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PK-PD cut-offs and their role in breakpoint setting

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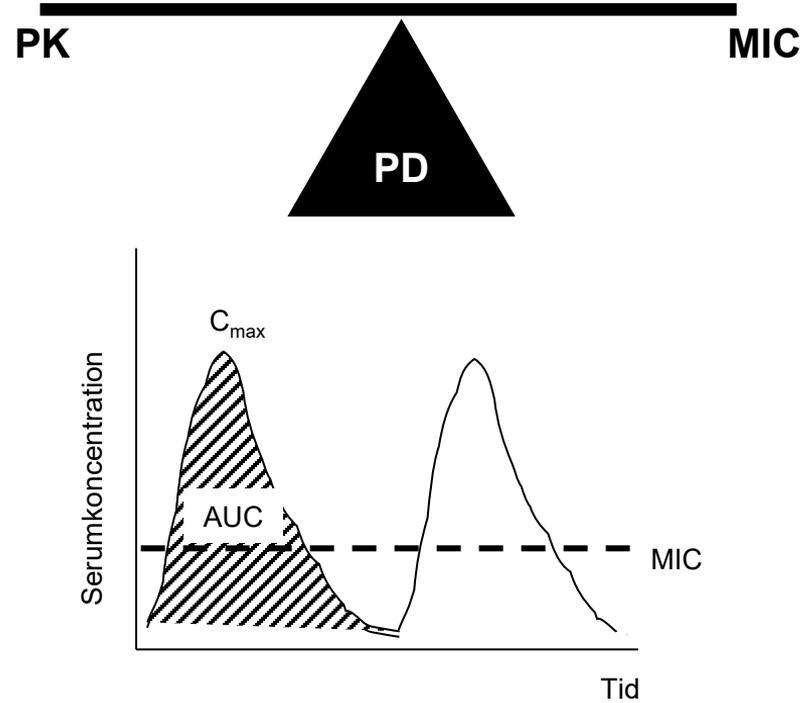
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Killing of bacteria: PK/PD



Targets for different antimicrobial groups



Antibiotics	PD parameter	Target
Penicillins	%fT>MIC	50
Cephalosporins	%fT>MIC	50
Carbapenems	%fT>MIC	40
Fluoroquinolones	fAUC/MIC	Gram-positive: 40 Gram-negative: 80
Aminoglycosides	AUC/MIC	30-40
Tigecycline	AUC/MIC	Gram-positive: 12.5 Gram-negative: 7
Vancomycin	fAUC/MIC	180 (<i>S. aureus</i>)

PK-PD breakpoints – past perspective



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PK-PD (Non-species related) breakpoints

EUCAST Clinical Breakpoint Tables v. 13.0, valid from 2023-01-01

[For abbreviations and explanations of breakpoints, see the Notes sheet](#)

These breakpoints are used only when there are no species-specific breakpoints or other recommendations (a dash or a note) in the species-specific tables.

If the MIC is greater than the PK-PD resistant breakpoint, advise against use of the agent.

If the MIC is less than or equal to the PK-PD susceptible breakpoint, suggest that the agent can be used with caution. The MIC may also be reported although this is not essential. Include a note that the guidance is based on PK-PD breakpoints only, and include the dosage on which PK-PD breakpoint is based.

[More information is available in the EUCAST Guidance Document on how to test and interpret results when there are no breakpoints.](#)

Penicillins	MIC breakpoints (mg/L)		Notes
	S ≤	R >	
Benzylpenicillin	0.25	2	1. For susceptibility testing purposes, the concentration of sulbactam is fixed at 4 mg/L. 2. For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/L. 3. For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L.
Ampicillin	2	8	
Ampicillin-sulbactam	2 ¹	8 ¹	
Amoxicillin	2	8	
Amoxicillin-clavulanic acid	2 ²	8 ²	
Piperacillin	8	16	
Piperacillin-tazobactam	8 ³	16 ³	

PK-PD (Non-species related) breakpoints

EUCAST Clinical Breakpoint Tables v. 14.0, valid from 2024-01-01

Pharmacokinetics and pharmacodynamics (PK/PD) are important tools in the process of setting and revising breakpoints, and for discussion of target attainment and exposure at the site of the infection in relation to daily dose, mode of administration, and the frequency of dosing. The calculated “PK/PD breakpoints” are mostly based on data and simulations involving a limited number of species. We have come to recognize the limitations of these. A common misunderstanding is that PK/PD breakpoints are overarching in relation to species-specific breakpoints and that these can be used when species-specific breakpoints are lacking. This is not the intention. Instead EUCAST has developed guidance on “When there are no breakpoints” ([See EUCAST guidance documents](#)) and removed the PK/PD breakpoints from the table. This is to underline that these should never be considered when breakpoints are lacking. During 2024 a document on the usefulness and limitations of PK/PD breakpoints will be developed.

Variability in PK-PD targets

Variation between strains

Species and type of value	E_{max}	EC ₅₀ (mg/liter)	H	Stasis	2-log reduction ^a
<i>E. coli</i> (n = 3)					
Minimum	4.36	31.9	2.33	27.1	42.7
Maximum	5.50	53.1	3.84	54.4	152
Median	5.47	34.4	3.77	28.4	52.2
Mean	5.13	39.8	3.31	36.6	82.3
CV%	13.0	29.1	25.7	42.0	73.6
<i>K. pneumoniae</i> (n = 4)					
Minimum	4.60	37.5	1.38	31.6	55.2
Maximum	5.34	49.3	3.90	47.7	108
Median	5.00	41.9	3.26	36.0	83.6
Mean	4.98	42.6	2.95	37.8	82.6
CV%	6.10	12.0	38.0	18.6	32.4
<i>S. aureus</i> (n = 3)					
Minimum	5.27	25.3	2.38	21.2	30.3
Maximum	5.94	39.0	5.66	33.1	66.9
Median	5.49	27.6	3.92	25.1	33.0
Mean	5.57	30.6	4.00	26.5	43.4
CV%	6.10	23.9	41.2	22.9	47.0
<i>S. pneumoniae</i> (n = 7)					
Minimum	5.97	16.9	0.670	5.23	16.1
Maximum	9.15	30.9	2.37	22.3	44.3
Median	7.49	22.8	1.86	12.9	26.3
Mean	7.29	24.3	1.70	14.0	29.8
CV%	14.4	20.9	32.9	45.4	34.7

- What should we choose?
- Worst case?
- Median or mean?
- Or perhaps we should opt for a randomly selected target
- In most cases we have limited knowledge about strain properties
- No standardised control strains are available to used to calibrate various models

Variation between species

5. Pharmacodynamics

	<i>Enterobacteriaceae</i>	<i>Streptococcus pneumoniae</i>	<i>S. aureus</i>
%fT>MIC for bacteriostasis	36-40	36-40	20-28
%fT>MIC for 2 log reduction			
%fT>MIC from clinical data			
Comments	<ul style="list-style-type: none"> %fT>MIC is the dominant pharmacodynamic index. 		
References	<ul style="list-style-type: none"> Craig. Diagn Microbiol Infect Dis 1995; 22: 89 		

Cefotaxime

5. Pharmacodynamics (PD)

Index	Various	Various	Various	Model
	<i>Enterobacterales</i>	<i>P. aeruginosa</i>	<i>S. pneumoniae</i>	<i>S. aureus</i>
fT>MIC for bacteriostasis	25-40	25-40	15-20	10-30
fT>MIC for 1-log ₁₀ reduction	35-55	35-55	25-40	15-40
fT>MIC for 2-log ₁₀ reduction	54	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 			

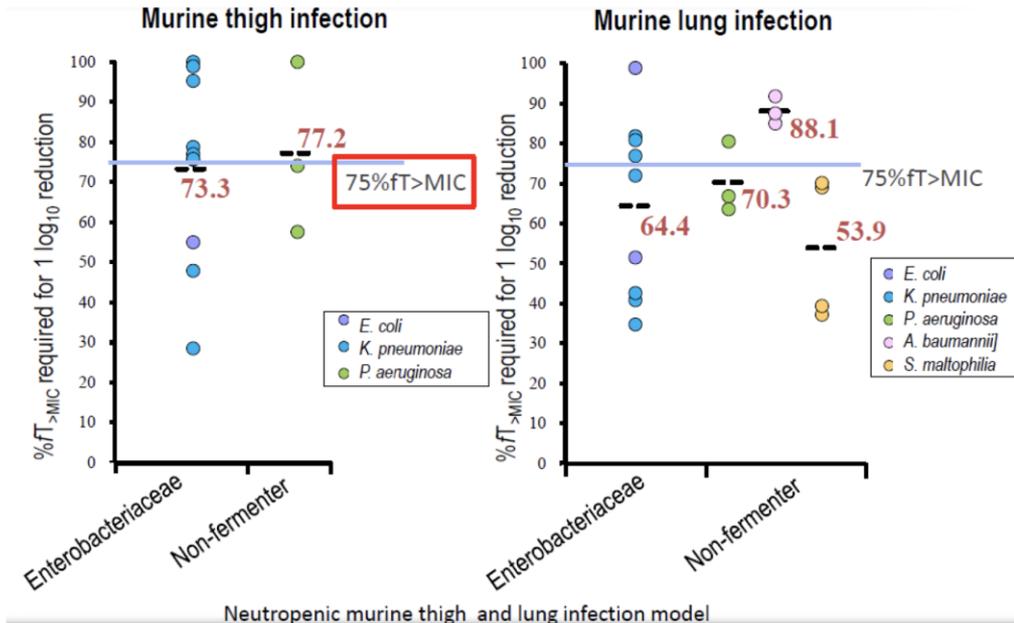
Meropenem

Source: EUCAST
Rationale Documents

Discussion on variation between species

- For agents active across a high number of species: questionable to present one PK-PD breakpoint fitting all species
- Should PK-PD breakpoints also be species-specific?
- What then is the utility of PK-PD breakpoints for species lacking breakpoints?
 - Possibly to compare to “related species” if this can be established
- Sometimes even challenging to break down PK-PD breakpoints according to Gram-stain
- Can be a problem if some species are for instance represented by low-pathogenic strains

Variation between infection types



Source: EUCAST
Rationale Document
Cefiderocol

Should we set a breakpoint for all indications?

Separate breakpoint for pneumonia?

Stasis enough for certain infection types?

Decisions we make will have consequences for SIR-reporting

Pharmacodynamic simulations

Variations across different infection types and renal clearance

Target fT>MIC	PK variable	Infection disease	Renal Function	Regimen ^a	MIC (µg/mL)						
					0.25	0.5	1	2	4	8	16
90%	Plasma	HAP/VAP/HCAP	Augmented	2 g q6h	100	100	99.8	99.8	98.7	90.8	61.2
			Normal	2 g q8h	100	100	100	99.7	97.8	91.0	56.1
			Mild	2 g q8h	100	100	100	100	99.4	96.3	79.7
			Moderate	1.5 g q8h	100	100	100	100	100	99.2	88.1
			Severe	1 g q8h	100	100	100	100	100	99.6	94.8
			ESRD	750 mg q12h	100	100	100	100	99.9	99.7	91.1
		BSI/sepsis	Augmented	2 g q6h	100	99.8	99.8	99.1	96.5	82.1	41.7
			Normal	2 g q8h	100	100	99.7	98.8	95.2	79.4	36.0
			Mild	2 g q8h	100	100	100	99.6	98.6	91.4	60.9
			Moderate	1.5 g q8h	100	100	100	100	99.7	97.3	76.5
			Severe	1 g q8h	100	100	100	100	99.8	98.8	87.7
			ESRD	750 mg q12h	100	100	100	100	99.9	98.4	81.3
		cUTI/AUP	Augmented	2 g q6h	100	99.8	99.8	98.7	95.0	76.8	37.7
			Normal	2 g q8h	100	100	99.6	97.9	93.4	74.0	32.0
			Mild	2 g q8h	100	100	100	99.5	97.7	88.7	56.5
			Moderate	1.5 g q8h	100	100	100	100	99.7	96.2	71.3
			Severe	1 g q8h	100	100	100	100	99.7	98.6	85.3
			ESRD	750 mg q12h	100	100	100	100	99.8	97.8	79.7
	ELF	HAP/VAP/HCAP	Augmented	2 g q6h	100	100	98.6	89.5	58.5	13.5	0.3
			Normal	2 g q8h	100	99.7	97.6	89.5	52.0	8.6	0.0
			Mild	2 g q8h	100	100	99.4	96.0	77.9	25.1	1.2
			Moderate	1.5 g q8h	100	100	100	99.0	87.1	36.1	1.9
			Severe	1 g q8h	100	100	100	99.4	94.0	51.0	4.2
			ESRD	750 mg q12h	100	100	100	100	90.2	38.7	3.9

Current Monte Carlo simulation do not consider extreme variation

Table 2.

Comparison of ertapenem pharmacokinetic data obtained in critically ill patients with data of healthy young volunteers previously reported by Pletz *et al.*¹³

Parameter	This study ^a (n = 17)	Pletz <i>et al.</i> , 2004 ^b single dose (n = 10)	Pletz <i>et al.</i> , 2004 ^b multiple dose (n = 10)
C _{max} (mg/L)	90.5 ± 26.1	253 (15)	275 (19)
AUC _{0-∞} (mg · h/L)	418.5 ± 171.6	817 (20) ^c	823 (19) ^d
T _{max} (h)	0.5 (0.5-1.0)	0.5 (0)	0.5 (0)
t _{1/2 β} (h)	4.15 ± 1.33	4.5 (23)	4.3 (11)
MRT (L)	5.72 ± 1.68	4.7 (13)	4.1 (18)
V _z (L)	17.3 ± 5.93	8.0 (25)	7.5 (20)
V _{ss} (L)	14.8 ± 3.78	5.7 (18)	5.0 (18)
CL _{TOT} (mL/min)	43.2 ± 23.7	20.4 (18)	20.2 (16)
CL _R (mL/min)	31.8 ± 23.3	9.38 (37)	8.62 (46)
f _u (%)	54.8 ± 19.09	45.1 (36)	41.2 (42)

^aData are reported as geometric means ± SD.

^bData are reported as geometric mean (coefficient of variation [in percent]).

^cAUC_{0-∞} for single-dose data (day 1).

^dAUC₀₋₂₄ for steady-state data (day 7).

What does the future hold for PK-PD "breakpoints"?

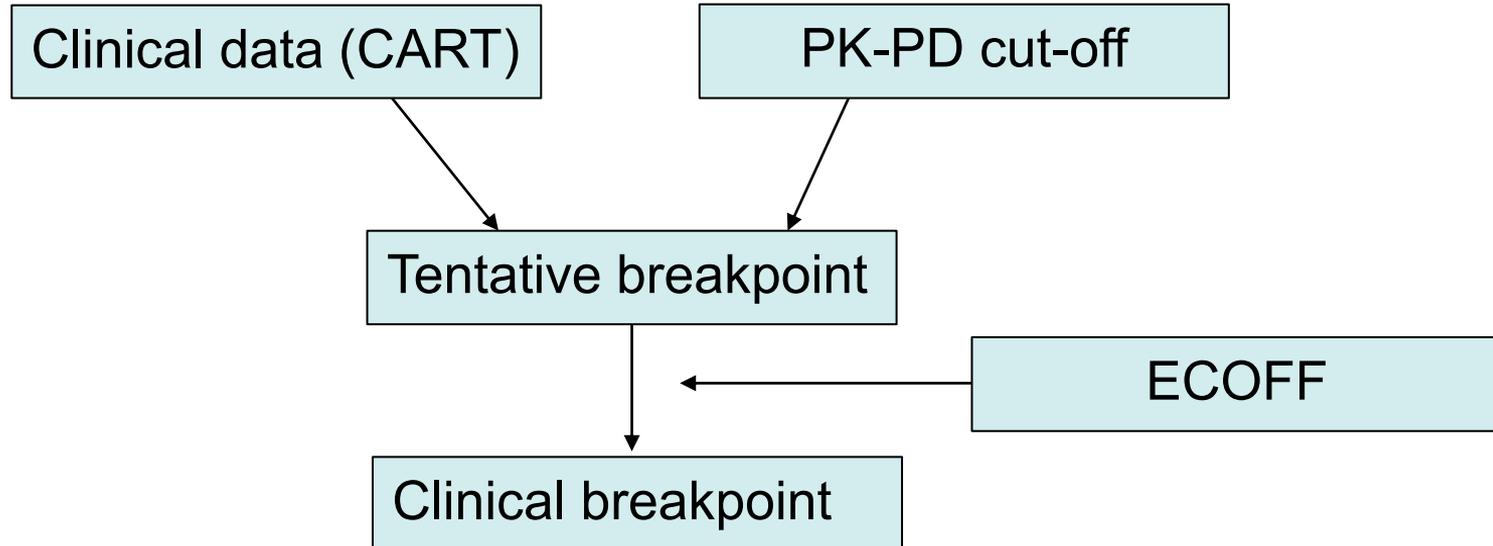


PK-PD breakpoints become PK-PD cut-offs...

PK-PD (Non-species related) breakpoints

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And you should now refer to the new guidance document: What to do when there are no breakpoints



EUCAST guidance on When there are no breakpoints in breakpoint tables? 2024-02-29

In breakpoint tables, there are some species/species groups and antimicrobial agents lacking numerical breakpoints to allow categorical interpretation to S, I or R or a dash to allow the reporting of “resistant” without testing.

The most probable sequence of events in the laboratory is as follows (see also the flowchart):

	MIC-values above which therapy with the agent should be discouraged		
Agents and notes for aerobic bacteria	Gram-positive organisms	Gram-negative organisms	Notes
Benzylpenicillin	0.25	0.5	If a beta-lactamase is detected, report resistant without further testing.
Ampicillin, Amoxicillin, Ampicillin-sulbactam, Amoxicillin-clavulanic acid (IV only)	0.5	8	The breakpoint of 8 mg/L pertains to intravenous high dose administration. If a beta-lactamase is detected, the value is only valid for amoxicillin-clavulanic acid and ampicillin-sulbactam.

Conclusions

- PK-PD cut-offs are dependent on a number of decisions to be made prior to PD simulation
 - Selection of target (considering strain, species, static vs cidal, infection type, random selection vs worst case vs mean)
 - Selection of PK-model
 - Consideration of MIC-variability
- PK-PD cut-offs are largely **species-specific**, which makes them mostly a tool (like ECOFFs) for setting species-specific breakpoints