

Meropenem	Rationale for the EUCAST clinical breakpoints, version 1.5	1st June 2009
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Introduction

Meropenem is a carbapenem, available only for parenteral use.

Meropenem 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. Meropenem can be used in the treatment of both Gram-positive and Gram-negative infections.

Meropenem is not considered active against *Stenotrophomonas maltophilia* and *Enterococcus* spp.

Resistance to meropenem 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. Meropenem 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 meropenem, often without causing clinical resistance. In *Pseudomonas aeruginosa*, porin loss and alteration in efflux pumps may also reduce meropenem susceptibility.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose (mg)	1 g x 3	1 g x 3	500 mg -1.0 g x 3	1 g x 3	500 mg -1 g x 3	500 mg -1 g x 3
Maximum dose schedule (mg)	2 g x 3	2 g x 3	2 g x 3	2 g x 3	2 g x 3	2 g x 3
Available formulations	iv	iv	iv	iv	iv	iv

	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>Enterobacter aerogenes</i>	0	0	32	100	390	1797	335	91	31	14	29	25	15	6	2	7	1	1	0	0.125
<i>Enterobacter cloacae</i>	69	216	524	486	614	4514	846	320	146	70	31	14	15	14	0	2	0	0	0	0.125
<i>Enterobacter sakazakii</i>	0	0	0	1	1	43	1	2	1	0	0	0	0	0	0	0	0	0	0	0.125
<i>Enterobacter spp.</i>	0	1	8	38	51	9	7	4	0	0	0	0	0	0	0	0	0	0	0	0.125
<i>Enterococcus avium</i>	0	0	0	0	0	0	0	0	0	1	0	2	12	9	3	0	0	0	0	ND
<i>Enterococcus casseliflavus</i>	0	0	0	0	0	0	0	1	0	0	5	4	2	3	1	0	0	0	0	ND
<i>Enterococcus faecalis</i>	0	0	0	5	5	11	66	64	169	613	2878	4130	2855	942	168	16	0	0	187	8
<i>Enterococcus faecium</i>	0	0	0	0	0	3	7	3	6	11	23	27	31	479	910	2	0	0	0	8
<i>Enterococcus gallinarum</i>	0	0	0	0	0	0	0	0	0	3	5	8	12	2	12	0	0	0	0	ND
<i>Escherichia coli</i>	0	0	953	3751	2381	286	76	41	12	8	1	1	0	0	0	0	0	0	0	0.125
<i>Haemophilus influenzae</i>	0	0	42	249	2632	2765	464	181	21	6	1	0	0	0	0	0	0	0	0	0.25
<i>Haemophilus parainfluenzae</i>	0	0	1	1	5	61	3	3	1	0	0	0	0	0	0	0	0	0	0	0.25
<i>Hafnia alvei</i>	0	0	6	10	19	3	0	2	1	0	0	0	0	0	0	0	0	0	0	0.125
<i>Klebsiella oxytoca</i>	0	0	100	318	724	2287	92	20	14	10	5	4	1	2	0	1	0	0	0	0.125
<i>Klebsiella pneumoniae</i>	0	0	271	989	2878	11766	1017	354	187	128	78	49	32	33	4	1	0	0	0	0.125
<i>Klebsiella spp.</i>	1	1	12	298	392	25	0	0	0	0	0	0	0	0	0	0	0	0	0	0.125
<i>Listeria monocytogenes</i>	0	0	0	0	0	3	100	31	0	0	0	0	0	0	0	0	0	0	0	0.25
<i>Moraxella catarrhalis</i>	10	25	7	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Morganella morganii</i>	0	0	7	16	87	678	487	142	34	12	1	1	1	0	0	0	0	0	0	0.25
<i>Neisseria gonorrhoeae</i>	0	14	0	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Peptostreptococcus magnus</i>	1	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	ND
<i>Peptostreptococcus micros</i>	0	0	0	0	5	3	0	1	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Peptostreptococcus prevotii</i>	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Peptostreptococcus spp.</i>	0	0	5	6	11	35	17	1	0	2	1	0	0	0	0	0	0	0	0	ND
<i>Prevotella bivia</i>	0	0	0	0	0	4	1	1	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Prevotella buccae</i>	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Prevotella corporis</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	ND
<i>Prevotella loeschei</i>	0	0	0	2	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	ND
<i>Prevotella melaninogenica</i>	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Prevotella oralis</i>	0	0	0	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	ND
<i>Proteus mirabilis</i>	0	0	10	78	502	3544	497	139	76	19	3	5	0	2	0	0	0	0	0	0.25
<i>Proteus vulgaris</i>	0	0	2	16	90	398	63	12	7	5	2	0	0	0	0	0	0	0	0	0.25
<i>Providencia rettgeri</i>	0	0	0	0	9	66	20	2	1	0	1	0	0	0	0	0	0	0	0	0.25
<i>Providencia spp.</i>	0	0	0	8	3	10	11	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Providencia stuartii</i>	0	0	1	2	12	138	38	15	3	5	4	1	0	1	0	0	0	0	0	0.25
<i>Pseudomonas aeruginosa</i>	0	0	7	40	144	2592	5929	10727	11880	8751	5164	3770	3248	3927	391	443	33	14	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>Pseudomonas fluorescens</i>	0	0	0	0	3	10	13	15	9	30	25	41	14	20	1	0	0	0	0	ND
<i>Pseudomonas stutzeri</i>	0	0	0	0	0	0	10	4	4	0	0	0	0	0	0	0	0	0	0	ND
<i>Salmonella enteritidis</i>	0	0	1	15	179	326	2	0	0	0	0	0	0	0	0	0	0	0	0	0.125
<i>Salmonella paratyphi</i>	0	0	0	1	7	60	0	1	0	0	0	0	0	0	0	0	0	0	0	0.125
<i>Salmonella</i> spp.	0	0	0	29	362	1178	9	8	0	1	0	0	1	0	0	0	0	0	0	0.125
<i>Salmonella typhi</i>	0	0	0	11	20	289	1	1	0	0	0	0	0	0	0	0	0	0	0	0.125
<i>Salmonella typhimurium</i>	0	0	0	2	51	121	1	0	0	0	0	0	0	0	0	0	0	0	0	0.125
<i>Serratia liquefaciens</i>	0	0	0	2	7	68	13	3	1	0	3	0	0	0	0	0	0	0	0	0.25
<i>Serratia marcescens</i>	0	0	13	36	269	5422	778	219	74	44	29	8	9	16	0	1	0	0	0	0.25
<i>Serratia</i> spp.	0	0	2	12	20	6	3	0	1	0	0	0	0	0	0	0	0	0	0	0.25
<i>Shigella flexneri</i>	0	0	0	29	93	187	3	0	0	1	0	0	0	0	0	0	0	0	0	ND
<i>Shigella sonnei</i>	0	0	0	19	14	383	1	0	1	0	0	0	0	0	0	0	0	0	0	ND
<i>Staphylococcus aureus</i>	0	0	31	205	988	2036	2467	823	198	95	34	49	31	11	12	6	0	2	0	0.5
<i>Staphylococcus capitis</i>	0	0	1	2	10	24	12	11	2	4	2	1	2	0	0	0	0	0	0	0.5
<i>Staphylococcus coagulase -ve</i>	0	0	0	1	9	25	26	25	10	7	4	6	12	18	0	0	0	0	0	0.5
<i>Staphylococcus epidermidis</i>	0	0	0	21	99	200	111	125	103	50	51	22	14	9	1	4	0	0	0	0.5
<i>Staphylococcus haemolyticus</i>	0	0	2	2	2	13	13	21	8	6	9	2	5	4	9	9	1	0	0	0.5
<i>Staphylococcus hominis</i>	0	0	0	2	5	23	24	49	21	19	6	6	1	3	6	1	0	0	0	0.5
<i>Staphylococcus lugdunensis</i>	0	0	0	0	2	7	4	17	5	2	5	2	0	0	0	0	0	0	0	0.5
<i>Staphylococcus saprophyticus</i>	0	0	0	0	0	3	24	48	8	2	3	4	1	3	4	0	0	0	0	0.5
<i>Staphylococcus simulans</i>	0	0	0	0	0	2	5	4	2	2	0	5	2	2	1	0	0	0	0	ND
<i>Staphylococcus warnerii</i>	0	0	1	0	1	2	29	4	2	1	3	4	0	4	0	0	0	0	0	ND
<i>Staphylococcus xylois</i>	0	0	0	0	0	3	4	1	1	0	8	3	1	1	1	0	0	0	0	ND
<i>Stenotrophomonas maltophilia</i>	0	0	0	0	0	4	6	16	33	22	21	72	154	3815	109	0	0	0	0	ND
<i>Streptococcus agalactiae</i>	0	0	18	53	279	523	39	12	4	2	2	2	0	1	1	2	0	0	0	0.125
<i>Streptococcus anaerobic</i>	0	0	5	5	7	32	9	1	0	2	1	0	0	0	0	0	0	0	0	ND
<i>Streptococcus anginosus</i>	0	0	1	1	3	2	0	1	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus anginosus</i>	0	0	0	1	5	16	4	1	1	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus constellatus</i>	0	0	1	1	4	3	4	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus constellatus</i>	0	0	2	2	2	8	9	1	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus</i> group C	0	0	10	2	1	14	2	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus</i> group F	0	0	0	0	1	4	5	3	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus</i> group G	0	0	35	12	9	74	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus intermedius</i>	0	0	0	2	7	8	3	0	3	0	0	1	0	0	0	0	0	0	0	ND
<i>Streptococcus milleri</i>	0	0	1	1	1	14	3	1	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus mitis</i>	0	0	1	9	32	30	17	7	14	8	6	3	0	1	0	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>Streptococcus mutans</i>	0	0	1	1	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus oralis</i>	0	0	0	1	5	14	2	1	1	1	3	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus pneumoniae</i>	0	10	49	38	6	4	4	7	9	0	0	0	1	0	0	0	0	0	0	0	0.064
<i>Streptococcus pyogenes</i>	0	58	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
<i>Streptococcus salivarius</i>	0	0	0	1	5	10	1	1	0	0	0	1	0	0	0	0	0	0	0	0	ND
<i>Streptococcus sanguis</i>	0	0	1	1	3	3	4	1	2	1	1	1	0	0	0	0	0	0	0	0	ND
<i>Streptococcus viridians</i> group	0	2	9	11	23	37	18	9	5	8	4	2	0	0	0	3	0	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							
		4/8	1/4	2/8		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					0.06/0.5	0.25/0.5
<i>Enterococcus</i> spp.	4/4						
Enterobacteriaceae	4/4	4/8			0.5/2	0.12/8	
<i>Pseudomonas</i> spp.	4/4	4/8				2/8	
<i>Acinetobacter</i> spp.	4/4	4/8				1/8	
<i>Haemophilus</i> spp.	4/4				0.5/2	1/2	0.5/-
<i>Moraxella</i> spp.	4/4				0.5/2	1/2	0.5/-
<i>Neisseria meningitidis</i>					0.25/-	0.06/0.5	0.5/-
<i>Neisseria gonorrhoeae</i>							
<i>Pasteurella multocida</i>							
Gram-negative anaerobes					1/1	1/1	
<i>Campylobacter</i> spp.							

4. Pharmacokinetics

Dosage (mg)	500 mg x 3 iv	1 g x 3 iv
Cmax (mg/L)	15-20	40-50
Cmin (mg/L)	0.1	0.2
Total body clearance (L/h)	14-18	14-18
T _{1/2} (h), mean (range)	1	1
AUC _{24h} (mg.h/L)	75-100	150-200
Fraction unbound (%)	91-98	91-98
Volume of distribution (L/kg)	18-25	18-25
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">Mouton et al., J Antimicrob Chemother 1991; 28:911Mouton et al., Clin Pharmacokinet 1995; 28:275Drusano et al., Scand J Infect Dis Suppl 1995; 96: 11AstraZeneca Pharm. http://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?id=6609 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 1000 mg x 3 iv are shown in Figure 1.

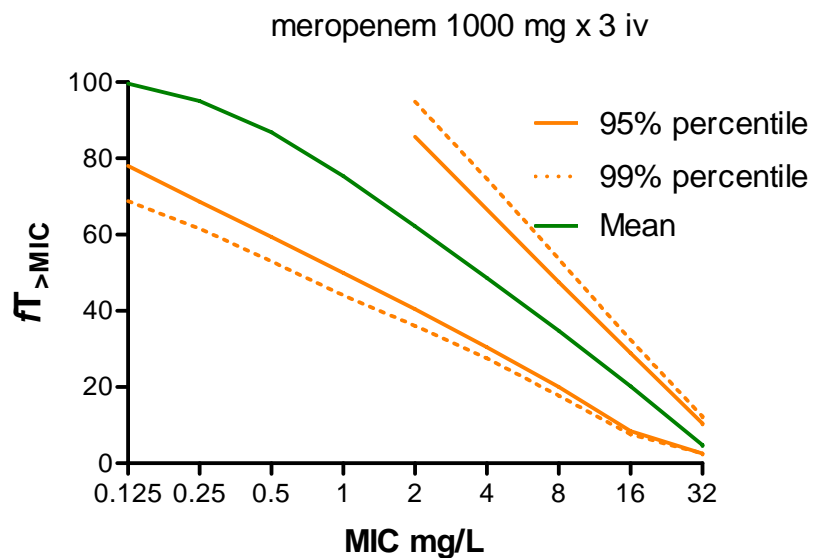


Figure 1. Probabilities of Target Attainment for Meropenem 1000 mg x 3 IV.

The following pharmacokinetic parameters were used to obtain the PTA:
Volume of distribution (Vd): 20.8 L, CV 13%
Elimination half-life (t): 1.04 h, CV 19%
Fraction unbound (Fu): 91%
Infusion time: 0.5 h

7. Clinical data

Clinical trials have shown the efficacy of meropenem in treatment of patients with septicaemia, post-operative sepsis, nosocomial pneumonia, community acquired pneumonia, complicated skin and soft tissue infections, complicated intra-abdominal infections and neutropenic sepsis. Acute meningitis caused by *S. pneumoniae*, *H. Influenzae* and *N. meningitidis* categorized as wild type can be treated with high-dose therapy.

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 1000 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 2g dose.</p> <p>These render wild type Enterobacteriaceae, <i>Acinetobacter</i> spp. and anaerobes susceptible.</p>
Species-related breakpoints	<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>Breakpoints for <i>Neisseria meningitidis</i> relate to treatment of meningitis only. Breakpoints were set at 0.25/0.25 mg/L as strains with MIC values above 0.25 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>Enterococcus</i> spp. were considered poor targets for meropenem 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 meropenem 1000 mg x 3 daily administered intravenously over 30 minutes as the lowest dose. 2g x 3 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
