The impact of PK/PD for clinical decisions.

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Disclosures

None

Clinical desicions and antimicrobial therapy

- **Is there PK/PD involved?**
  - Which drug to use based on the indication?
    - Example urinary tract infections and nitrofurantoin
  - Which drug to us based on the lab-report?
    - Example: cefuroxim S for *E coli*
  - Which dose to use?

Clinical desicions and antimicrobial therapy

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Clinical desicions and antimicrobial therapy

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  - Which dose to use? Yes

Laboratory Report

Urine culture

Escherichia coli >10^5 kve/ml

Amoxicillin	R
Amoxi/clav	R
Cefuroxim	S
Ceftazidime	S
Ciprofloxacin	I

etc

- Provides Clinician/Consultant guidelines how to optimally treat a patient

How does the laboratory distinguish between S or R?

- Breakpoints

European committee on susceptibility testing (EUCAST)

- Harmonisation of methods
- Harmonisation of breakpoints in Europe

Situation in 2001

E.coli vs. cefotaxime		S≤ / R>
BSAC	The United Kingdom	2 / 2
CA-SFM	France	4 / 32
CRG	The Netherlands	4 / 8
DIN	Germany	2 / 8
CLSI	U.S.A.	8 / 32
NWGA	Norway	1 / 2
SRGA	Sweden	0.5 / 1

The reference method

European Committee for Standardization
Comité Européen de Normalisation
Europäisches Komitee für Normung

↓

International Organization for Standardization

2003 20 june DIN Berlin
CEN TC140/WG10

2004 22 april DIN Berlin
Combined meeting with
ISO ISO/TC 212 WG4
Vienna Agreement

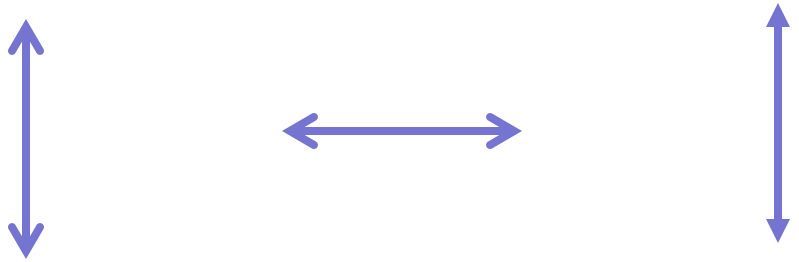
2005 Vote on first draft and comments by all Member Countries

2006 Final version 27 October 2006,
8th CEN, 6th ISO meeting
ISO 20776-1

2007 Final version validation ISO 20776-2.

Antimicrobial therapy in general

Efficacy of the drug



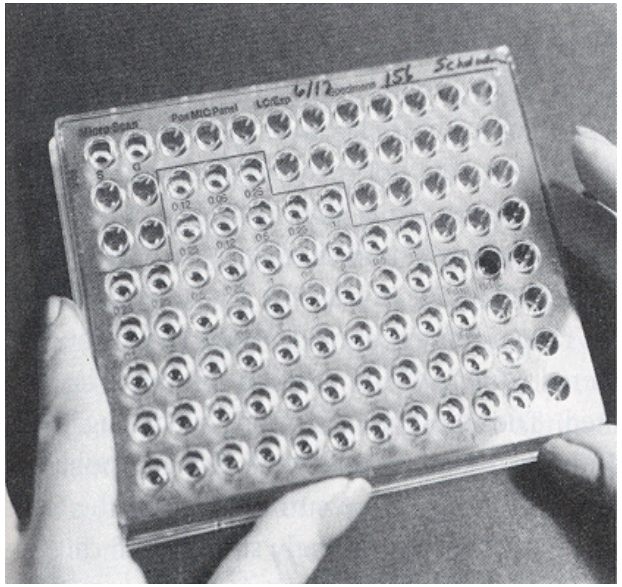
Potency of a drug
(MIC)

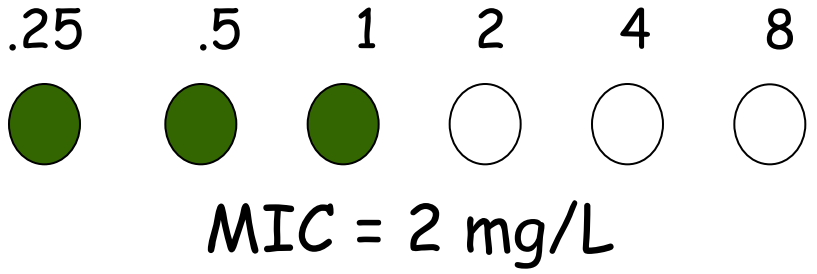
Exposure to the bug
In vivo
(PK)

MIC
Measure of Potency – antibacterial activity

MIC

Lowest concentration
with no visible growth
after 18 hour incubation





ACTVITY
***in vitro* (MIC)**

CONCENTRATIONS
***in vivo* (PK)**

DOSING
regimen

ANTIMICROBIAL EFFICACY
(*Microbiological Cure*)

Other factors

CLINICAL EFFICACY
(*Clinical Cure*)

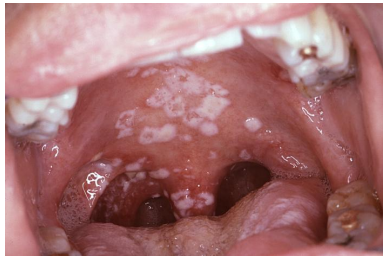
Mouton et al., *Drug Resistance Updates 2011*

1st Question:

Does the dose matter?

Probability of cure after treatment with fluconazole Oropharyngeal Candidiasis n=132

Treatment with fluconazol
Doses 100 – 400 mg



Culture-results with
MIC-values

Individual Dose

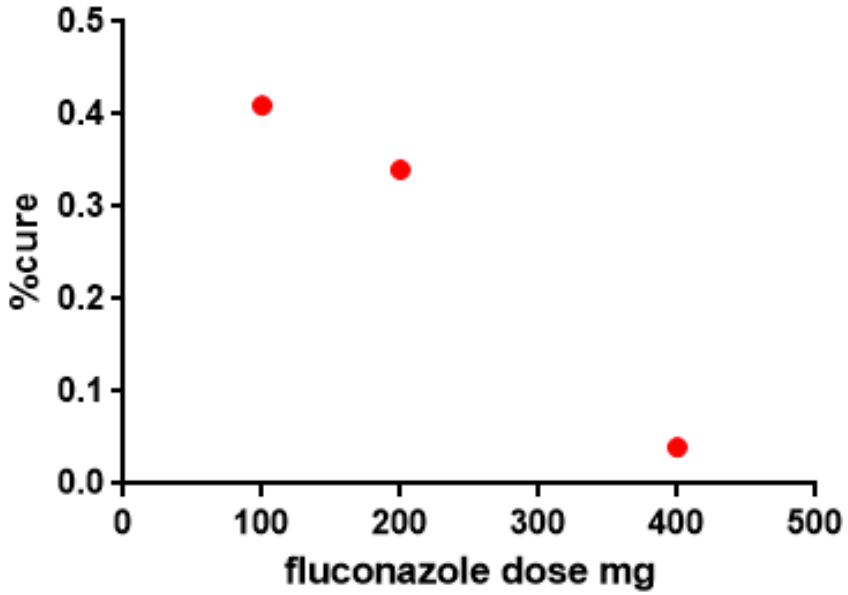
MIC-values per individual

Determine Dose/MIC for each patient

Microbiological outcome (candida cured)
Clinical outcome

Rodriguez- Tudela et al, AAC 2007

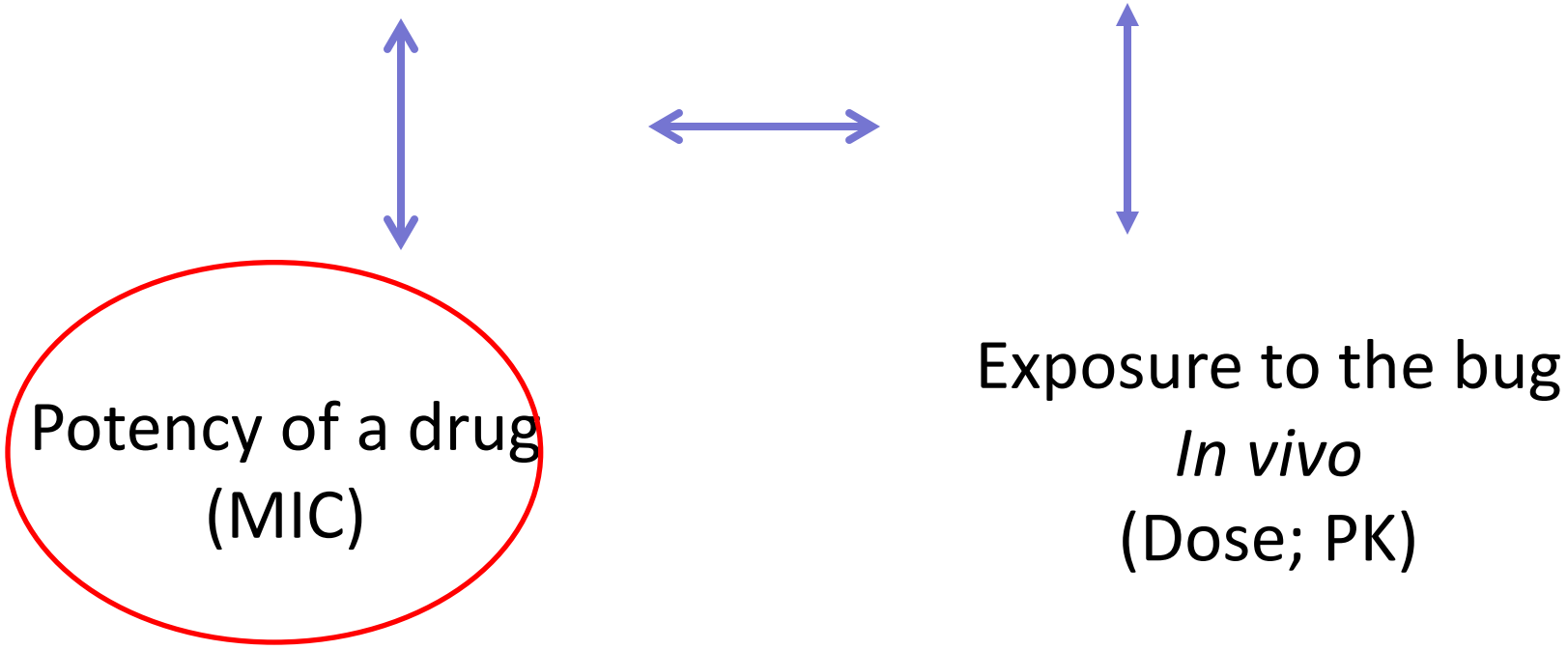
Probability of cure after treatment with fluconazole Oropharygeal Candidiasis n=132



Dose vs % cure

Higher dose – Lower efficacy?

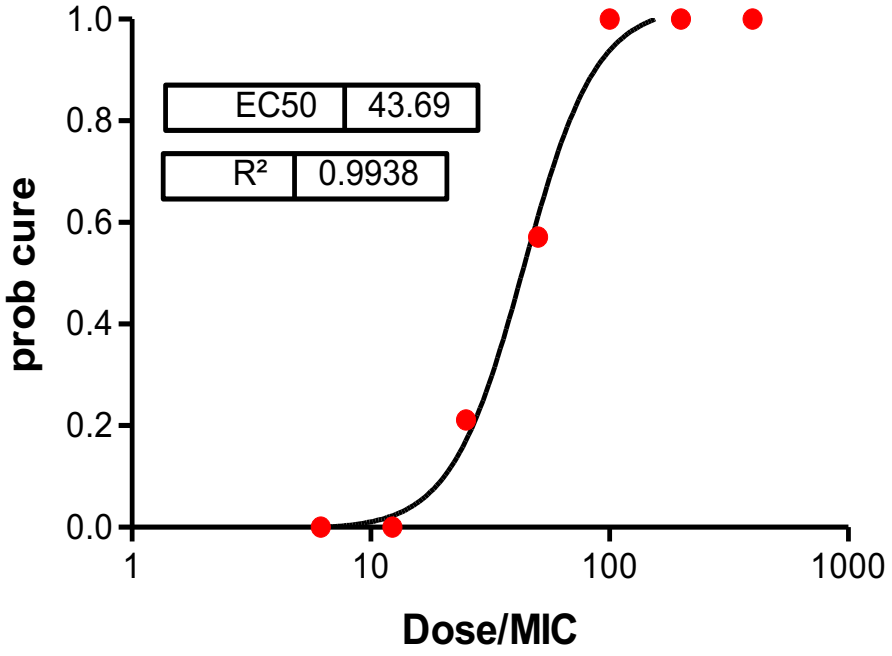
Efficacy of the antimicrobial



2nd Question:

Does the Dose matter
in relation to the MIC (potency?)?

Probability of cure after treatment with fluconazole Oropharygeal Candidiasis n=132



- Prob cure correlates with Dose/MIC
- POSITIVE correlation with dose
- INVERSE correlation with MIC

Each data point represents the proportion of patients cured within a group representing a certain AUC/MIC value

Rodriguez- Tudela et al, AAC 2007

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***in vitro* (MIC)**

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***in vivo* (PK)**

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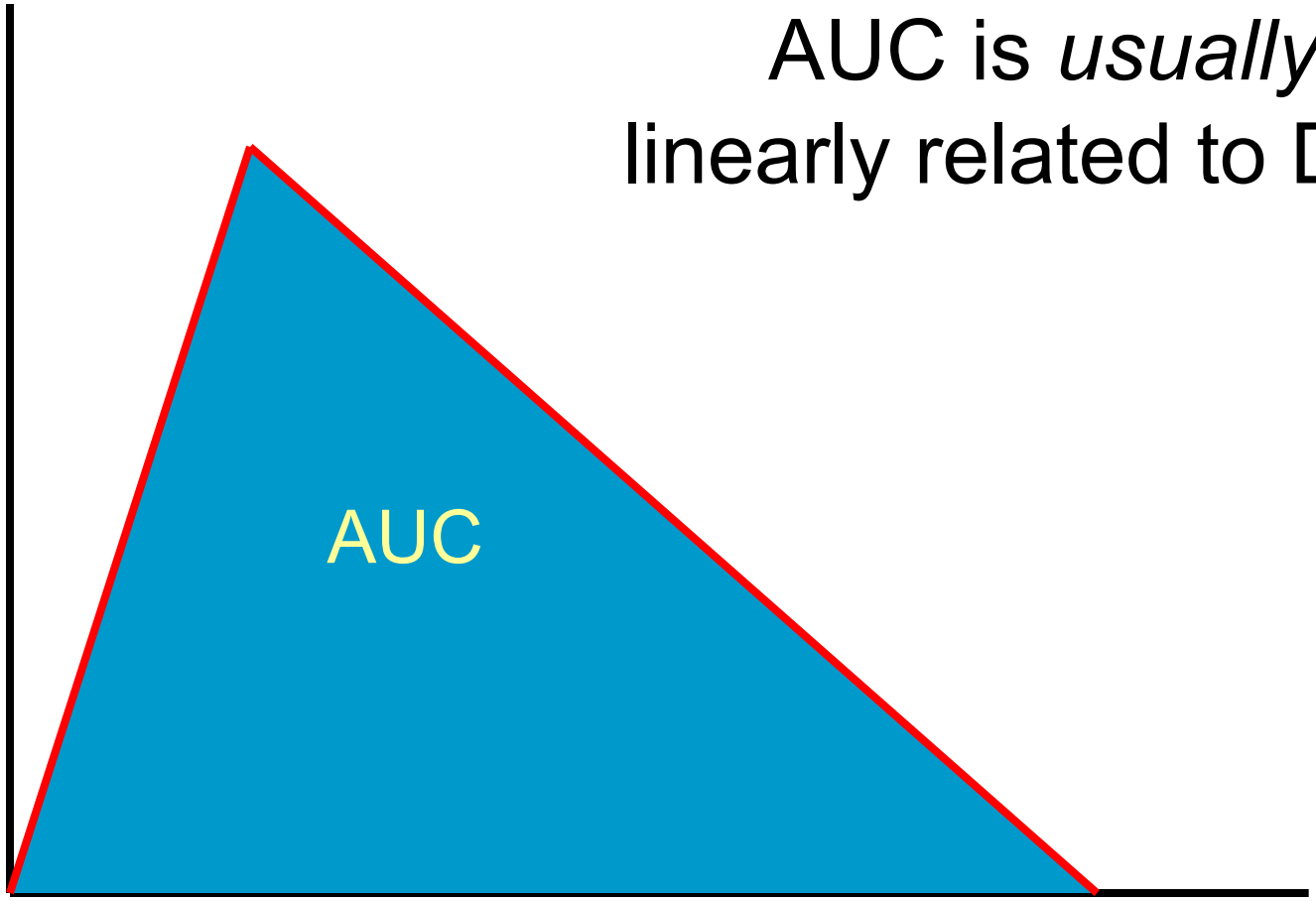
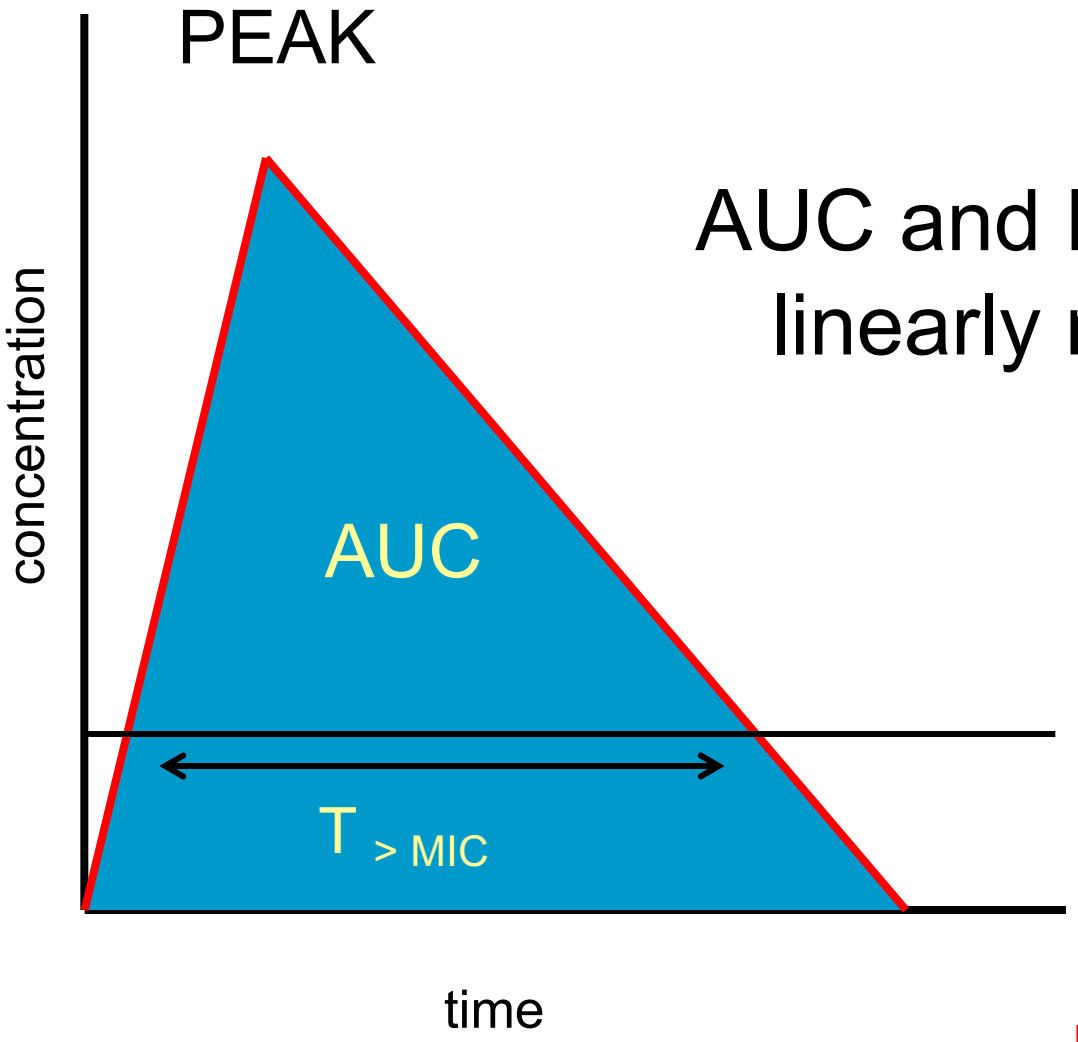
Mouton et al., *Drug Resistance Updates 2011*

Pharmacokinetic parameters : Measures of Exposure

AUC is *usually* linearly related to Dose



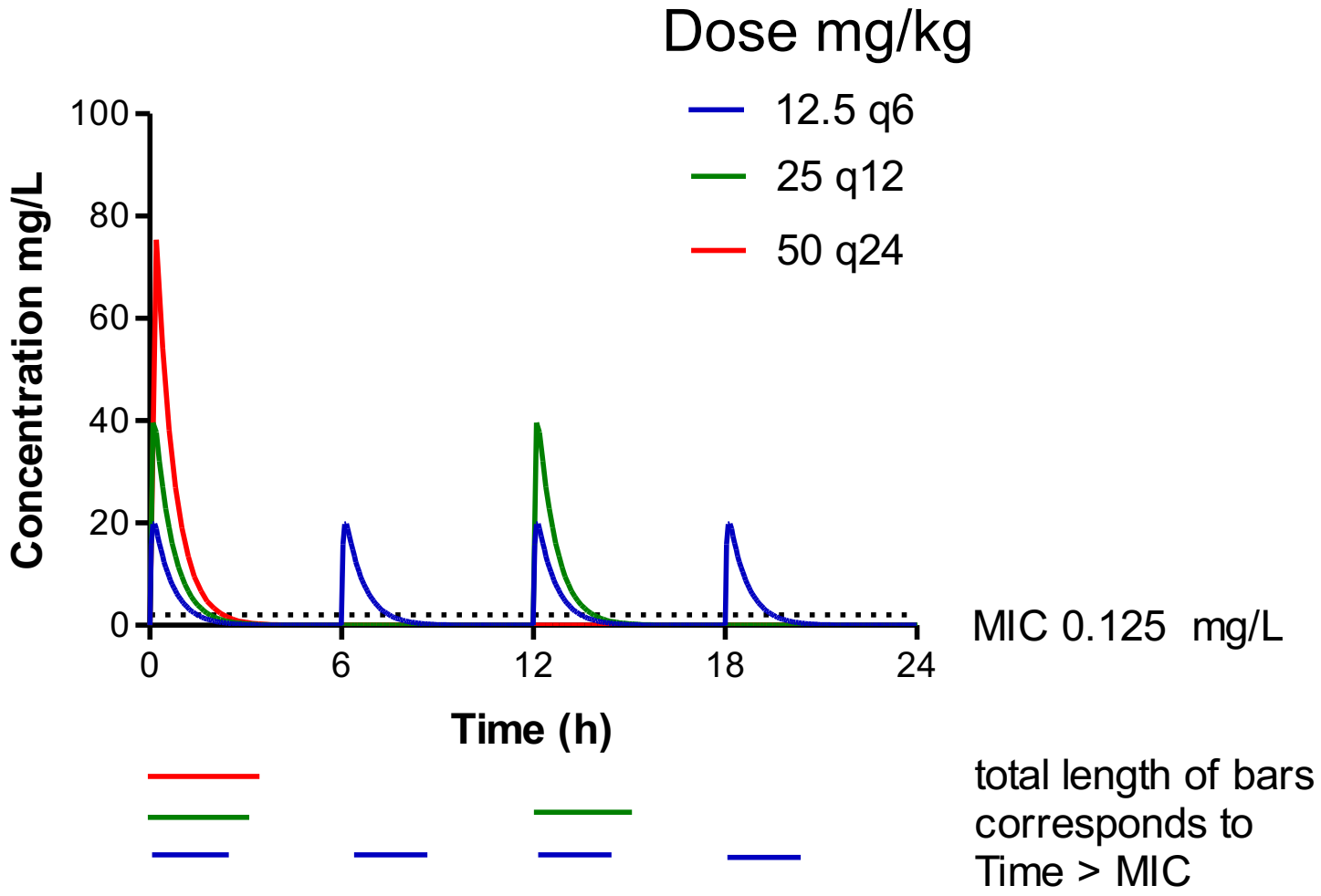
Pharmacokinetic parameters : Measures of Exposure



AUC and Peak are *usually* linearly related to Dose

Mouton et al. 2007 21-44
In Antimicrobial Pharmacodynamics in Theory and Clinical Practice

Does the dosing regimen matter?



Mouton et al. Drug Resist Updat. 2011 14:107-17

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Mouton et al., *Drug Resistance Updates 2011*

Ceftazidime in patients with nosocomial pneumonia

- randomized, double-blind phase 3 clinical trial (NCT00210964):
  - comparing the efficacy of ceftobiprole with the combination CAZ and linezolid
  - Ceftazidime 3dd 2 gr 2h infusion
  - **Extensive and sparse sampling of ceftazidime**

N=390 patients included

NO clear dose response relationship

BUT…….

Muller et al, JAC 2013 68:900-906

Ceftazidime in patients with nosocomial pneumonia

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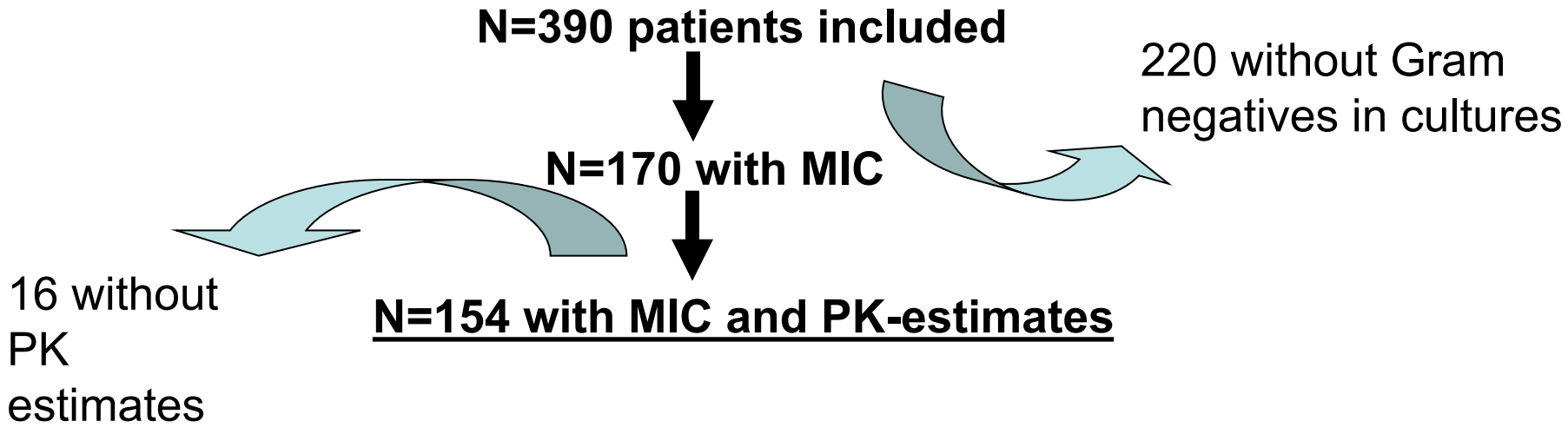
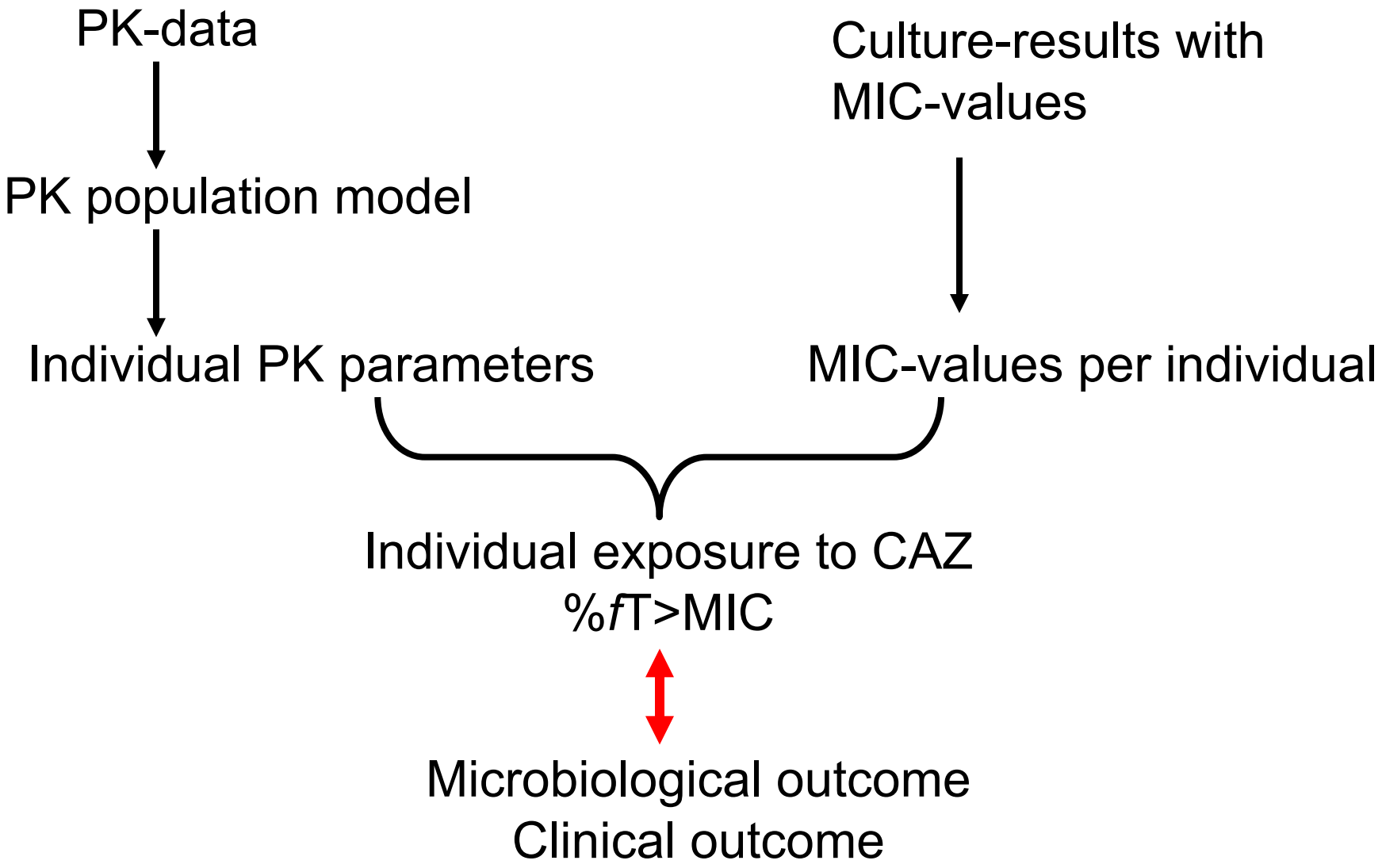
  - comparing the efficacy of ceftobiprole with the combination CAZ and linezolid
  - Ceftazidime 3dd 2 gr 2h infusion
  - Extensive and sparse sampling of ceftazidime
  - MICs of strains



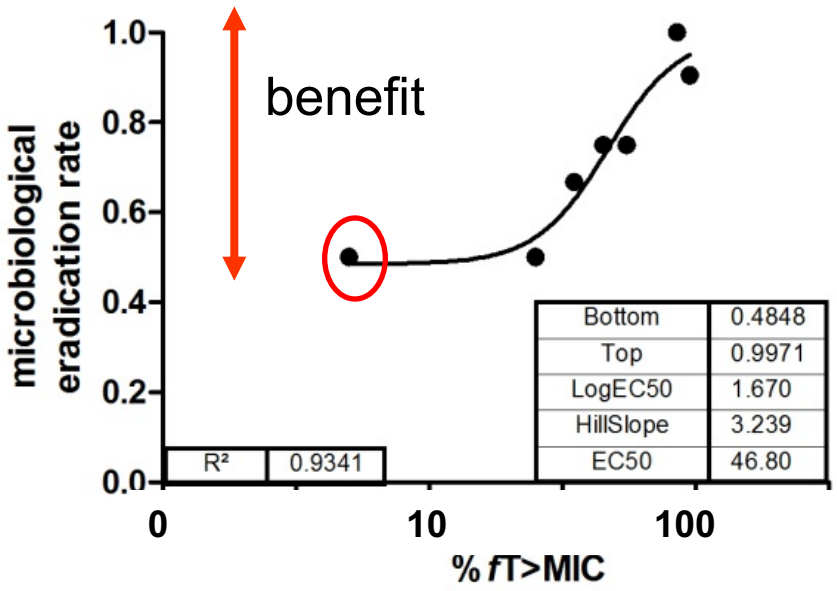
Muller et al, JAC 2013 68:900-906

Clinical phase 3 study



Exposure-response Emax model

microbiological eradication

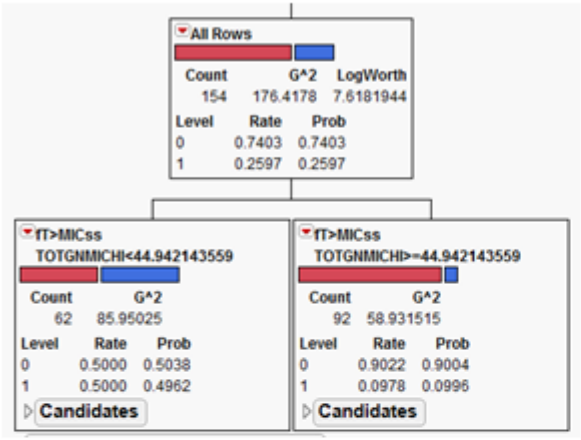


- Individual exposures to CAZ
- Categorised (%*f*T>MIC per 10%)
- Eradication rate per group
- 154 patients

Muller et al, JAC 2013 68:900-906

Ceftazidime in patients with nosocomial pneumonia

CART analysis



- to differentiate between lower and higher response rate

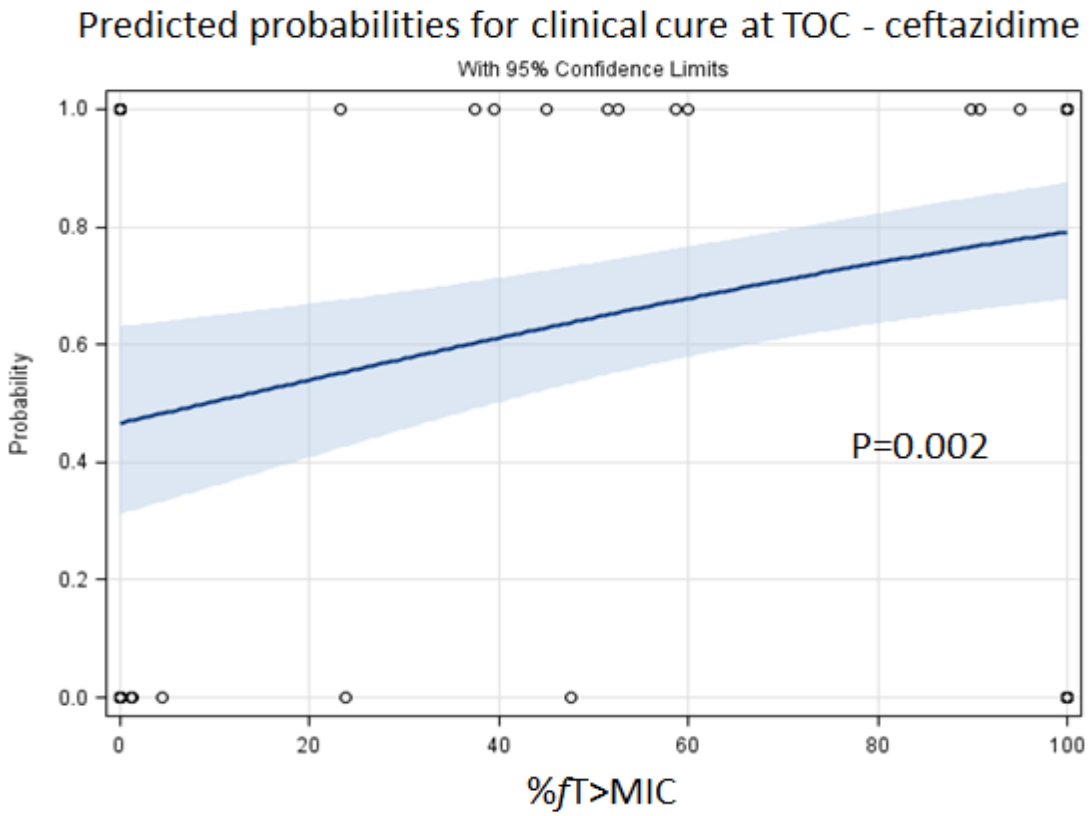
%*f*T>MIC breakpoint = 44.9 %

P< 0.0001

%*f*T>MIC	Success	Failure
≥44.9	83 (90.2%)	9 (9.8%)
<44.9	31 (50%)	31 (50%)

Muller et al, JAC 2013 68:900-906

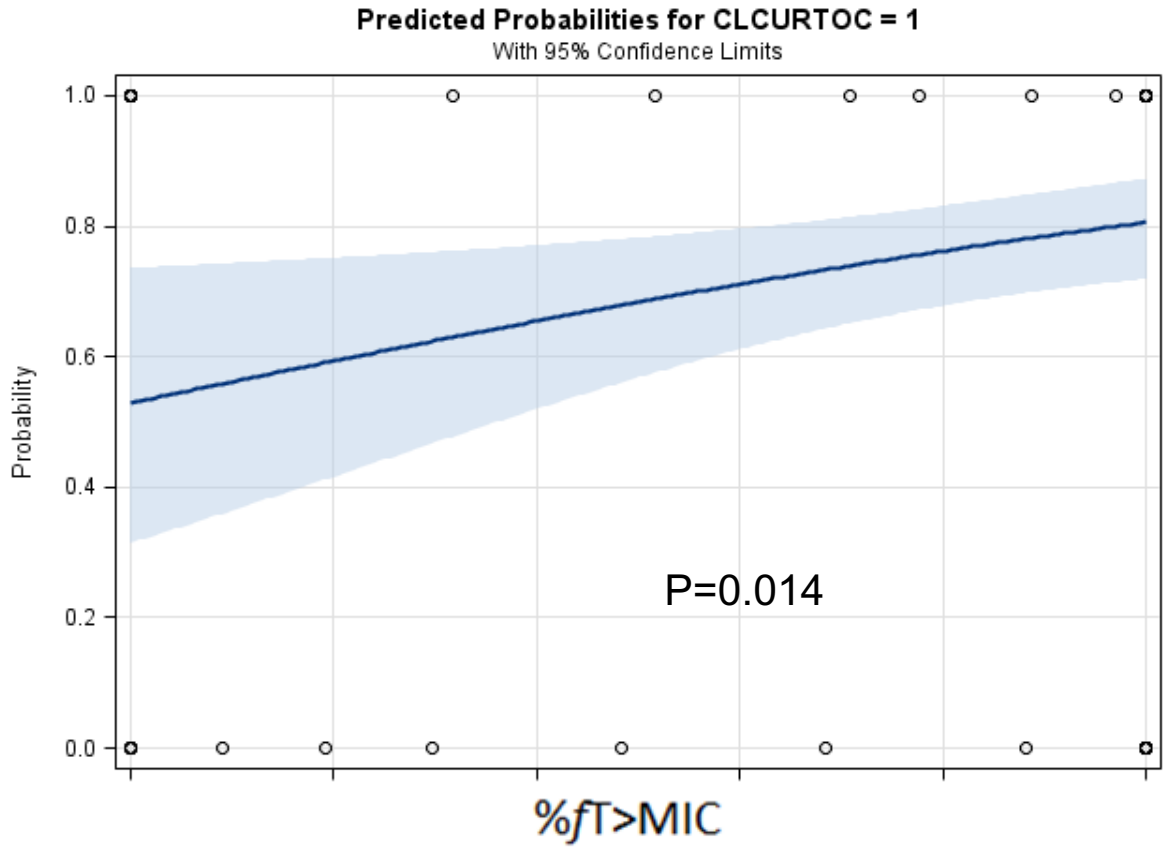
Probability plot of the logistic regression analysis for ceftazidime showing the relationship between %*f*T>MIC (Gram-negatives at baseline/EOT) and probability of cure at TOC



BENEFIT

Muller et al, JAC 2013 68:900-906

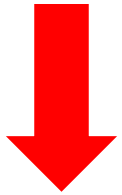
Probability plot of the logistic regression analysis for ceftobiprole showing the relationship between %*f*T>MIC and probability of cure at TOC – nosocomial pneumonia



BENEFIT

Muller et al, AAC 2014 58:2512

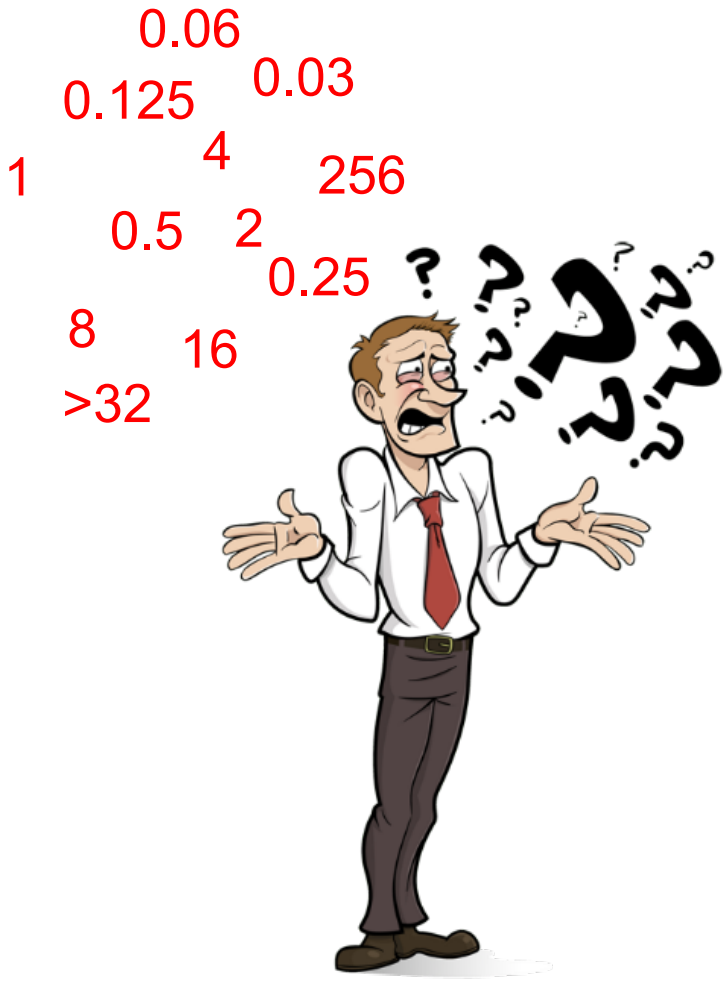
The PK/PD relationship is based on MIC AND PK exposure



Optimize dose based on:

- Exposure response relationship
- PK characteristics
- MIC (distribution)

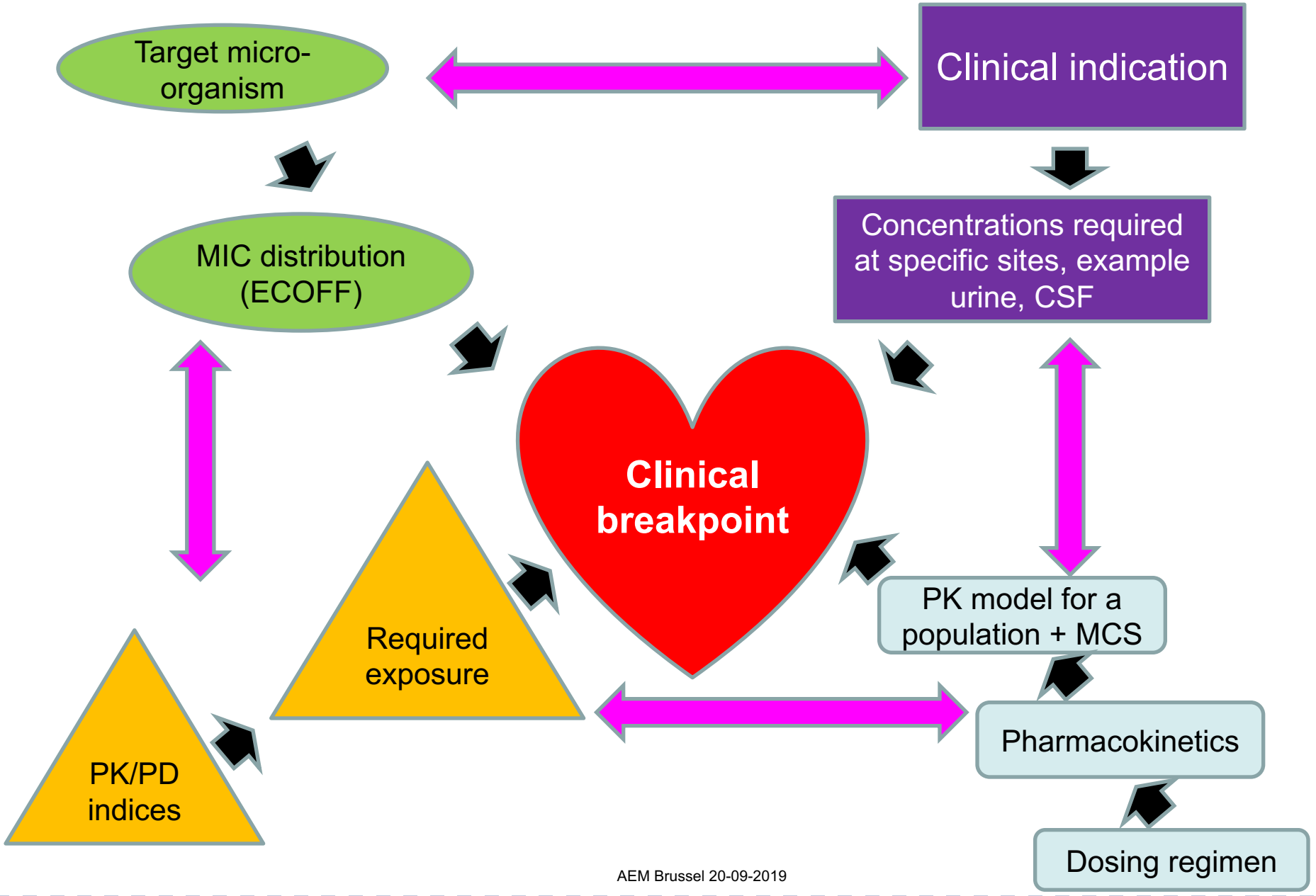
Setting clinical breakpoints…why?



Report an advise to the clinic

- Is there a high probability that the therapy will work or not?

Back to breakpoints….many factors



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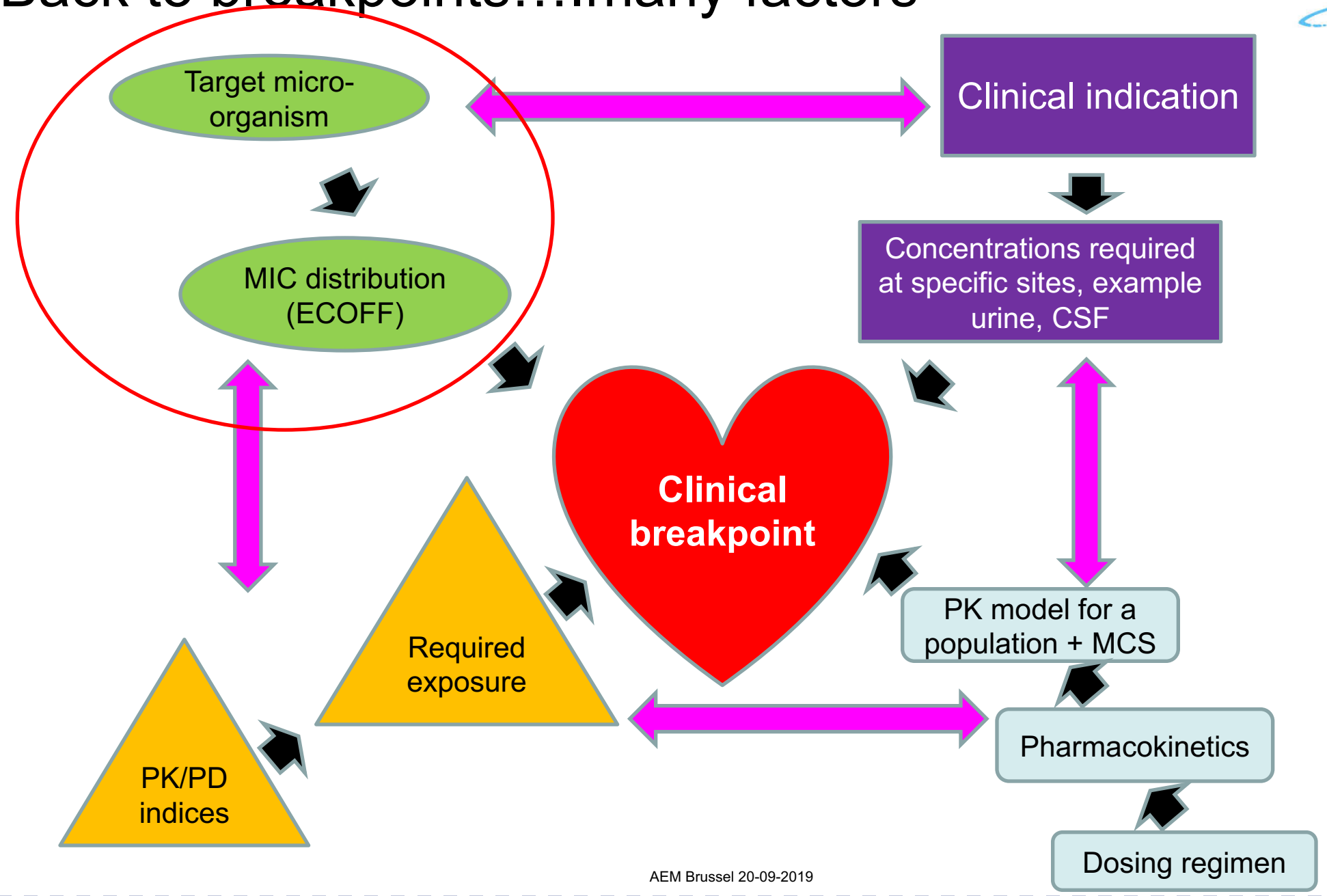

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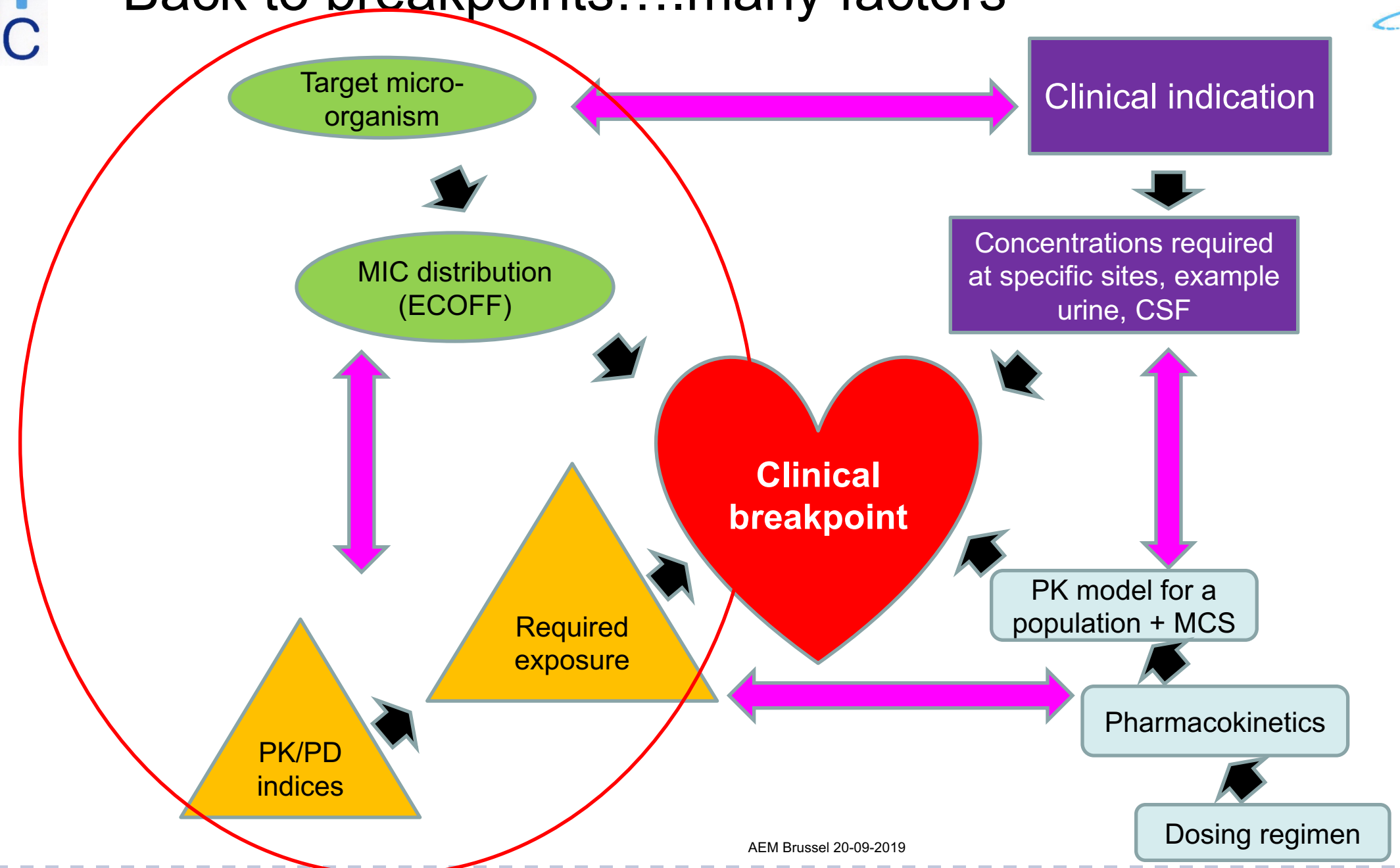
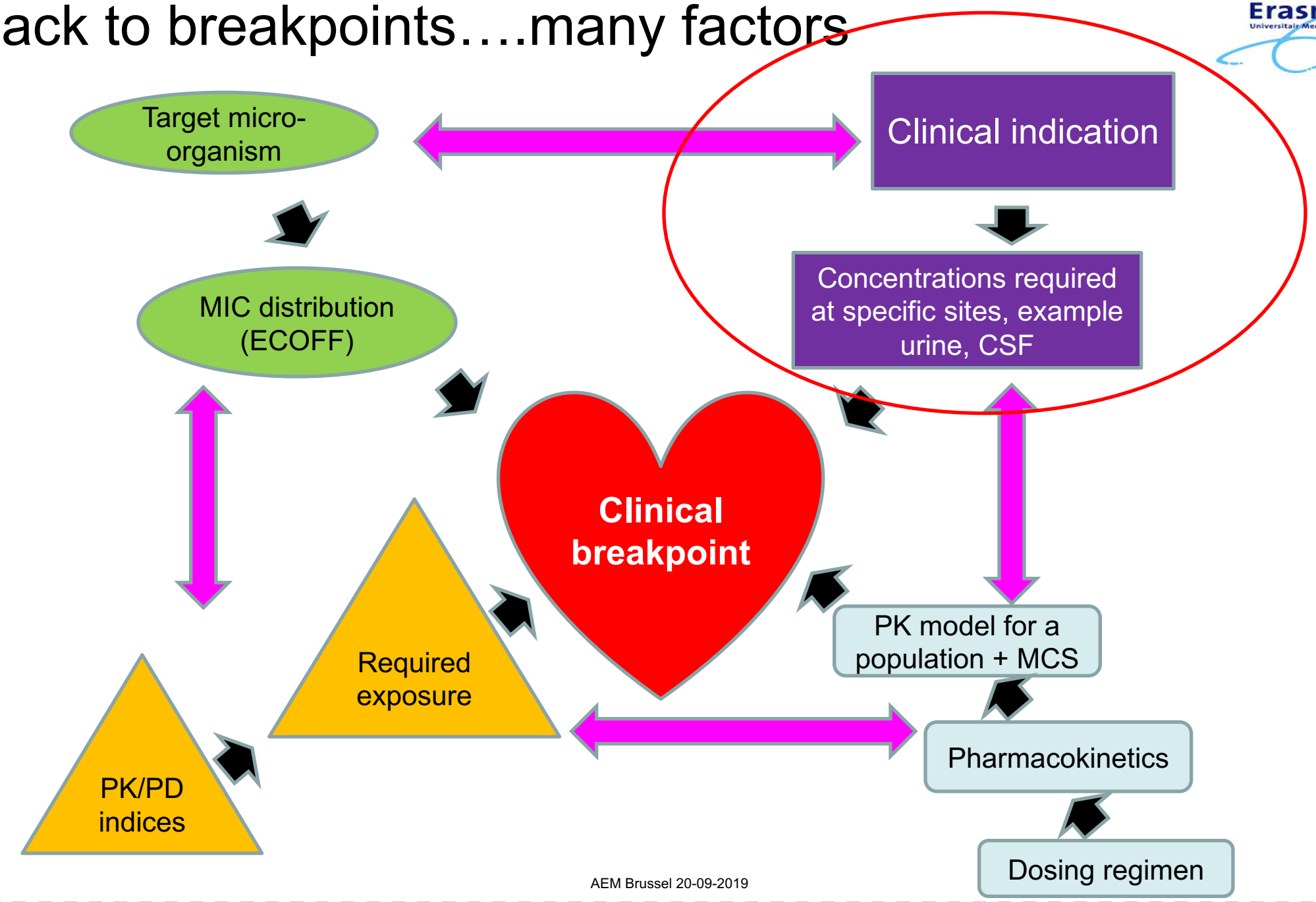


Summary on the exposure MIC relation

- MIC measure of potency
- PK/PD indices determined by fractionation studies
  - » AUC/MIC: aminoglycosides, vancomycin
  - » %*f*T>MIC: beta-lactams
  - » Peak/MIC: possibly colistin (?)
- How much exposure of the antibiotic to the bug is needed to achieve antibacterial effect?
  - – From animal-studies a minimal value for these indices is determined.

Back to breakpoints….many factors



Site specific breakpoints?

- There are some site specific breakpoints:
  - Concentrations reached in CSF are much lower compared to urine or in the lungs

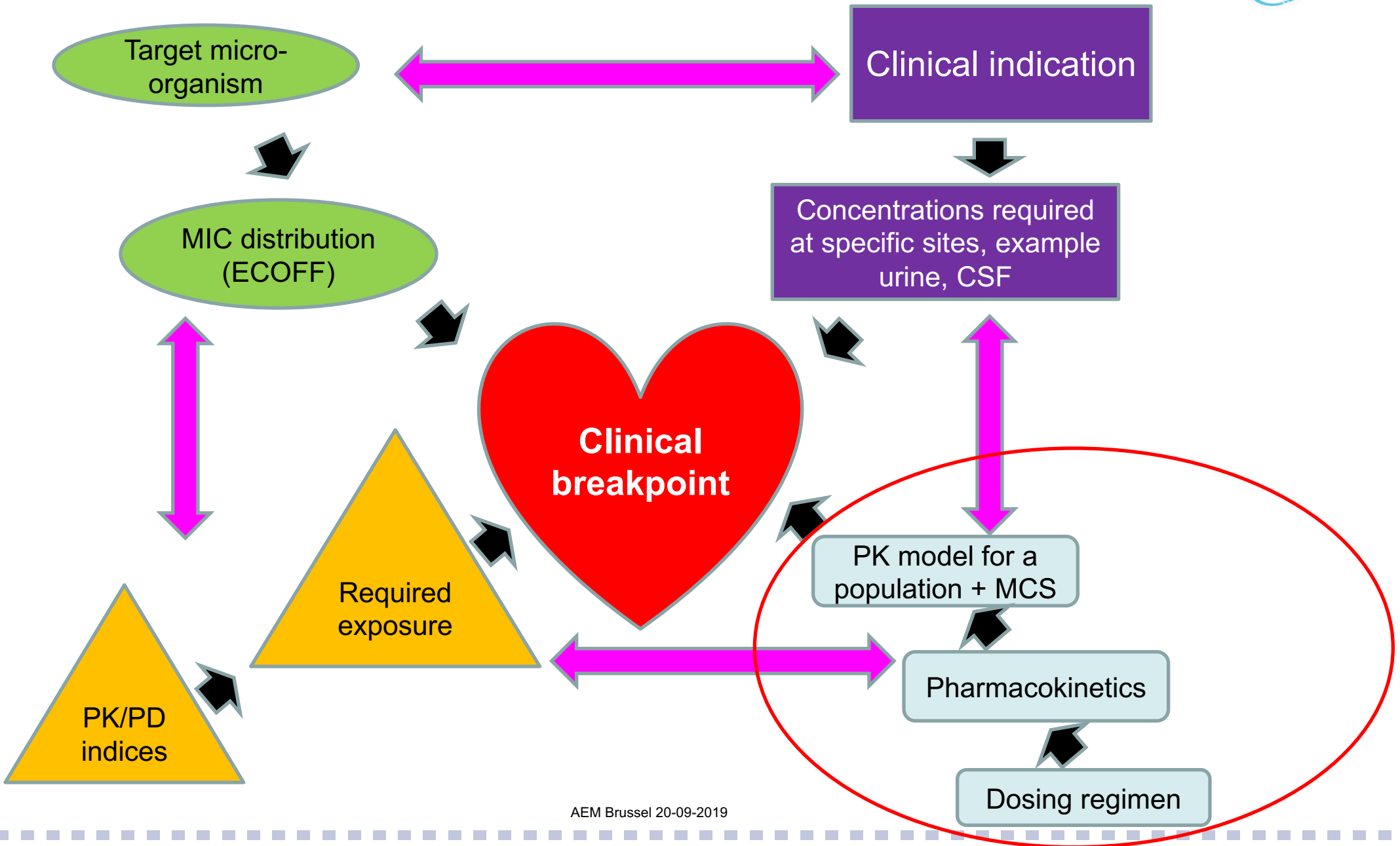
Streptococcus pneumoniae

Expert Rules and Intrinsic Resistance Tables

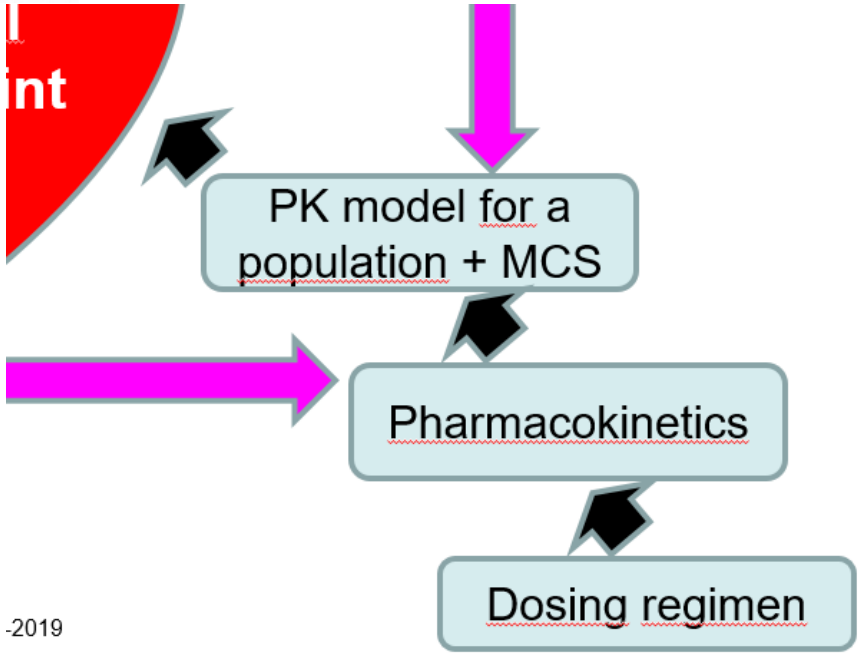
MIC determination (broth microdilution according to ISO standard 2
Medium: Mueller-Hinton broth + 5% lysed horse blood and 20 mg/L β-N
Inoculum: 5x10^5 CFU/mL
Incubation: Sealed panels, air, 35±1°C, 18±2h
Reading: Unless otherwise stated, read MICs at the lowest concentratio inhibits visible growth.
Quality control: *Streptococcus pneumoniae* ATCC 49619. For agents r EUCAST QC Tables.

Penicillins[1,2]	MIC breakpo (mg/L)	
	S ≤	R >
Benzylpenicillin (indications other than meningitis)[3]	0.06[1]	2[1]
Benzylpenicillin (meningitis)	0.06[1]	0.06[1]

Back to breakpoints….many factors



PK and MCS in breakpoint setting



-2019

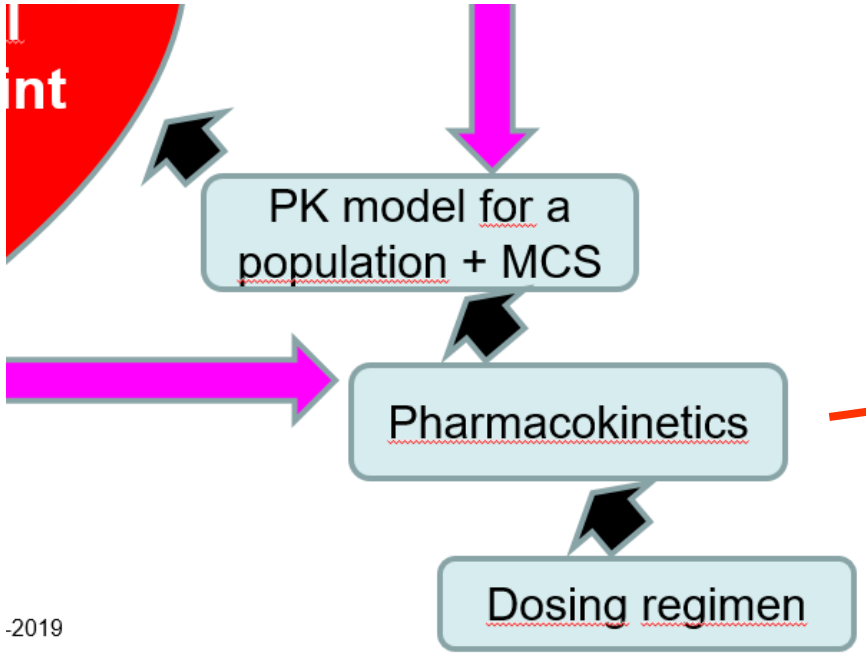
What are the dosing regimen currently used?

1. Dosage Amoxicillin

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose	250-500 mg x 3 oral 1 g x 3 iv	500 mg x 3 oral 1 g x 2 iv	500 mg-1 g x 3 oral 1 g x 3 – 4 iv	500 mg-1 g x 3 oral	500 mg x 3 oral	500 mg-1 g x 3 oral
Maximum dose schedule	2 g x 6 iv	3 g x 6 iv	2 g x 6 iv	2 g x 6 iv	1 g x 3-4	1 g x 3-4
Available formulations	oral, iv	oral, iv	oral, iv	oral, iv	oral	oral

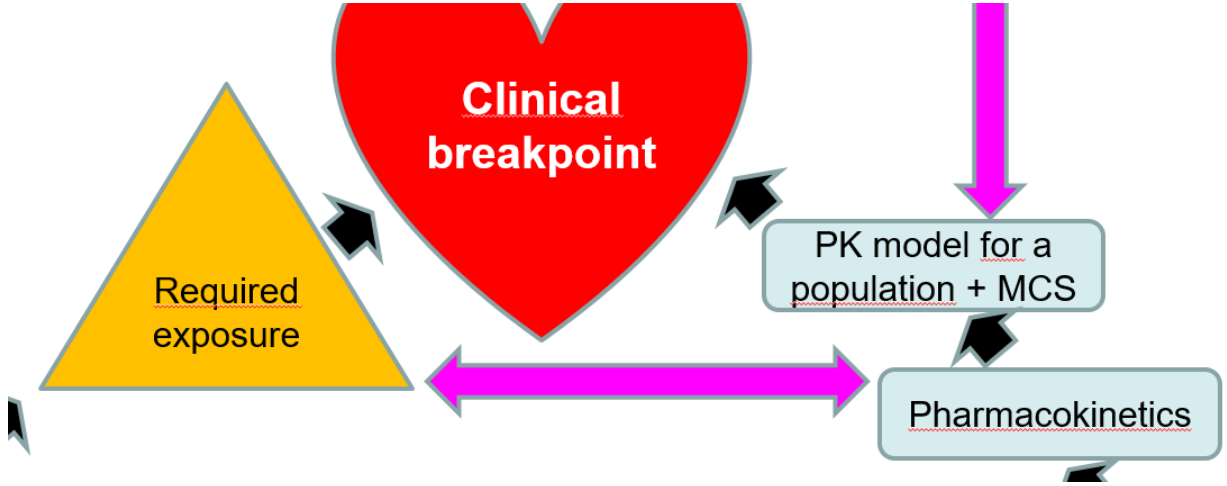
 Amoxicillin Rationale for the EUCAST clinical breakpoints, version 1.0 22nd November 2010

PK and MCS in breakpoint setting



-2019

What are the concentrations reached in humans?



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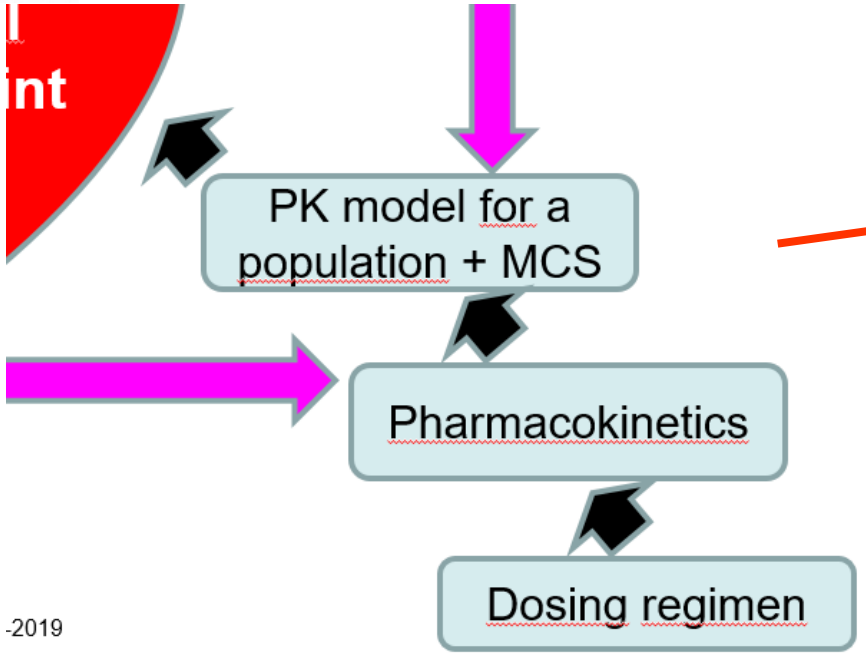


-2019

Not only for an average patient, but for the population

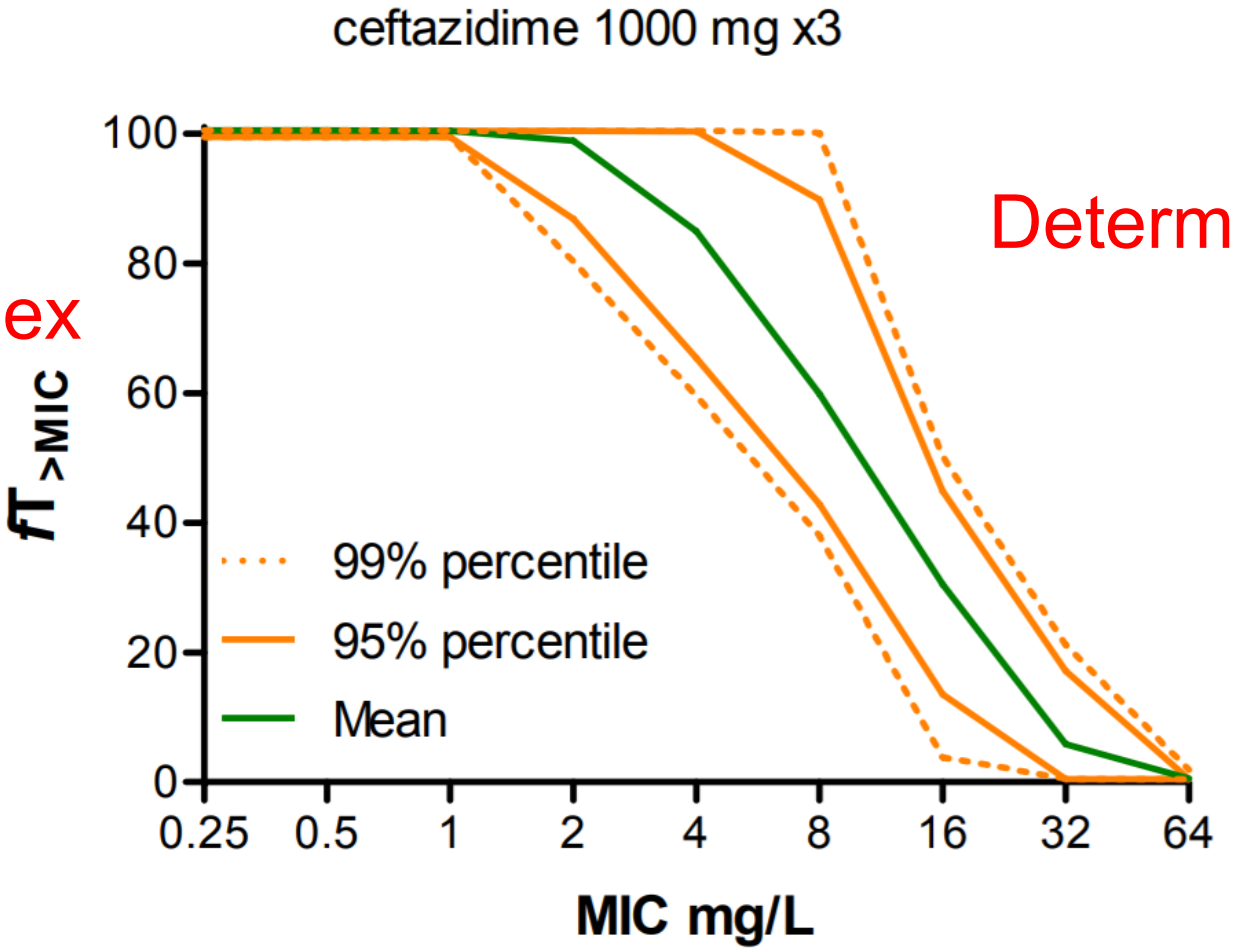
Perform Monte Carlo simulation with a population model representing the average patient with different dosing regimen.

The target needs to be reached in 95-99% of the population

NB: Garbage in is Garbage out
The models used for breakpoint setting are average patients: NOT ICU, NOT sepsis, NOT obesity etc

Example ceftazidime MCS

PK/PD index



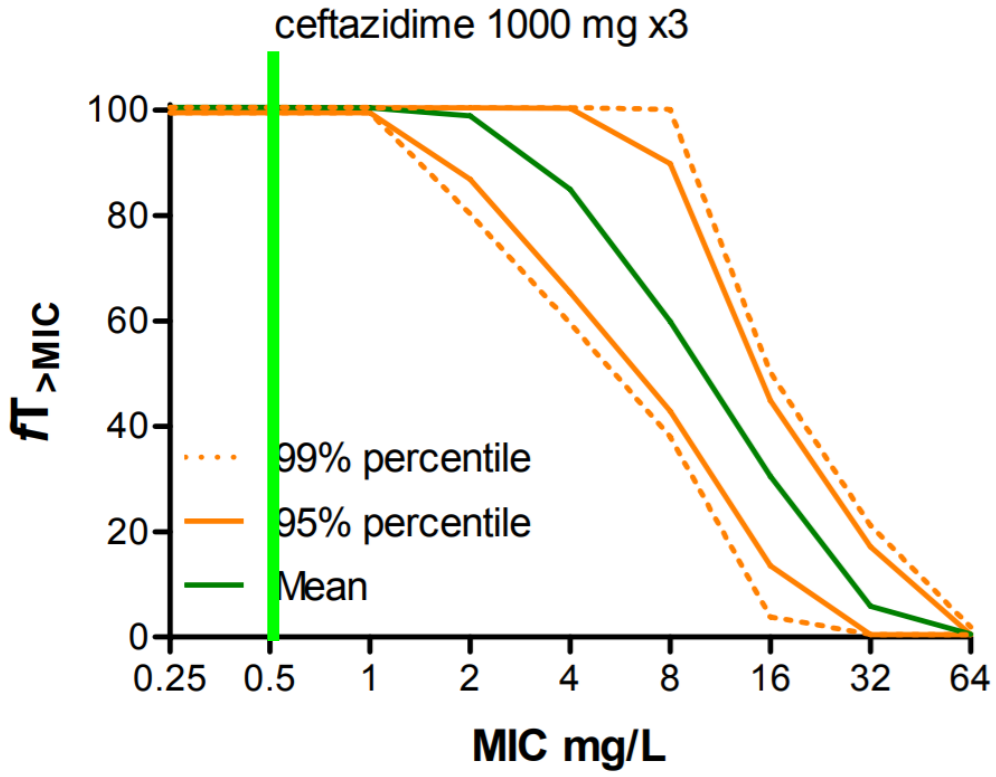
Determined by the PK model

Potency

Klebsiella and ceftazidime

	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
Klebsiella pneumoniae	0	0	10	9	89	592	1346	1425	611	281	145	88	104	113	146	136	92	112	27		0.5
Klebsiella spp	0	0	0	15	125	343	351	158	71	43	13	3	3	0	2	0	1	0	0		0.5

Normal range ends at 0.5 mg/L



Strains with MICs up to 0.5 mg/L can be called susceptible with this dose.

If you look at the population, there is a high likelihood on therapeutic success.

EUCAST Definitions from januari 2019

- S - Susceptible, standard dosing regimen: A microorganism is categorised as "Susceptible, standard dosing regimen", when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.

- R - Resistant: A microorganism is categorised as "Resistant" when there is a high likelihood of therapeutic failure even when there is increased exposure.

EUCAST Definitions from januari 2019

- S - Susceptible, standard dosing regimen: A microorganism is categorised as "Susceptible, standard dosing regimen", when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.
- I – Susceptible, increased exposure*: A microorganism is categorised as "**Susceptible, Increased exposure***" when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.
- R - Resistant: A microorganism is categorised as "Resistant" when there is a high likelihood of therapeutic failure even when there is increased exposure.

- **Susceptible, Increased exposure**
  - Increased exposure: urine
  - Prescribe ceftazidime 3dd 2 gram in stead of 3dd 1 gram