	2g x 3	0.5-1g x 3	1g x 3
Maximum dose schedule	2g x 3	2g x 3	2g x 3	2g x 3	2g x 3	2g x 3
Available formulations	iv	iv	iv	iv	iv	iv



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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	2	0	0	5	25	57	102	216	702	1744	1157	716	884	462	215	1013	2	ND
<i>Acinetobacter lwoffii</i>	0	0	0	0	1	0	3	42	32	121	171	133	85	45	84	16	1	2	14	ND
<i>Acinetobacter</i> spp	0	0	0	1	0	0	3	28	64	123	169	249	150	56	28	45	8	5	23	ND
<i>Bacteroides fragilis</i>	0	0	0	0	0	0	0	0	1	0	0	1	3	15	26	3	12	37	0	ND
<i>Bacteroides fragilis</i> group	0	0	0	0	0	0	0	0	2	0	0	1	4	16	28	4	16	56	0	ND
<i>Burkholderia cepacia</i>	0	0	0	0	0	0	0	1	5	13	20	9	5	2	8	3	4	1	0	ND
<i>Citrobacter freundii</i>	0	0	0	0	1	10	9	86	41	29	15	11	11	15	36	30	6	0	0	1
<i>Citrobacter koseri</i>	0	0	0	0	2	8	24	22	14	4	1	1	0	2	1	0	1	0	0	1
<i>Citrobacter</i> spp	0	0	0	0	3	16	311	364	226	440	206	38	33	45	299	5	5	3	7	1
<i>Enterobacter aerogenes</i>	0	0	1	1	3	45	106	192	122	57	55	42	51	85	98	121	66	237	2	1
<i>Enterobacter cloacae</i>	0	3	19	29	145	438	474	728	456	206	105	110	154	186	196	281	123	84	64	1
<i>Enterobacter</i> spp	0	0	0	0	1	16	733	1435	784	1771	901	205	200	338	1937	2	0	0	0	ND
<i>Escherichia coli</i>	0	0	21	53	243	1671	5422	5294	1228	323	200	141	128	138	140	79	25	25	5	0.5
<i>Haemophilus influenzae</i>	0	0	0	0	31	127	114	30	5	9	5	0	0	2	0	0	0	0	0	0.5
<i>Klebsiella oxytoca</i>	0	0	4	9	58	368	532	385	159	99	83	66	18	17	15	14	13	12	8	0.5
<i>Klebsiella pneumoniae</i>	0	0	10	9	89	592	1346	1425	611	280	143	88	104	112	143	136	92	112	27	0.5
<i>Klebsiella</i> spp	0	0	0	15	76	252	296	147	64	39	12	2	2	0	1	0	1	0	0	0.5
<i>Moraxella catarrhalis</i>	0	0	0	6	27	28	10	7	1	1	0	0	0	0	0	0	0	0	0	0.125
<i>Morganella morganii</i>	0	2	5	18	67	64	48	38	34	15	12	10	7	19	4	3	0	1	0	0.25
<i>Neisseria gonorrhoeae</i>	0	2	3	12	16	5	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Proteus mirabilis</i>	0	0	6	86	517	461	92	50	37	30	10	9	2	4	2	2	0	3	0	0.125
<i>Proteus vulgaris</i>	0	0	0	10	52	82	12	2	6	1	1	1	1	1	0	0	0	0	0	0.125



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<i>Providencia</i> spp	0	0	0	0	1	9	28	43	6	2	0	4	0	0	0	0	0	0	0.5	
<i>Providencia stuartii</i>	0	0	0	0	1	1	1	6	4	2	8	6	2	3	1	1	0	1	0	0.5
<i>Pseudomonas aeruginosa</i>	0	0	0	1	4	8	30	291	959	5909	12190	6205	2721	1689	795	726	167	117	106	8
<i>Pseudomonas fluorescens</i>	0	0	0	0	1	1	0	4	5	24	68	57	18	10	9	4	0	0	113	8
<i>Salmonella</i> spp	0	0	0	0	0	4	168	415	2144	1663	1089	17	8	10	16	1	0	0	0	2
	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>Serratia marcescens</i>	0	0	1	1	12	89	614	836	379	924	526	83	70	43	156	7	21	15	0	0.5
<i>Serratia</i> spp	0	0	0	0	2	13	36	111	63	35	20	7	2	0	0	0	1	0	1	0.5
<i>Stenotrophomonas maltophilia</i>	0	0	0	0	0	1	4	40	72	146	180	97	76	98	138	314	31	8	1	ND
<i>Streptococcus pneumoniae</i>	0	0	2	1	14	49	107	189	105	161	335	28	30	21	6	0	0	0	0	0.5
<i>Streptococcus pyogenes</i>	0	0	0	1	2	74	87	54	16	1	0	1	4	0	0	0	0	0	0	0.5
<i>Streptococcus viridans</i>	0	0	0	0	2	2	6	19	28	18	12	19	7	7	9	2	2	2	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).



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

¹2005

²CLSI breakpoints converted to EUCAST terminology.



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4. Pharmacokinetics				
Dosage (mg)	1000 x 3	2000 x 3	25 mg/kg x 3	
Cmax (mg/L)	80-120	185-233		
Cmin (mg/L)				
Total body clearance (L/h)	7.0		9.0	
T ½ (h), mean (range)	1.5-2	1.7	1.6	
AUC24h (mg.h/L)		1002		
Fraction unbound (%)	80-90	84	82.3	
Volume of distribution (L/kg)		0.17-0.20	0.18	
Comments	<ul style="list-style-type: none">• Two values are given where references differ. Cells are left empty when data are not readily available.• There are no active metabolites.			
References	<ul style="list-style-type: none">• Bryskier A. In Antimicrobial Agents 2005. ASM; 174• Finch R. In Antibiotic and Chemotherapy 1997. Churchill-Livingstone; 252-3• Mouton et al., Antimicrob Agents Chemother 1990; 34: 2307• Paufeuernborn et al., Antimicrob Agents Chemother 1993; 37: 1835• Drusano et al., Antimicrob Agents Chemother 1984; 26: 388• Walstad et al., J Antimicrob Chemother 1983; 12 Suppl A: 275• Sommers et al., Antimicrob Agents Chemother 1983; 23: 892• Vinks et al., Antimicrob Agents Chemother 1996; 40: 1091• Buijk et al., J Antimicrob Chemother 2002; 49:121			



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5. Pharmacodynamics				
%fT>MIC for bacteriostasis	25-40			
%fT>MIC for 2 log reduction	45-55			
%fT>MIC from clinical data	65			
Comments	<ul style="list-style-type: none">• %fT>MIC is the dominant pharmacodynamic index.			
References	<ul style="list-style-type: none">• Craig, Infect Dis Clin N Am 2003; 17: 479• Bakker-Woudenberg et al., Antimicrob Agents Chemother 2006; 50: 2919			



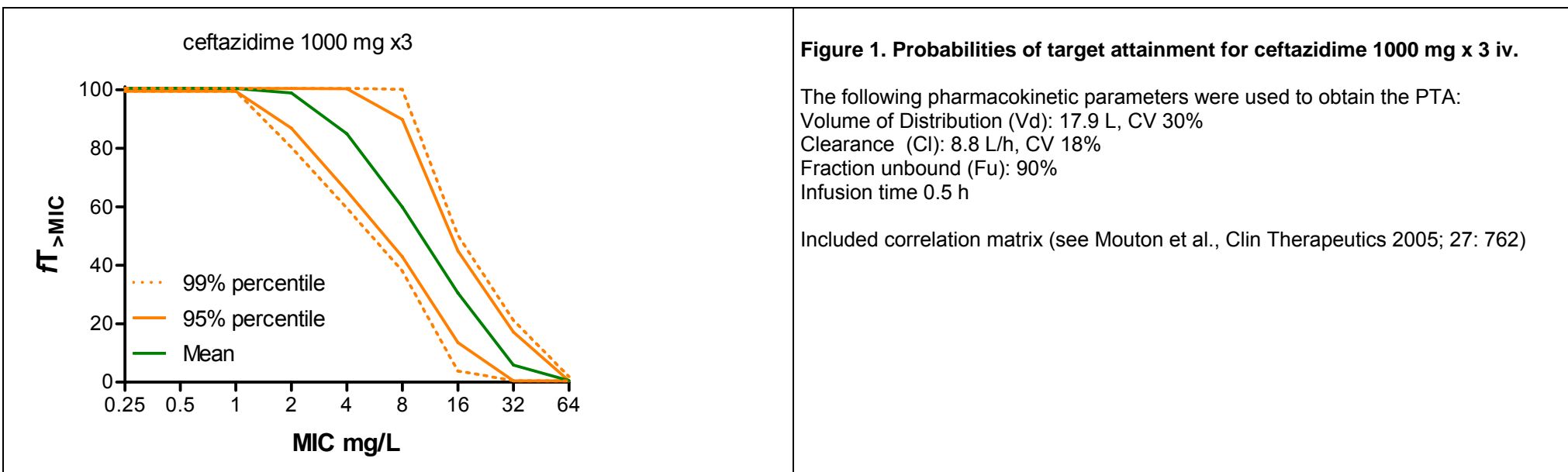
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6. Monte Carlo simulations and Pk/Pd breakpoints

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





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7. Clinical data

Clinical trials have shown the efficacy of ceftazidime treatment of patients with septicaemia and severe urinary and wound infections in immunocompromised patients, nosocomial pneumonia and respiratory tract infections in cystic fibrosis patients with microorganisms categorized as wild type.



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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 approximately 50% $fT > MIC$. The 95% confidence interval of the 1g 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 2g dose. These breakpoints render wild type Enterobacteriaceae and <i>Pseudomonas</i> spp, susceptible.</p>
Species-related breakpoints	<p>For Enterobacteriaceae the breakpoints are S ≤ 1 mg/L R > 8 mg/L. The S/I breakpoint was reduced from 4 to 1 mg/L to avoid reporting ESBL-producing organisms with MICs of 2-4 mg/L as susceptible.</p> <p>For <i>Pseudomonas</i> spp. the breakpoints are S ≤ 8 mg/L R > 8 mg/L. S/I breakpoint was increased from 4 to 8 mg/L to avoid dividing the wild type MIC distribution. The breakpoints relate to high dose therapy.</p>
Species without breakpoints	<p>Species other than Enterobacteriaceae and <i>Pseudomonas</i> spp. were considered poor targets for ceftazidime 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 <i>Pseudomonas</i> spp. the breakpoints relate to high dose therapy only.</p>
Additional comment	



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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