

The role of MIC testing in therapeutic drug monitoring and beyond

– implications for the clinical microbiology laboratory

Anna-Karin Smekal
Senior Consultant Clinical Microbiology
Specialist Physician Infectious Diseases
Karolinska University Hospital
Stockholm

TDM =Therapeutic Drug Monitoring

- **Purpose:**
 - To avoid toxicity and to optimise clinical efficacy
 - Historically employed for antimicrobials with narrow therapeutic range and mostly to prevent toxicity

- Traditionally TDM is used in a Nordic setting for:
 - Vancomycin; "Mississippi mud"
 - Aminoglycosides



- From a Swedish perspective TDM for other antimicrobials can only be performed at four of seven University hospitals

European experts: Recommendations regarding TDM in ICU-patients from 2020

Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper#



Mohd H. Abdul-Aziz¹, Jan-Willem C. Alffenaar^{2,3,4}, Matteo Bassetti⁵, Hendrik Bracht⁶, George Dimopoulos⁷, Deborah Marriott⁸, Michael N. Neely^{9,10}, Jose-Artur Paiva^{11,12}, Federico Pea¹³, Fredrik Sjovall¹⁴, Jean F. Timsit^{15,16}, Andrew A. Udy^{17,18}, Sebastian G. Wicha¹⁹, Markus Zeitlinger²⁰, Jan J. De Waele²¹, Jason A. Roberts^{1,22,23,24*} on behalf of the Infection Section of European Society of Intensive Care Medicine (ESICM), Pharmacokinetic/pharmacodynamic and Critically Ill Patient Study Groups of European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Group of International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) and Infections in the ICU and Sepsis Working Group of International Society of Antimicrobial Chemotherapy (ISAC)

Intensive Care Med (2020) 46:1127–1153

Take-home message:

The Panel Members recommend routine TDM to be performed for aminoglycosides, beta-lactam antibiotics, linezolid, teicoplanin, vancomycin and voriconazole in critically ill patients.

Why TDM of β -lactams in the critically ill patient?

- Severe infections like sepsis and septic shock are common causes of admissions to intensive care units (ICU) globally. The use of antibiotics in ICU-patients is high.
 - In a recent worldwide point prevalence study, 50% of the ICU-patients had a proven or suspected infection and the in-hospital mortality in this group was 30%
- The beta-lactams like cefotaxime, piperacillin-tazobactam and meropenem are cornerstones of treatment in the ICU due to their bactericidal effect and rapid killing of the bacteria.
- Despite knowledge that targeted, rapidly initiated and adequately dosed antibiotics are crucial to the outcome the mortality and morbidity in ICU-patients with infections remains high
- Why?

Antibiotic dosing regimens are often developed from data on pharmacokinetics (PK) from healthy individuals. In ICU-patients, both the infection and ICU-care itself alter the PK with risk of underdosing of antibiotics like the β -lactams.

Insufficient β -lactam concentrations in the early phase of severe sepsis and septic shock

Standard dosing of piperacillin and meropenem fail to achieve adequate plasma concentrations in ICU patients

Fabio Silvio Taccone¹, Pierre-François Laterre², Thierry Dugernier³, Herbert Spapen⁴, Isabella Xavier Wittebole², Daniel De Backer¹, Brice Layeux⁶, Pierre Wallemacq⁵, Jean-Louis Vincent¹

J. Petersson^{1,2}, C. G. Giske^{3,4} and E. Eliasson^{5,6}

¹Function Perioperative Medicine and Intensive Care, Karolinska University hospital Solna, Stockholm, Sweden

²Section of Anesthesiology and Intensive Care Medicine, Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden

³Clinical Microbiology, Karolinska University Hospital Solna, Stockholm, Sweden

⁴Division of Clinical Microbiology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden

⁵Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden

⁶Clinical Pharmacology, Karolinska University Hospital Huddinge, Stockholm, Sweden

Acta Anaesthesiologica Scandinavica **60** (2016)

DALI: Defining Antibiotic Care Unit Patients: Are Current β -Lactam Antibiotic Doses Sufficient for Critically Ill Patients?

Jason A. Roberts^{1,2}, Sanjoy K. Paul^{3,4}, Murat Akova⁵, Matteo Bassetti⁶, Jan J. De Waele⁷, Kirsi-Maija Kaukonen⁹, Despoina Koulenti^{1,8}, Claude Martin^{10,11}, Philippe Montravers¹², Andrew Rhodes¹⁴, Therese Starr², Steven C. Wallis¹ and Jeffrey Lipman^{1,2}; for the DALI Study Group

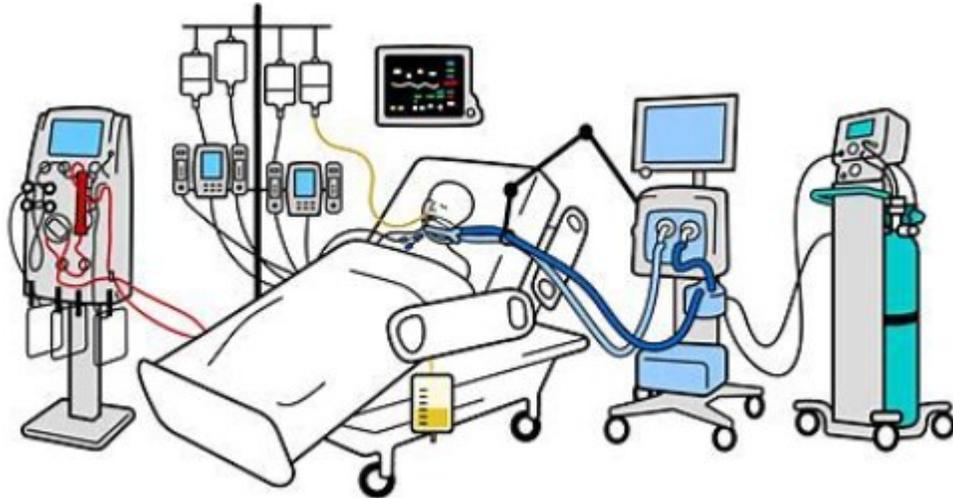
Low attainment to PK/PD-targets for β -lactams in a multi-center study on the first 72 h of treatment in ICU patients

Anna-Karin Smekal^{1,2}, Mia Furebring³, Erik Eliasson⁴ & Miklos Lipcsey^{1,5}

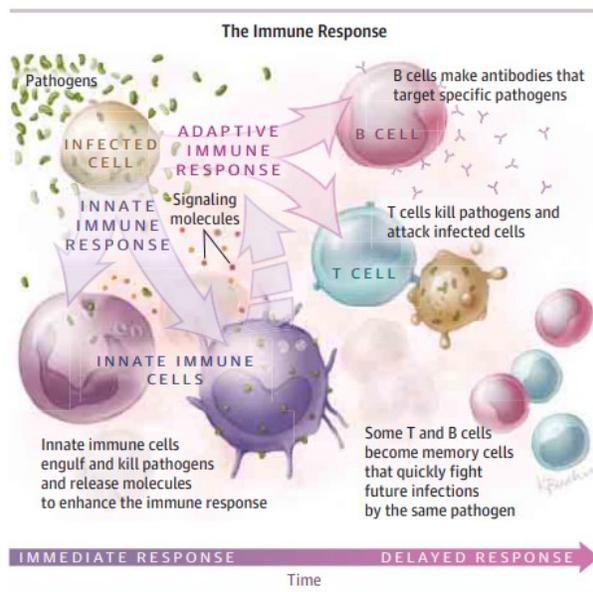
Sci Rep. 2022

Why TDM of β -lactams in the critically ill patient?

- **Overall goal:** optimisation of therapy by reaching PK/PD-target attainment, ie adequate antibiotic concentrations.
- Avoid collateral damage of more aggressive beta-lactam dosing to account for altered drug PK of ICU-patients. Side-effects like neurotoxicity underreported (exception: cefepime)
- Optimal exposure also prevents development of resistance in causative bacterium

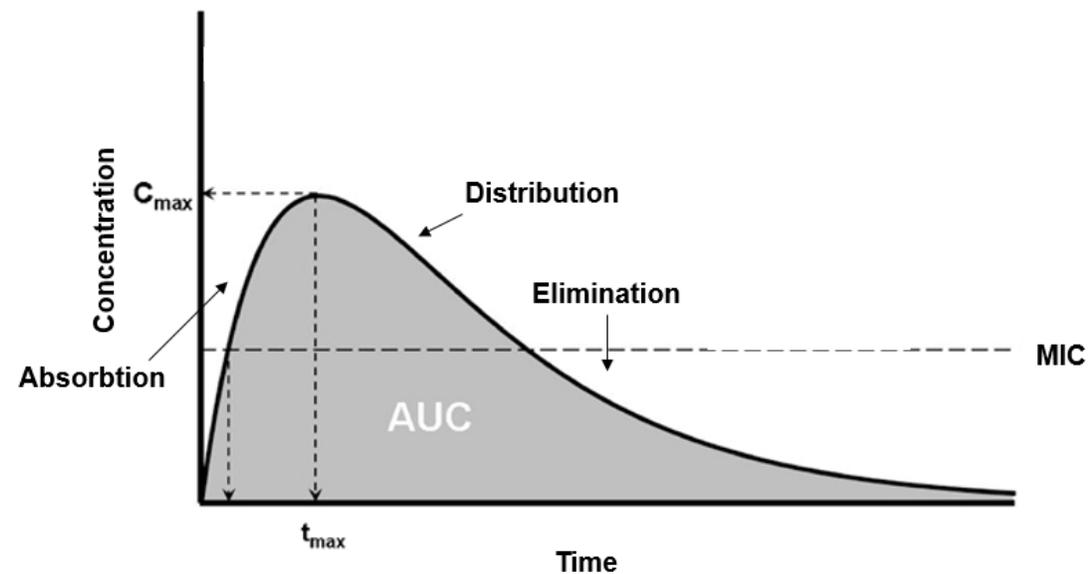


Host factors influencing the cure of infection



JAMA April 28, 2015 Volume 313, Number 16

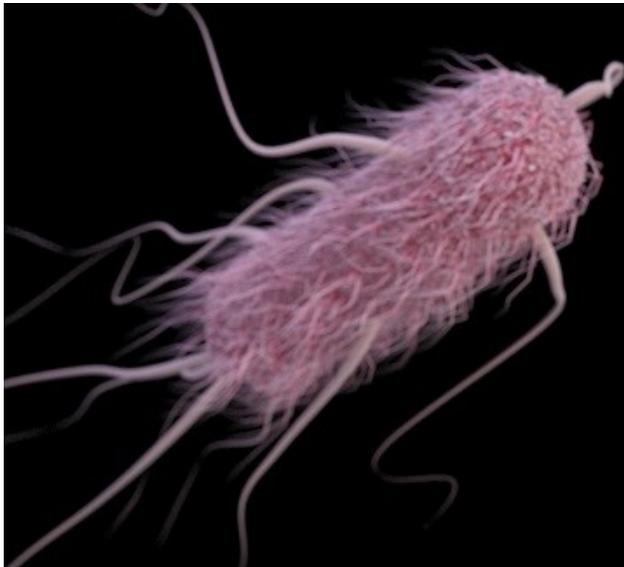
Immune system



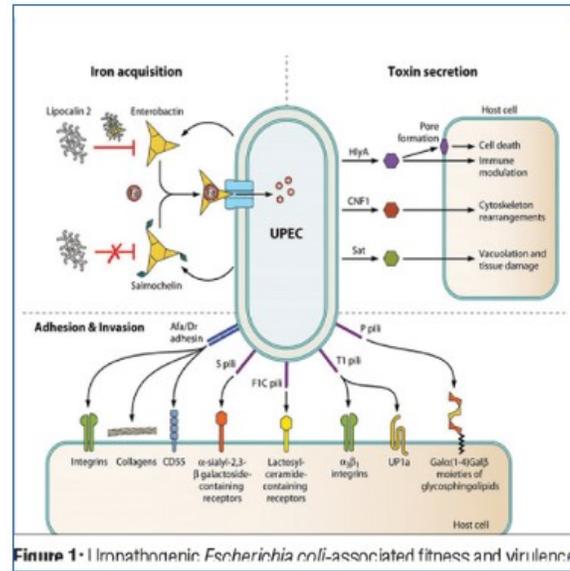
PK of the antibiotics

Bacterial factors

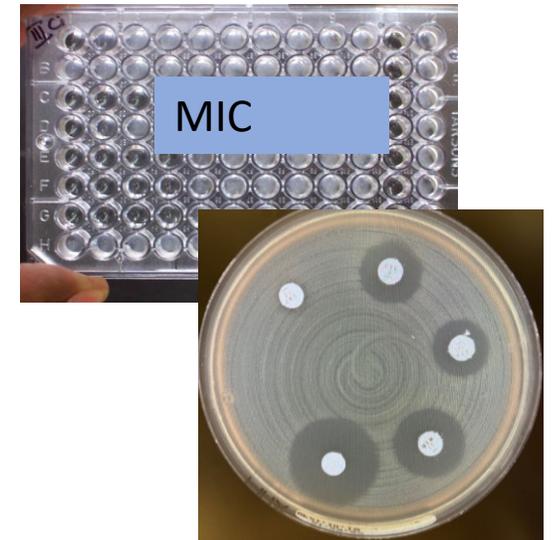
-influencing the cure of infection



=



+



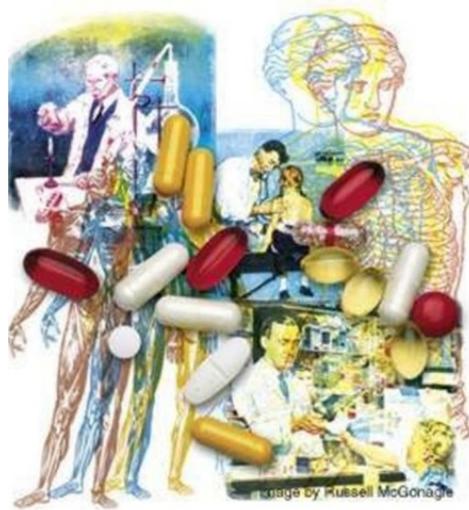
Virulence factors

MIC/ Susceptibility

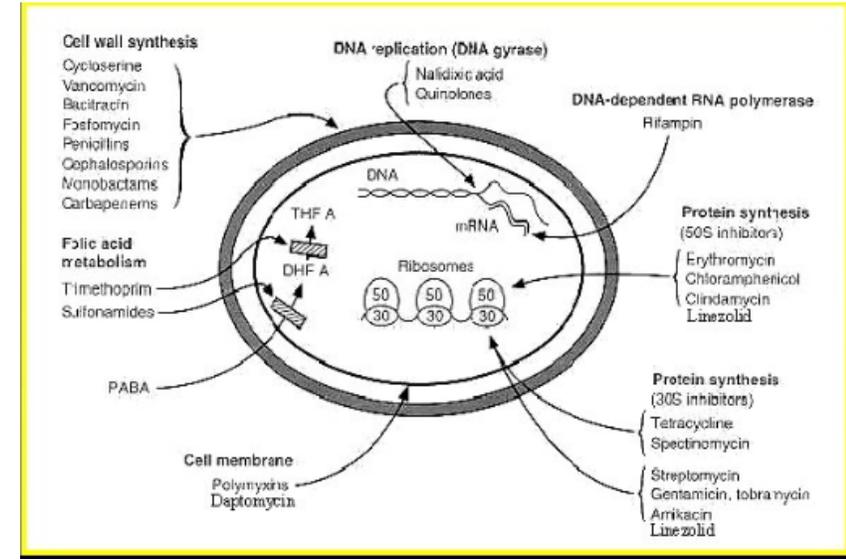
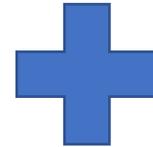
Antibiotic factors- influencing the cure of an infection



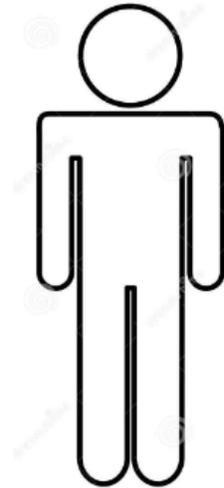
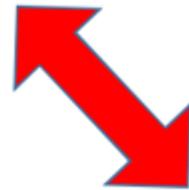
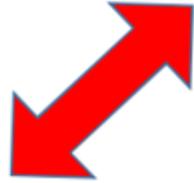
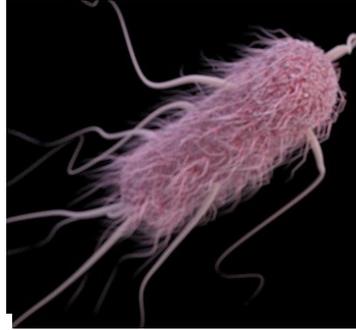
PD of AB



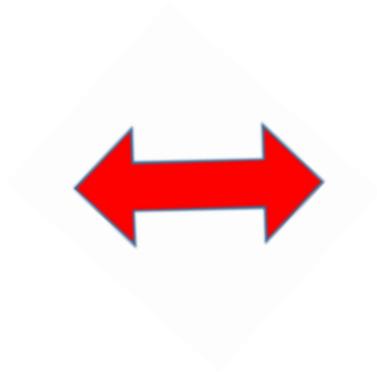
PD of the antibiotic



Mechanism of action

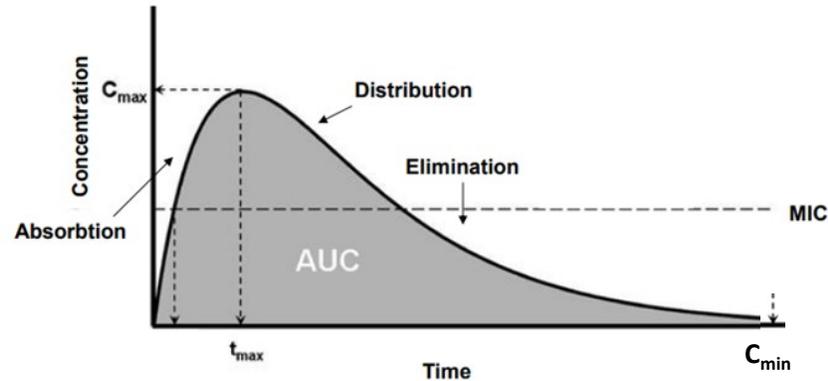


PK/PD



A short reminder on PK/PD of antimicrobials

- **Pharmacokinetics (PK): The way the body processes the drug**
 - In terms of how the concentration of a single dose changes over time
 - Depending on the four PK-parameters (Absorption, Distributions, Metabolism and Elimination)
 - Leading to a specific exposure of the drug



- **Pharmacodynamics (PD): How the drug exposure impacts the body**
 - In terms of how a single dose impacts the body, the "dose-response" relationship.
 - Depending on the pathogen causing the infection and its MIC, or the susceptibility, of the pathogen

PK/PD-index

- Based on the work of Bill Craig on neutropenic mice (pneumonia)
- Describes the correlation between the exposure (PK), the MIC and the effective killing of the causative bacteria (PD), i. e the treatment efficacy
- For antimicrobial agents there are three different PK/PD-index

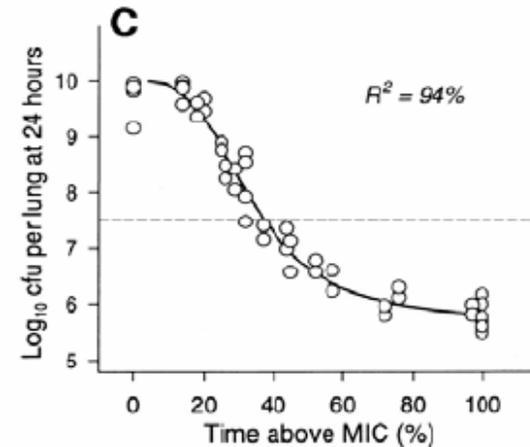
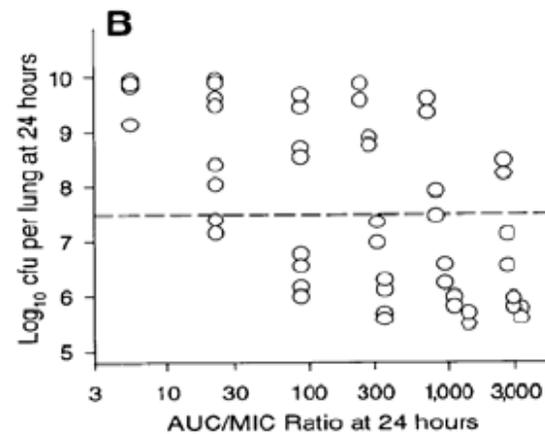
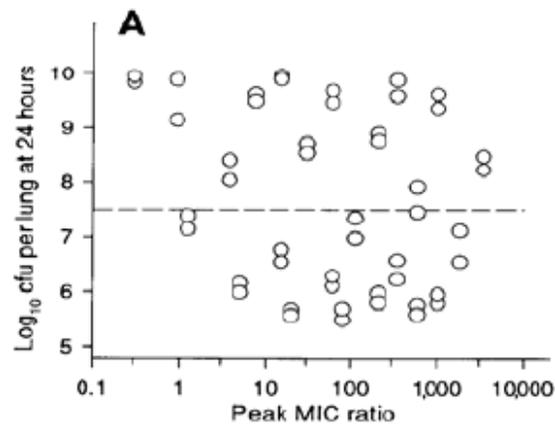


Table 1. The three PK/PD-indices.

PK/PD-index correlating to bacterial killing/treatment efficacy	Explanation of PK/PD-index	Antimicrobial agent
$T > MIC$	Percentage of time the serum concentration exceeds the MIC	Penicillins, cephalosporins, carbapenems, monobactams, macrolides, clindamycin
$AUC_{0-24\text{ h}}/MIC$	The area under the concentration curve divided by MIC during 24 hours.	Fluoroquinolones, vancomycin, tigecycline, aminoglycosides
C_{\max}/MIC	The peak concentration divided by MIC	(Previously used for aminoglycosides)

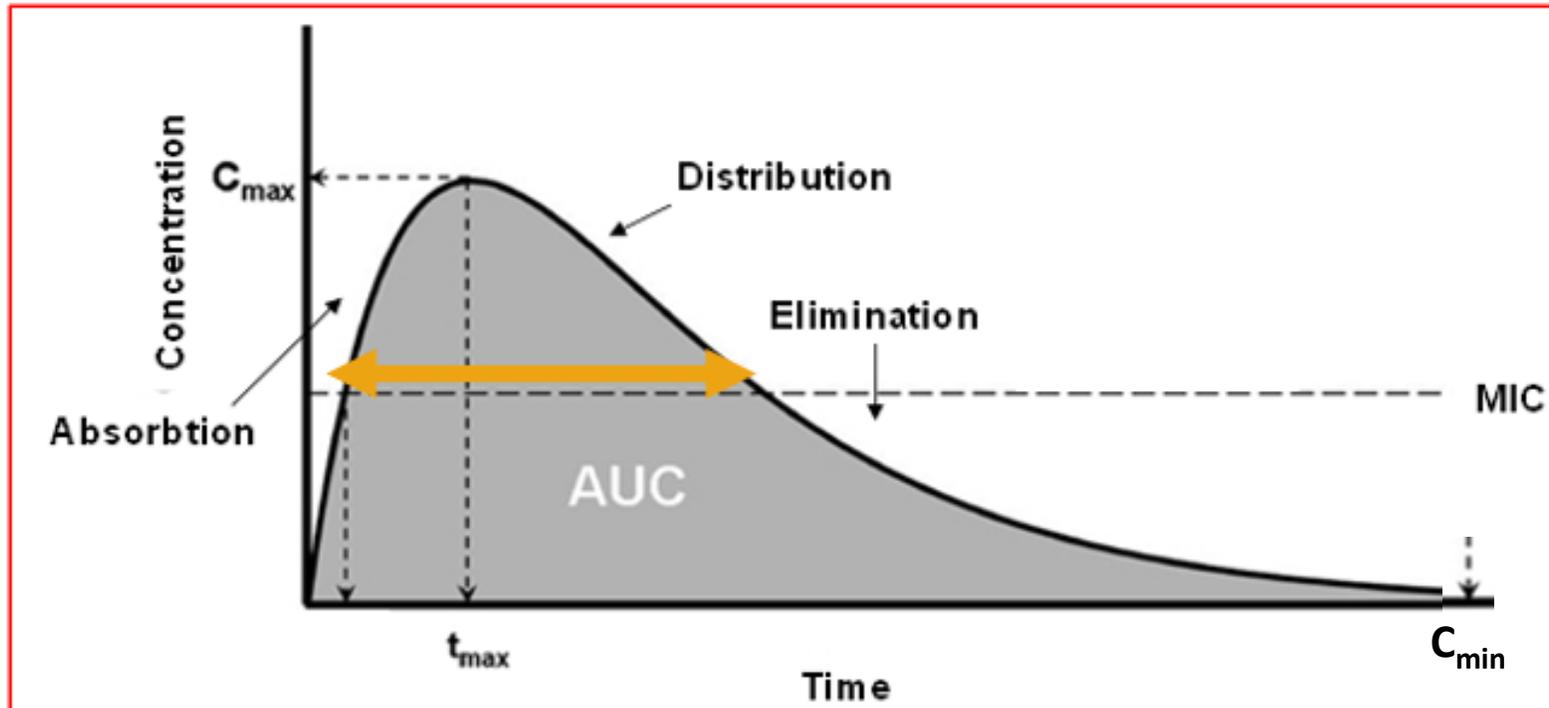
The magnitude of the PK/PD-index needed for antimicrobial efficacy

- Cut-off value also known as the pharmacodynamic target (PDT) or PK/PD-target
- For beta-lactams: the percentage of time the free plasma concentration of the drug remains above the MIC (%fT>MIC)
- The optimal PK/PD-target in ICU-patients is still under discussion

Antibacterial class	PK/PD index	Pre-clinical PK/PD target for efficacy	Clinical PK/PD target for efficacy
Beta-lactams			
Carbapenems	% fT _{>MIC}	40% fT _{>MIC}	50–100% fT _{>MIC}
Cephalosporins	% fT _{>MIC}	60–70% fT _{>MIC}	45–100% fT _{>MIC}
Penicillins	% fT _{>MIC}	50% fT _{>MIC}	50–100% fT _{>MIC}

Abdul-Aziz, Crit Care Med, 2020

Beta-lactams	TDM recommendation by Panel: "YES"	
	C _{min} monitoring One sample 30 min or just before the next dosing Sampling should occur 24–48 h post-initiation of therapy	100% fT _{>MIC}
	C _{ss} monitoring for continuous infusion One sample at any time point during the infusion	C _{ss} > MIC



In this example the plasma concentration remains above the MIC for around half of the dosing interval (=50% T>MIC).

Beta-lactams

TDM recommendation by Panel: "YES"

C_{min} monitoring

One sample

30 min or just before the next dosing

Sampling should occur 24–48 h post-initiation of therapy

C_{ss} monitoring for continuous infusion

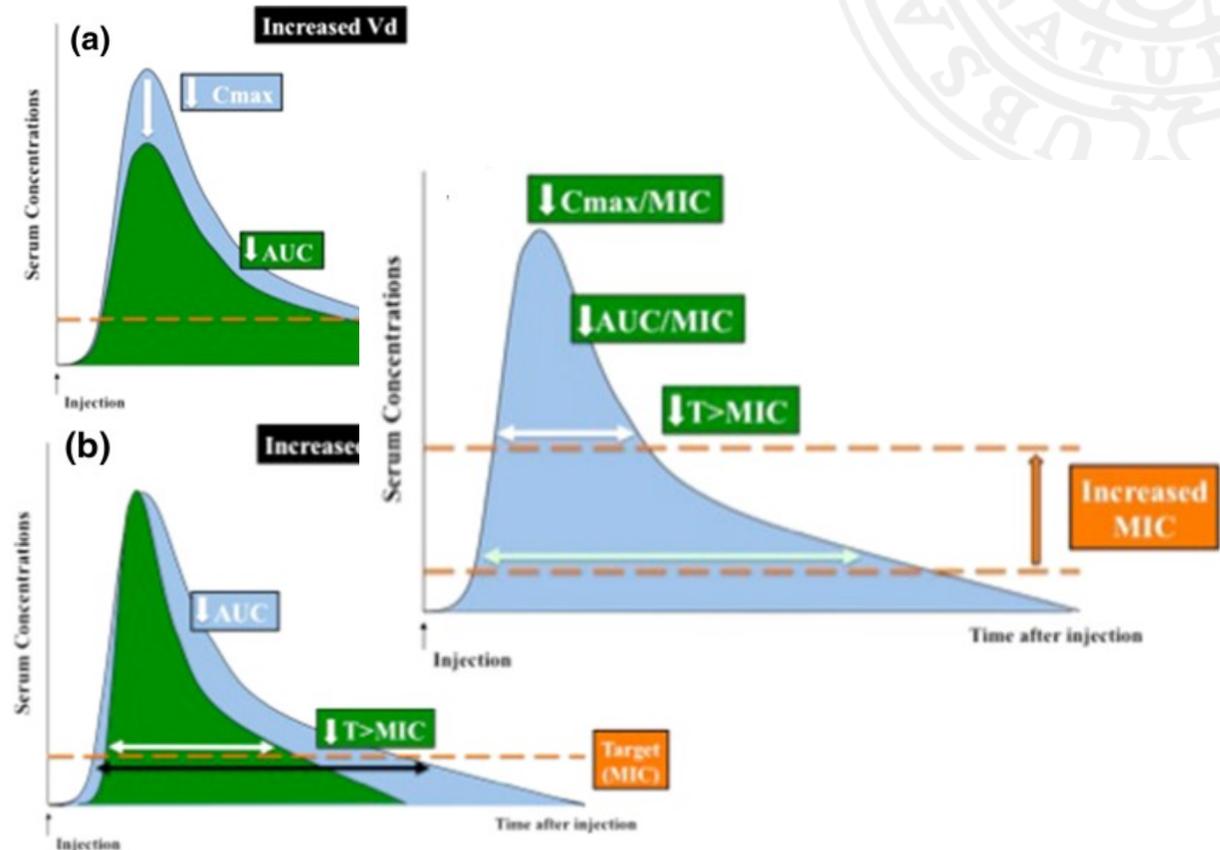
One sample at any time point during the infusion

100% $fT_{>MIC}$

$C_{ss} > MIC$

Impact of critical illness on pharmacokinetics (PK) of β -lactams in ICU-patients

- PK-alterations in critically ill ICU-patients depends on:
 - physiological changes caused by the infection
 - interventions associated with modern ICU-care
- For β -lactams that are small, hydrophilic and renally cleared drugs the important PK-alterations are:
 - **A) Increased volume of distribution (V_D)** $\rightarrow C_{max}$ and $T>MIC$ decreases
 - **B) Increased drug clearance (CI)** $\rightarrow T>MIC$ decreases
 - Altered protein binding and hypoalbuminemia enhances A+ B for β -lactams with high protein binding.



Roberts JA, Taccone FS, Lipman J. Understanding PK/PD. Intensive Care Med. 2016 Nov;42(11):1797-1800.

Summary: Increased risk that standard dosing regimen during the first days of treatment of β -lactams leads to underexposure in ICU-patients. Therapeutic drug monitoring could overcome this.



TDM and MIC

J Antimicrob Chemother 2018; **73**: 564–568
doi:10.1093/jac/dkx427 Advance Access publication 5 December 2017

Journal of
Antimicrobial
Chemotherapy

MIC-based dose adjustment: facts and fables

Johan W. Mouton^{1*}, Anouk E. Muller^{1,2}, Rafael Canton³, Christian G. Giske⁴, Gunnar Kahlmeter⁵ and John Turnidge⁶

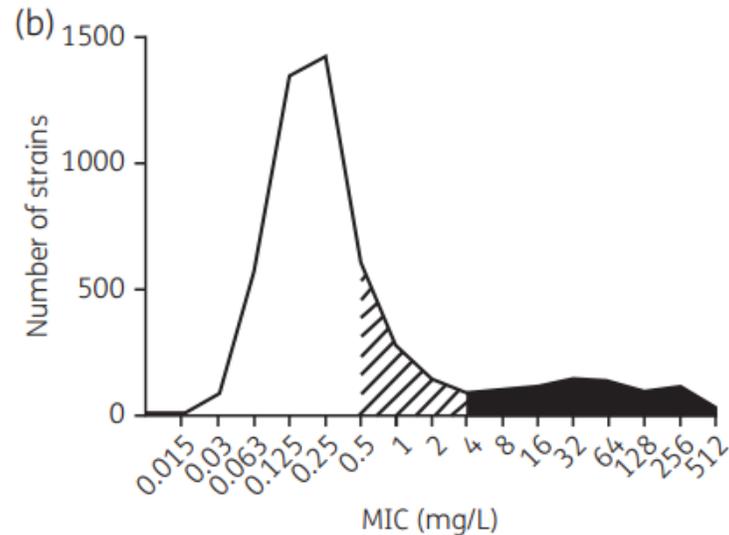


Table 1. Suggested interpretation of the MIC for target attainment under various conditions

MIC found	Interpretation for target attainment
Within WT, \leq ECOFF	ECOFF
$>$ ECOFF	MIC + two 2-fold dilutions ^a

^aNumber of dilutions could be higher or lower than two depending on the proficiency of the lab and the drug-species distribution.

High target attainment for β -lactam antibiotics in intensive care unit patients when actual minimum inhibitory concentrations are applied

H. Woksepp^{1,2}  · A. Hällgren³ · S. Borgström⁴ · F. Kullberg⁵ · A. Wimmerstedt⁶ ·
A. Oscarsson^{7,8} · P. Nordlund⁹ · M-L. Lindholm⁴ · J. Bonnedahl¹⁰ · L. Brudin¹¹ ·
B. Carlsson¹² · T. Schön^{13,14}

J Antimicrob Chemother 2023; **78**: 2895–2901

<https://doi.org/10.1093/jac/dkad327> Advance Access publication 28 October 2023

**Journal of
Antimicrobial
Chemotherapy**

Swedish multicentre study of target attainments with β -lactams in the ICU: which MIC parameter should be used?

Anna-Karin Smekal^{1,2*}, Mia Furebring³, Miklos Lipcsey ^{1,4} and Christian G. Giske^{2,5}

MIC-parameters in the PK/PD-calculations

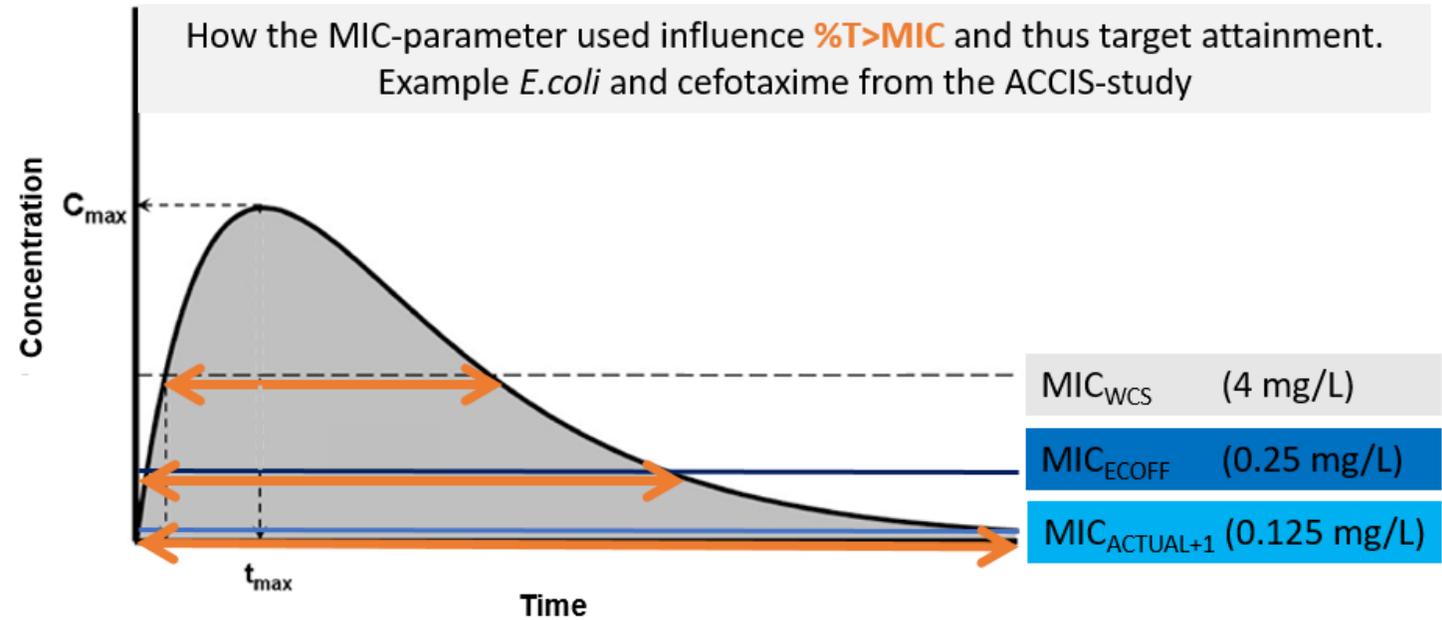
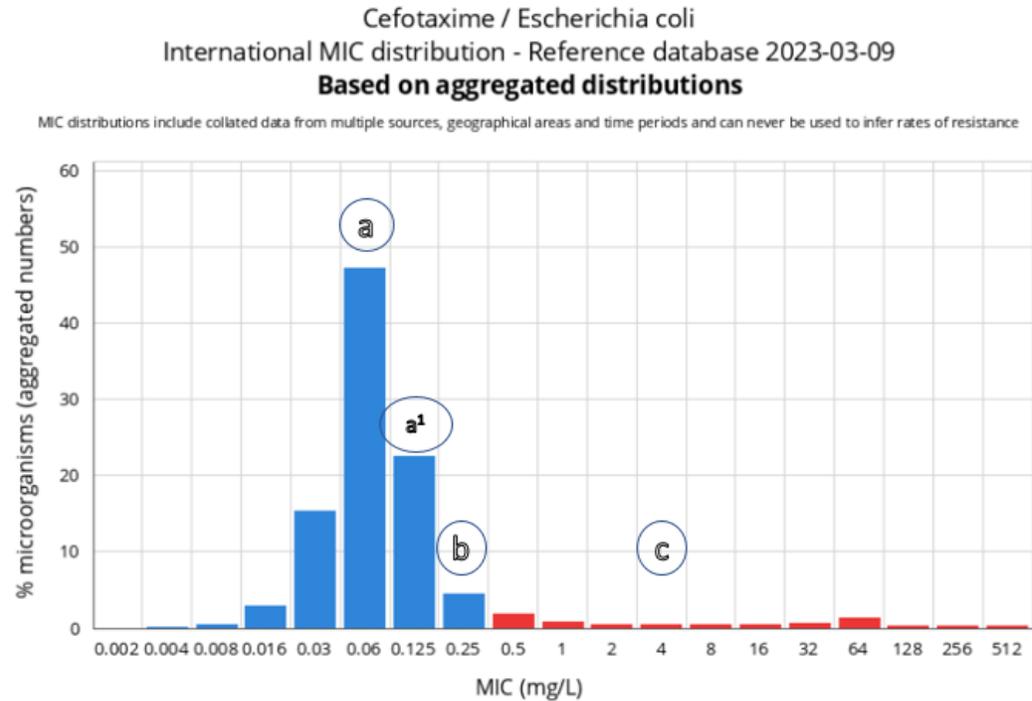


- **Three MIC-parameters were developed** and used in the target attainment calculations based on EUCAST MIC-distributions and the article "MIC-based dose adjustment: facts and fables" by Mouton et al (2018)

MIC-parameter	Definition	Usage in the PK/PD—calculations of the study (n=patients)
$MIC_{ACTUAL+1}$	The actual MIC for the isolated pathogens adjusted by adding one 2-fold dilution MIC-step to account for technical variation of BMD	Used for all patients where a causative pathogen was isolated and MIC-testing with BMD was performed
MIC_{ECOFF}	The epidemiological cut-off value (ECOFF); a value separating the wild type (WT) population from the population with acquired resistance mechanisms	Used for all patients where a causative pathogen was isolated and BMD or disc diffusion according to EUCAST was performed
MIC_{WCS}	The worst-case scenario of bacterial susceptibility, i.e. the MIC_{ECOFF} for the possible pathogen with the highest ECOFF for the antibiotic in question, reflecting the highest MIC the empiric treatment should cover.	Used for all patients in the study. MIC_{WCS} used: <u>Cefotaxime</u> : MIC_{ECOFF} for <i>S. aureus</i> of 4 mg/L <u>Piperacillin-tazobactam</u> : MIC_{ECOFF} for <i>P. aeruginosa</i> of 16 mg/L <u>Meropenem</u> : MIC_{ECOFF} for <i>P. aeruginosa</i> of 2 mg/L



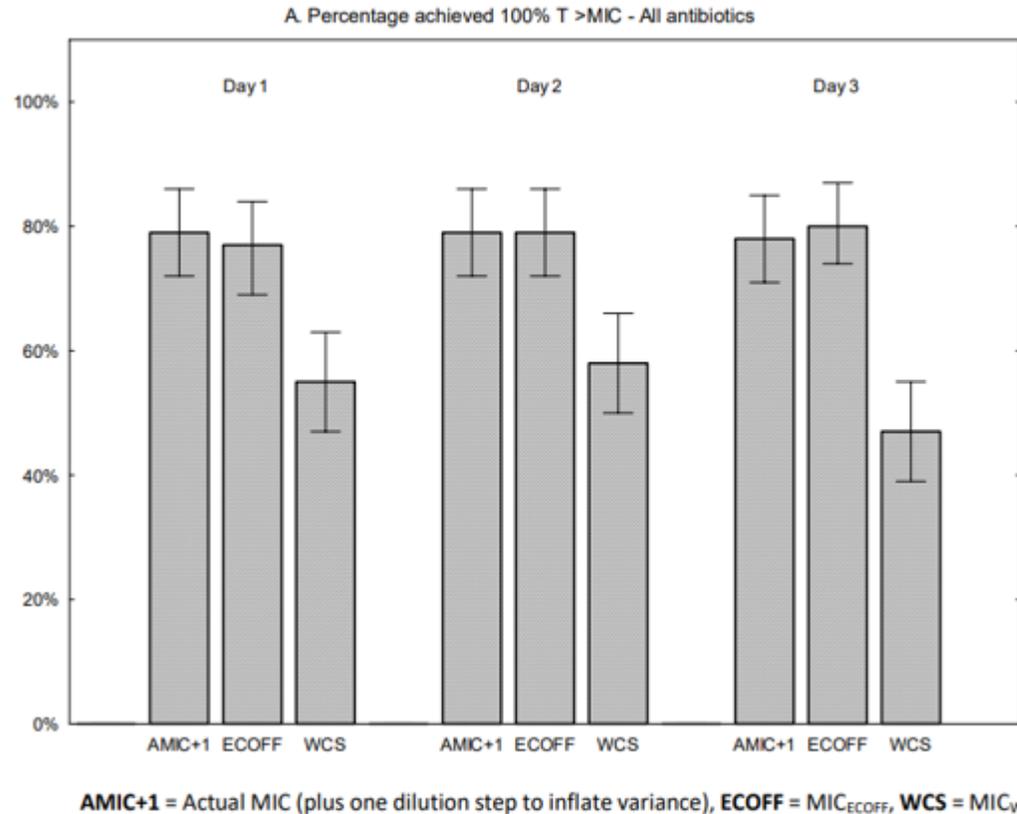
The impact of the MIC-parameter (PD) on target attainment



- a) MIC_{ACTUAL} : The actual MIC of testing
- a¹) MIC_{ACTUAL+1} : MIC_{ACTUAL} adjusted for method variation
- b) MIC_{ECOFF} : The epidemiological cut-off value
- c) MIC_{WCS} : The worst case scenario of bacterial susceptibility



Target attainment depending on the MIC-parameter

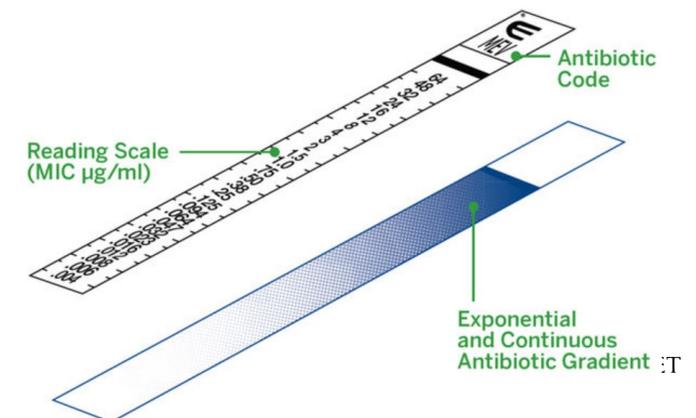
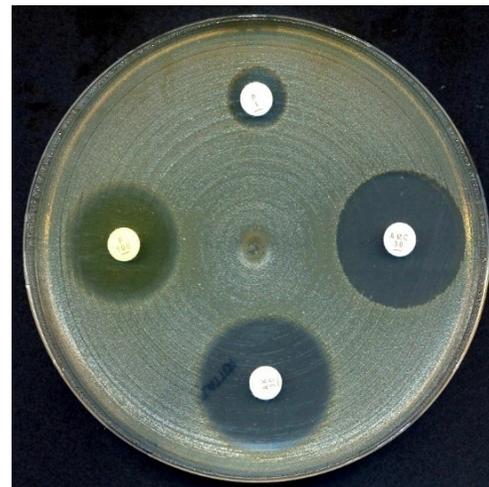
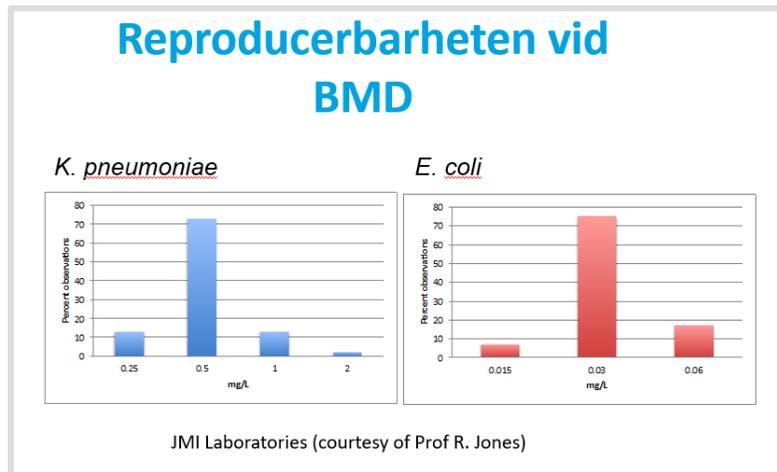


In the whole ACCIS-study cohort the use of MIC_{WCS} overestimated target attainment failure compared to the use of MIC_{ECOFF} based on the causative pathogen

Fig A. Percentage with 95% CI of all patients achieving 100% T > MIC on day 1, 2 and 3 depending on the MIC-parameter used in the calculation (MIC_{ACTUAL + 1}, MIC_{ECOFF} or MIC_{WCS}).

Basic concepts of minimal inhibitory concentration (MIC)

- MIC is not a strict value but rather an observational minimum concentration range based on MIC-distributions
- MIC-testing in the WT-population should not be performed!
- MIC-testing has a variability of +/- 1 dilution step even with the reference methods under optimal conditions and with well-trained staff
 - Broth microdilution (BMD) is the reference method for aerobic bacteria, with some exceptions
 - Agar dilution is the reference method for anaerobic bacteria
 - EUCAST disk diffusion method is well calibrated against reference MIC and is a good surrogate marker for MIC. Most other surrogate MIC-methods including gradient test are not.



QC of discs compared to gradient test

EUCAST warnings concerning antimicrobial susceptibility testing products or procedures

The EUCAST Development Laboratories, from time to time discover products (including discs, gradient tests, devices and/or procedures) which are not performing to the expected standard. When this is the case we inform the manufacturer of the problem on this page. We do not systematically test all products so the lack of a warning does not imply that there is no problem with the product in question. Laboratories who have identified problems with a susceptibility test method, and suspect that this may be a problem with a particular product, may contact EUCAST for advice. Use the [EUCAST subject related contact form](#).



4. Vancomycin susceptibility testing in *Enterococcus faecalis* and *E. faecium*

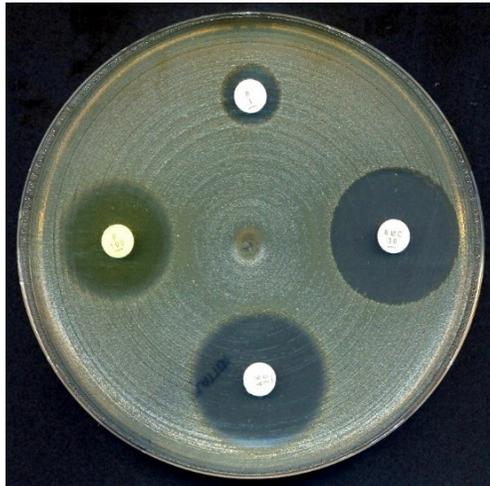
using MIC gradient tests – a modified [Warning against the use of gradient tests for determining benzylpenicillin MICs in *S. pneumoniae*](#)
Laboratory has had no reason to modify (21 November, 2019; data and data analysis added 27 November; updated 4 May 2022).

bioMérieux has added a ["Follow-up information to customers"](#) on this issue.

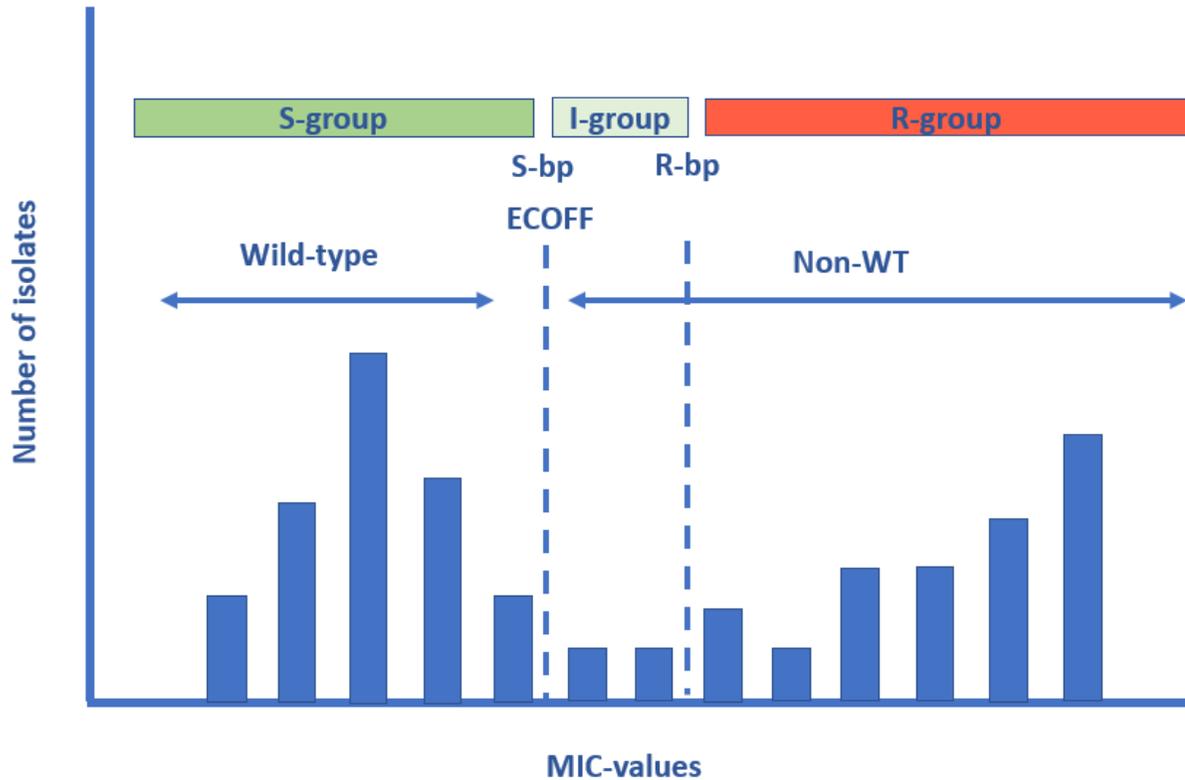
There is no further information from either company to indicate product development. The EDL is now conducting further tests (January, 2022).

Is MIC-testing needed for TDM-purposes?

- Most Nordic laboratories are testing isolates with the EUCAST disc diffusion method which does not give you an MIC-value...or?
- Gradienttest is just a surrogate marker for MIC.
 - Not superior in any way to disc diffusion.
 - In almost all cases no added value compared to disc diffusion, especially in WT isolates



How to use your disc diffusion results in TDM situations



Example 1:

If the antibiotic/pathogen combination is reported S (WT) and no I-group exist: The MIC-value = clinical S-breakpoint=ECOFF.
Enterobacterales/Piperacillin-tazobactam MIC 8 mg/L

Penicillins	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Piperacillin-tazobactam	8	8	16	30-6	20	20	19

Example 2:

If the antibiotic/pathogen combination is reported I (WT): The MIC-value = clinical R-breakpoint=ECOFF
P. aeruginosa/Piperacillin-tazobactam MIC 16 mg/L

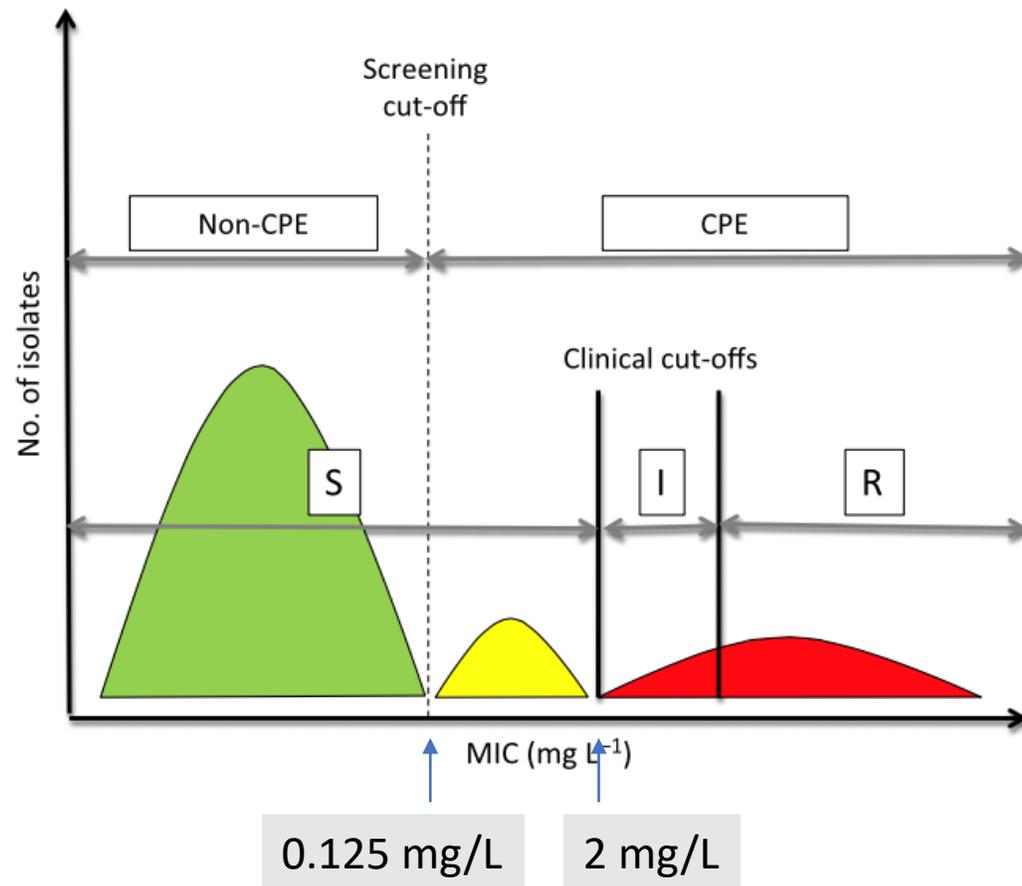
Penicillins	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Piperacillin-tazobactam	0.001	16		30-6	50	18	18-19

How to use your disc diffusion results in TDM situations- Special situations

- S. aureus: Screening for beta-lactams using cefoxitin
- Cefoxitin S: Go to the MIC-distributions on EUCAST website
 - Cefotaxime/S. aureus: ECOFF = 4 mg/L
 - Meropenem/S.aureus: ECOFF =0.5 mg/L
 - Piperacillin-tazobactam/S.aureus: ECOFF = 4 mg/L
 - Kloxacillin/S.aureus: tentative value 1 mg/L (insufficient data)

	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Distributions	Observations	(T)ECOFF
Cefotaxime	0	0	2	0	1	2	17	102	378	2140	2330	341	92	25	241	10	6	15	0	30	5702	4

How to use your disc diffusion results in TDM situations- Special situations



- Enterobacterales and meropenem
 - MIC ≤ 0.125 mg/L: strain belongs to the WT, i.e. ≥ 26 mm
 - MIC ≤ 2 mg/L: strain is susceptible, i.e. ≥ 22 mm
 - Major difference in calculations depending on if the strain is S/WT or S/non-WT
 - This can be determined with disk diffusion

....and then just follow the French solution...

Table 2 Target trough total (Cmin) or free (fCmin) plasma concentration following intermittent administration and target total (Css) or free (fCss) steady-state plasma concentration following continuous administration for the main beta-lactam antibiotics

	Free fraction (%)	Recommended target concentrations [#]		MIC threshold [‡] [130]	Ref.
		Documented infection	Non-documented infection		
Amoxicillin	≈ 80%	fCmin or fCss ≥ 4x MIC Cmin or Css < 80 mg/L	Cmin 40–80* mg/L [§] Css 40–80 mg/L	8 mg/L (ECOFF <i>E. coli</i>)	[131]
Cefazolin	≈ 15–20%	fCmin or fCss ≥ 4x MIC Cmin or Css < 80 mg/L	Cmin 40–80 mg/L [§] Css 40–80 mg/L	2 mg/L (ECOFF <i>S. aureus</i>)	[132]
Cefepime	80%	fCmin or fCss ≥ 4x MIC Cmin < 20 mg/L Css < 35 mg/L	Cmin 5–20 mg/L Css 5–35 mg/L	1 mg/L (<i>Enterobacteriaceae</i>) ^{§§}	[21, 72, 73]
Cefotaxime	≈ 60–80%	fCmin or fCss ≥ 4x MIC Cmin or Css < 60 mg/L	Cmin 25–60 mg/L Css 25–60 mg/L	4 mg/L (ECOFF <i>S. aureus</i>)	[133]
Ceftazidime	≈ 90%	fCmin or fCss ≥ 4x MIC Cmin or Css < 80 mg/L	Cmin 35–80 mg/L [§] Css 35–80 mg/L	8 mg/L (ECOFF <i>P. aeruginosa</i>)	[77]
Ceftriaxone	≈ 10%	fCmin ≥ 4x MIC Cmin < 100 mg/L	Cmin 20–100 mg/L	0.5 mg/L (ECOFF <i>E. cloacae</i>)	[129]
Cloxacillin	≈ 10%	fCmin or fCss ≥ 4x MIC Cmin ou Css < 50 mg/L	Cmin 20–50 mg/L [§] Css 20–50 mg/L	0.5 mg/L (ECOFF <i>S. aureus</i>)	[131]
Ertapenem	≈ 10%	fCmin ou fCss ≥ 4x MIC Cmin < 10 mg/L	Cmin 5–10 mg/L	0.125 mg/L (<i>H. influenzae</i>) ^{§§§}	[117, 134]
Imipenem	≈ 80%	fCmin ≥ 4x MIC Cmin < 5 mg/L	Cmin 2.5–5 mg/L	0.5 mg/L (ECOFF <i>E. coli</i>)	[135]
Meropenem	≈ 100%	fCmin ou fCss ≥ 4x MIC Cmin ou Css < 16 mg/L	Cmin 8–16 mg/L [§] Css 8–16 mg/L	2 mg/L (ECOFF <i>P. aeruginosa</i>)	[136]
Piperacillin	≈ 80%	fCmin ou fCss ≥ 4x MIC Css < 160 mg/L	Css 80–160 mg/L	16 mg/L (ECOFF <i>P. aeruginosa</i>)	[75]

REVIEW

Open Access



Optimization of the treatment with beta-lactam antibiotics in critically ill patients—guidelines from the French Society of Pharmacology and Therapeutics (Société Française de Pharmacologie et Thérapeutique—SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Société Française d’Anesthésie et Réanimation—SFAR)

Romain Guilhaumou¹, Sihem Benaboud², Youssef Bennis³, Claire Dahyot-Fizelier⁴, Eric Dailly⁵, Peggy Gandia⁶, Sylvain Goutelle⁷, Sandrine Lefeuvre⁸, Nicolas Mongardon⁹, Claire Roger¹⁰, Julien Scala-Bertola¹¹, Florian Lemaître¹² and Marc Garnier^{13*}

Thank you!