Mentimeter

NordicAST

PK-PD breakpoints are dead – long live the PK-PD cut-offs!

Barbara Holzknecht, Herlev Hospital / Statens Serum Institut, DK
Christian Giske, Karolinska Institutet and Karolinska Univ. Hosp., SE

NordicAST workshop 27-28 May 2025

9

Mentimeter

PK-PD breakpoints – past perspective

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.
Ampicillin			
Ampicillin-su			
Amoxicillin			
Amoxicillin-c			
Piperacillin			
Piperacillin-t			

PK/PD cut-off values

EUCAST Clinical Breakpoint Tables v. 15.0, valid from 2025-01-01

Pharmacokinetics and pharmacodynamics (PK/PD) are important, but not the only tools for setting and revising clinical breakpoints. PK/PD targets are often based on a limited number of species. The selection of clinical PK/PD targets is highly dependent on the targeted patient population. Critically ill patients or immunocompromised patients will normally require higher antimicrobial exposure, and thus the PK/PD targets will be higher. As clinical PK/PD targets are often lacking, preclinical PK/PD targets determined in *in vitro* and animal models are often used. These models are not always validated with clinical data. Moreover, the animal models are usually limited to the neutropenic mouse thigh and lung infection model and may not have a translational value for all type of infections. Different PK/PD targets can be determined depending on i) the species, ii) the level of effect (stasis, 1-3 log kill, prevention of emergence of resistance), and iii) the within-species strain variation of PK/PD-targets.

Moreover, simulated pharmacokinetics (healthy vs. patients, different patient populations with different degree of renal/hepatic insufficiencies, levels of plasma proteins and other important covariates) will play a major role in determining PK/PD cut-offs. Critically ill patients have much higher variation in PK than other groups of patients. Calculations are usually made based on free drug concentrations in the plasma or epithelial lining fluid, which are presumed to relate to the concentration at the site of infection. Individual variations in protein binding may also affect the pharmacodynamically important drug exposure. Finally, PK/PD cut-offs may be based on various levels of probability of target attainment like 99%, 95% or 90%. All these factors may result in different PK/PD cut-off values that span in several two-fold dilutions.

A common misunderstanding is that PK/PD cut-offs can be used when clinical breakpoints are lacking. This is not the intention. Instead EUCAST has developed guidance on "When there are no breakpoints" (**see EUCAST guidance document**) and removed the PK/PD cut-offs from the breakpoint tables. This is to underline that these values should never be used when clinical breakpoints are lacking.

Agenda

- A short intro to basic principles and terms in PK-PD
- How are clinical breakpoints set?
- Challenges when using PK-PD cut-offs in breakpoint setting

A short intro to basic principles and terms in PK-PD

Mentimeter

Pharmacokinetics (PK)

"what the body does to the drug"

Pharmakodynamics (PD)

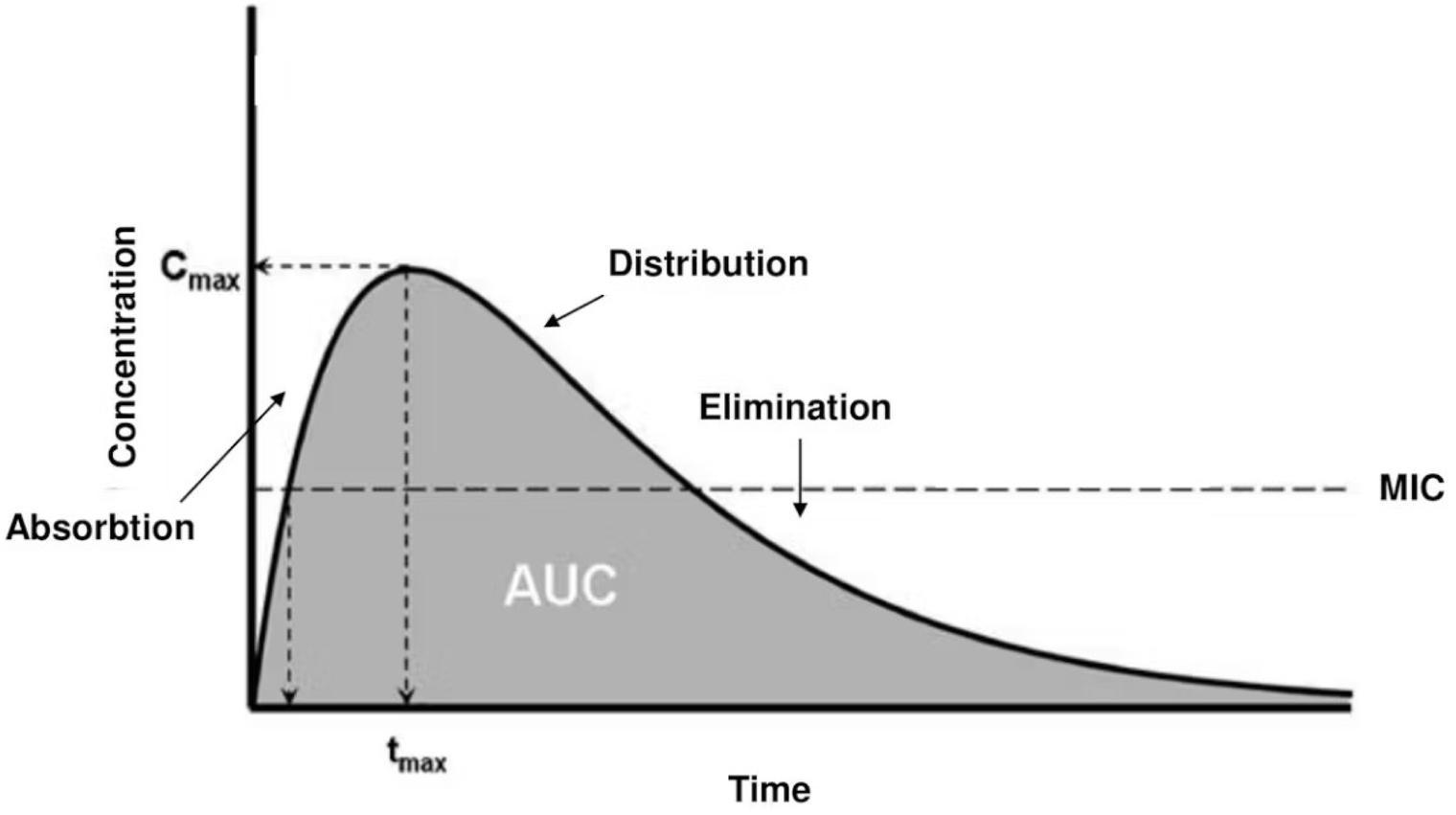
"what the drug does to the microorganism"

NordicAS

Mentimeter

PK

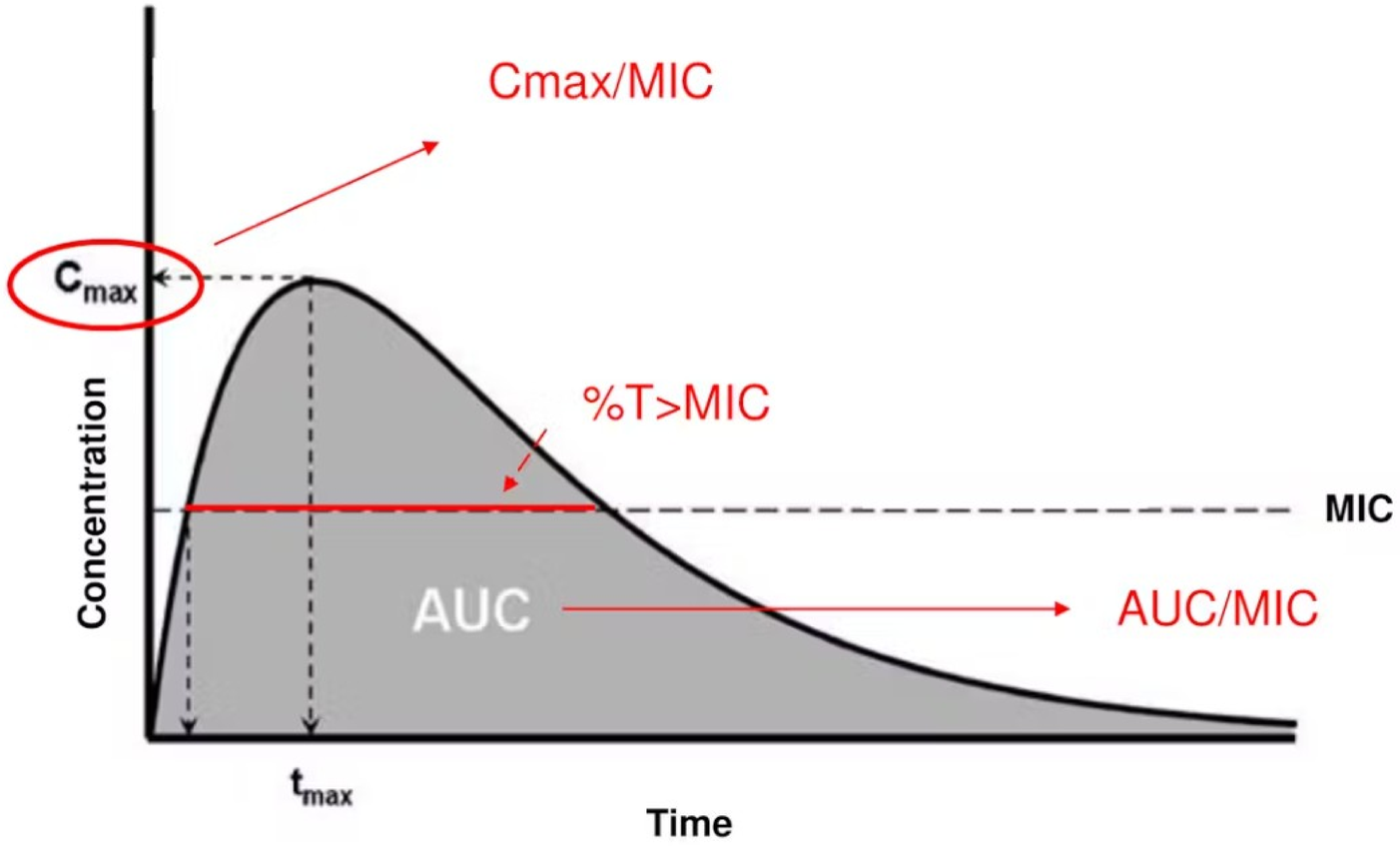
The free (unbound) drug is active!



NordicAS

Mentimeter

PK-PD indices



NordicAS

Mentimeter

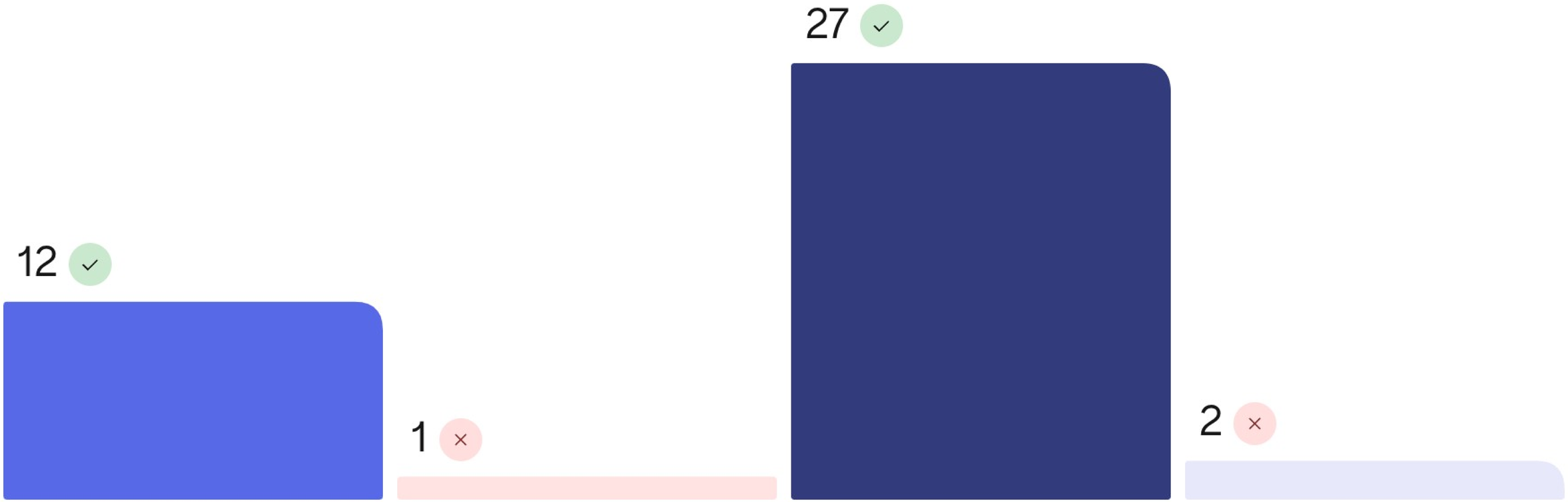
Targets for different antimicrobial groups

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

NordicAS

Mentimeter

Which of the following statement(s) is/are right?



3

29

Mentimeter

How are clinical breakpoints set?

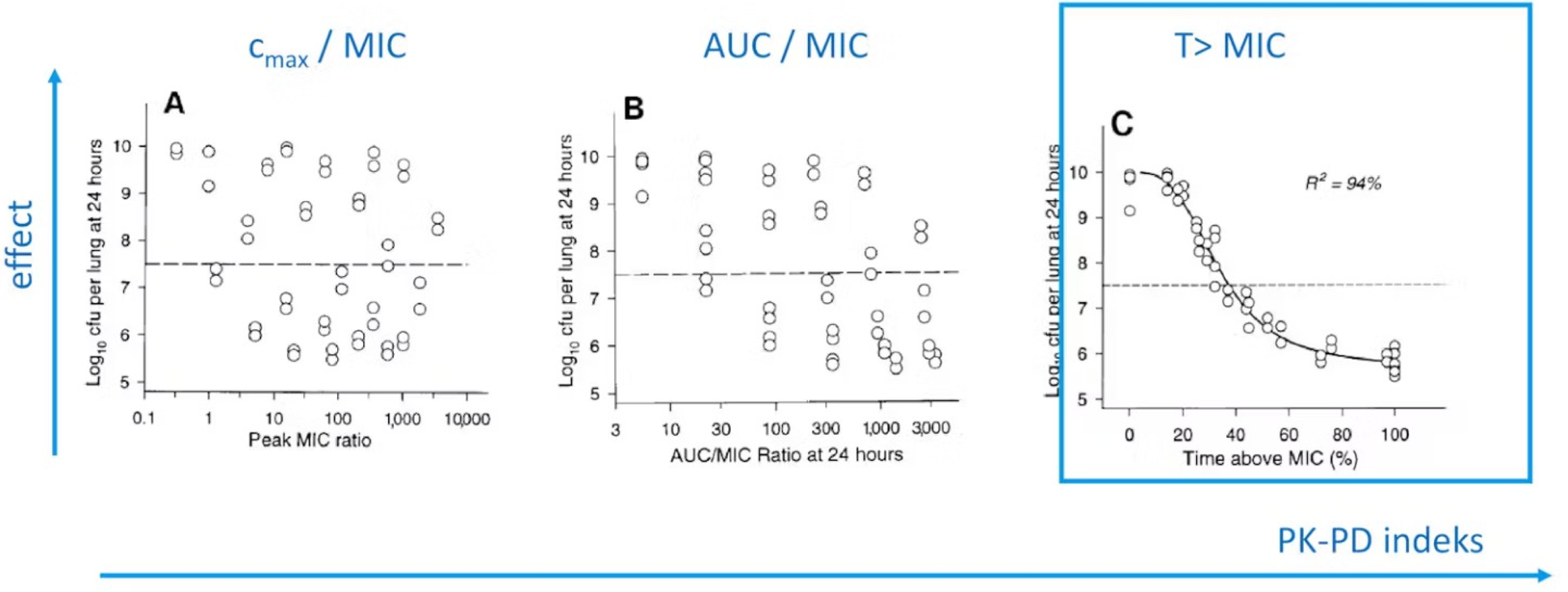
Mouton et al. Clin Microbiol Infect 2012; 18: E37–E45.
Mouton: Setting Clinical MIC Breakpoints from a PK/PD Point of View: It Is the Dose That Matters; in:
Fundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics, Springer 2014; ISBN 978-0-387-75612-7

NordicAS

Mentimeter

1. Which PK-PD index is correlated to effect (bacterial stasis/killing)?

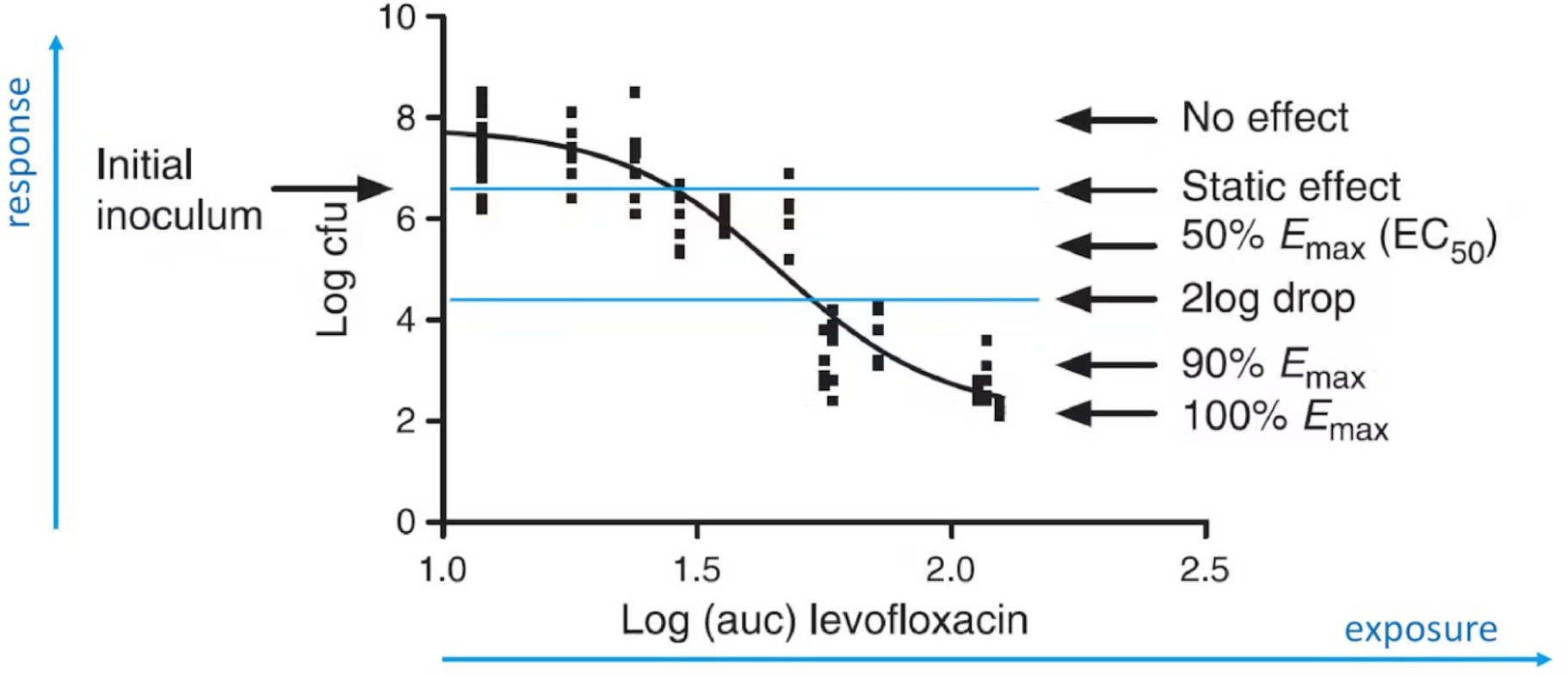
Often data from animal models



Craig. Clin Inf Dis 1998;26:1–12

NordicAS

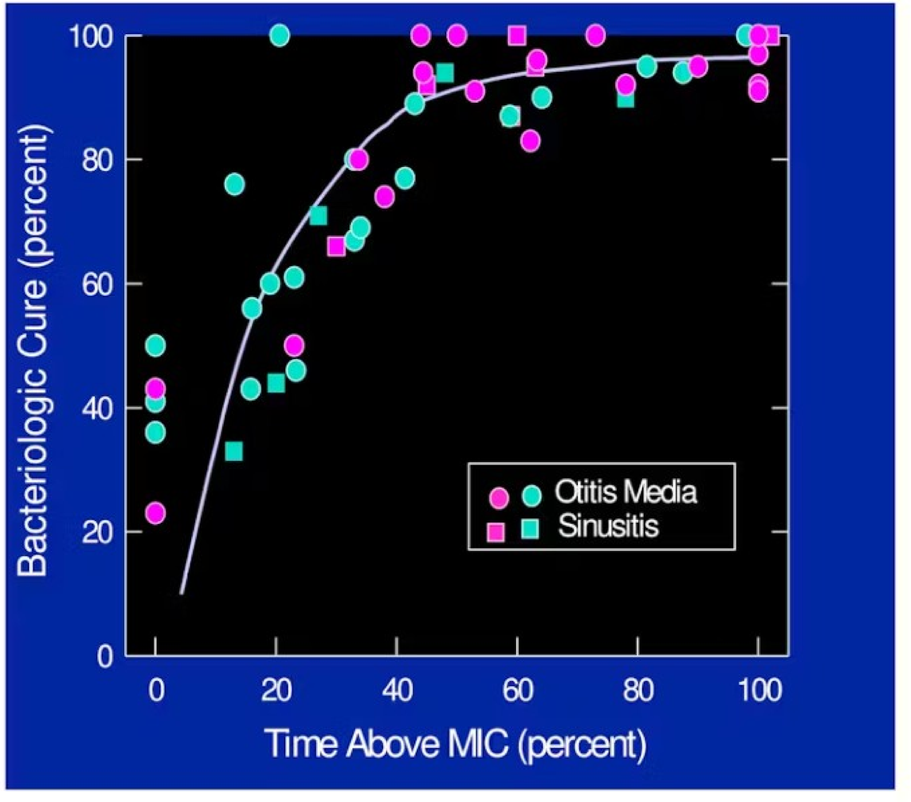
2. What is the pharmacodynamic **target**?



Mouton et al. Clin Microbiol Infect 2012; 18: E37–E45.

Validation in clinical studies: example double tympanocentesis studies

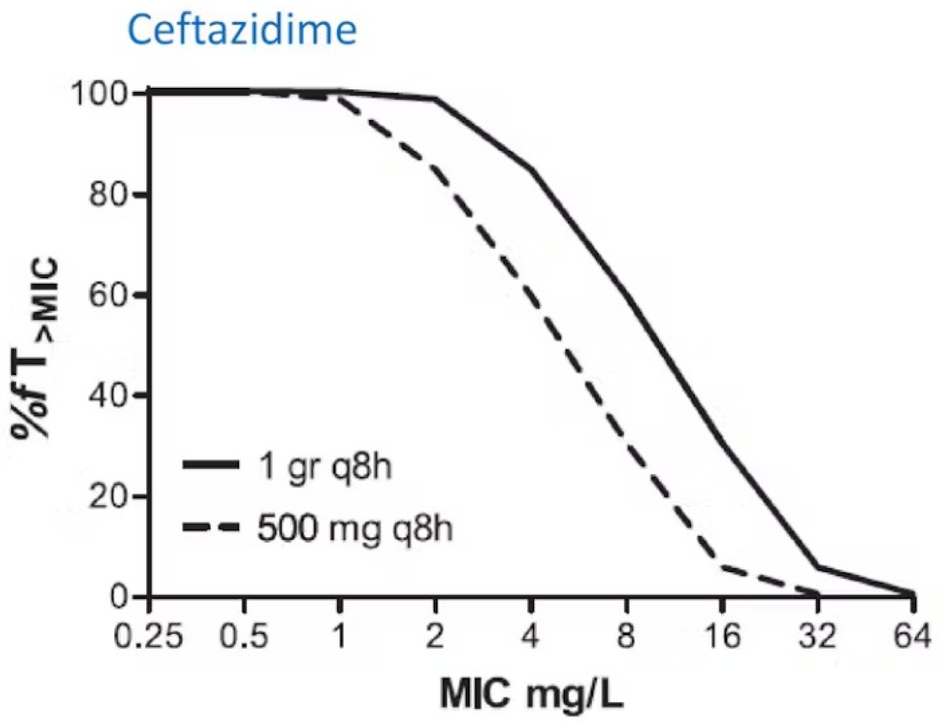
Sampling of middle ear fluid before and after treatment



Pink: *S. pneumoniae*
Green: *H. influenzae*

Dagan R et al.

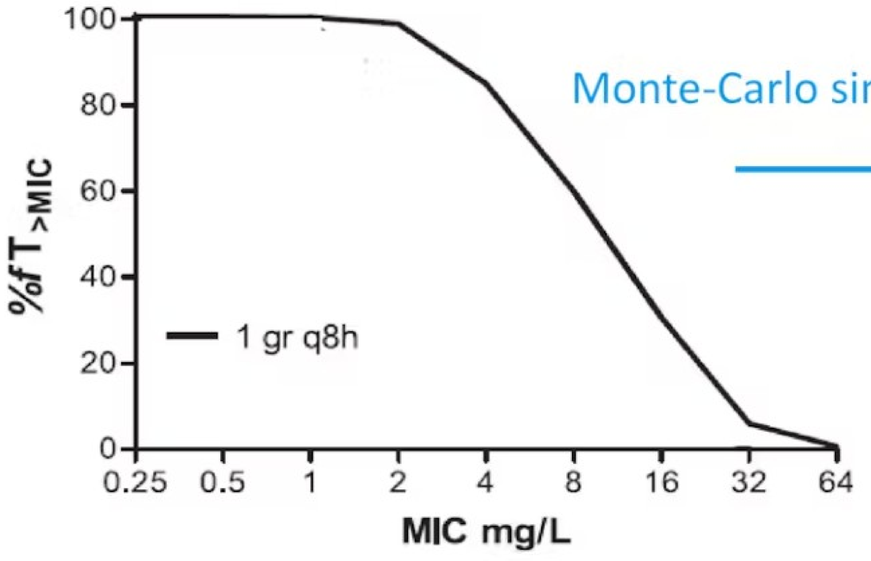
3. Which exposure does a certain dosing regimen result in?



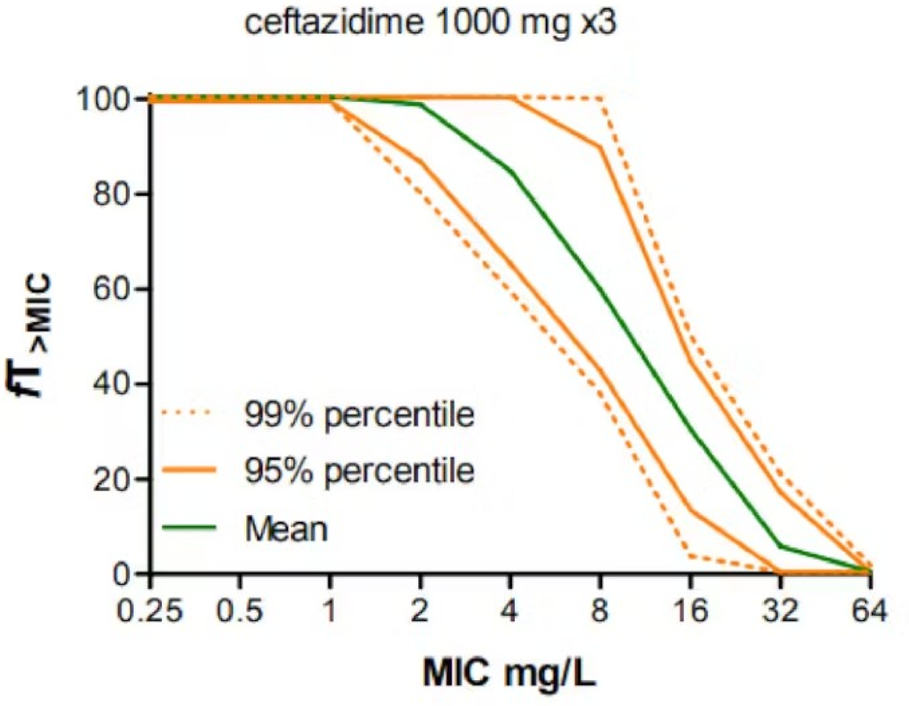
Mouton et al. Clin Microbiol Infect 2012; 18: E37–E45

4. Population variation

Ceftazidime



Monte-Carlo simuation



Mouton et al. Clin Microbiol Infect 2012; 18: E37–E45
EUCAST rationale document: https://www.eucast.org/publications-and-documents/rd

5. For species-specific breakpoints:
How does the **wild type distribution** look like and what is the **ECOFF**?

Mentimeter

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

MIC and zone distributions and ECOFFs

- Organization
- Consultations
- EUCAST News
- New definitions of S, I and R
- Clinical breakpoints and dosing
- Rapid AST in blood cultures
- Expert rules and expected phenotypes
- Resistance mechanisms
- Guidance documents
- SOP
- MIC and zone distributions and ECOFFs
  - New and revised ECOFFs
- AST of bacteria
- AST of mycobacteria
- AST of fungi
- AST of veterinary pathogens
- Frequently Asked Questions (FAQ)
- Meetings
- Rationale documents and publications
- Presentations and statistics

MIC and zone diameter distributions and ECOFFs

1. EUCAST MIC and zone diameter distributions and ECOFFs
2. Correlation between MIC values and inhibition zone diameters

The EUCAST software, originally created in 2003, for displaying distributions of MIC-values (generated with methods calibrated to reference broth microdilution or for some agents and species, agar dilution) and inhibition zone diameters (generated with EUCAST standardised disk diffusion methodology) was re-programmed during 2020 and re-launched on 24 November, 2020. Each graph is shown in two versions where one is constructed by just adding up all approved distributions, and the other by giving each distribution equal weight before constructing the aggregated distribution. The later is generated through converting numbers to per cent before aggregation. This prevents large distributions from dominating or even "obliterating" smaller distributions and allows all distributions equal weight. During 2021-2022 distributions are curated in accordance with EUCAST SOP10.2 and all distributions and ECOFF values gradually reviewed. A dedicated software for the calculation of zone diameter ECOFFs has been created and will be applied during 2023.

The distributions are based on collated data from a total of more than 30 000 distributions containing more than several million MIC values and zone diameters. The distributions include data from national and international studies such as resistance surveillance programs and and MIC distributions from published articles, the pharmaceutical industry drug development programmes, veterinary programmes and from individual laboratories. Histograms display wild type and non-wild type organisms, together with EUCAST epidemiological cut-off values (ECOFFs) and tentative ECOFFs (TECOFF).

Antimicrobial wild type distributions of microorganisms

Mic distributions include collated data from multiple sources, geographical areas and time p

Search database

MIC and Inhibition zone diameter distributions of

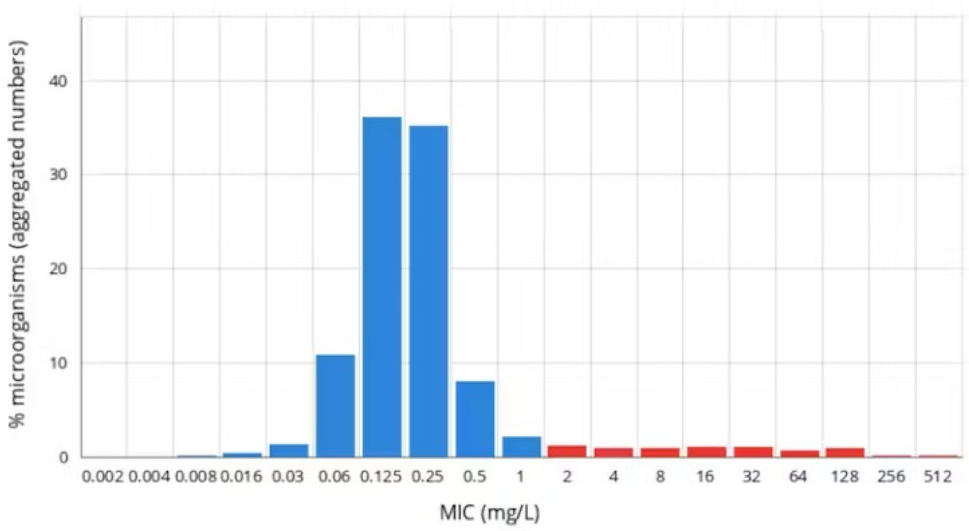
MIC and inhibition zone diameter distributions

Distributions are shown as "aggregated distributions" and as "aggregated weighted distrib

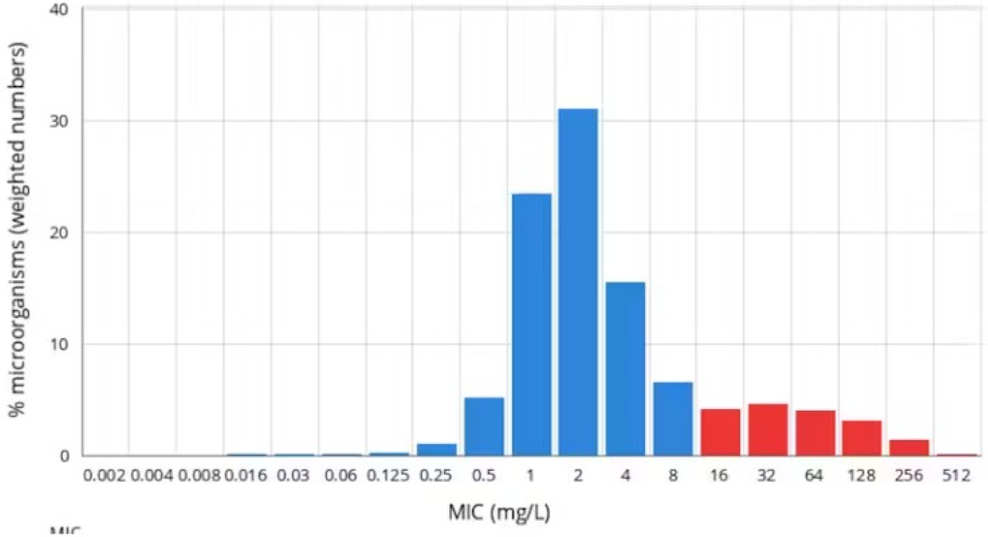
NordicAST

3. Wild type distribution and ECOFF

Ceftazidime / *E. coli*
ECOFF 1 mg/L



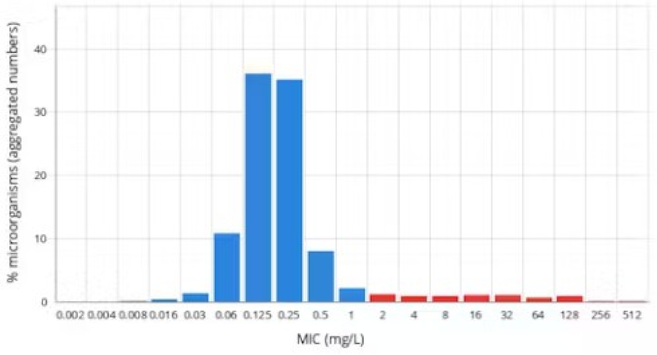
Ceftazidime / *P. aeruginosa*
ECOFF 8 mg/L



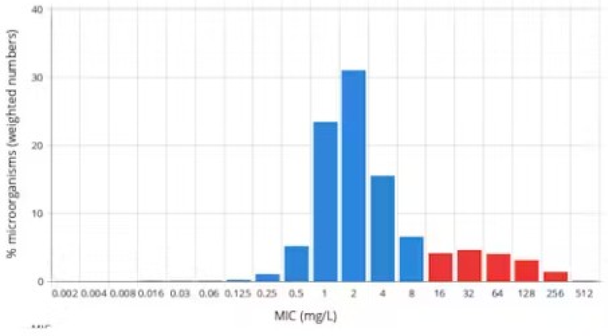
Mentimeter

Ceftazidime breakpoints

E. coli

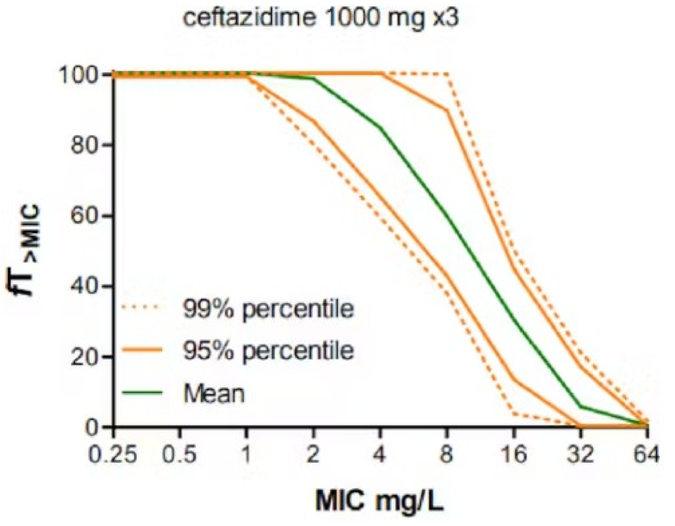


Pseudomonas spp.



+

EUCAST standard dose



→

Clinical breakpoints

E. coli:

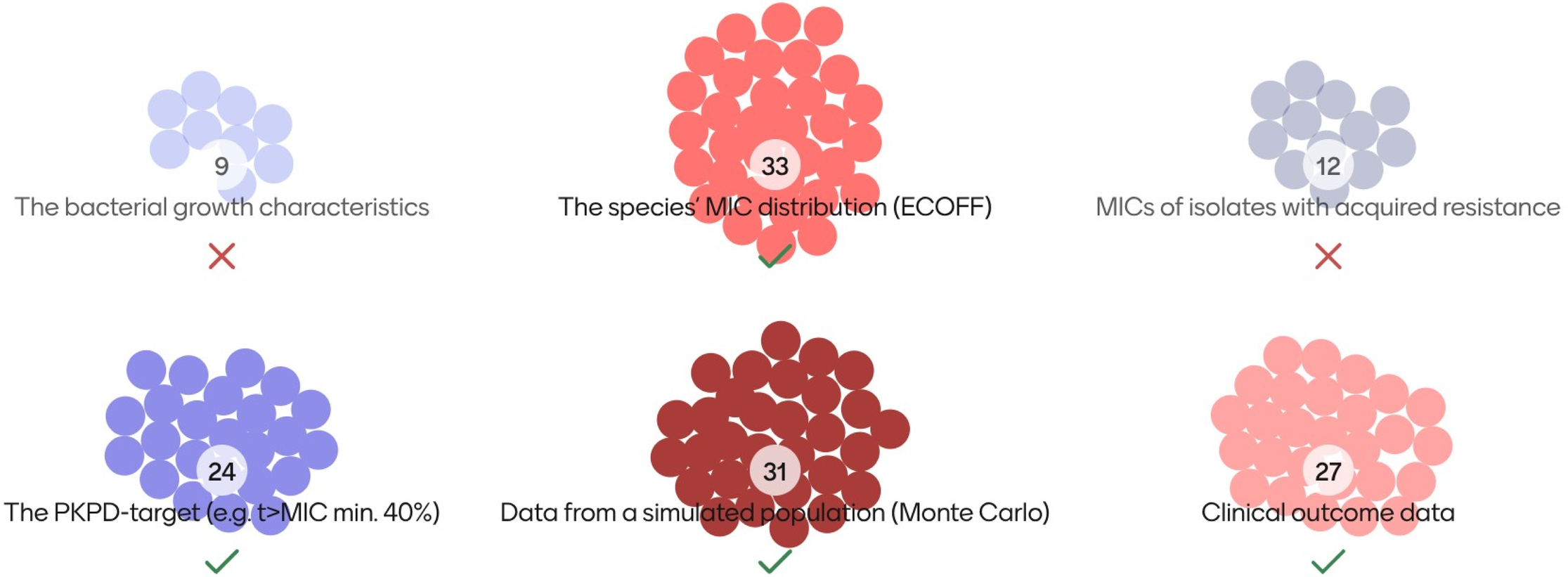
S≤1; R>4

Pseudomonas spp.

S≤0,001; R>8

Mentimeter

When setting breakpoints, the following parameters are taken into account:



5 33

Mentimeter

Further reading – EUCAST rationale documents

AST of veterinary pathogens

Frequently Asked Questions (FAQ)

Meetings

Rationale documents and publications

- Rationale Documents
- Consultations
- Publications in journals
- Technical notes
- Posters
- External documents
- Reports

Presentations and statistics

Videos and online seminars

Warnings!

Translations

two for RDs in line for update. As RDs are updated to the new format, old versions will be archived and not immediately available but can be obtained from the webmaster on request. Former scientific secretary John Turnidge is updating RDs to new formats.

Rationale documents pertaining to antifungal agents are published on the AFST website.

Rationale documents pertaining to veterinary agents and issues are published on the VetCAST website.

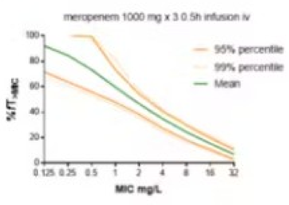
Section 1 - **RDs updated and converted to new format** (alphabetical order)

- Amikacin 3.1 (2024-September); Amikacin 3.0 (2024-01-04)
- Aztreonam-avibactam (2024-07-03)
- Bedaquiline - See AST of Mycobacteria
- Cefepime-enmetazobactam (2024-07-03)
- Cefiderocol 2.0 (2023-04-04)
- Ceftriaxone 1.0 (2023-04-04)
- Delamanid - See AST of Mycobacteria
- Doripenem v 2.0 (2024-01-04)
- Ertapenem v 3.0 (2024-01-04)
- Fosfomycin IV 4.0 (2022-11-22)

Pharmacodynamics

Index	Various models	Various models	Various models	Various models
	Enterobacterales	*P. aeruginosa*	*S. pneumoniae*	*S. aureus*
	Range	Range	Range	Range
f%T>MIC for bacteriostasis	25-40	25-40	15-20	10-30
f%T>MIC for 1-$\log_{10}$ kill	35-55	35-55	25-40	15-40

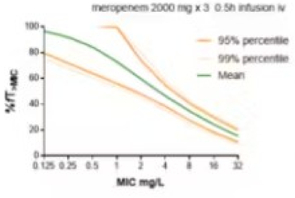
Monte Carlo simulations



The following pharmacokinetic parameters were used to obtain the PTA (Wijma, 2018, based on data from Krueger, 2005)

Vc: 10.5 L, CV 17.7%
Cl : 15.6 L/h, CV 15.3%
Q : 7.17 L/h, CV 66.8%
Vp : 5.09 L, CV 44.9%

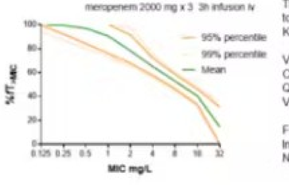
Fraction unbound (Fu): 90%
Infusiontime 0.5 h
Note : Covariance matrix used in simulations



The following pharmacokinetic parameters were used to obtain the PTA (Wijma, 2018, based on data from Krueger, 2005)

Vc: 10.5 L, CV 17.7%
Cl : 15.6 L/h, CV 15.3%
Q : 7.17 L/h, CV 66.8%
Vp : 5.09 L, CV 44.9%

Fraction unbound (Fu): 90%
Infusiontime 0.5 h
Note : Covariance matrix used in simulations



The following pharmacokinetic parameters were used to obtain the PTA (Wijma, 2018, based on data from Krueger, 2005)

Vc: 10.5 L, CV 17.7%
Cl : 15.6 L/h, CV 15.3%
Q : 7.17 L/h, CV 66.8%
Vp : 5.09 L, CV 44.9%

Fraction unbound (Fu): 90%
Infusiontime 3 h
Note : Covariance matrix used in simulations

NordicAST

Mentimeter

PK-PD breakpoints – past perspective

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.
Ampicillin			
Ampicillin-su			
Amoxicillin			
Amoxicillin-c			
Piperacillin			
Piperacillin-ta			

PK/PD cut-off values

EUCAST Clinical Breakpoint Tables v. 15.0, valid from 2025-01-01

Pharmacokinetics and pharmacodynamics (PK/PD) are important, but not the only tools for setting and revising clinical breakpoints. PK/PD targets are often based on a limited number of species. The selection of clinical PK/PD targets is highly dependent on the targeted patient population. Critically ill patients or immunocompromised patients will normally require higher antimicrobial exposure, and thus the PK/PD targets will be higher. As clinical PK/PD targets are often lacking, preclinical PK/PD targets determined in *in vitro* and animal models are often used. These models are not always validated with clinical data. Moreover, the animal models are usually limited to the neutropenic mouse thigh and lung infection model and may not have a translational value for all type of infections. Different PK/PD targets can be determined depending on i) the species, ii) the level of effect (stasis, 1-3 log kill, prevention of emergence of resistance), and iii) the within-species strain variation of PK/PD-targets.

Moreover, simulated pharmacokinetics (healthy vs. patients, different patient populations with different degree of renal/hepatic insufficiencies, levels of plasma proteins and other important covariates) will play a major role in determining PK/PD cut-offs. Critically ill patients have much higher variation in PK than other groups of patients. Calculations are usually made based on free drug concentrations in the plasma or epithelial lining fluid, which are presumed to relate to the concentration at the site of infection. Individual variations in protein binding may also affect the pharmacodynamically important drug exposure. Finally, PK/PD cut-offs may be based on various levels of probability of target attainment like 99%, 95% or 90%. All these factors may result in different PK/PD cut-off values that span in several two-fold dilutions.

A common misunderstanding is that PK/PD cut-offs can be used when clinical breakpoints are lacking. This is not the intention. Instead EUCAST has developed guidance on "When there are no breakpoints" (**see EUCAST guidance document**) and removed the PK/PD cut-offs from the breakpoint tables. This is to underline that these values should never used when clinical breakpoints are lacking.

But what are the real challenges?

- Coping with **variability in PK-PD targets**
  - Variation between strains and species
  - Static vs 1-log vs 2-log vs suppression of resistance
  - Variation between infection types
  - Worst case vs mean vs random selection
- **Pharmacodynamic simulations**
  - Extreme situations (ICU, obesity, altered renal function)
  - Simulating variation in MICs?

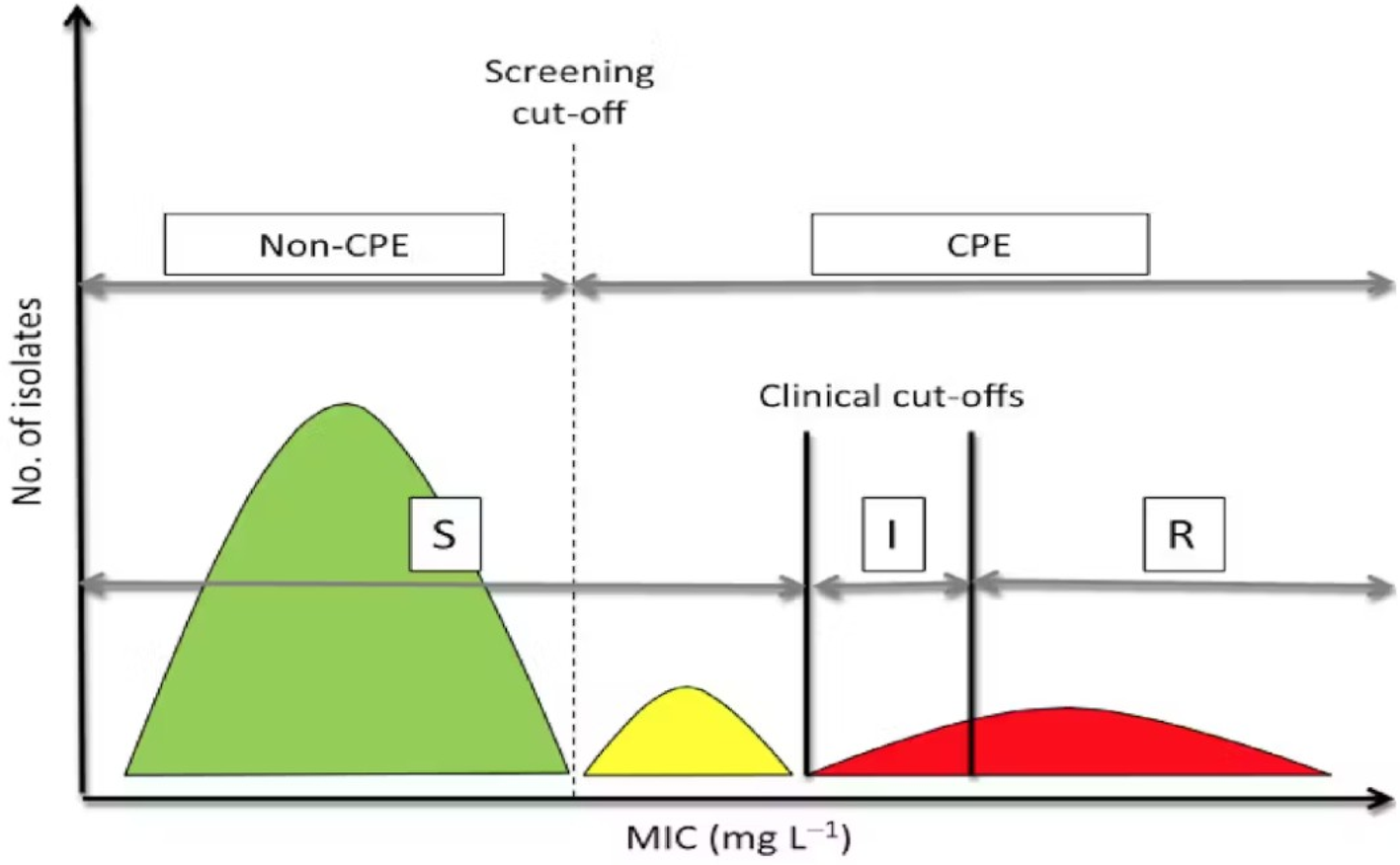
Mentimeter

What are the challenges with setting PK-PD breakpoints?

- **PK-PD relations**
  - Pharmacodynamic target
  - Pharmacodynamic simulation
  - Decisions to be made on PK-model
  - Decisions to be made on target attainment
- **Clinical data**
  - Preferably outcome vs exposure (or MIC vs outcome)
- **MIC-data**
  - Ensure that the wild-type distribution is not bisected by suggested values

NordicAS

Where can the breakpoint be set?



Tängdén T and Giske CG. J Intern Med. 2015;277(5):501-12.

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]
E. coli ($n = 3$)					
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
K. pneumoniae ($n = 4$)					
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
S. aureus ($n = 3$)					
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
S. pneumoniae ($n = 7$)					
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

Mentimeter

5. Pharmacodynamics

	Enterobacteriaceae	*Streptococcus pneumoniae*	*S. aureus*
%*f*T>MIC for bacteriostasis	36-40	36-40	20-28
%*f*T>MIC for 2 log reduction			
%*f*T>MIC from clinical data			
Comments	• %fT>MIC is the dominant pharmacodynamic index.		
References	• Craig. Diagn Microbiol Infect Dis 1995; 22: 89		

Cefotaxime

Pharmacodynamics

Index	Various models	Various models	Various models	Various models
	Enterobacterales	***P. aeruginosa***	***S. pneumoniae***	***S. aureus***
	Range	**Range**	**Range**	**Range**
f%T>MIC for bacteriostasis	25-40	25-40	15-20	10-30
f%T>MIC for 1-$\log_{10}$ kill	35-55	35-55	25-40	15-40

Meropenem

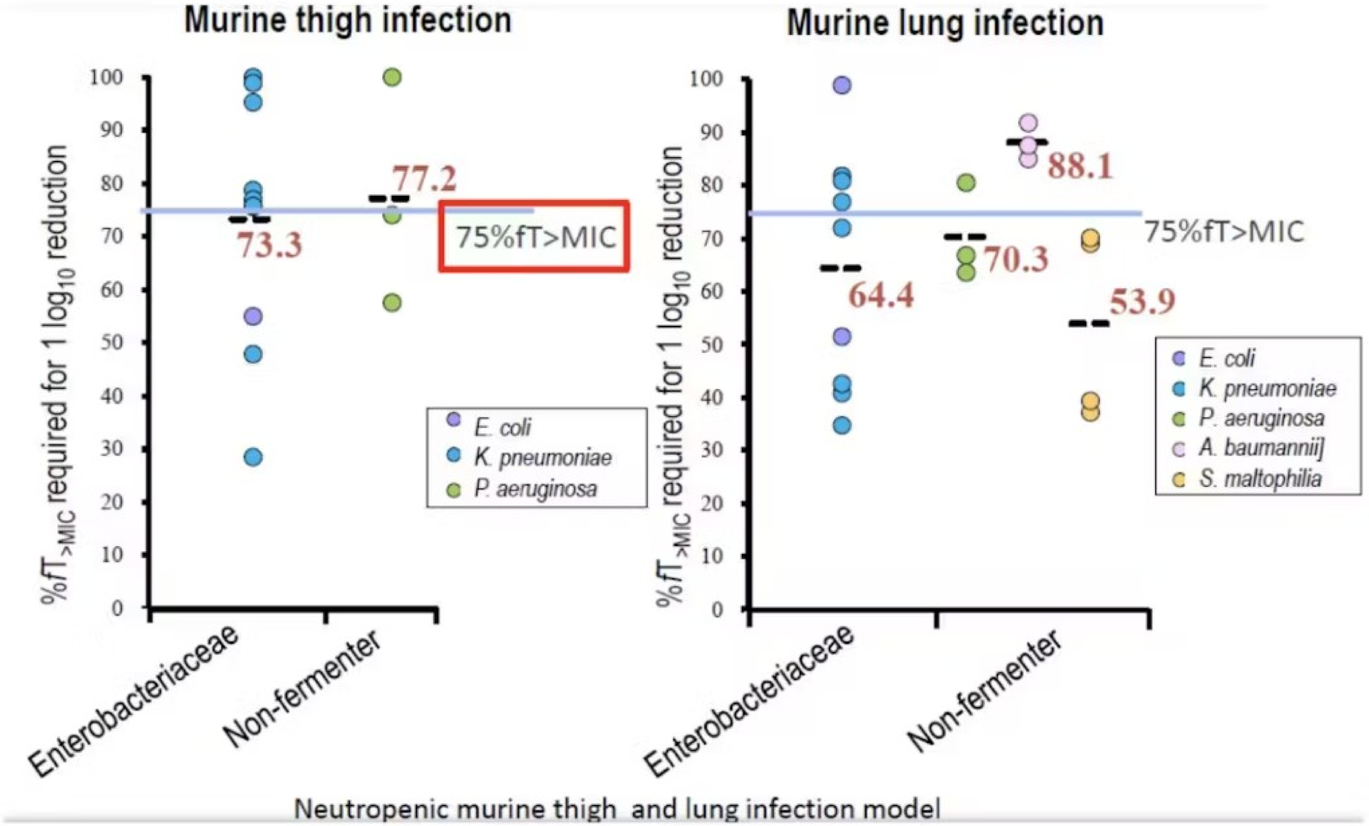
Source: EUCAST Rationale Documents

NordicAST

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

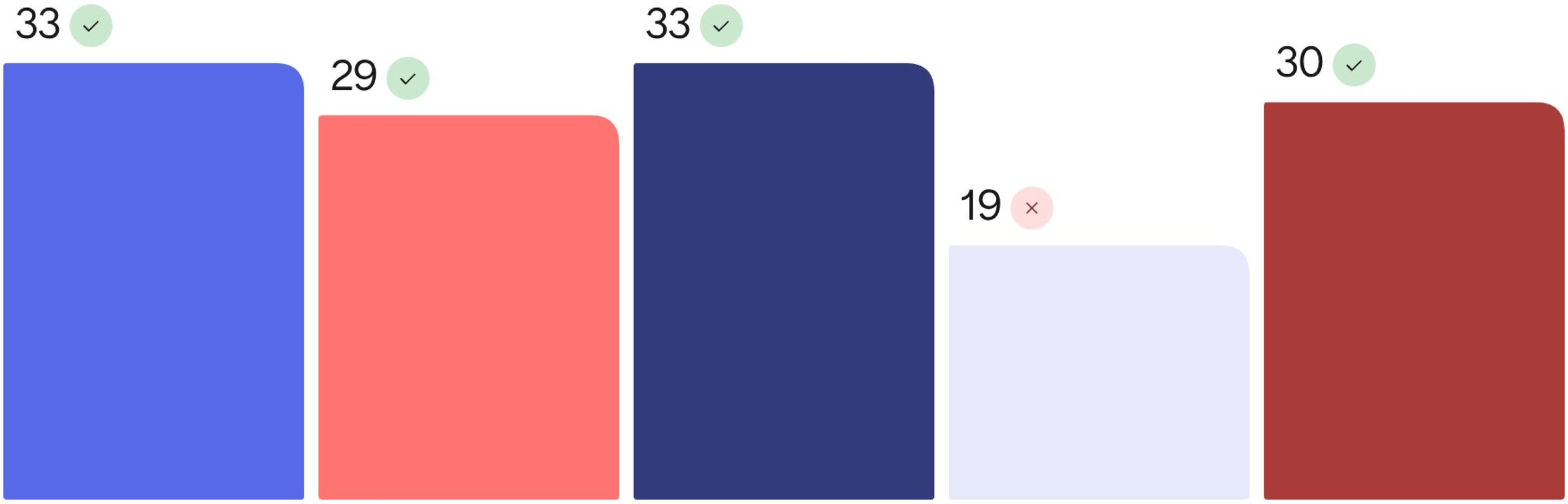


Source: EUCAST Rationale Document Cefiderocol

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

Mentimeter

Pharmacodynamic targets can vary for different



3
34

Mentimeter

Pharmacodynamic simulations

NordicASC

Variations across different infection types and renal clearance

Mentimeter

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

NordicASP

Current Monte Carlo simulations do not consider extreme variation

Mentimeter

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 *et al.*, 2004[b] single dose (n = 10)	Pletz *et al.*, 2004[b] multiple dose (n = 10)
C_{max} (mg/L)	90.5 ± 26.1	253 (15)	275 (19)
$AUC_{0-\infty}$ (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)

[a]Data are reported as geometric means ± SD.

[b]Data are reported as geometric mean (coefficient of variation [in percent]).

[c]$AUC_{0-\infty}$ for single-dose data (day 1).

[d]AUC_{0-24} for steady-state data (day 7).

Burkhard O, et al. JAC 2007;59(2):277-84

NordicASP

Combination of obesity and altered clearance – example with meropenem

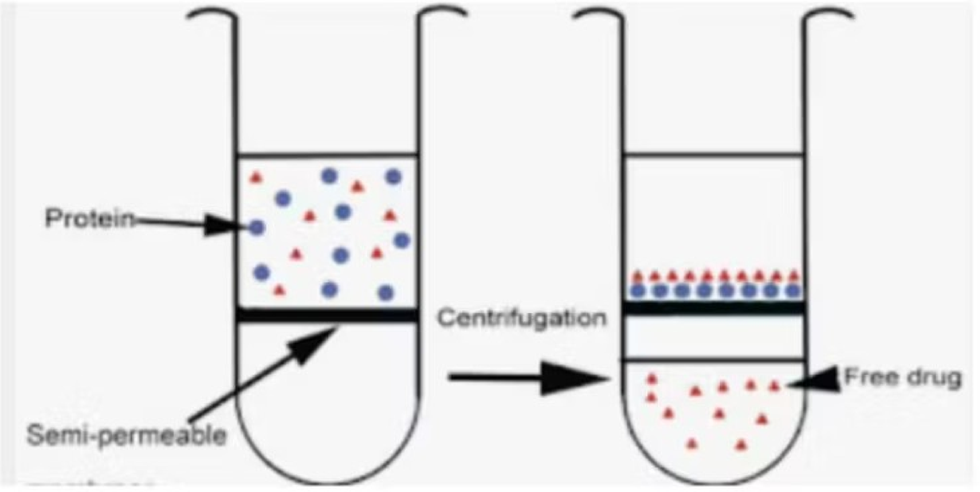
Dose (mg) q8h (infusion interval)	BMI group	CL_{CR} (ml/min)	Attainment of PTA for MIC (mg/liter) 0.5	1	2	4	8	16
1,000 (II)	Nonobese	30	+	+	+	+	+	–
		50	+	+	+	+	+	–
		150	–	–	–	–	–	–
	Obese	30	+	+	+	+	+	–
		50	+	+	+	+	+	–
		150	+	–	–	–	–	–
	Morbidly obese	30	+	+	+	+	+	–
		50	+	+	+	+	+	–
		150	+	+	–	–	–	–
1,000 (PI)	Nonobese	30	+	+	+	+	+	–
		50	+	+	+	+	+	–
		150	+	+	+	+	–	–
	Obese	30	+	+	+	+	+	–
		50	+	+	+	+	+	–
		150	+	+	+	+	–	–
	Morbidly obese	30	+	+	+	+	+	–
		50	+	+	+	+	+	–
		150	+	+	+	+	–	–

Dose (mg) q8h (infusion interval)	BMI group	CL_{CR} (ml/min)	Attainment of PTA for MIC (mg/liter) 0.5	1	2	4	8	16
2,000 (II)	Nonobese	30	+	+	+	+	+	+
		50	+	+	+	+	+	+
		150	+	–	–	–	–	–
	Obese	30	+	+	+	+	+	+
		50	+	+	+	+	+	+
		150	+	+	–	–	–	–
	Morbidly obese	30	+	+	+	+	+	+
		50	+	+	+	+	+	+
		150	+	+	+	–	–	–
2,000 (PI)	Nonobese	30	+	+	+	+	+	+
		50	+	+	+	+	+	+
		150	+	+	+	+	+	–
	Obese	30	+	+	+	+	+	+
		50	+	+	+	+	+	+
		150	+	+	+	+	+	–
	Morbidly obese	30	+	+	+	+	+	+
		50	+	+	+	+	+	+
		150	+	+	+	+	+	–

Alobaid A et al. AAC; 2016:60:4577–4584.

Variation in protein binding

- Concentrations of total and unbound ertapenem were determined by ultrafiltration and HPLC in 29 plasma samples from six ICU patients treated with 1 g of ertapenem once daily
- Protein binding was ~20% in plasma from healthy volunteers at clinically relevant concentrations
- In ICU patients, protein binding was substantially higher (range 30.9%–53.6%)
- Binding studies indicated that hypoalbuminemia alone did not explain these differences
- Liebchen U et al. JAC 2014; 11:3108–3111



Ultrafiltration method

Variation in protein binding

Mentimeter

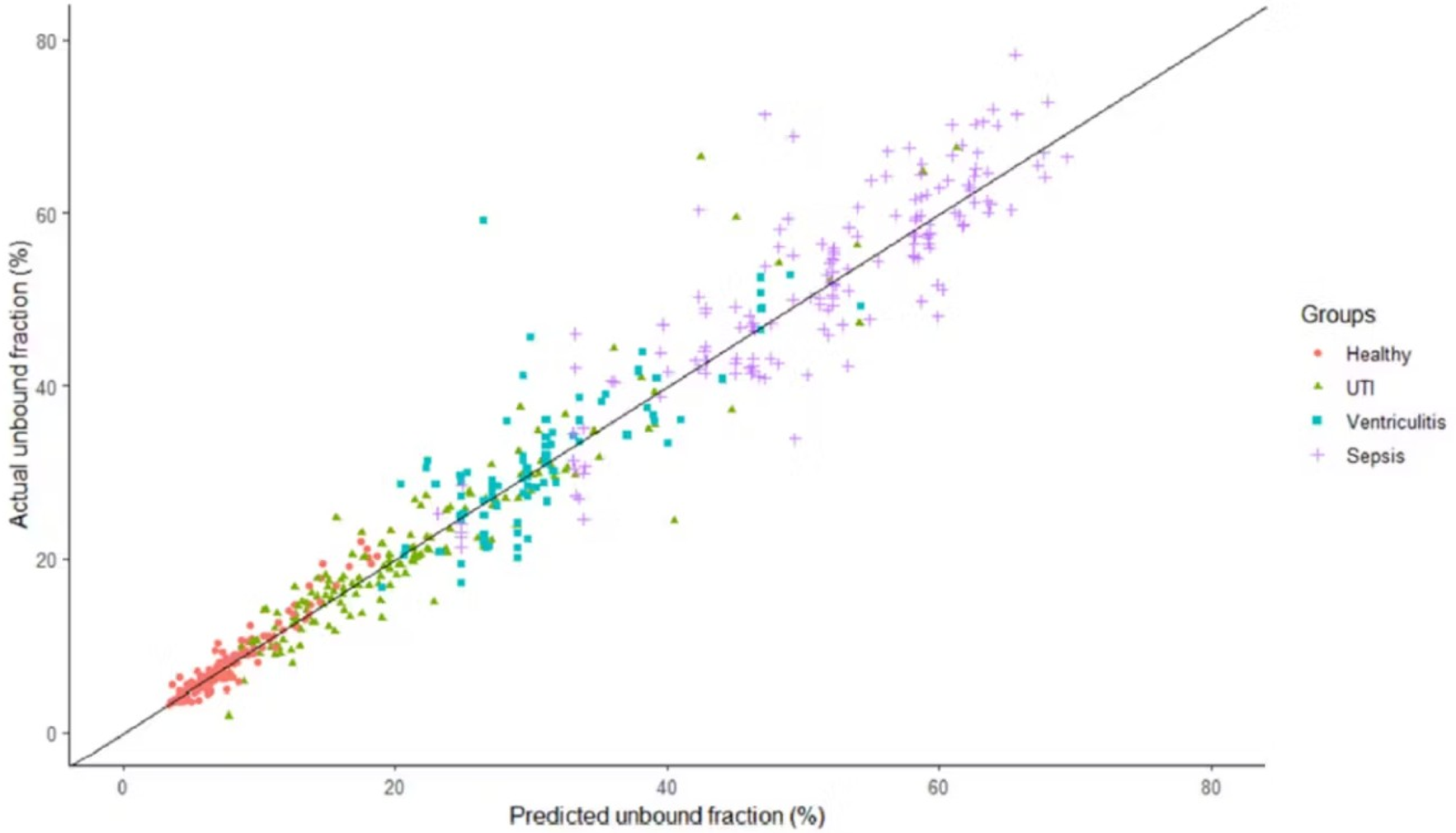
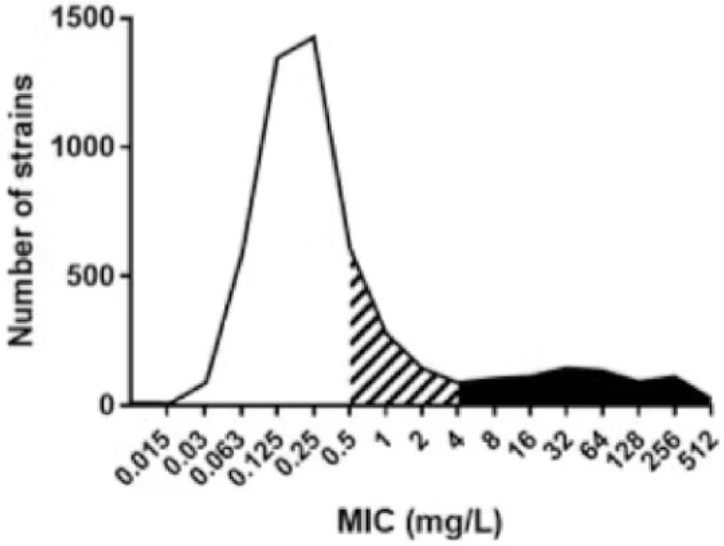


FIGURE 2 Observed unbound fraction *vs.* predicted for different groups. UTI: urinary tract infection. Solid line = line of identity.

Li et al. Br J Clin Pharmacol. 2025;1–11.

Not only variation in plasma concentration should be considered in pharmacodynamic simulations

Mentimeter



MIC found	Interpretation for target attainment
Within WT, ≤ ECOFF	ECOFF
>ECOFF	MIC + two 2-fold dilutions [1]

[1]The number of dilutions could be higher or lower than two depending on proficiency of the lab and the drug-species distribution

- Variability: both technical and biological
- Usually not considered ount in recommendations regarding individualized dosing
- Might be included in complex simulations

Mouton JW et al. JAC 2018;73(3):564-568.

NordicAS

Mentimeter

What is correct?

Variation is highest in critically ill patients.

Higher targets are needed for critically ill patients.

Protein binding is constant across patient groups.

4

37

Mentimeter

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

NordicASC

PK-PD breakpoints become PK-PD cut-offs…

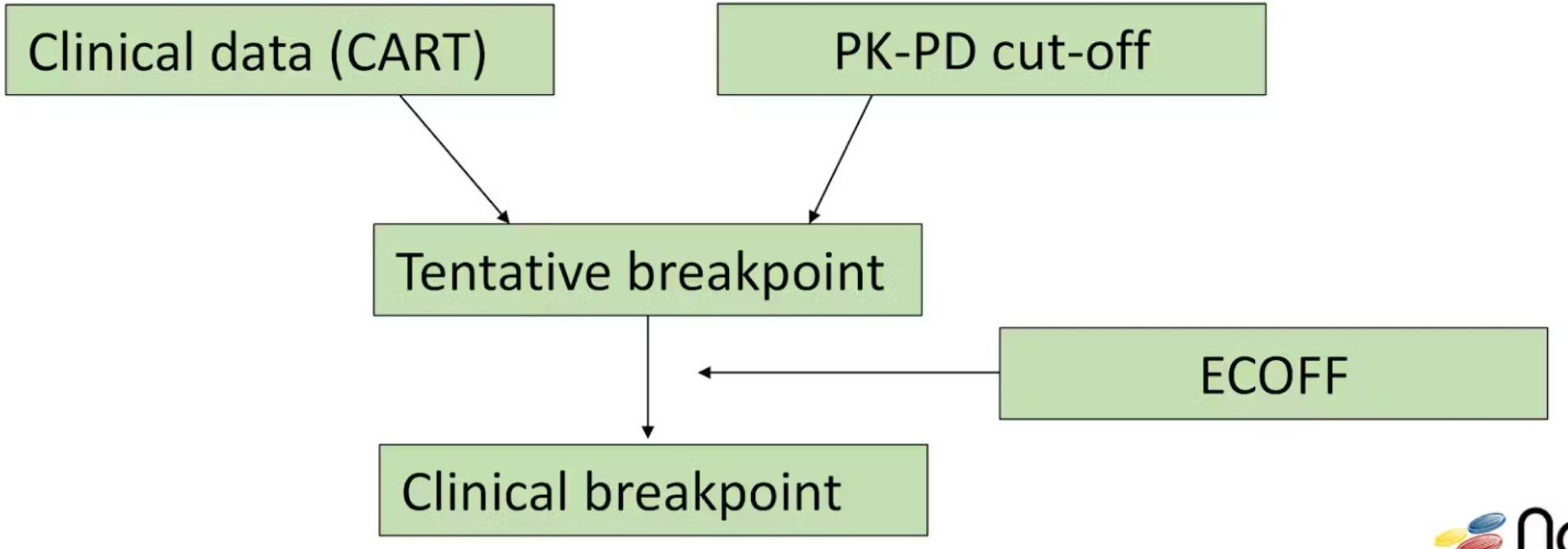
Mentimeter

PK/PD cut-off values **EUCAST Clinical Breakpoint Tables v. 15.0, valid from 2025-01-01**

Pharmacokinetics and pharmacodynamics (PK/PD) are important, but not the only tools for setting and revising clinical breakpoints. PK/PD targets are often based on a limited number of species. The selection of clinical PK/PD targets is highly dependent on the targeted patient population. Critically ill patients or immunocompromised patients will normally require higher antimicrobial exposure, and thus the PK/PD targets will be higher. As clinical PK/PD targets are often lacking, preclinical PK/PD targets determined in *in vitro* and animal models are often used. These models are not always validated with clinical data. Moreover, the animal models are usually limited to the neutropenic mouse thigh and lung infection model and may not have a translational value for all type of infections. Different PK/PD targets can be determined depending on i) the species, ii) the level of effect (stasis, 1-3 log kill, prevention of emergence of resistance), and iii) the within-species strain variation of PK/PD-targets.

Moreover, simulated pharmacokinetics (healthy vs. patients, different patient populations with different degree of renal/hepatic insufficiencies, levels of plasma proteins and other important covariates) will play a major role in determining PK/PD cut-offs. Critically ill patients have much higher variation in PK than other groups of patients. Calculations are usually made based on free drug concentrations in the plasma or epithelial lining fluid, which are presumed to relate to the concentration at the site of infection. Individual variations in protein binding may also affect the pharmacodynamically important drug exposure. Finally, PK/PD cut-offs may be based on various levels of probability of target attainment like 99%, 95% or 90%. All these factors may result in different PK/PD cut-off values that span in several two-fold dilutions.

A common misunderstanding is that PK/PD cut-offs can be used when clinical breakpoints are lacking. This is not the intention. Instead EUCAST has developed guidance on "When there are no breakpoints" (**see EUCAST guidance document**) and removed the PK/PD cut-offs from the breakpoint tables. This is to underline that these values should never be used when clinical breakpoints are lacking.



NordicAST

Future PK-PD cut-offs

Mentimeter

- Higher complexity is needed
- Consensus needed regarding selection of targets
- Standardised control strains to be used across models to calibrate data better
- Monte Carlo simulations including also MIC-variation
- Consideration for species-specific breakpoints
- Might be used in precision medicine along with applications that can integrate data (unless this is done in the breakpoint tables)
- Assays for measuring free fraction should become the new standard in TDM – protein binding could be more variable than expected

NordicAST

Conclusions

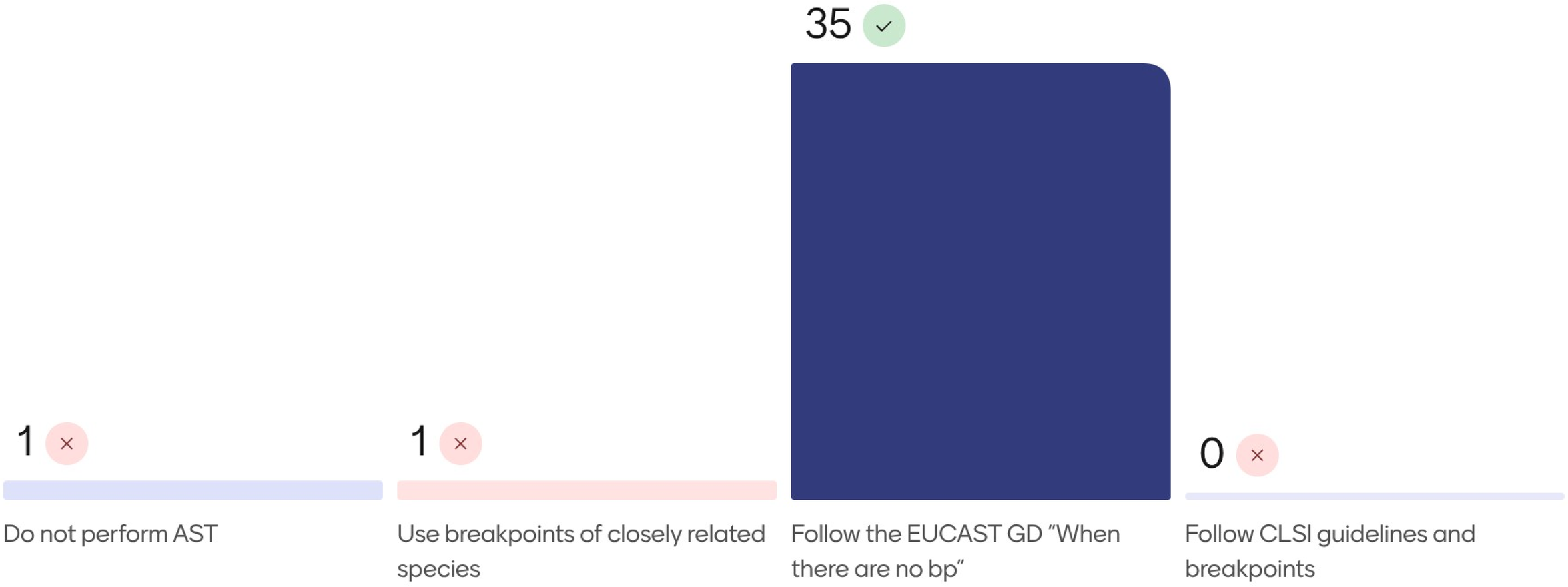
- PK-PD cut-offs are dependent on a number of decisions to be made prior to PD simulation
  - Selection of target (considering strain, species, static vs cidal, infection type, random selection vs worst case vs mean)
  - Selection of PK-model
  - Consideration of MIC-variability

- PK-PD cut-offs are largely species-specific, which makes them mostly a tool (like ECOFFs) for setting species-specific breakpoints

- A higher complexity is needed for setting species-specific PK-PD cut-offs, accounting for higher variability

Mentimeter

What to do when there are no species-specific breakpoints?



4

37

Mentimeter

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

EUCAST guidance on
When there are no breakpoints in breakpoint tables?

Table 1. Antimicrobial agents relevant for the treatment of aerobic bacteria with guidance for bacteria lacking breakpoints in standard EUCAST breakpoint tables.

Determine an MIC and compare with numerical values to assess the microbiological activity of the agent against the species. The clinical use of agents for which MIC-values are higher than those listed below should be discouraged, while agents for which the MIC is the same or lower can be considered for therapy. Avoid reporting isolates S, I or R – instead add a comment to discourage or consider therapy. The proposed values are based on (i) a compromise between current EUCAST susceptible (S or I) breakpoints for species already in the tables, (ii) wild type distributions for microorganisms when available and (iii) PK/PD cut-off values.

	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.
Piperacillin-tazobactam	1	8	Species specific breakpoints for gram-positive organisms are 0.25 – 1 mg/L, and for gram-negative organisms 8 – 16 mg/L
Cefotaxime	0.5	0.5	Cefotaxime and ceftriaxone – resistance to either

1