



EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Piperacillin-tazobactam

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. Piperacillin-tazobactam: Rationale for the clinical breakpoints, version 1.0, 2010. <http://www.eucast.org>.

Introduction

Piperacillin is a ureidopenicillin which, in the absence of tazobactam (a beta-lactamase inhibitor), is inactivated by most beta-lactamases. Piperacillin is available in combination with tazobactam for parenteral use.

Piperacillin-tazobactam is active against Enterobacteriaceae, *Pseudomonas* spp., methicillin susceptible *Staphylococcus* spp., streptococci, ampicillin-susceptible *Enterococcus* spp., *Haemophilus influenzae* and many anaerobic bacteria. Resistance to piperacillin-tazobactam can be conferred by PBP changes, hyperproduction or acquisition of certain beta-lactamases and, less commonly, by efflux. There is no evidence that piperacillin-tazobactam has clinically useful activity against *Acinetobacter* spp.

Piperacillin-tazobactam is used for therapy of intra-abdominal infections, fever of unknown origin in neutropenic patients, nosocomial pneumonia, skin and soft tissue infections including diabetic foot infections, urinary tract infection, bone and joint infection, gynaecological infection and bloodstream infections.

1. Dosage¹

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	4g x 3	4 g x 3	2g x 4	4g x 3	4 g x 3	4 g x 3
Maximum dose schedule	4g x 4	4 g x 4	4g x 4	4g x 4	4 g x 4	4 g x 4
Available formulations	iv	iv	iv	iv	iv	iv

¹Dosage given is the piperacillin component of the piperacillin-tazobactam combination in the ratio 8:1.

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	79	9	10	10	53	10	20	9	19	28	56	50	70	77	162	179	0	ND
<i>Acinetobacter calcoaceticus</i>	0	0	1	1	0	1	0	0	0	0	0	1	4	0	3	1	0	0	0	ND
<i>Acinetobacter lwoffii</i>	0	0	0	0	0	0	6	2	169	22	17	25	31	20	9	6	37	1	3	ND
<i>Acinetobacter</i> spp.	0	0	0	17	2	0	29	7	700	225	176	267	373	453	345	436	1697	118	25	ND
<i>Aeromonas hydrophila</i>	0	0	0	0	0	0	0	0	3	1	8	0	0	1	0	0	0	1	0	ND
<i>Alcaligenes xylosoxidans</i>	0	0	0	0	0	0	1	1	12	4	6	1	2	1	0	0	1	1	0	ND
<i>Bacteroides fragilis</i>	0	0	0	0	0	41	238	275	109	54	56	34	26	3	3	2	1	0	0	1
<i>Bacteroides fragilis</i> group	0	0	2	3	7	118	215	335	202	160	241	228	183	82	34	23	7	22	8	1
<i>Bacteroides thetaiotaomicron</i>	0	0	0	0	0	0	0	0	0	0	1	4	3	11	3	0	0	3	0	ND
<i>Burkholderia cepacia</i>	0	0	0	1	0	0	1	6	18	14	6	11	5	10	5	3	5	1	1	ND
<i>Chryseobacterium meningosepticum</i>	0	0	0	0	0	0	0	0	0	0	2	0	4	4	0	1	0	0	0	ND
<i>Chryseobacterium</i> spp.	0	0	0	0	0	0	0	0	0	0	1	3	10	1	2	0	2	0	0	ND
<i>Citrobacter freundii</i>	0	0	0	0	0	1	0	0	62	294	777	234	142	142	120	160	135	24	36	8
<i>Citrobacter koseri</i>	0	0	0	0	0	1	0	1	14	68	370	90	48	22	3	4	3	1	0	8
<i>Citrobacter</i> spp.	0	0	0	0	0	4	0	0	4	121	313	79	80	34	17	18	12	9	43	8
<i>Clostridium perfringens</i>	0	0	11	24	33	17	2	3	0	3	1	0	2	0	0	0	0	0	0	0.125
<i>Corynebacterium jeikeium</i>	0	0	0	0	0	0	0	0	2	0	0	1	0	1	7	0	18	2	5	ND
<i>Enterobacter aerogenes</i>	0	0	0	0	2	0	2	5	43	238	1006	624	297	329	417	327	144	70	53	8
<i>Enterobacter agglomerans</i>	0	0	0	0	0	0	0	3	25	20	5	5	0	0	0	0	0	0	0	ND
<i>Enterobacter cloacae</i>	0	0	0	2	9	15	42	166	669	1582	4020	1560	665	526	663	776	961	146	87	8
<i>Enterobacter dissolvens</i>	0	0	0	0	0	0	0	0	1	4	24	4	2	1	2	0	0	0	0	8
<i>Enterobacter sakazakii</i>	0	0	0	0	0	0	0	0	1	9	18	7	7	2	1	2	2	0	0	8
<i>Enterobacter</i> spp.	0	0	0	0	0	0	3	15	50	101	100	30	17	12	7	6	8	2	17	8
<i>Enterococcus avium</i>	0	0	0	0	0	0	0	0	0	1	0	1	2	6	23	2	20	4	0	ND
<i>Enterococcus casseliflavus</i>	0	0	0	0	0	0	0	1	0	0	0	3	19	5	1	0	3	0	1	ND
<i>Enterococcus faecalis</i>	0	0	0	6	5	6	12	13	86	327	1025	4302	1317	328	133	30	73	21	4	16
<i>Enterococcus faecium</i>	0	0	0	0	0	0	0	0	3	14	12	31	47	105	93	67	1682	318	507	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>Enterococcus gallinarum</i>	0	0	0	0	0	0	0	0	1	0	0	2	8	27	17	6	8	1	10	ND
<i>Escherichia coli</i>	0	0	8	6	9	47	101	214	2933	16028	20167	5222	1828	1176	765	484	730	160	53	8
<i>Haemophilus influenzae</i>	0	8	97	116	78	30	16	13	11	7	2	1	1	1	0	0	0	0	1	0.064
<i>Klebsiella oxytoca</i>	0	0	1	2	2	6	9	28	274	1106	1376	430	172	79	47	43	344	135	44	8
<i>Klebsiella pneumoniae</i>	0	0	0	0	2	7	12	22	386	2316	7188	4336	1496	903	455	336	1222	227	158	8
<i>Klebsiella</i> spp.	0	0	0	0	1	1	3	8	33	101	307	155	33	17	3	3	1	14	3	8
<i>Kluyvera</i> spp.	0	0	0	0	0	0	0	0	10	13	8	3	1	0	0	0	0	0	0	ND
<i>Listeria monocytogenes</i>	0	0	0	0	0	0	0	1	6	18	48	50	6	0	0	0	0	0	0	8
<i>Morganella morganii</i>	0	0	0	1	2	3	54	109	739	159	62	43	29	17	14	11	7	0	0	2
<i>Neisseria meningitidis</i>	0	1	10	10	4	1	31	0	119	2	0	0	0	0	0	0	0	0	0	ND
<i>Proteus mirabilis</i>	0	0	0	1	4	15	220	641	3319	528	127	72	37	28	25	18	8	1	1	2
<i>Proteus</i> spp.	0	0	0	0	0	4	19	25	19	17	5	1	0	3	0	0	0	0	1	ND
<i>Proteus vulgaris</i>	0	0	0	0	6	4	42	47	239	61	15	3	6	4	1	0	1	0	0	2
<i>Providencia rettgeri</i>	0	0	0	0	0	0	1	2	70	15	5	3	0	3	0	0	0	0	0	2
<i>Providencia stuartii</i>	0	0	0	1	0	0	0	1	15	33	60	64	26	11	2	5	2	0	0	8
<i>Pseudomonas aeruginosa</i>	0	0	0	0	0	2	10	15	412	768	2506	9185	4940	3144	1627	1302	2939	496	143	16
<i>Pseudomonas fluorescens</i>	0	0	0	0	0	0	1	0	5	24	69	95	74	41	14	8	19	3	118	16
<i>Pseudomonas stutzeri</i>	0	0	0	0	0	0	0	2	6	15	14	1	0	0	0	0	0	0	0	ND
<i>Salmonella enteritidis</i>	0	0	0	0	0	0	0	0	4	9	205	327	17	4	0	0	1	0	0	8
<i>Salmonella paratyphi</i>	0	0	0	0	0	0	0	0	0	3	22	42	2	0	0	0	0	0	0	8
<i>Salmonella</i> spp.	0	0	0	0	0	0	0	0	16	139	656	702	109	15	7	7	8	9	7	8
<i>Salmonella typhi</i>	0	0	0	0	0	0	0	0	5	106	152	42	12	1	1	1	1	2	0	8
<i>Salmonella typhimurium</i>	0	0	0	0	0	0	0	0	1	8	52	65	38	4	3	3	2	6	7	8
<i>Serratia liquefaciens</i>	0	0	0	0	0	0	0	0	14	93	129	27	8	5	12	6	5	2	142	8
<i>Serratia marcescens</i>	0	0	1	0	0	0	1	2	282	1120	1313	506	186	155	210	137	138	27	1	8
<i>Serratia</i> spp.	0	0	0	0	0	0	0	3	5	125	152	41	13	15	17	32	7	4	173	8
<i>Shigella flexneri</i>	0	0	0	0	0	0	0	1	59	47	146	57	10	0	0	0	1	0	0	8
<i>Shigella sonnei</i>	0	0	0	0	0	0	0	0	16	165	231	11	3	0	0	0	0	0	0	8
<i>Staphylococcus aureus</i>	0	0	0	8	3	4	104	254	914	737	761	341	99	65	33	37	25	39	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>Staphylococcus aureus</i> MSSA	0	0	0	0	0	0	1	1	66	114	81	17	2	0	1	0	0	0	0	ND
<i>Staphylococcus auricularis</i>	0	0	0	0	0	0	1	2	9	10	4	0	2	0	1	0	2	0	1	ND
<i>Staphylococcus capitis</i>	0	0	0	0	1	1	8	11	79	31	15	10	11	6	3	9	4	0	0	ND
<i>Staphylococcus coagulase negative</i>	0	0	0	1	7	44	131	124	205	225	142	51	32	21	7	7	23	34	1	ND
<i>Staphylococcus coagulase negative MRSE</i>	0	0	0	0	0	0	0	1	4	37	76	30	28	11	4	4	11	22	0	ND
<i>Staphylococcus epidermidis</i>	0	0	0	5	5	10	92	130	663	819	823	477	271	123	79	82	91	28	1	ND
<i>Staphylococcus haemolyticus</i>	0	0	1	1	1	0	2	5	25	42	21	33	39	31	20	34	131	38	9	ND
<i>Staphylococcus hominis</i>	0	0	0	1	1	0	2	3	76	46	40	51	80	22	6	11	20	0	0	ND
<i>Staphylococcus lugdunensis</i>	0	0	0	0	1	1	1	3	19	33	6	1	3	1	3	1	4	0	0	ND
<i>Staphylococcus saprophyticus</i>	0	0	0	0	0	1	6	1	17	27	39	13	11	7	2	2	7	3	0	ND
<i>Staphylococcus simulans</i>	0	0	0	0	0	0	0	2	14	10	7	10	8	2	0	1	6	0	1	ND
<i>Staphylococcus warneri</i>	0	0	0	0	0	0	2	1	34	32	7	4	11	8	4	1	2	1	0	ND
<i>Staphylococcus xylois</i>	0	0	0	0	0	0	1	2	6	6	9	1	4	4	1	2	1	0	0	ND
<i>Stenotrophomonas maltophilia</i>	0	0	0	0	0	0	0	0	2	11	16	70	229	443	453	359	1237	256	61	ND
<i>Streptococcus agalactiae</i>	0	0	4	8	7	30	156	372	1775	120	3	3	0	1	1	0	2	2	0	1
<i>Streptococcus anginosus</i>	0	0	0	1	2	10	32	36	78	15	4	2	2	5	1	1	1	5	0	1
Streptococcus group C	0	0	0	1	2	4	3	1	0	0	0	0	0	0	0	0	0	0	0	ND
Streptococcus group F	0	0	0	0	0	0	1	3	38	2	0	0	0	0	0	0	0	0	0	ND
Streptococcus group G	0	0	0	11	47	144	49	6	13	1	0	0	0	0	0	0	0	0	0	0.25
<i>Streptococcus milleri</i>	0	0	0	0	2	6	8	9	61	13	2	0	1	0	0	0	0	0	0	1
<i>Streptococcus mutans</i>	0	0	0	0	0	0	3	0	15	1	0	1	1	0	0	0	0	0	0	ND
<i>Streptococcus oralis</i>	0	1	15	32	52	11	20	23	16	8	5	7	3	3	0	0	0	0	0	ND
<i>Streptococcus pneumoniae</i>	2	12	421	694	183	72	13	43	145	24	48	47	12	0	0	0	0	0	0	0.064
<i>Streptococcus pyogenes</i>	0	0	3	22	188	290	73	8	64	3	1	1	0	0	0	0	0	0	0	0.25
<i>Streptococcus salivarius</i>	0	0	0	0	0	0	0	3	47	11	8	2	2	4	0	0	0	0	0	ND
<i>Streptococcus sanguis</i>	0	0	0	0	0	0	5	1	49	15	8	7	5	3	2	0	0	0	0	ND
<i>Streptococcus viridans</i>	0	2	17	49	70	54	149	132	88	35	23	30	22	11	2	2	0	1	0	ND
<i>Yersinia</i> spp.	0	0	0	0	0	0	1	4	2	28	11	1	2	0	0	1	1	0	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).

3. Breakpoints prior¹ to harmonisation (mg/L) S_≤ / R>							
	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI²
General breakpoint							
		0.25/16	0.25/4	0.12/1		1/4	
Species specific breakpoints:							
Enterobacteriaceae	16/16	8/64			8/16	16/16	16/64
<i>Pseudomonas</i> spp.	16/16	16/64				16/16	64/64
<i>Acinetobacter</i> spp.	16/16	16/64				16/32	
<i>Staphylococcus</i> spp.							8/8
<i>Streptococcus</i> spp.						0.25/1	
<i>Streptococcus pneumoniae</i>						0.06/1	
<i>Enterococcus</i> spp.						16/16	
<i>Haemophilus influenzae</i>							1/1
<i>Moraxella catarrhalis</i>							1/1
Corynebacteria							
<i>Neisseria meningitidis</i>							
<i>Neisseria gonorrhoeae</i>							
<i>Pasteurella multocida</i>							
Anaerobes, Gram-positive		8/64			8/16		
Anaerobes, Gram-negative		8/64			8/16		
<i>Campylobacter</i> spp.							
<i>Helicobacter pylori</i>							

¹2005

²CLSI breakpoints converted to EUCAST terminology.

4. Pharmacokinetics					
Dosage (mg)	4000 (piperacillin component) x 3				
Bioavailability					
Cmax (mg/L)	368				
Cmin (mg/L) 6 hr	1.6				
Total body clearance (L/g/h)	14.5				
T ½ (h), mean (range)	0.5-0.9				
AUC24h (mg.h/L)	281				
Fraction unbound (%)	79				
Volume of distribution (L/kg)	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. 				
References	<ul style="list-style-type: none"> Bryson HM and Brogden RN <i>Drugs</i>1994; 47: 506-535 				

5. Pharmacodynamics

	Enterobacteriaceae	<i>P. aeruginosa</i>	Staphylococci	<i>Streptococcus pneumoniae</i>	
%T>MIC for stasis : exp	30 – 35	30 – 35	15 – 20	25 – 35	
%T>MIC for 2 log drop : exp				35 – 45	
%T>MIC from clinical data					
Comments	<ul style="list-style-type: none"> • Cells are left empty when data are not readily available. • Beta-lactam antibiotics are bactericidal. The effect is dependent on the time during which the free concentration in serum is above the MIC value for the bacterium. 				
References	<ul style="list-style-type: none"> • Gerber AU et al. <i>J Infect Disease</i> 1986; 153: 90-97 • Craig WA et al. 33rd ICAAC 1993; Abstract 86 • Craig WA. In <i>Antimicrobial Pharmacodynamics Theory and Clinical Practice</i> 2002. Eds. C Nightingale, TT Murakawa, PG Ambrose. Marcel Dekker Inc, Basel: 1-22 • MacGowan AP. <i>Clin Microbiol Infect</i> 2004; 52: 6-11 				

6. Monte Carlo simulations and PK/PD Breakpoints

The following iv piperacillin pharmacokinetics were modelled:

volume of distribution (L)	18 ± 10% (1.8)
dose (mg)	4000
half-life (h)	1.0 ± 12% (0.12)
dose interval (h)	8
free fraction	0.78 – 0.84, average 0.81
number of trials	1,000

MIC (mg/L)	Piperacillin target attainment rates at T>MIC of (%)				
	20	30	40	50	60
64	30.5	0	0	0	0
32	100	60.5	2.4	0	0
16	100	100	74.3	13.3	0
8	100	100	99.4	81.4	28.4
4	100	100	100	99.3	85.3
≤ 2	100	100	100	100	99.1

A T>MIC of 40% suggests a pharmacodynamic breakpoint of $S \leq 8\text{mg/L}$.

7. Clinical data

The bacteriological and clinical efficacy of piperacillin-tazobactam has been demonstrated in several trials involving patients with intra-abdominal infections, nosocomial pneumonia, fever of unknown origin in neutropenic patients, skin and soft tissue infections, urinary tract infection, bone and joint infection, gynaecological infection and blood stream infection.

- Solomkin JS *Ann Surg* 2003; 237: 235-45
- Schmitt DV et al. *Infection* 2006; 34: 127-134
- Bow EJ et al. *Clin Infect Dis* 2006; 43: 447-59
- Lipsky BA et al *Lancet* 2005; 366: 1695-703
- Bryson HM and Brogden RN *Drugs* 1994; 47: 506-535

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 organisms in animal model infections requires 40% $fT > MIC$. The 95% confidence interval of the 4g dose administered by bolus intravenous injection results in an S breakpoint of ≤ 8 mg/L. The R breakpoint of > 16 mg/L is based on a dosing interval of 6 h instead of 8 h. These breakpoints render wild type Enterobacteriaceae, <i>P. aeruginosa</i> and most anaerobic bacteria susceptible.</p>
Species-related breakpoints	<p>For Enterobacteriaceae and anaerobic bacteria the breakpoints are S ≤ 8 mg/L / R > 16 mg/L.</p> <p>For <i>P. aeruginosa</i> the breakpoints are S ≤ 16 mg/L / R > 16 mg/L. The S breakpoint was increased from 8 to 16 mg/L to avoid splitting the wild-type population.</p>
Species without breakpoints	<p>For <i>Staphylococcus</i> spp. susceptibility to piperacillin-tazobactam is inferred from the cefoxitin/oxacillin susceptibility.</p> <p>For group A, B, C and G streptococci and <i>S. pneumoniae</i> susceptibility to piperacillin-tazobactam is inferred from the benzylpenicillin susceptibility.</p> <p>For streptococci other than group A, B, C and G streptococci and <i>S. pneumoniae</i>, <i>Enterococcus</i> spp. and beta-lactamase negative <i>H. influenzae</i>, susceptibility to piperacillin-tazobactam is inferred from the ampicillin susceptibility. For beta-lactamase producing <i>H. influenzae</i> susceptibility to piperacillin-tazobactam is inferred from amoxicillin-clavulanic acid susceptibility.</p> <p><i>Acinetobacter</i> were considered poor targets for piperacillin-tazobactam and for that reason did not receive breakpoints.</p>
Clinical qualifications	<p>In endocarditis caused by streptococci other than group A, B, C and G streptococci and <i>S. pneumoniae</i> refer to national or international endocarditis guidelines.</p>
Dosage	<p>Breakpoints apply to piperacillin-tazobactam dosage of 4 g x 3 (4 g x 4 in infections caused by <i>P. aeruginosa</i>).</p>
Additional comment	

9. EUCAST clinical MIC breakpoints

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

10. Exceptions noted for individual national committees

None