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Optimizing antimicrobial therapy in the elderly

Johan W. Mouton MD PhD FIDSA
Professor pharmacokinetics and pharmacodynamics

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Dosing should be such that the level of antimicrobial activity is associated with a high likelihood of therapeutic success.

therapeutic success

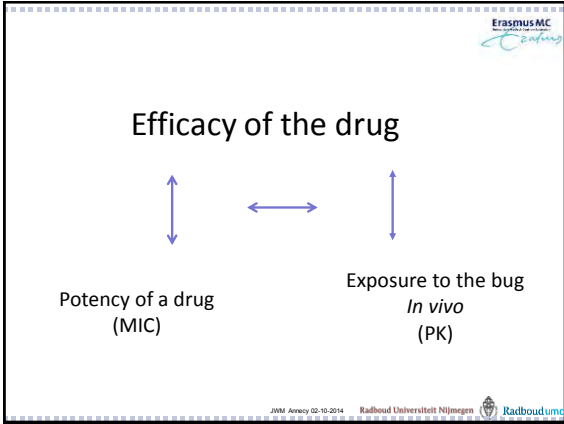
DOSE

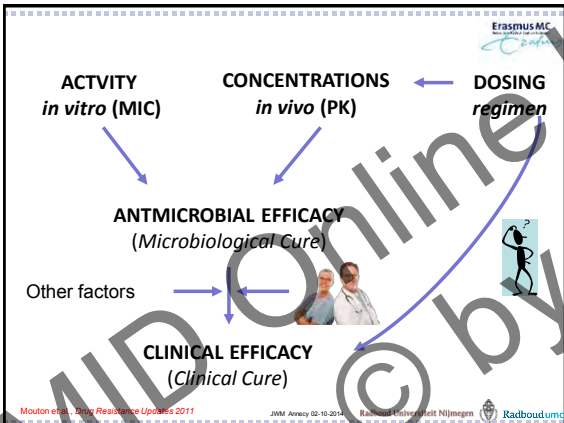
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Dose Finding - The Past

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MIC
Measure of Potency – antibacterial activity

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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Pharmacokinetic parameters :
Measures of Exposure

AUC is usually linearly related to Dose

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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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MIC

Lowest concentration with no visible growth after 18 hour incubation

PK

X-acin 500 mg

.25 .5 1 2 4 8

MIC = 2 mg/L

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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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Pharmacokinetic Parameter (and Dose) MIC

Potency

- EXPOSURE RESPONSE RELATIONSHIP

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

Treatment with fluconazol
Doses 50 – 800 mg

↓

Individual AUC

Culture-results with
MIC-values

↓

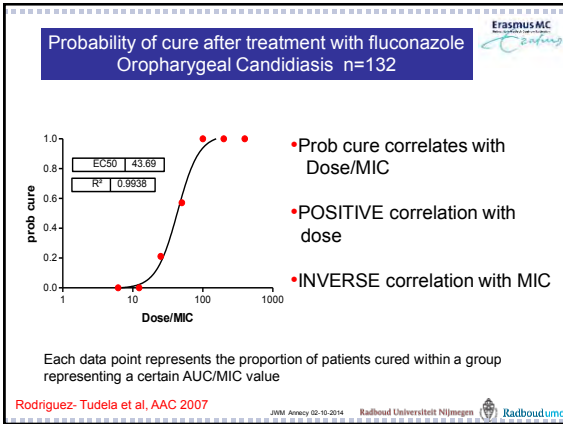
MIC-values per individual

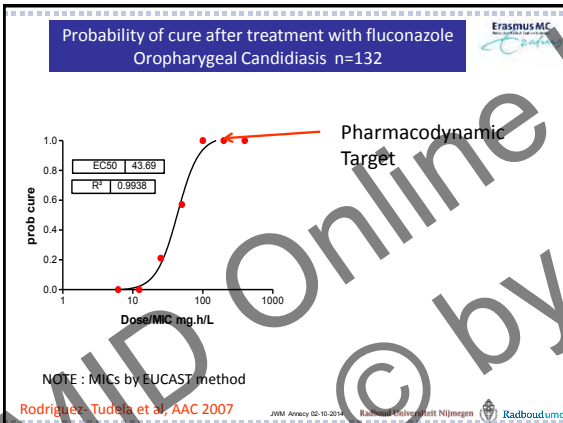
} Determine AUC/MIC for each patient

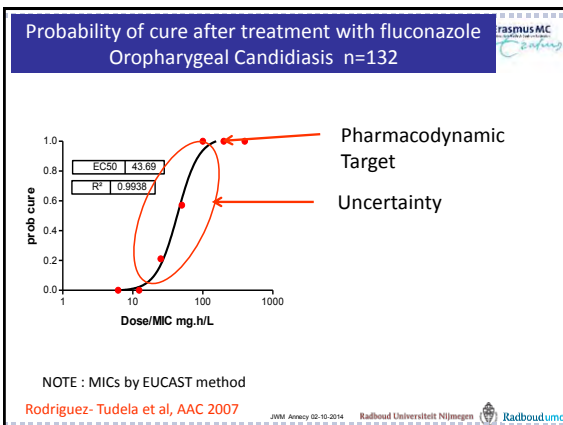
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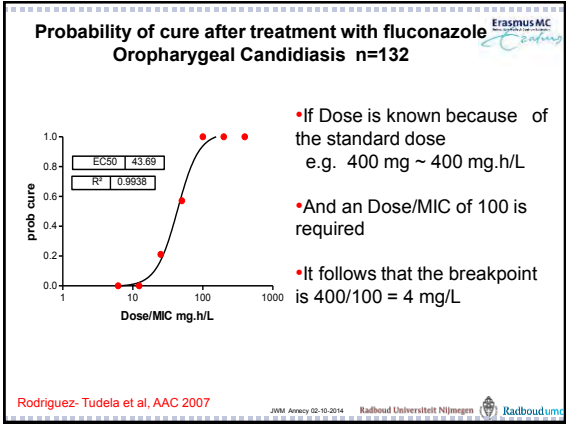
Microbiological outcome (candida cured)
Clinical outcome

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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 intermediate 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)

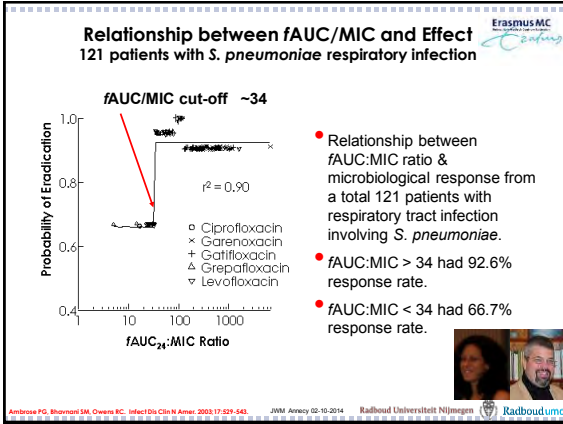
A micro-organism is defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure. A micro-organism is categorized as resistant by applying the appropriate breakpoint in a defined phenotypic test system.

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

LAB REPORT

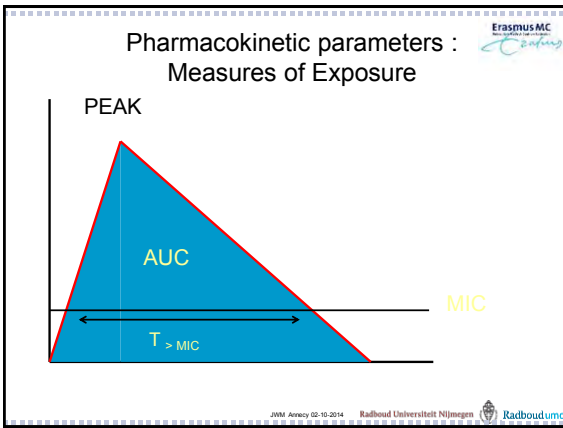
Sensitivity	Organism 1	Escherichia coli
Hoeveetheid	>=10E5 kve/ml	5 Urine Coliform
Panel gevoeligheid amoxicilline/clavula	Sensitive (0.06 mg/l)	Sensitive (0.06 mg/l)
amoxicilline	Sensitive (0.06 mg/l)	Sensitive (0.06 mg/l)
cefuroxim	Sensitive (0.06 mg/l)	Sensitive (0.06 mg/l)
cefotaxim	Sensitive (0.5 mg/l)	Sensitive (0.5 mg/l)
cefazoline	Sensitive (0.25 mg/l)	Sensitive (0.25 mg/l)
ciprofloxacine	Sensitive (<=0.06 mg/l)	Sensitive (1 mg/l)
doxycycline	Sensitive (1 mg/l)	Sensitive (<=32 mg/l)
nitrofurantoin	Sensitive (<=32 mg/l)	Intermediate (1 mg/l)
norfloxacin	Intermediate (1 mg/l)	Sensitive (<=64 mg/l)
sulfamethoxazol	Sensitive (<=64 mg/l)	Intermediate (0.25 mg/l)
tobramycine	Intermediate (0.25 mg/l)	Resistant (>64 mg/l)
trihexoprim	Resistant (>64 mg/l)	Sensitive (1 mg/l)
cotrimoxazole	Sensitive (1 mg/l)	Sensitive (0.13 mg/l)
cefazidim	Sensitive (0.13 mg/l)	

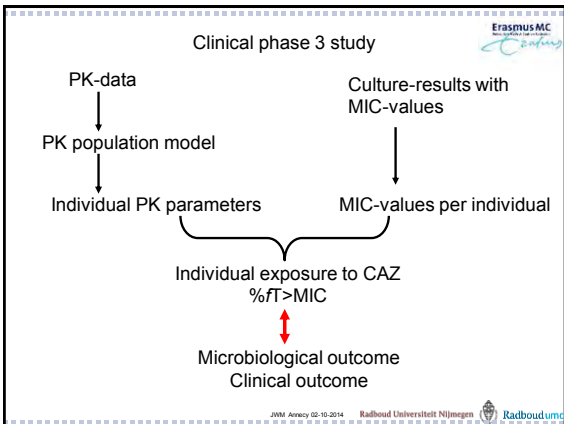
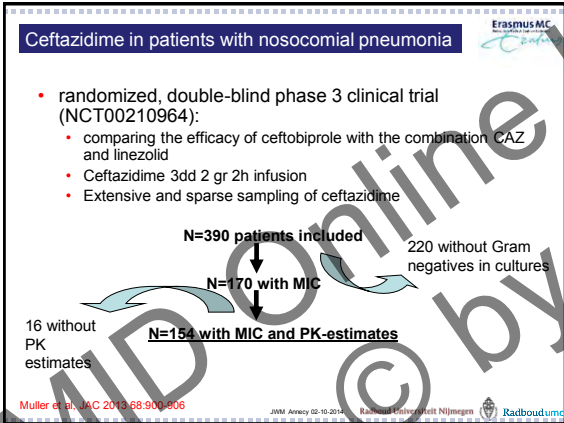
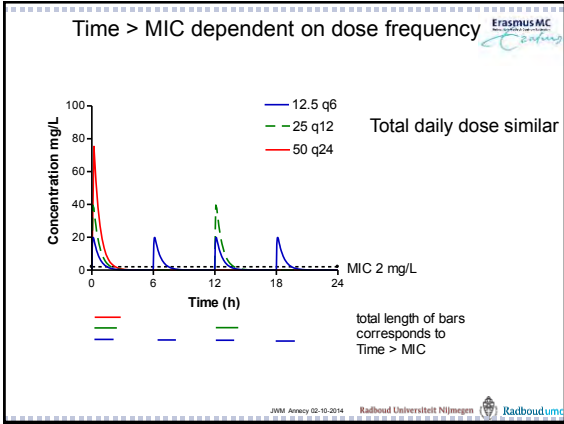
- Provides Clinician/Consultant guidelines how to optimally treat a patient (Freely translated from EUCAST guideline)

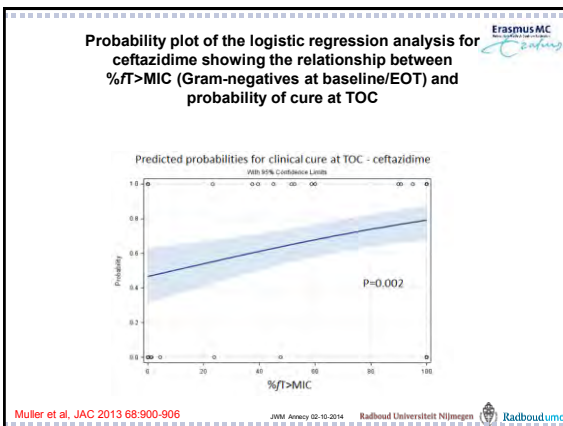
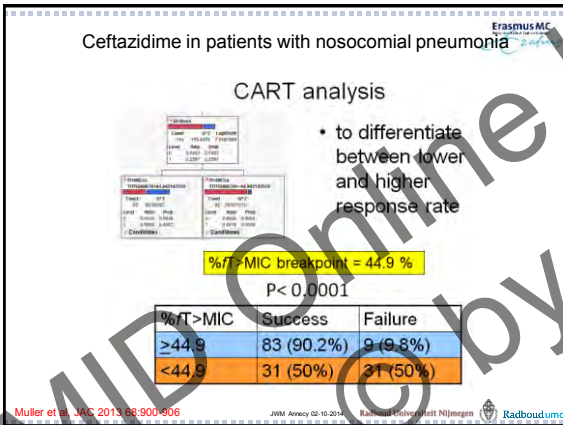
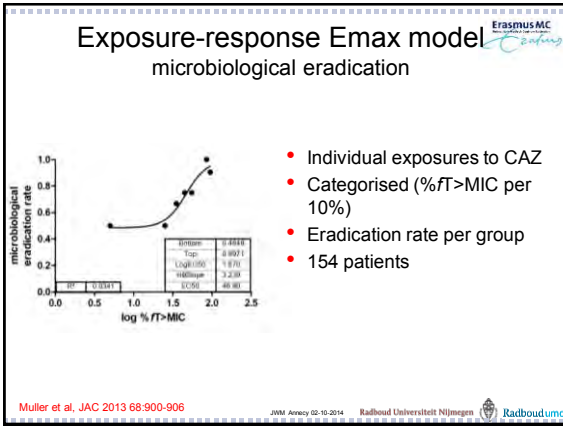


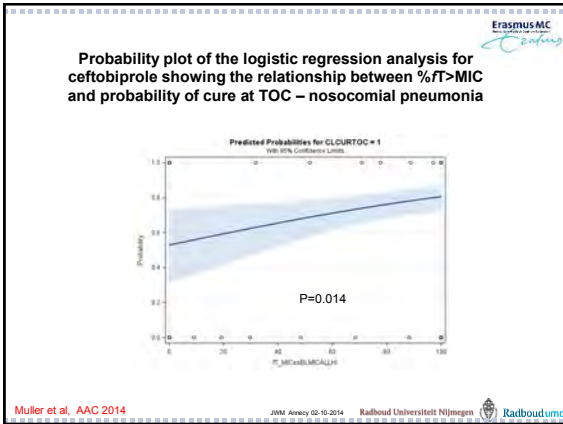
Are All Antimicrobials Created Equal???

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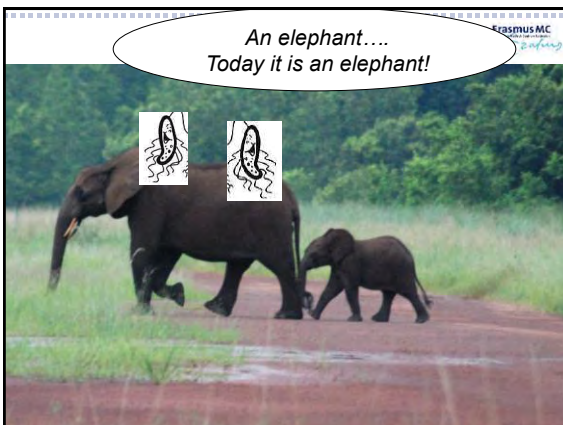












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THE TARGET IS THE MICRO-ORGANISM

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Neutropenic Mouse Thigh-Infection Model

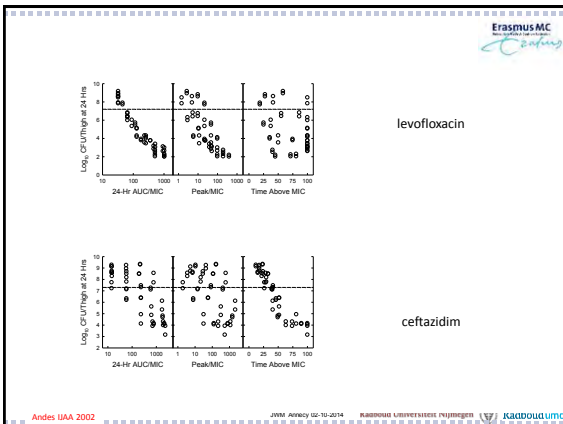
1. Neutropenia induced by 2 injections of cyclophosphamide on days -4 and -1

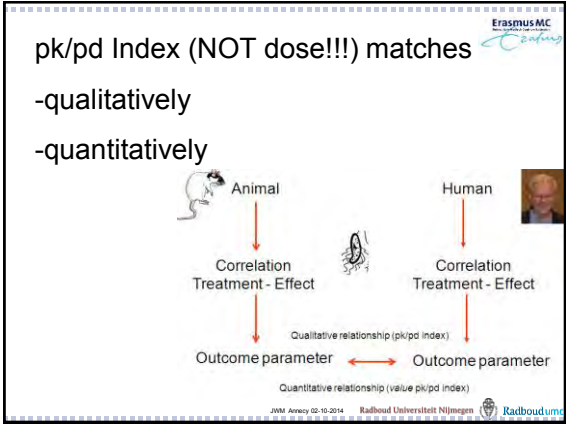
2. Bacteria injected into thighs on day 0 (10^6)

3. Treatment (usually given SQ) started 2 hr after infection and continued for 1-5 days

4. Thighs removed, homogenized, serially diluted and plated for CFU determinations

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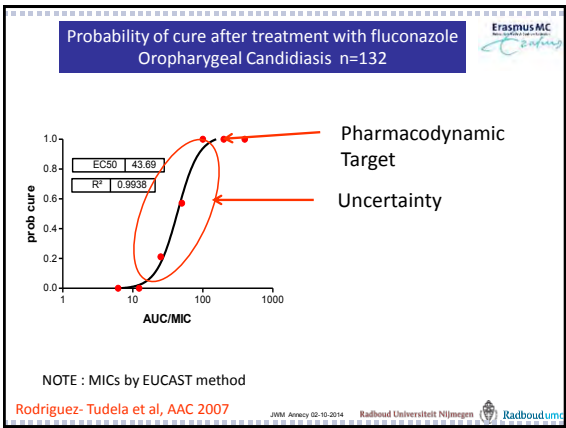




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T>MIC	AUC
Penicillins	Aminoglycosides
Cephalosporins	Fluoroquinolones
Carbapenems	Metronidazole
Monobactams	Lipopeptides
Tribactams	Ketolides
	Macrolides
	Clindamycin
	Streptogramins
	Glycopeptides
	Glycylcyclines
	Oxazolidinones
	Tetracyclines
	Azoles

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LAB REPORT

Sensitivity

Organism 1

Escherichia coli

Hoeveelheid >=1.0E5 kve/ml

Panel gevoeligheid 5 Urine Coliform

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norfloxacin Intermediate (1 mg/l)

sulfamethoxazol Sensitive (>=64 mg/l)

tobramycine Intermediate (0.25 mg/l)

trimehoprim 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)

BASED ON EXPOSURES OF COMMON DOSES

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BASED ON EXPOSURES OF COMMON DOSES

IN ADULTS - < 50 Y (mostly)

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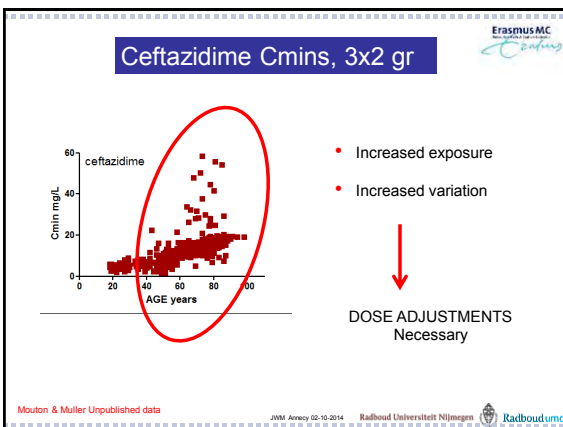
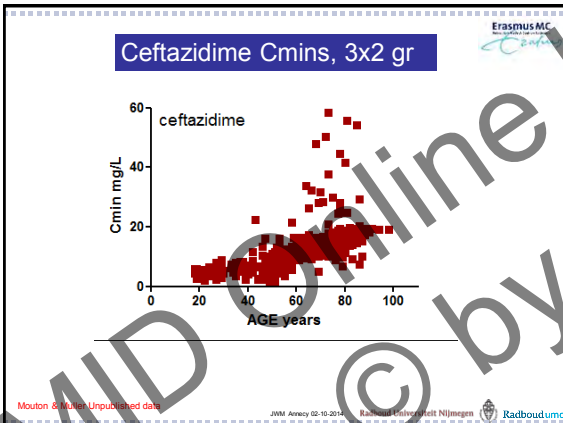
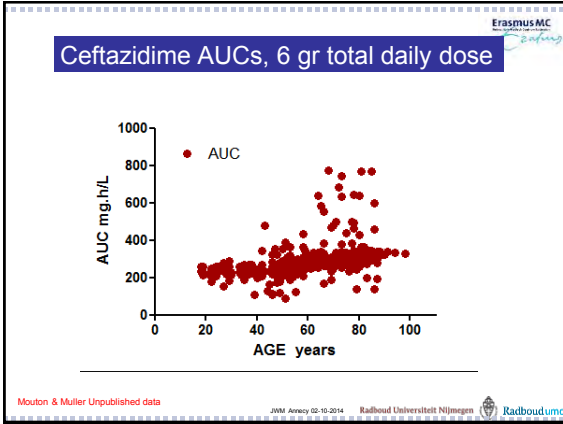
EXPOSURES IN Elderly?

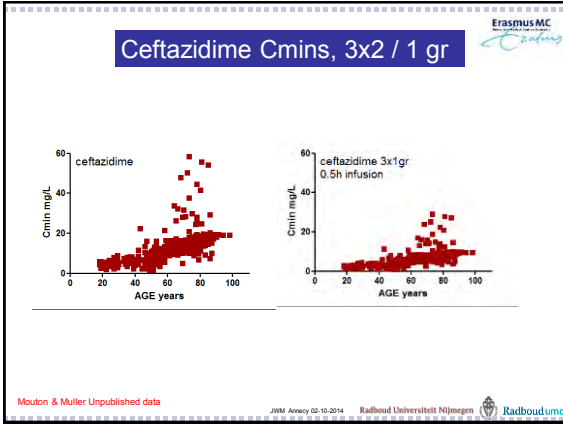
Consequences for dosing?

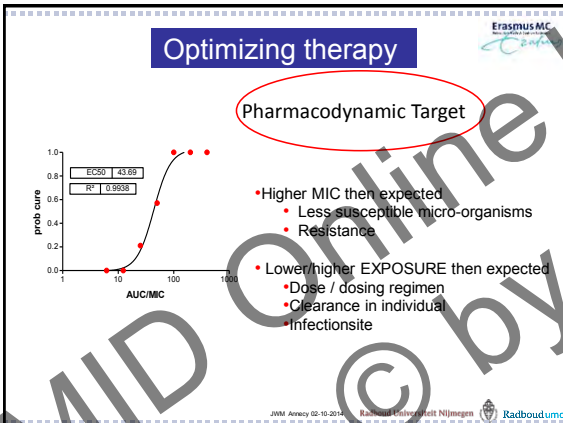
Overdosing?

Underdosing?

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So what can we conclude from all this?

- Pharmacodynamic targets have been described for many antimicrobials
- Clinical breakpoints are based on exposures in adults – but not the elderly!
- Exposures in the elderly show more variation
- Exposures in special populations need to be determined and dosing adjusted where applicable – if at all possible

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