

Erasmus MC  
Centrum

## EUCAST breakpoints

**Johan W. Mouton MD PhD FIDSA**  
Professor pharmacokinetics and pharmacodynamics

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## Disclosures

Research grants – advisory boards – speaker

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## LAB REPORT

Sensitivity	
Organism 1	Escherichia coli
Hoeveelheid	>=10E5 kve/ml
Panel gevoeligheid	5 Urine Coliform
amoxicilline/clavula	Sensitive ( 0,06 mg/l )
amoxicilline	Sensitive ( 0,06 mg/l )
cefuroxim	Sensitive ( 0,06 mg/l )
cefotaxim	Sensitive ( 0,5 mg/l )
cefazoline	Sensitive ( 0,25 mg/l )
ciprofloxacine	Sensitive ( <+0,06 mg/l )
doxycycline	Sensitive ( 1 mg/l )
nitroksantoline	Sensitive ( <+32 mg/l )
nofloxacine	Intermediate ( 1 mg/l )
sulfamethoxazol	Sensitive ( <+64 mg/l )
tobrangicine	Intermediate ( 0,25 mg/l )
timelhopim	Resistant ( >64 mg/l )
cotrimoxazole	Sensitive ( 1 mg/l )
ceftazidim	Sensitive ( 0,13 mg/l )

- Provides Clinician/Consultant guidelines how to optimally treat a patient (Freely translated from EUCAST guideline)

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Is susceptibility (MICs) related to (clinical) outcome?

If yes, which values (breakpoints) make the difference?

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Efficacy of the drug

Potency of a drug (MIC)

Exposure to the bug *In vivo* (PK)

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ACTIVITY *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 JWM Bochem 20-09-2016 Radboud Universiteit Nijmegen Radboudumc

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### MIC Measure of Potency

**MIC**  
Lowest concentration with no visible growth after 18 hour incubation

.25 .5 1 2 4 8

MIC = 2 mg/L

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

Treatment with fluconazol Doses 50 – 800 mg

Culture-results with MIC-values

Individual Dose

MIC-values per individual

Determine Dose/MIC for each patient

Microbiological outcome (candida cured)  
Clinical outcome

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

EC50 | 43.69  
R<sup>2</sup> | 0.9938

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

Rodriguez- Tudela et al, AAC 2007 JWM Bochum 20-09-2016 Radboud Universiteit Nijmegen Radboudumc

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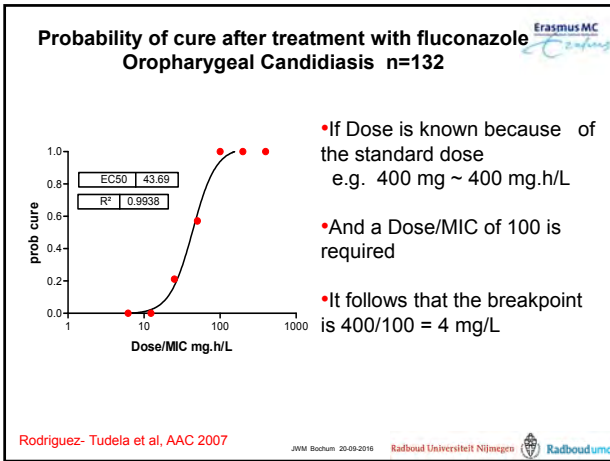
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It is thus however, slightly more complicated than just dose.....

- Usually, dose – effect relationships are not really known
  - development
- How to adjust for altered clearance

Dose is just a means to reach adequate concentrations

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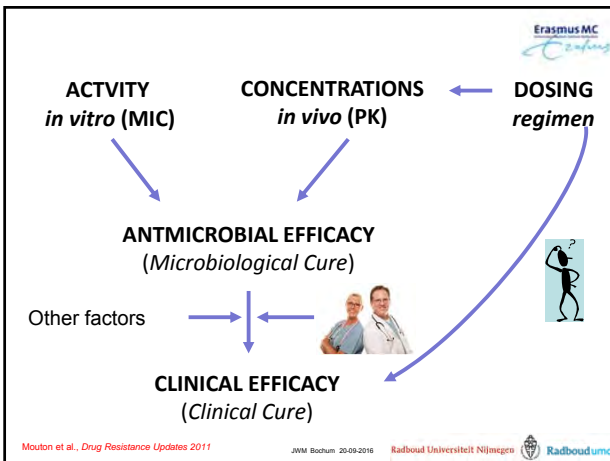
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### Antimicrobial Treatment

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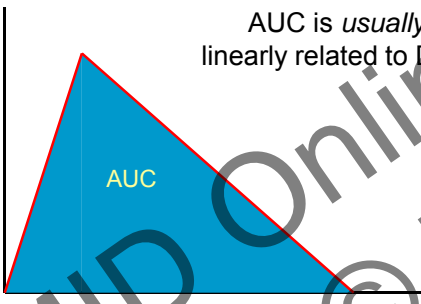

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### Pharmacokinetic parameters : Measures of Exposure

AUC is *usually*  
linearly related to Dose

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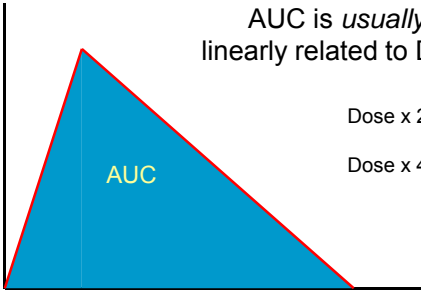
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### Pharmacokinetic parameters : Measures of Exposure

AUC is *usually*  
linearly related to Dose



Dose x 2 = AUC x 2

Dose x 4 = AUC x 4

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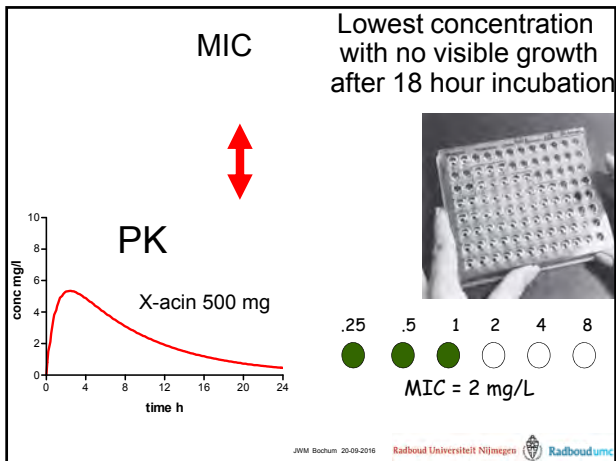
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**Pharmacokinetic Parameter (and Dose)**

**MIC**

• Thus, we have to:

- Establish a relationship between the MIC in vitro and concentrations in vivo (thus, dosing regimens)
- Determine which dosing regimens are optimal for Treatment in relation to the MIC

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**EUCAST** EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

**Susceptible (S)**

A micro-organism is defined as susceptible by a level of antimicrobial activity associated with a high likelihood of therapeutic success. A micro-organism is categorized as susceptible by applying the appropriate breakpoint in a defined phenotypic test system.

Note: This breakpoint may be altered with legitimate changes in circumstances

**Intermediate (I)**

A micro-organism is defined as intermediate by a level of antimicrobial activity associated with indeterminate therapeutic effect. A micro-organism is categorized as intermediate by applying the appropriate breakpoints in a defined phenotypic test system.

Note: This breakpoint may be altered with legitimate changes in circumstances.

**Resistant (R)**

Bacteria are defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure. A micro-organism is categorized as resistant by applying the appropriate breakpoint in a defined phenotypic test system.

Note: This breakpoint may be altered with legitimate changes in circumstances

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WE AIM FOR:

A high likelihood of success for every one (S)

Hitting the PK/PD target

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### SETTING A BREAKPOINT –PK/PD (example 1)

DETERMINE THE PK/PD TARGET e.g. *value of the PK/PD Index*  
(animal studies, clinical studies)

↓

ESTIMATE EXPOSURE from the dosing regimen and PK, including population variability

↓

CALCULATE PK/PD BREAKPOINT from  $PK/PD\ target = PK/PD\ Index$

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### SETTING A BREAKPOINT –PK/PD (example 1)

DETERMINE THE PK/PD TARGET e.g. *value of the PK/PD Index*  
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ESTIMATE EXPOSURE from the dosing regimen and PK, including population variability

↓

CALCULATE PK/PD BREAKPOINT from  $PK/PD\ target = PK/PD\ Index$

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Any idea where we are today?

No idea...  
maybe a mouse?

Might be a human,  
though...

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An elephant...  
Today it is an elephant!



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**THE TARGET IS THE MICRO-ORGANISM**

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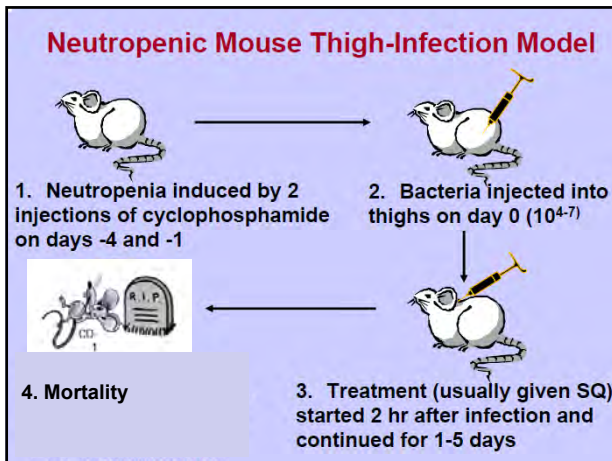
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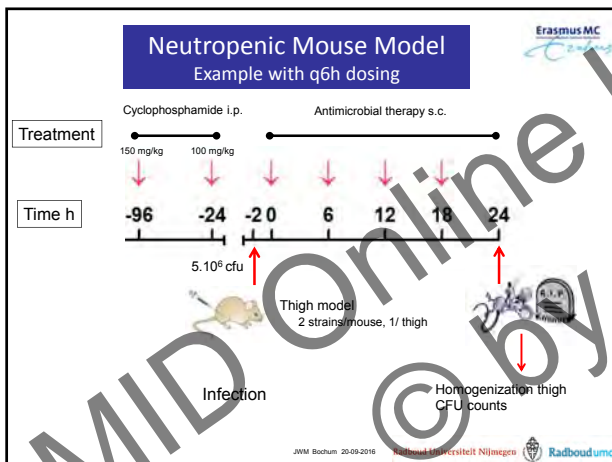
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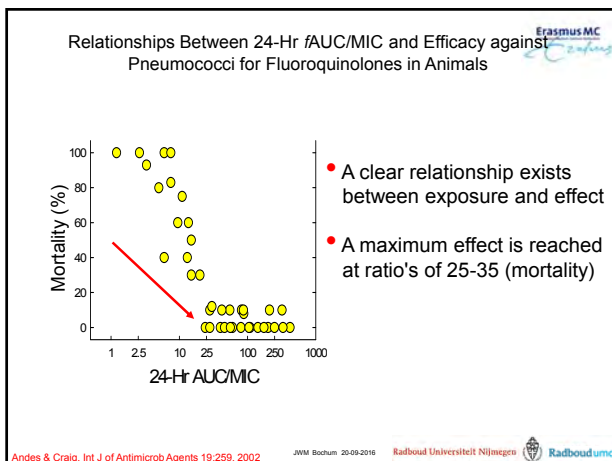
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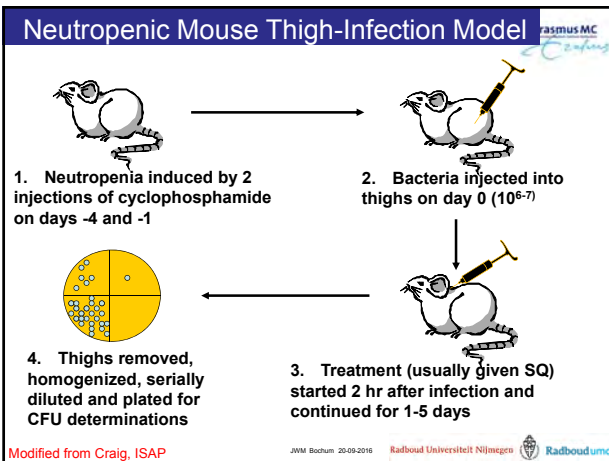
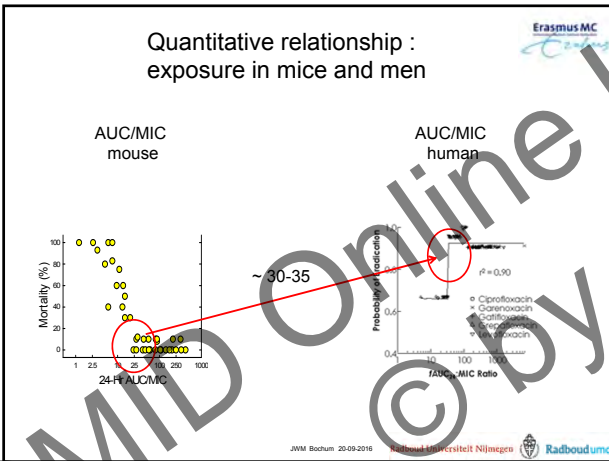
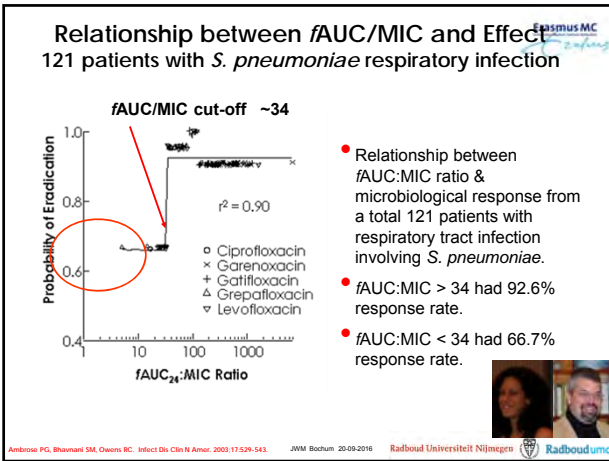
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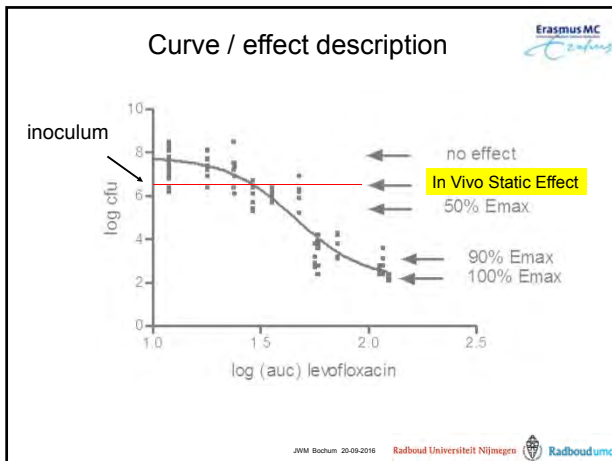
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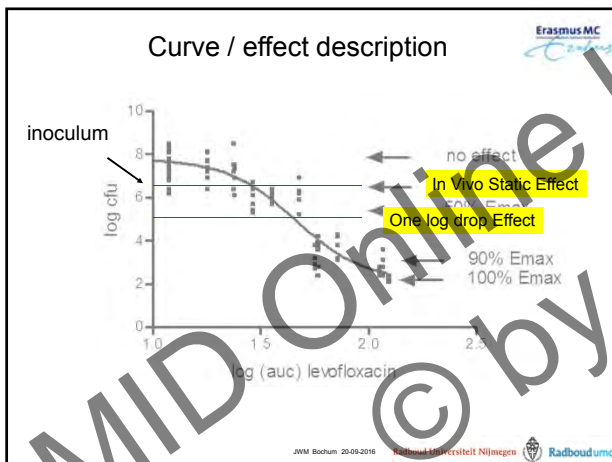
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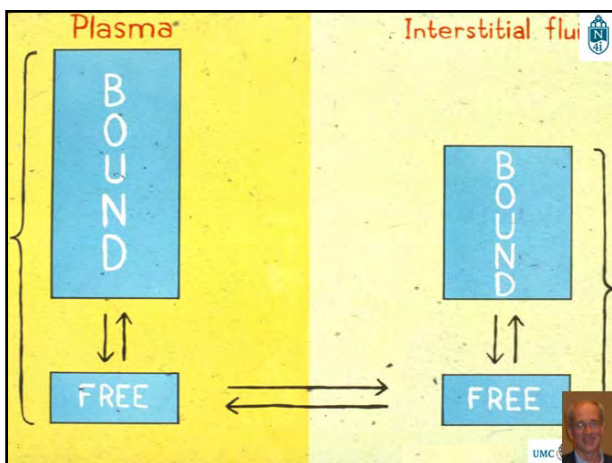
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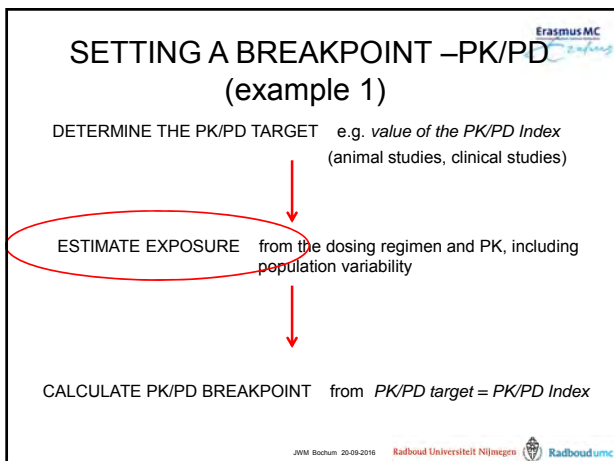
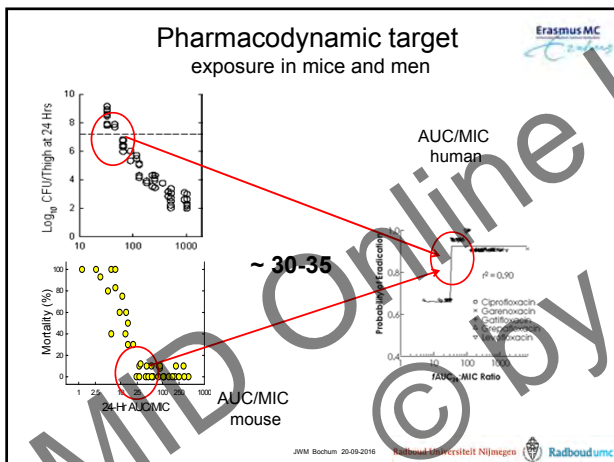
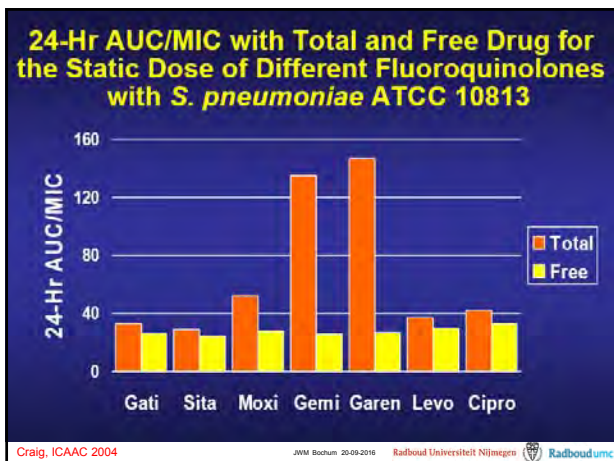
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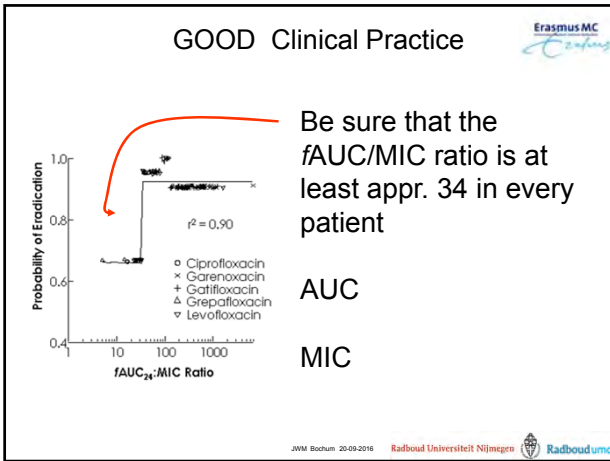
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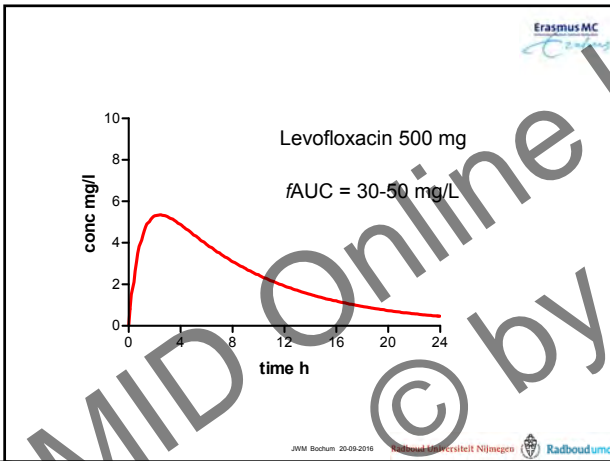
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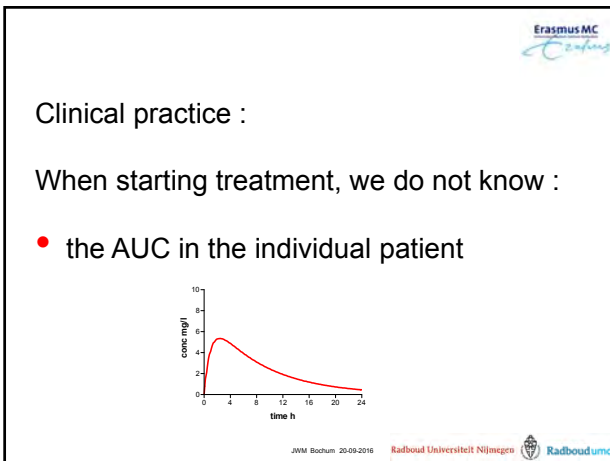
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Pharmacokinetics

Some people are more equal than others...

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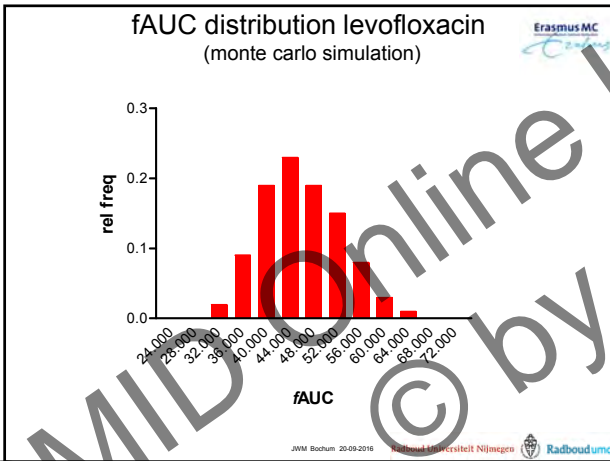
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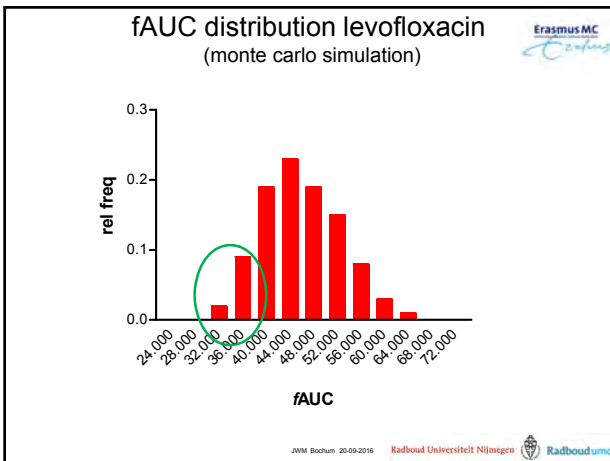
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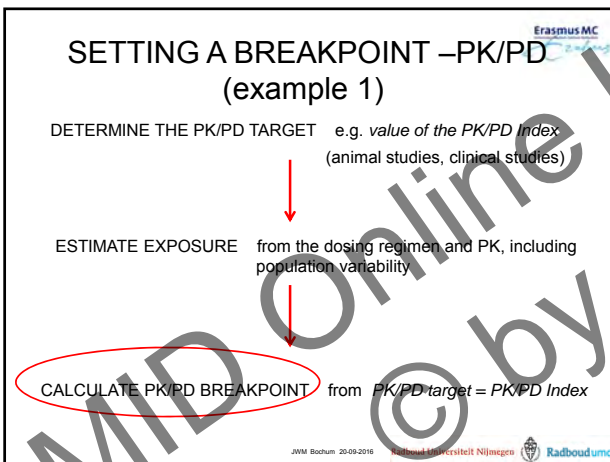
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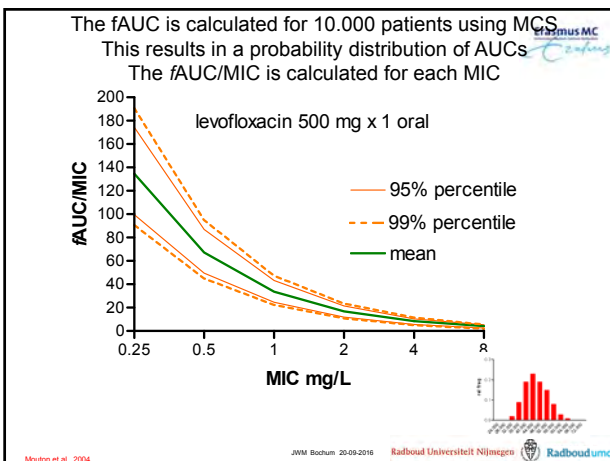
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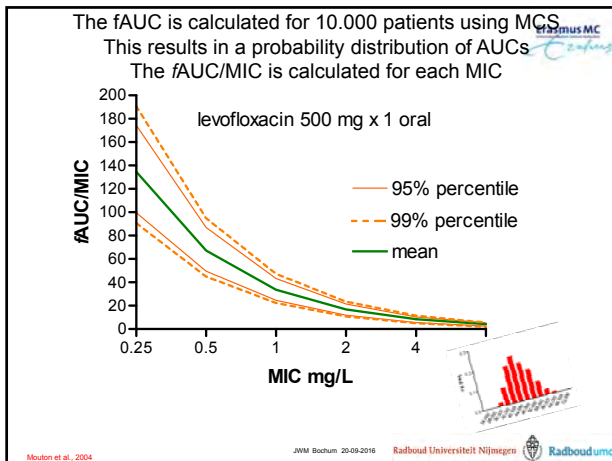
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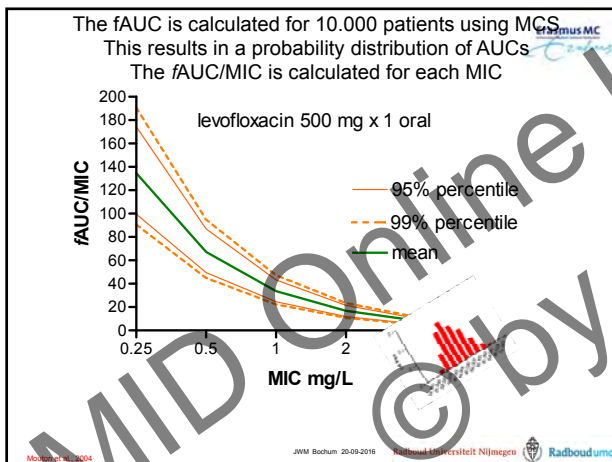
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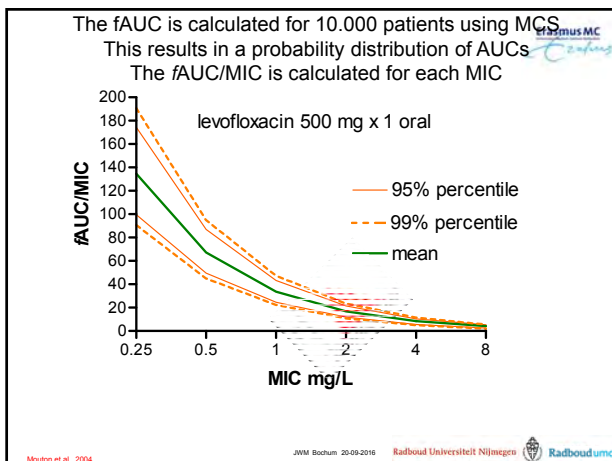
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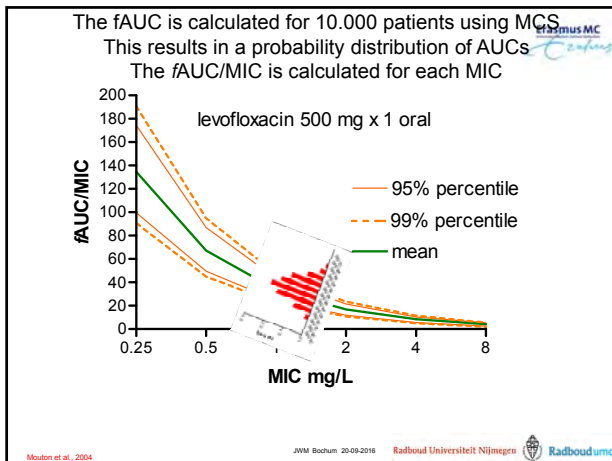
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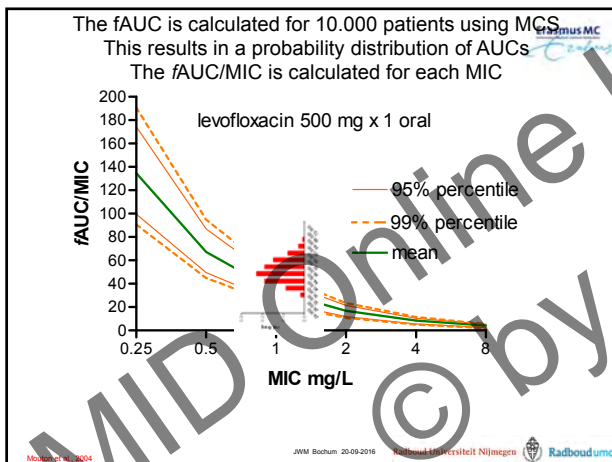
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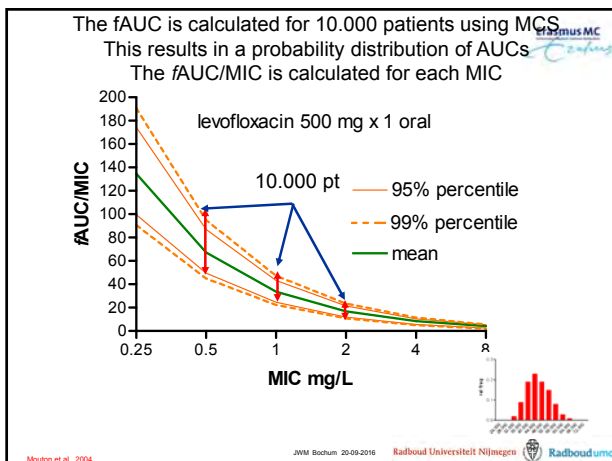
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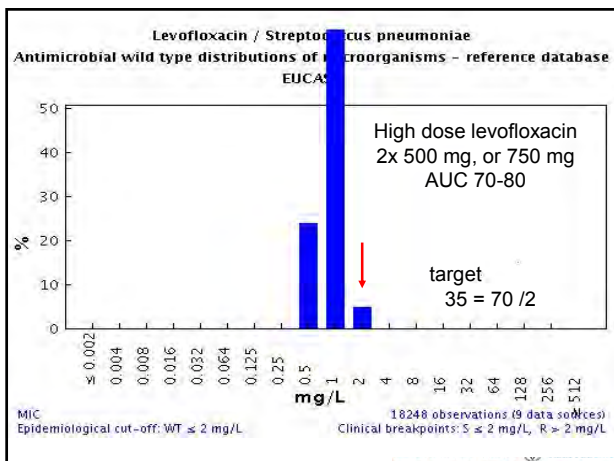
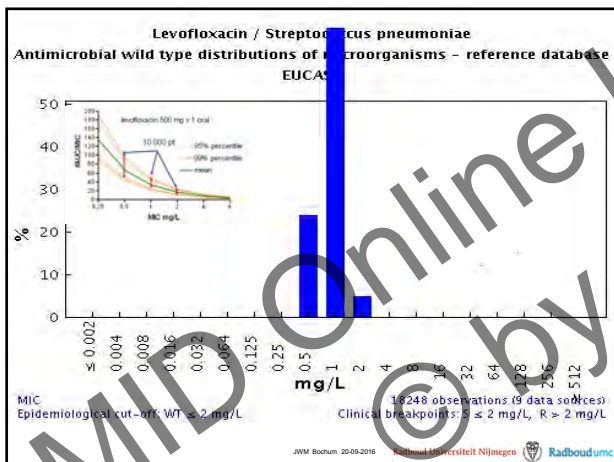
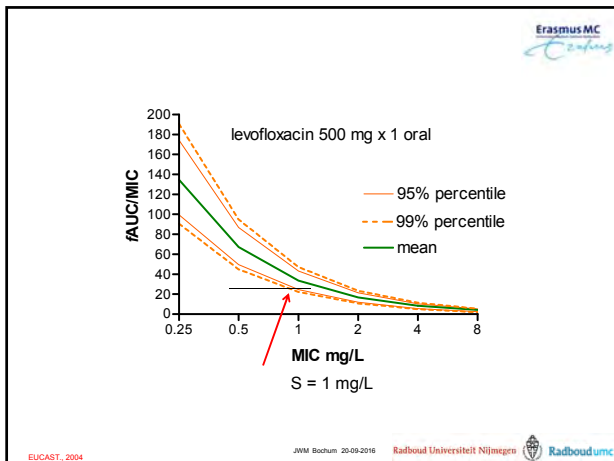
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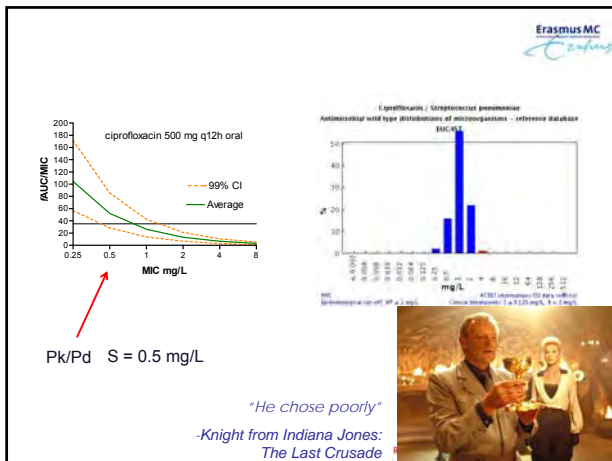
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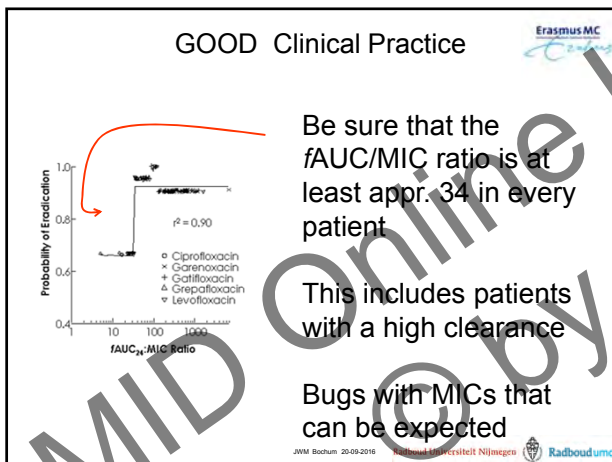
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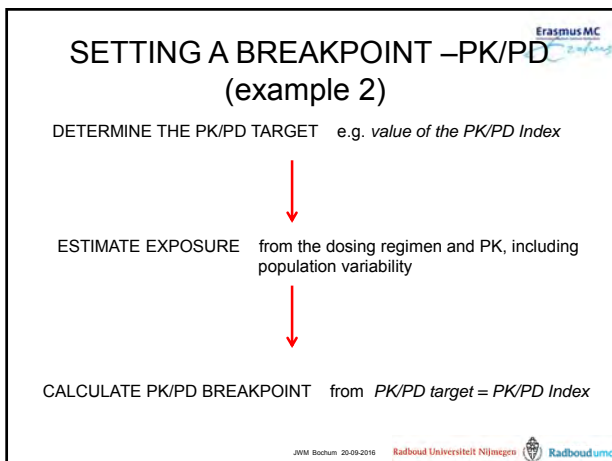
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Are All Antimicrobials Created Equal???

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Pharmacokinetic parameters :  
Measures of Exposure

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Time > MIC dependent on dose frequency

Total daily dose similar

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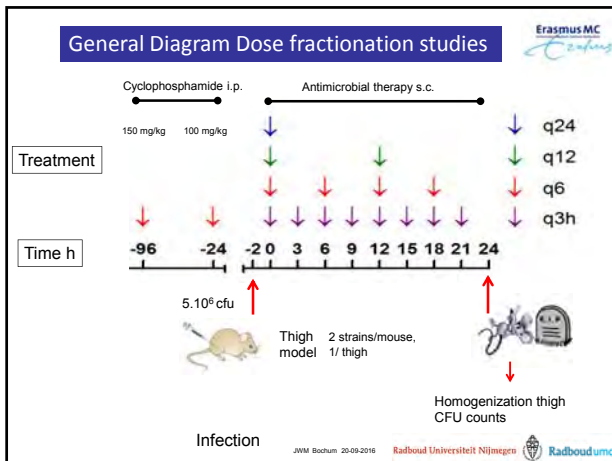
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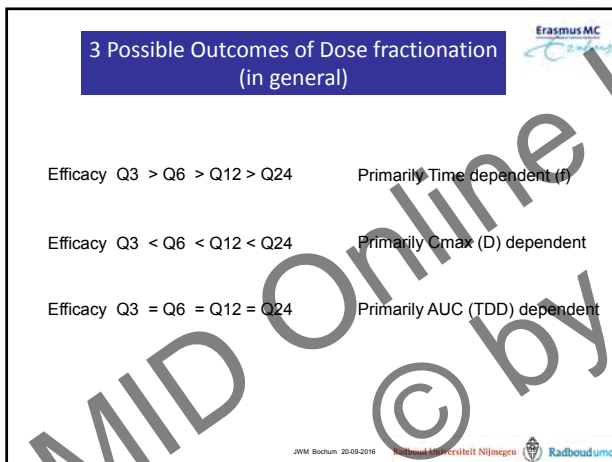
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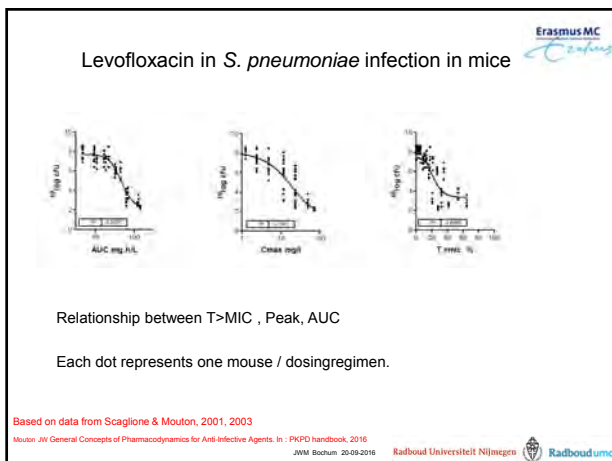
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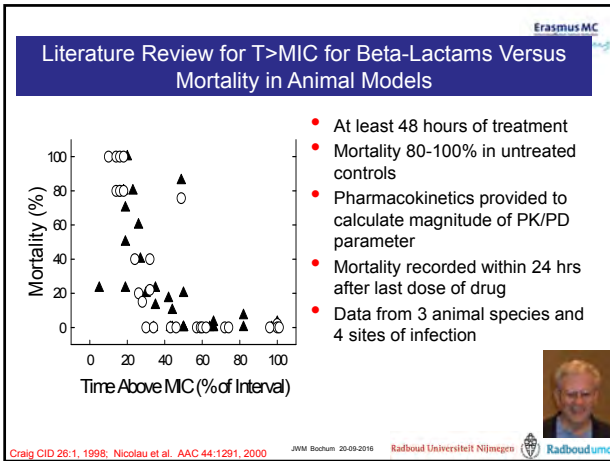
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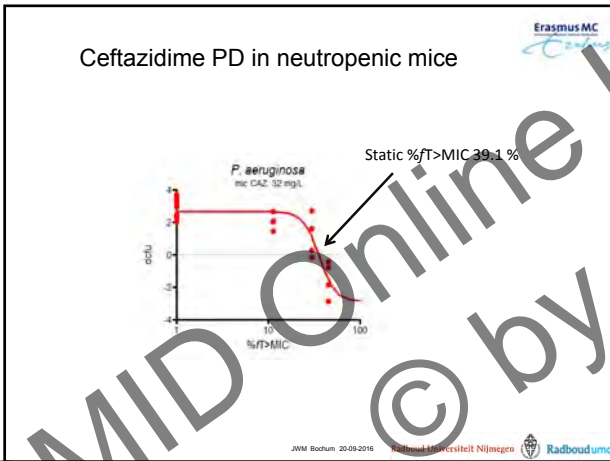
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### Time > MIC Required for a Static Effect After 24-hours of Therapy with Four Cephalosporins

Time Above MIC (Percent of Dosing Interval)

Drug	Enterobacteriaceae	<i>S. pneumoniae</i>
Ceftriaxone (T)	72 (66-79)	74 (69-78)
Ceftriaxone (F)	38 (34-42)	39 (37-41)
Cefotaxime	38 (36-40)	38 (36-40)
Ceftazidime	36 (27-42)	39 (35-42)
Cefpirome	35 (29-40)	37 (33-39)

Data from Craig

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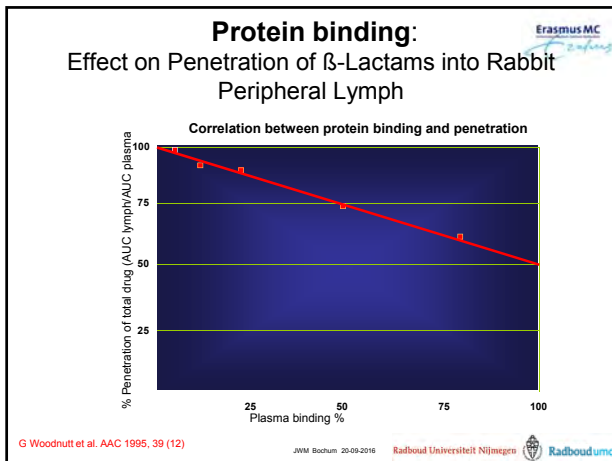
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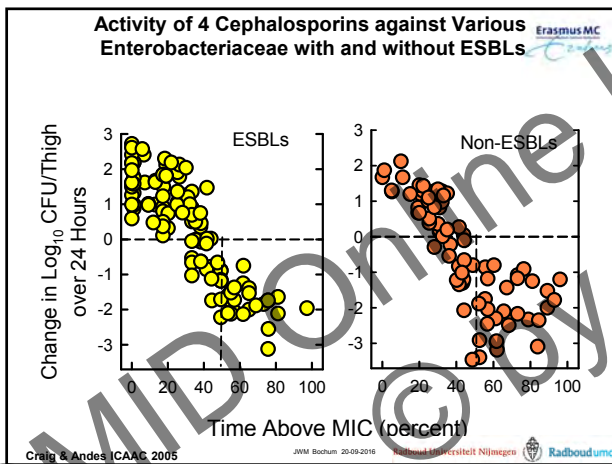
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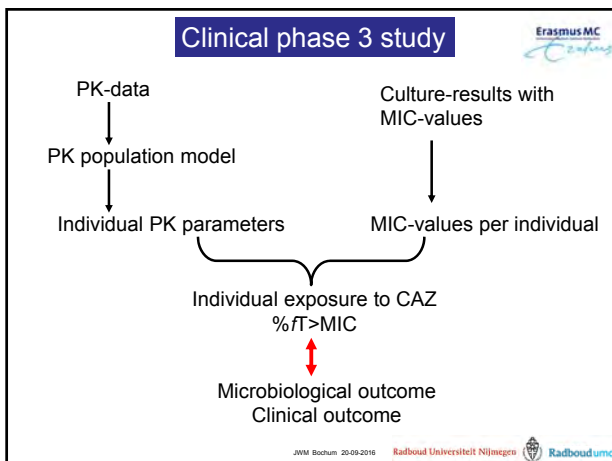
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**Ceftazidime in patients with nosocomial pneumonia**

- 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
- Numbers of patients in CAZ arm:
  - N=390 patients included
  - 220 without Gram negatives in cultures
  - N=170 with MIC
  - 16 without PK estimates
  - N=154 with MIC and PK-estimates**

Muller et al, JAC 2013 68:900-906

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**PK/PD of ceftazidime in Clinical Study**

- 154 patients with nosocomial pneumonia (including VAP)
- PK parameters determined in every patient
  - Sparse sampling; covariates; population PK
- MICs of infecting micro-organisms
- Individual exposures to CAZ (%fT>MIC)
  - Categorised (%fT>MIC per 10%)
- Eradication rate per exposure group

Muller et al, JAC 2013 68:900-906

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**Exposure-response Emax model  
ceftazidime – micro eradication**

Bottom	0.4548
Top	0.9971
LogEC50	1.670
HillSlope	3.230
EC50	46.80

- Baseline response 50%
- Max response 99.7%
- 50% Effective PD index (EI<sub>50</sub>): 47 %fT>MIC

Muller et al, JAC 2013 68:900-906

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**Ceftazidime in patients with nosocomial pneumonia**

**CART analysis**

- to differentiate between lower and higher response rate

**%fT>MIC breakpoint = 44.9 %**

P < 0.0001

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

Predicted probabilities for clinical cure at TOC - ceftazidime  
 With 95% Confidence Limits  
 P=0.002

Muller et al, JAC 2013 68:900-906  
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**Ceftobiprole %fT>MIC (Gram-negatives at baseline/EOT) and probability of cure at TOC (nosocomial pneumonia [excl. VAP, n=82])**

Predicted probabilities for clinical cure at TOC - ceftobiprole  
 With 95% Confidence Limits  
 P=0.033

Muller et al., AAC 2014  
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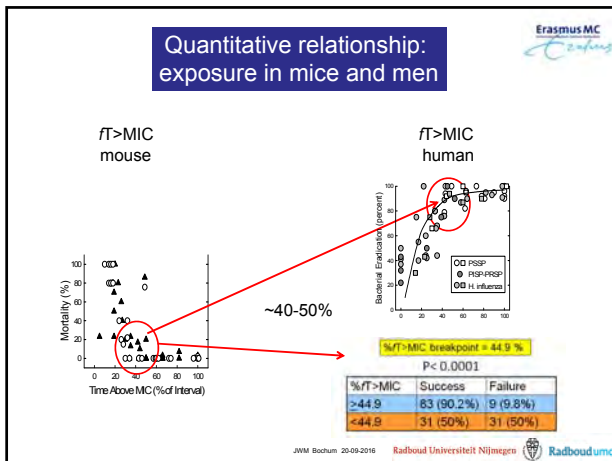
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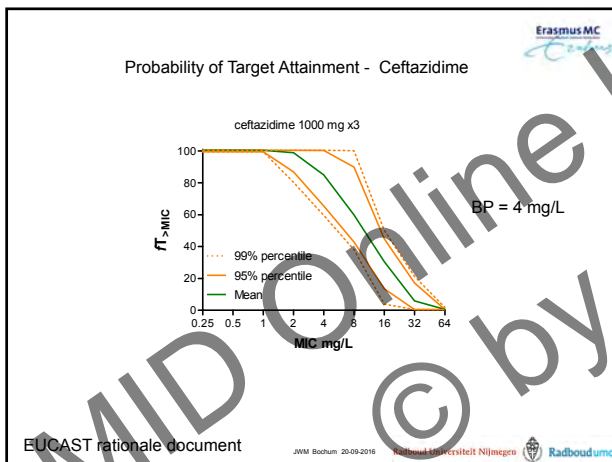
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### It is not only for Mice !!

Disease state, drug	Clinically-derived PK/PD target (reference(s))	Animal infection model/ organism studied	Animal-derived PK/PD target (reference(s))
<b>Hospital-acquired pneumonia</b>			
Quinolones	$AUC_{0-24}/MIC$ ratio, 62-75 [11, 12]	Neutropenic mouse thigh, gram-negative bacilli	$AUC_{0-24}/MIC$ ratio, 70-90 for 90% animal survival or 2 log-unit HR [13, 14]
<b>Community-acquired respiratory tract infections</b>			
Quinolones	$AUC_{0-24}/MIC$ ratio, 34 [22]	Immunocompetent mouse thigh; <i>Streptococcus pneumoniae</i>	$AUC_{0-24}/MIC$ ratio, 25-34 for 90% animal survival or 2 log-unit HR [23]
$\beta$ -lactams	$T>MIC$ , 40% of the dosing interval [14]	Immunocompetent mouse thigh; <i>S. pneumoniae</i>	$T>MIC$ , 30-40% of the dosing interval for 90% animal survival [14]
Tellithromycin	$AUC_{0-24}/MIC$ ratio, 3.375 [20]	Neutropenic mouse thigh; <i>S. pneumoniae</i>	$AUC_{0-24}/MIC$ ratio, 1000 for stasis [24]
<b>Bacteremia</b>			
Oritavancin	$fT>MIC$ , 22% of the dosing interval for <i>Staphylococcus aureus</i> [25]	Neutropenic mouse thigh; <i>S. aureus</i>	$fT>MIC$ , 20% of the dosing interval for a 0.5 log-unit HR [26]
Linezolid	$AUC_{0-24}/MIC$ ratio, 85 for <i>S. aureus</i> or <i>Enterococcus faecium</i> [27]	Neutropenic mouse thigh; <i>S. aureus</i>	$AUC_{0-24}/MIC$ ratio, 83 for stasis [28]
<b>Complicated skin and skin structure infections</b>			
Tigecycline	$AUC_{0-24}/MIC$ ratio, 17.9 [29]	Neutropenic mouse thigh; <i>S. aureus</i>	$AUC_{0-24}/MIC$ ratio, 15-20 for stasis [29]
Linezolid	$AUC_{0-24}/MIC$ ratio, 110 [27]	Neutropenic mouse thigh; <i>S. aureus</i>	$AUC_{0-24}/MIC$ ratio, 83 for stasis [28]

NOTE:  $AUC_{0-24}/MIC$ , the ratio of the area under the concentration-time curve at 24 h to the MIC;  $C_{max}/MIC$ , the ratio of the maximal drug concentration to the MIC;  $T>MIC$ , duration of time a drug concentration remains above the MIC.

Ambrose et al. CID 2007  
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## EUCAST Website resources


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**EUCAST**

<http://www.EUCAST.org>  
All EUCAST documents FREE DOWNLOAD

<http://mic.eucast.org/Eucast2>  
MIC and zone diameter distributions

MIC distributions 

Zone diameter distributions 

MIC-zone diameter correlations 

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## Implications for breakpoints

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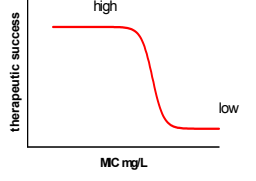
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## Susceptibility (MICs) are related to (clinical) outcome

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Susceptibility (MICs) are related to (clinical) outcome?

Breakpoint values make the difference –but include PK!!!

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**Conclusions**

- PK/PD breakpoints reflect the relationship between exposure and clinical outcome
- PK/PD breakpoints are dependent on dose (I), pharmacokinetic profile and pharmacodynamic target
- The pharmacodynamic target MAY differ by species (e.g. Gram- vs Gram+)
- EUCAST PK/PD breakpoints are based on clinical data if available and otherwise on animal data and other data. Rationale documents describe the background.

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