

Imipenem	Rationale for the EUCAST clinical breakpoints, version 1.3	1st June 2009
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Introduction

Imipenem is a carbapenem, available only for parenteral use.

Imipenem is relevant for therapy of septicaemia, post-operative sepsis, nosocomial pneumonia, community acquired pneumonia, and complicated skin and soft tissue infections caused by *Staphylococcus* spp., *Streptococcus* spp. (including *Streptococcus pneumoniae*), *Haemophilus influenzae*, Enterobacteriaceae and *Pseudomonas* spp. Imipenem can be used in the treatment of both Gram-positive and Gram-negative infections.

Imipenem is not considered active against *Stenotrophomonas maltophilia* and *Enterococcus faecium*.

Resistance to imipenem is conferred by PBP changes also mediating high-level penicillin resistance in *S. pneumoniae*, by PBP changes mediating β -lactam resistance in *H.influenzae*, and by production of carbapenemases in *Pseudomonas* spp. and Enterobacteriaceae. Imipenem is not affected by classical ESBL and AmpC β -lactamases in Enterobacteriaceae. In Enterobacteriaceae, combinations of an ESBL or AmpC enzyme and impermeability confer reduced susceptibility to imipenem, often without causing clinical resistance. In *Pseudomonas aeruginosa*, porin loss and alteration in efflux pumps may also reduce imipenem susceptibility.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose (mg)	500 mg x 4	500 mg x 3	500 mg x 3-4	500 mg x 4	500mg -1 g x 3-4	500 mg x 3
Maximum dose schedule (mg)	1 g x 4	1 g x 4	1 g x 4	1 g x 4	1 g x 4	1 g x 4
Available formulations	iv	iv	iv	iv	iv	iv

2. MIC distributions and epidemiological cut-off (ECOFF) values

	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	10	24	45	218	822	1344	1088	781	594	342	213	560	91	74	10	18	8	1
<i>Acinetobacter calcoaceticus</i>	0	0	0	0	0	0	1	2	5	10	4	0	0	0	0	1	0	0	0	ND
<i>Acinetobacter lwoffii</i>	0	0	0	0	1	103	67	62	91	22	18	5	8	19	10	3	0	0	0	1
<i>Acinetobacter</i> spp.	0	0	0	7	21	387	1164	1958	1965	1486	929	273	234	1119	7	0	1	0	0	1
<i>Aeromonas hydrophila</i>	0	0	0	0	0	0	12	26	11	12	6	6	2	2	0	0	1	0	0	ND
<i>Aeromonas</i> spp.	0	0	0	0	0	1	19	24	18	9	3	8	5	6	6	0	0	0	0	ND
<i>Alcaligenes xylosoxidans</i>	0	0	0	0	0	1	0	3	2	6	8	7	1	2	0	0	0	0	0	ND
<i>Bacteroides distasonis</i>	0	0	0	0	1	5	11	8	3	0	0	0	0	0	0	0	0	0	0	ND
<i>Bacteroides fragilis</i>	0	0	0	1	132	243	496	306	78	40	18	4	7	3	0	0	0	0	0	0.5
<i>Bacteroides fragilis</i> group	0	2	15	32	95	92	134	28	15	0	0	1	0	0	0	1	0	0	0	ND
<i>Bacteroides ovatus</i>	0	0	0	0	1	7	43	10	3	0	0	0	0	0	0	0	0	0	0	ND
<i>Bacteroides</i> spp.	0	0	0	1	3	3	4	9	9	4	2	0	0	0	0	0	0	0	0	ND
<i>Bacteroides thetaiotaomicron</i>	0	0	0	0	6	12	27	23	26	23	5	1	2	0	0	0	0	0	0	ND
<i>Bacteroides uniformis</i>	0	0	0	0	0	1	16	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Bacteroides vulgatus</i>	0	0	0	0	1	5	7	2	1	0	0	0	0	0	0	0	0	0	0	ND
<i>Burkholderia cepacia</i>	0	0	0	0	0	0	6	10	2	2	6	8	8	7	14	13	0	0	0	ND
<i>Chryseobacterium</i> spp.	0	0	0	0	0	0	0	0	0	0	1	3	2	0	1	11	1	0	0	ND
<i>Citrobacter freundii</i>	0	0	0	2	6	20	269	545	864	471	81	31	5	7	5	0	0	0	33	2
<i>Citrobacter koseri</i>	0	0	0	3	3	41	364	124	85	7	3	1	2	0	0	0	0	0	0	1
<i>Citrobacter</i> spp.	0	0	0	0	2	53	430	450	662	336	73	18	1	2	0	0	0	0	0	1
<i>Clostridium difficile</i>	0	0	0	0	0	0	0	0	0	2	2	8	0	0	0	592	0	0	0	ND
<i>Clostridium</i> spp.	0	0	3	3	18	45	23	29	18	9	8	3	0	0	0	0	0	0	0	ND
<i>Corynebacterium jeikeium</i>	0	0	0	0	0	4	0	3	4	2	0	0	0	47	0	0	0	0	0	ND
<i>Corynebacterium</i> spp.	0	0	1	0	3	3	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Enterobacter aerogenes</i>	0	0	1	4	4	38	254	753	1139	996	377	80	38	20	18	14	3	1	49	1
<i>Enterobacter agglomerans</i>	0	0	0	0	0	0	0	19	72	81	8	3	0	0	0	0	0	0	0	ND
<i>Enterobacter cloacae</i>	0	7	20	68	193	659	1623	3452	3920	1109	328	63	29	28	10	2	0	0	59	1
<i>Enterobacter dissolvens</i>	0	0	0	0	0	0	4	6	7	1	1	0	0	0	0	0	0	0	0	ND
<i>Enterobacter sakazakii</i>	0	0	0	0	0	1	8	7	22	8	3	0	0	0	0	0	0	0	0	ND
<i>Enterobacter</i> spp.	0	0	0	0	0	47	714	2337	4094	1708	621	85	15	16	4	0	0	0	75	1
<i>Enterococcus avium</i>	0	0	0	0	0	1	0	9	15	26	5	9	2	37	0	0	0	0	0	ND
<i>Enterococcus casseliflavus</i>	0	0	0	0	0	0	0	5	30	7	8	5	1	5	0	0	0	0	0	ND
<i>Enterococcus faecalis</i>	0	0	0	5	8	27	160	367	2402	6644	4662	1238	339	174	69	5	2	0	184	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>Shigella sonnei</i>	0	0	0	0	0	30	215	59	121	1	0	0	0	0	0	0	0	0	0	ND
<i>Shigella</i> spp	0	0	0	0	0	1	31	130	19	3	1	1	0	0	0	0	0	0	0	1
<i>Staphylococcus aureus</i>	0	12	541	1641	1882	966	305	176	122	63	84	19	13	4	4	4	0	1	0	0.125
<i>Staphylococcus capitis</i>	0	0	0	0	0	105	34	9	36	6	3	4	4	13	0	0	0	0	0	ND
<i>Staphylococcus coagulase -ve</i>	6	25	157	269	242	147	107	46	38	24	14	15	10	10	16	18	0	0	0	0.125
<i>Staphylococcus epidermidis</i>	0	0	0	48	48	40	45	64	28	15	17	2	5	6	1	1	5	0	0	0.125
<i>Staphylococcus haemolyticus</i>	0	0	4	5	8	1	3	2	1	2	3	1	0	1	2	4	0	0	0	0.125
<i>Staphylococcus hominis</i>	0	0	6	12	10	2	3	6	2	2	0	0	0	0	2	0	0	0	0	0.125
<i>Staphylococcus lugdunensis</i>	0	0	0	2	4	4	2	2	1	0	2	1	0	1	1	0	0	0	0	0.125
<i>Staphylococcus saprophyticus</i>	0	0	0	16	23	6	5	0	2	0	0	0	0	0	2	0	0	0	0	0.125
<i>Streptococcus agalactiae</i>	0	20	45	106	88	23	1	0	1	3	0	0	0	0	0	0	0	0	0	0.125
<i>Streptococcus anginosus</i>	0	9	6	10	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus constellatus</i>	0	0	4	4	3	1	0	0	1	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus</i> group G	0	86	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus intermedius</i>	0	0	2	7	4	4	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus mitis</i>	0	0	0	5	10	7	10	11	3	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus oralis</i>	0	18	13	8	6	3	3	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus oralis</i>	0	1	10	13	12	2	2	1	2	2	2	0	0	0	0	0	0	0	0	ND
<i>Streptococcus pneumoniae</i>	0	376	290	112	161	103	88	50	10	2	3	1	0	0	0	0	0	0	0	ND
<i>Streptococcus pyogenes</i>	0	231	130	97	61	19	1	1	1	0	0	0	0	0	0	0	0	0	0	0.064
<i>Streptococcus viridians</i> group	0	2	7	24	28	24	17	10	16	6	1	0	0	0	0	1	0	0	0	0.125

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 (IE) no epidemiological cut-off has been determined.

3. Breakpoints prior to harmonisation (mg/L) S_≤/R_>

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
General breakpoints							
	4/4	4/8	2/8	2/4	See below	4/8	4/8
Species related breakpoints							
<i>Staphylococcus</i> spp.					2/4		4/8
<i>Streptococcus</i> spp.						0.06/2	
<i>Streptococcus pneumoniae</i>	4/4	0.5/2				0.06/0.5	0.12/0.5
<i>Enterococcus</i> spp.	4/4					1/8 (<i>E. faecalis</i>)	
Enterobacteriaceae	4/4	4/8			0.5/2	1/8	4/8
<i>Pseudomonas</i> spp.	4/4	4/8				4/8	4/8
<i>Acinetobacter</i> spp.	4/4	4/8				1/8	
<i>Haemophilus</i> spp.	4/4				1/2	1/2	4/-
<i>Moraxella</i> spp.	4/4				1/2	1/2	4/-
<i>Neisseria meningitidis</i>						IE	
<i>Neisseria gonorrhoeae</i>						IE	
<i>Pasteurella multocida</i>						IE	
Gram-negative anaerobes		4/8			1/1	1/1	
<i>Campylobacter</i> spp.		4/8					

4. Pharmacokinetics

Dosage (mg)	500 mg x 4	1 g x 4
C _{max} (mg/L)	30-40 mg/L	60-70 mg/L
C _{min} (mg/L)	0.25-0.5	0.5-1
Total body clearance (L/h)	11-15	11-15
T _{1/2} (h), mean (range)	1	1
AUC _{24h} (mg.h/L)	100-150	200-300
Fraction unbound (%)	80	80
Volume of distribution (L/kg)	14-16	14-16
Comments	<ul style="list-style-type: none">• Cilastatin protein binding is 40%.• Cilastatin has no antimicrobial activity but is necessary to avoid degradation of imipenem.• Two values are given where references differ. Cells are left empty when data are not readily available.	
References	<ul style="list-style-type: none">• Wise et al., J Antimicrob Chemother 1986; 18S:E93• Mouton et al., Clin Pharmacokinet 2000; 39:185• Drusano et al., Antimicrob Agents Chemother 1984 26:715• Merck & Co. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=7539#n1m34090-1 accessed 27-08-2008	

5. Pharmacodynamics

	Enterobacteriaceae, <i>Pseudomonas aeruginosa</i>	<i>Streptococcus pneumoniae</i>	<i>Staphylococcus aureus</i>
% fT>MIC for bacteriostasis (experimental)	25-40	15-20	10-30
% fT>MIC for 2 log reduction (experimental)	35-55	25-40	15-40
%fT>MIC from clinical data	54		
Comments	<ul style="list-style-type: none"> • Pk/Pd data for carbapenems are presented as class effects. There are no indications that the Pk/Pd properties differ between carbapenem agents. • Cells are left empty when data are not readily available. 		
References	<ul style="list-style-type: none"> • DeRyke CA, et al. Antimicrob Agents Chemother 2007; 51:1481. • Li C, et al. Antimicrob Agents Chemother 2007; 51:1725 • Maglio D, et al. Antimicrob Agents Chemother 2005; 49:276 • Xuan D, et al. Antimicrob Agents Chemother 2002; 46:2990 • Andes D, et al. ICAAC 2003 abstr. A308 • Takata T, et al., J Infect Chemother 2004; 10:76 • Sugihara K, et al. ICAAC 2008 abstr. A027 • MacGowan AP et al, Antimicrob. Agents Chemother. 2008, 52: 1401-06 		

6. Monte Carlo simulations and Pk/Pd breakpoints

Probabilities of Target Attainment (PTA) for 500 mg x 4 iv are shown in Figure 1.

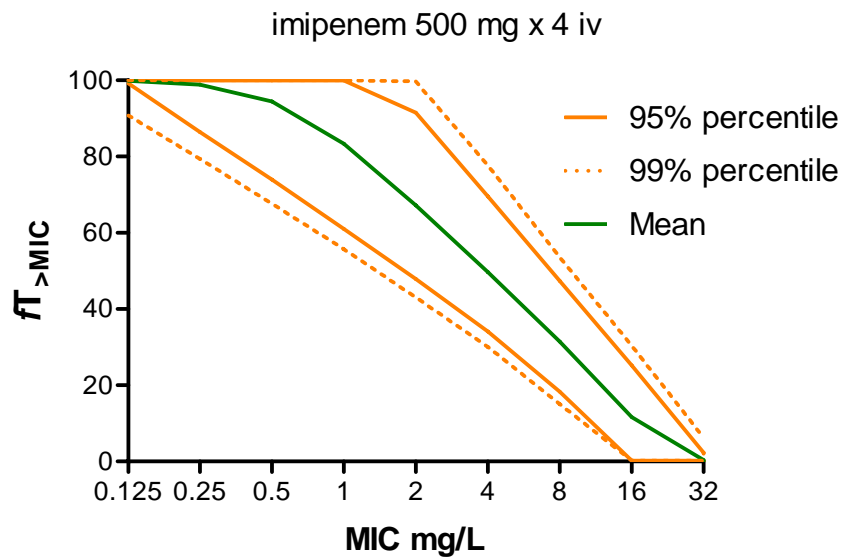


Figure 1. Probabilities of Target Attainment for Imipenem 500 mg x 4 IV.

The following pharmacokinetic parameters were used to obtain the PTA:
Volume of distribution (Vd): 15 L, CV 20%
Elimination half-life (t): 1.0 h, CV 15%
Fraction unbound (Fu): 80%
Infusion time 0.5 h

7. Clinical data

Clinical trials have shown the efficacy of imipenem in treatment of patients with septicaemia, post-operative sepsis, nosocomial pneumonia, community acquired pneumonia, and complicated skin and soft tissue infections caused by micro-organisms 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 500 mg dose administered by 30 min infusion results in an S/I breakpoint of 2 mg/L. The I/R breakpoint of 8 mg/L is based on a 1g dose.</p> <p>These breakpoints render wild type Enterobacteriaceae, <i>Acinetobacter</i> spp. and anaerobes susceptible.</p>
Species-related breakpoints	<p>The S/I breakpoint for <i>Pseudomonas</i> spp. and <i>Enterococcus</i> spp. was increased from 2 to 4 mg/L to avoid dividing the wild type MIC distribution. The breakpoints for <i>Pseudomonas</i> spp. relate to high dose frequent therapy.</p> <p>For <i>Streptococcus pneumoniae</i>, streptococci groups A, B, C, G, other streptococci, <i>Haemophilus</i> spp. and <i>Moraxella catarrhalis</i>, breakpoints were set at 2/2 mg/L as strains with MIC values above 2 mg/L are rare or not yet reported.</p> <p>Susceptibility of staphylococci is inferred from the methicillin susceptibility.</p>
Species without breakpoints	<p><i>Neisseria meningitidis</i> were considered poor targets for imipenem therapy and for that reason did not receive breakpoints.</p> <p>There was considered to be insufficient evidence to set breakpoints for <i>Neisseria gonorrhoeae</i>.</p>
Clinical qualifications	
Dosage	<p>EUCAST breakpoints apply to imipenem 500 mg x 4 daily administered intravenously over 30 minutes as the lowest dose. 1g x 4 daily was taken into consideration for severe infections and in setting the I/R breakpoint.</p>
Additional comment	

9. Current EUCAST breakpoints

The current EUCAST breakpoints are shown on <http://www.eucast.org>

10. Exceptions noted for individual national committees
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None
