Nijmegen Institute for Infection, Inflammation & Immunity

Individualised therapy in ICU patients beta-lactam agents

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EPASG/ISAP Workshop 2013

When is Individualized Therapy Useful?

- If the target of therapy is known
  - Mode of administration
  - peak, trough, steady state
- Good correlation between target and effect
- (Adjustments can easily – and reliably - be made)

Trauma Patient

- 21 years old
- Hit a tree
- On the ICU since three days
- Suspicion of VAP
- No significant culture results at this moment
- Treatment with BSC is started

- Ceftazidime is started by continuous infusion, 3 gram/day. The reasons for CI are :

  it has been demonstrated to be more efficaceous?

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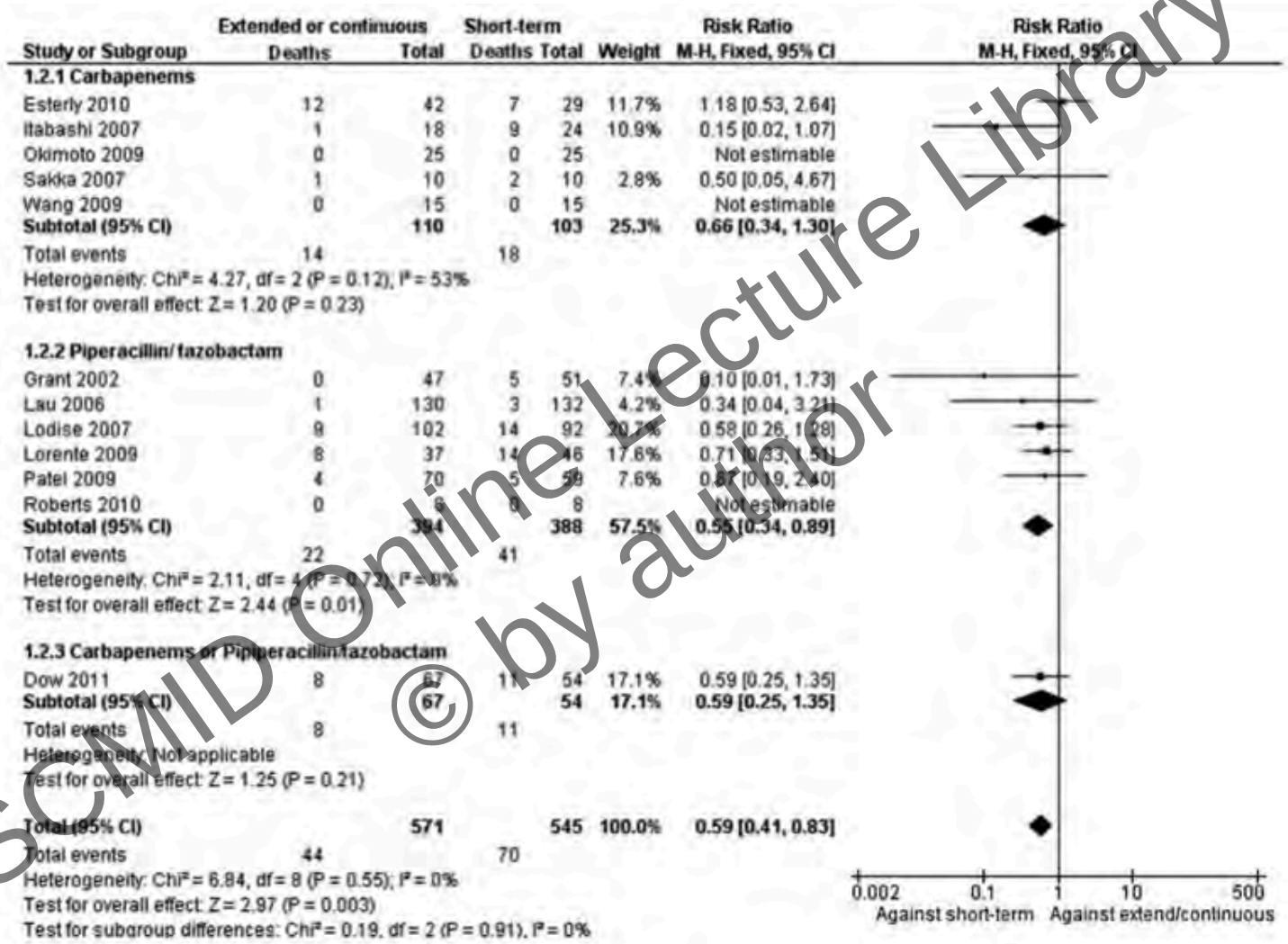


Figure 3. Forest plot depicting the risk ratios of mortality of patients receiving extended or continuous versus short-term infusion of carbapenems and piperacillin/tazobactam, stratified by the administered antibiotics. Vertical line, "no difference" point between the 2 regimens; squares, risk ratios; diamonds, pooled risk ratios; horizontal lines, 95% confidence interval. Abbreviation: CI, confidence interval.

Falagas et al CID 2013

Endpoint	Intervention Group	Control Group	*P*
Plasma antibiotic concentration >MIC	18 (81.8%)[a]	6 (28.6%)[a]	.001
Clinical cure (test of cure date)	23 (76.7%)	15 (50.0%)	.032
Clinical cure (test of cure date with treatment exclusions)	21 (70.0%)	13 (43.3%)	.037
Clinical cure (last day of blinding)	9 (30.0%)	6 (20.0%)	.37
Time to clinical resolution (days)	11 (6.75–24.25)[b]	16.5 (7–28)[b]	.14
Time to resolution of CRP (days)	6 (2.5–22.5)[c]	5 (3–27)[c]	.79
ICU length of stay (postrandomization)	7.5 (4–12)	9 (5–14.25)	.50
ICU-free days			
All	19.5 (12.75–24)	17 (.75–22)	.14
ICU survivors	20.5 (16–24)[d]	18 (12.75–22)[d]	.22
ICU survival	28 (93.3%)	26 (86.7%)	.67
Hospital survival	27 (90.0%)	24 (80.0%)	.47

Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; MIC, minimum inhibitory concentration.

[a] Plasma samples were available for 22 and 21 patients in the intervention and control groups, respectively (subgroup analysis).

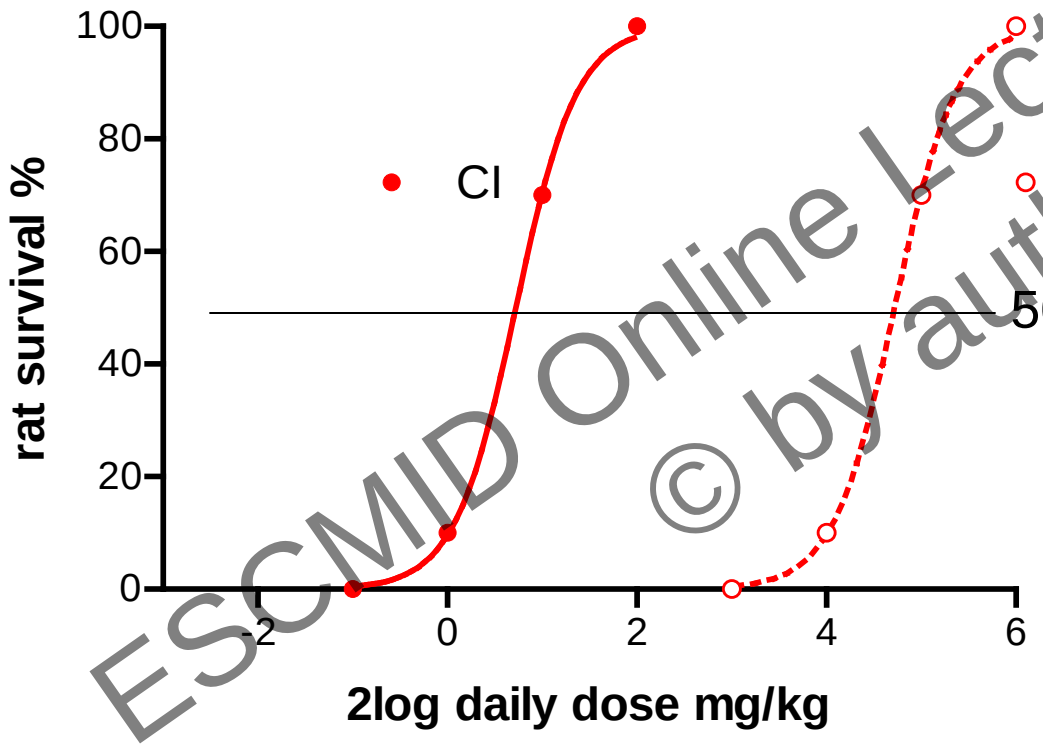
[b] Time to clinical resolution was set at 28 d for 7 and 13 patients in the intervention and control groups, respectively, as clinical resolution did not occur during this period.

[c] Postrandomization CRP levels were available for 25 and 24 patients in the intervention and control groups, respectively (subgroup analysis); time to resolution of CRP was set at 28 d for 6 patients in each group as CRP was not measured below 100 mg/L during this period.

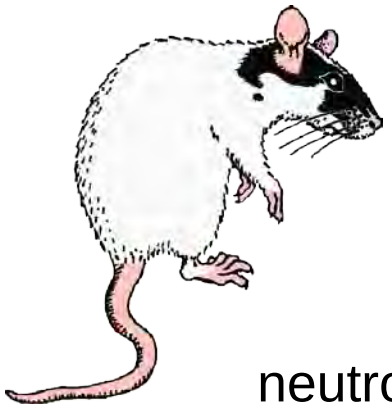
[d] Subgroup analysis (28 and 26 patients in intervention and control groups, respectively).

Dulhunty et al, CID 2013

Rat survival :
4 days Continuous Infusion vs Q6h



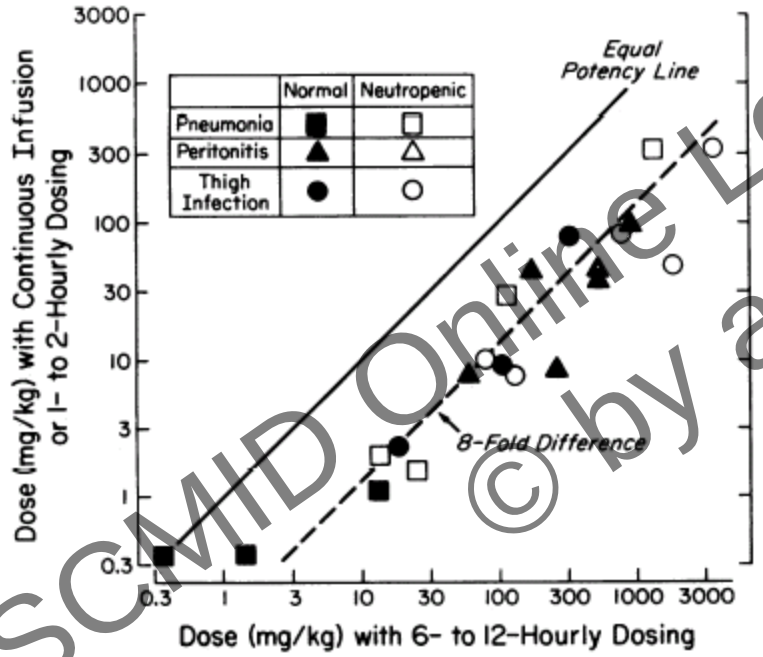
Regimen	PD50 mg/kg
CI	1.52
Q6h	24.37



neutropenic

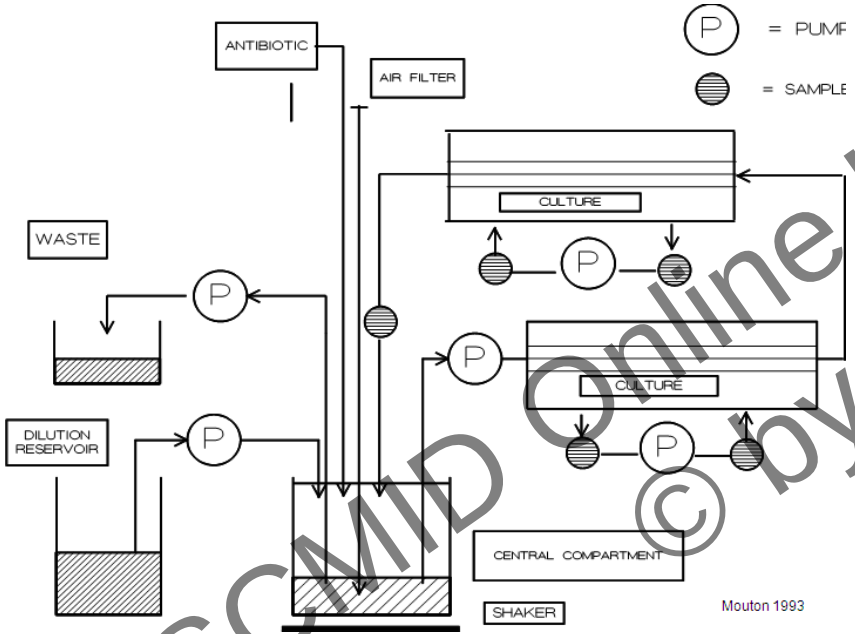
Adapted from Roosendaal AAC 1986

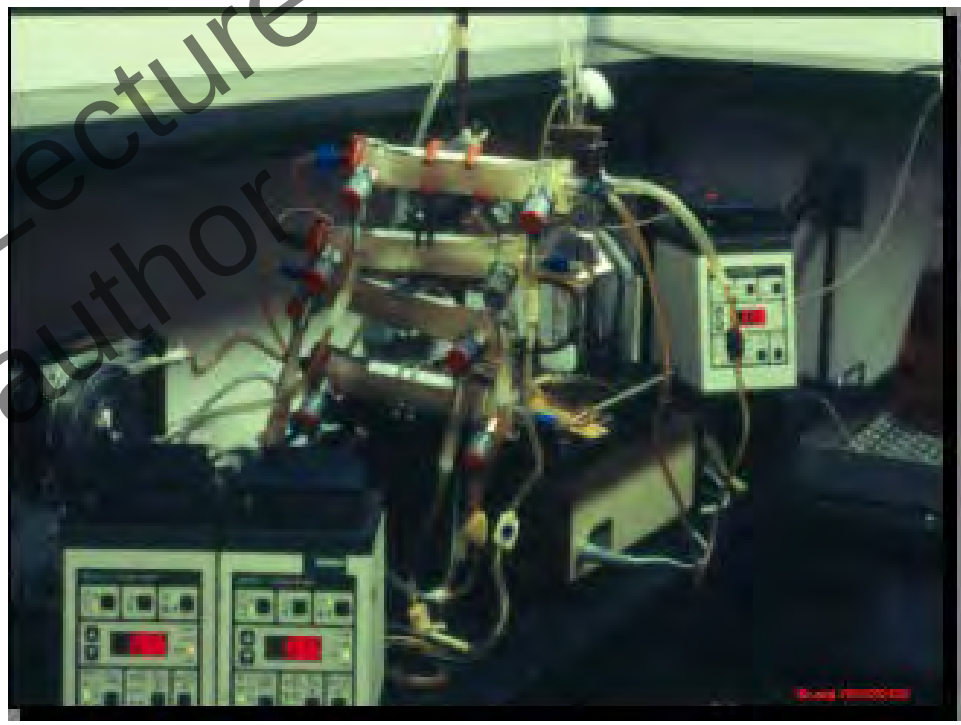
Effect of longer vs shorter intervals or CI in animals



- Effect of larger dosing intervals vs CI or q1 or 2h
- 8 fold difference in potency

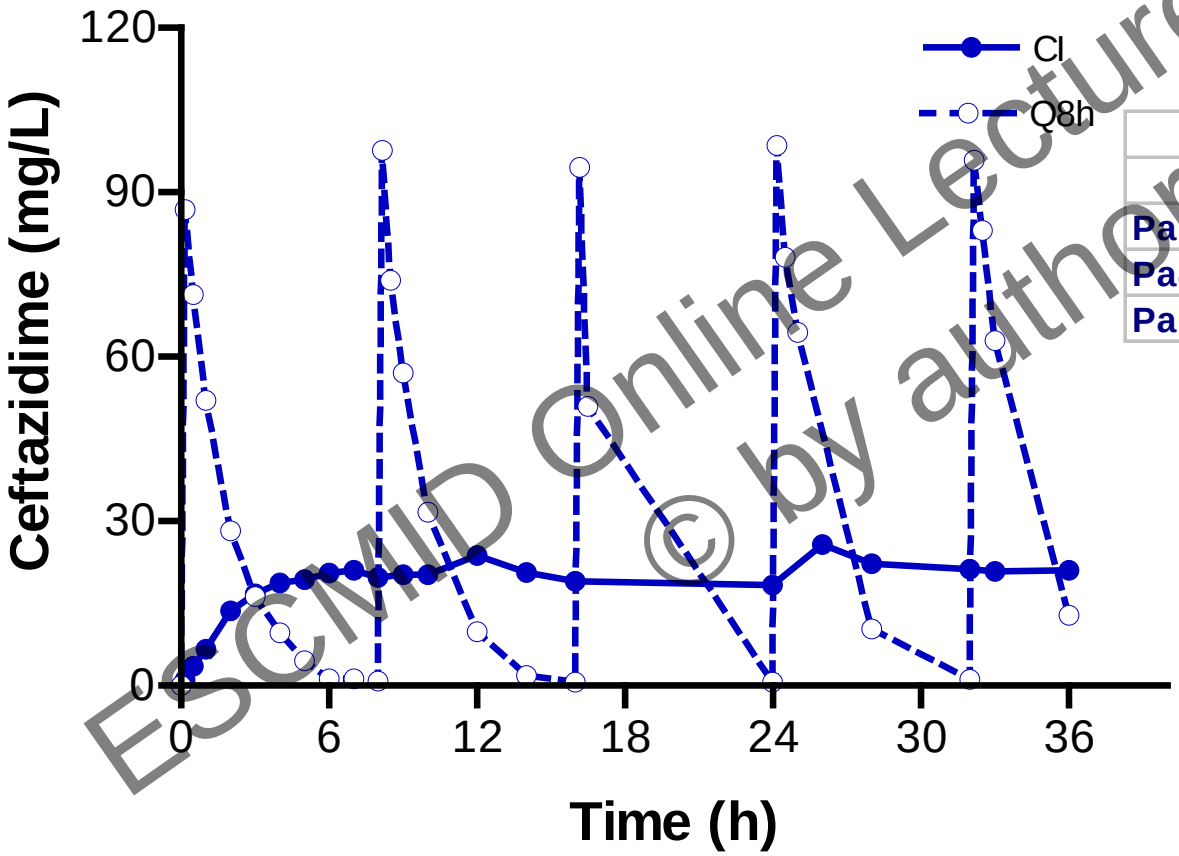
Craig and Ebert AAC 1992





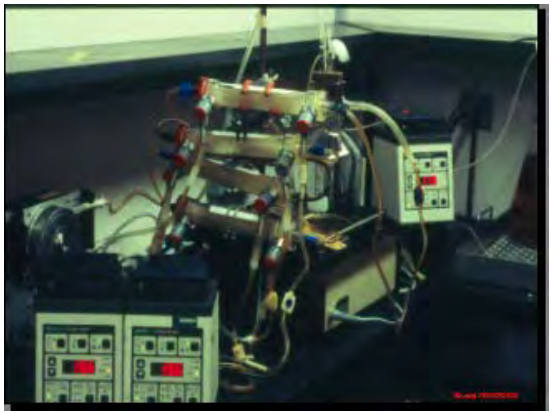
Mouton & den Hollander AAC 1995

CI vs Q8h in an IVPM
P. aeruginosa



	dcfu		
	CI	Q8h	Diff
Pa1	-2.9	-0.7	2.2*
Pa4	-3.9	-1.1	2.8*
Pa16	3.2	2.9	-0.3

* p<0.05



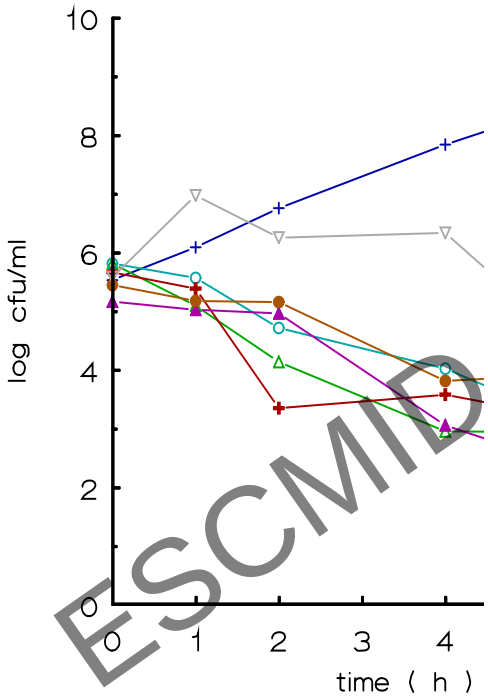
Mouton et al, AAC 1995, 97

UMC St Radboud

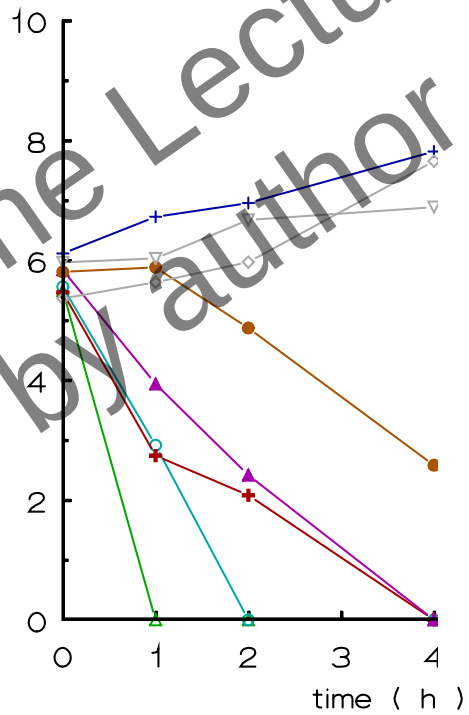
Why is continuous infusion useful?

Patterns of activity:
Kill curves of P. aeruginosa

ceftazidime



tobramycin

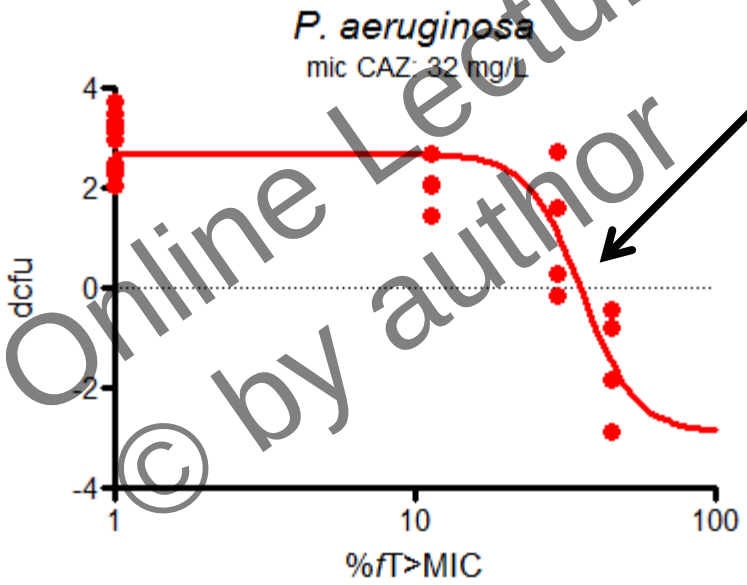


Mouton JW Thesis 1993

UMC St Radboud

Mouse model of infection (thigh)

Static %*f*T>MIC 39.1 %



Predicted *f*T>MIC needed for in vivo static effect -- Mice

	Mouse[1]	
regimen	mg/kg	%fT>MIC
q2	2.12	37.3
q3	4.60	38.1
q4	9.29	37.6
q6	35.6	36.5
q8	129.7	35.7
q12	-	-

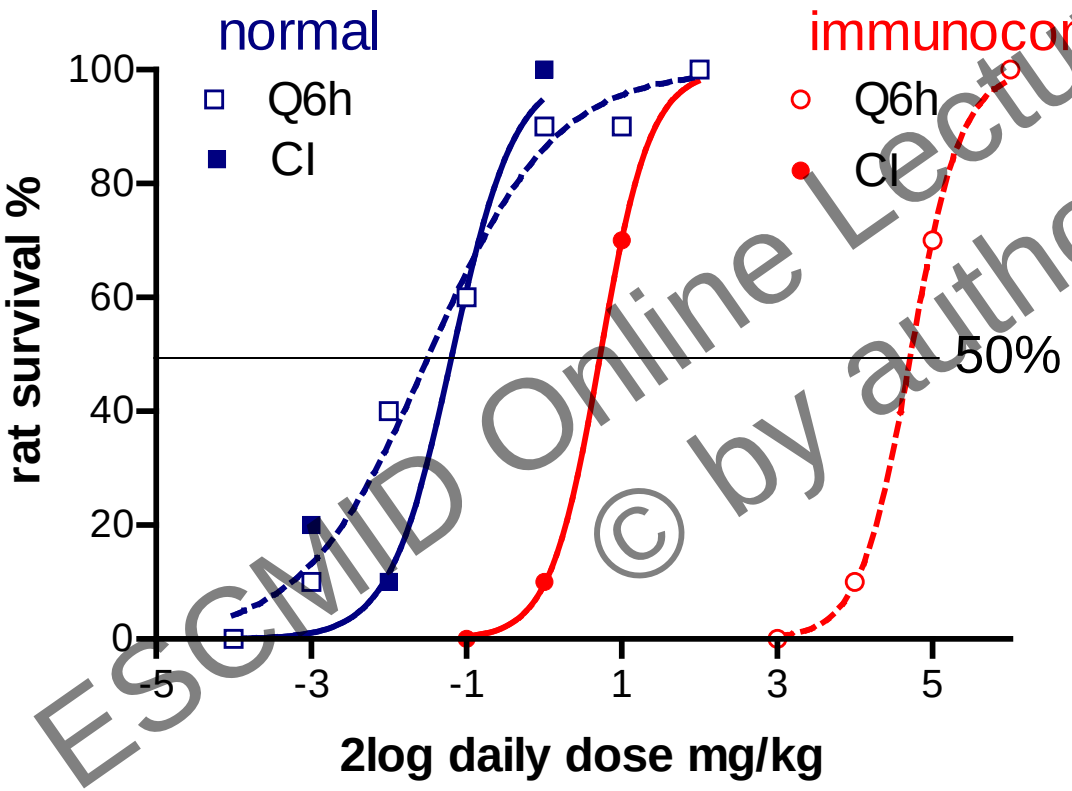
MIC = 1 mg/L

Mouton et al AAC 2007

Pharmacodynamics of beta-lactams

- ~40 % *f*T>MIC results in a static effect
- This can be explained by the characteristics of the drug
- For most (non-severe) infections, this is probably enough because of the presence of the immune system

Rat survival :
4 days Continuous Infusion vs Q6h

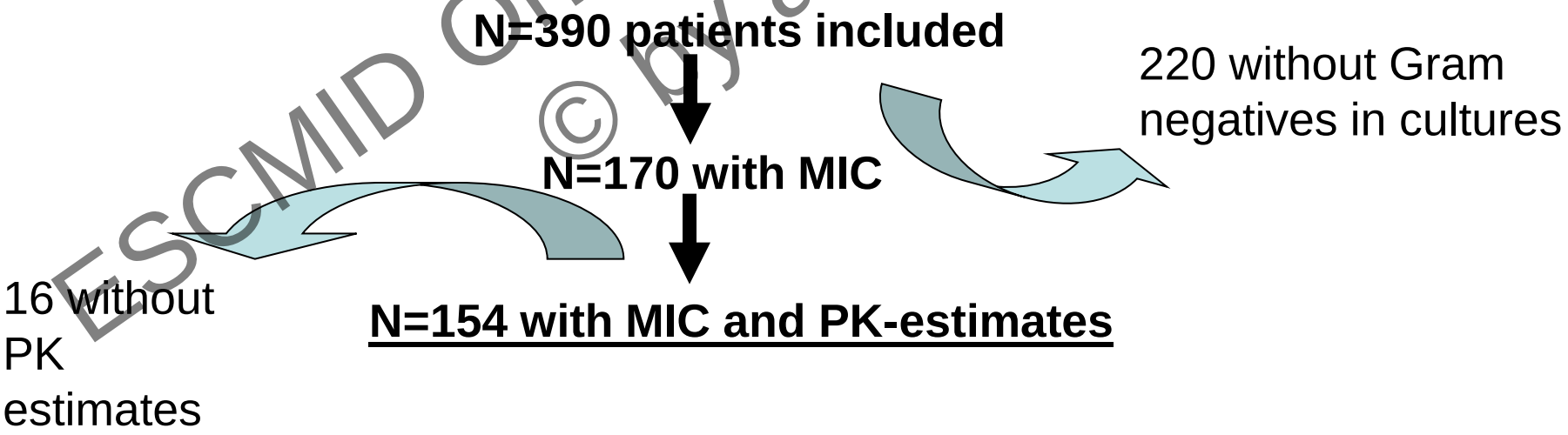


Regimen	PD50 mg/kg
CI	0.36
Q6h	0.35
CI	1.52
Q6h	24.37

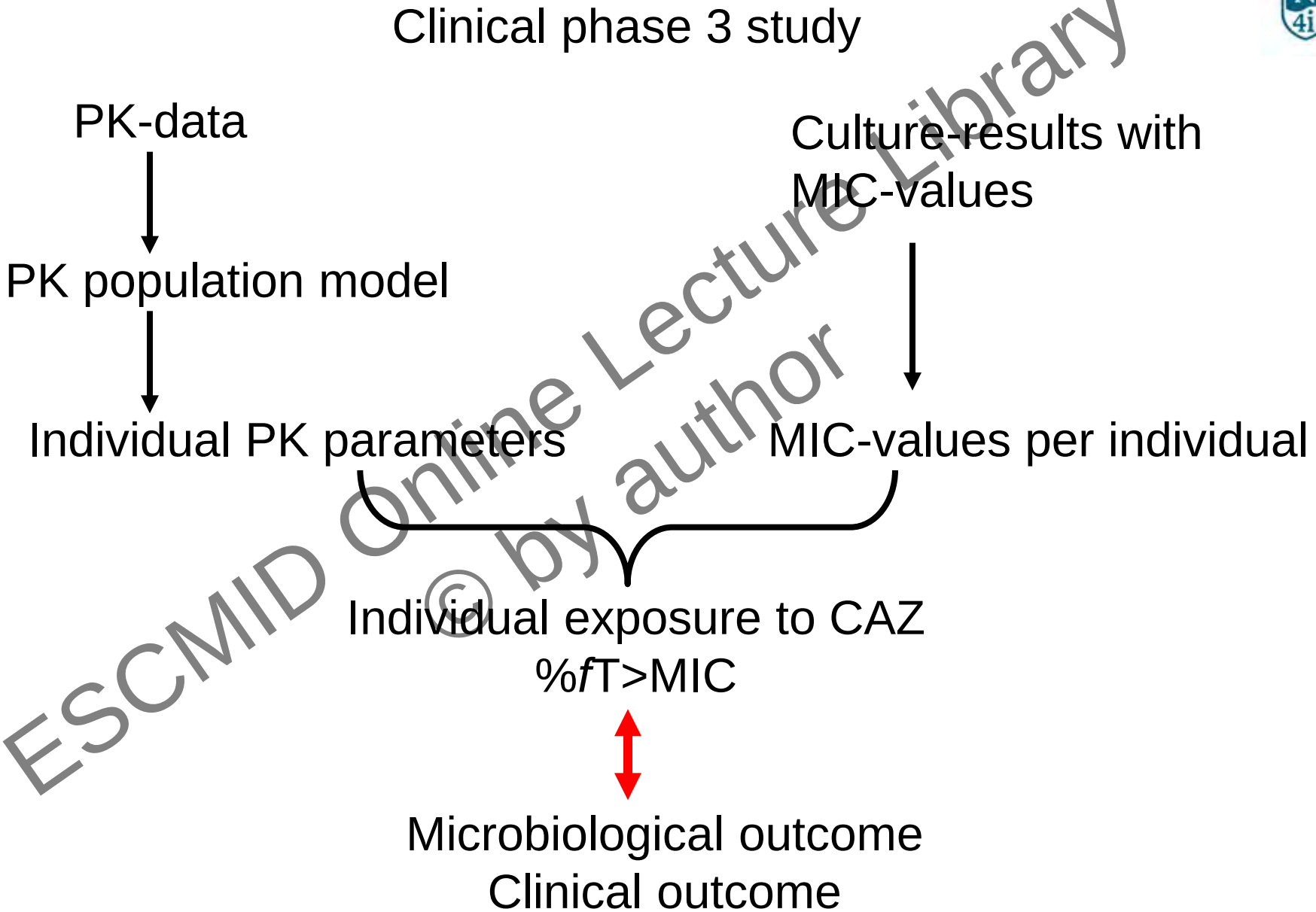
Adapted from Roosendaal AAC 1986

Ceftazidime in patients with nosocomial pneumonia

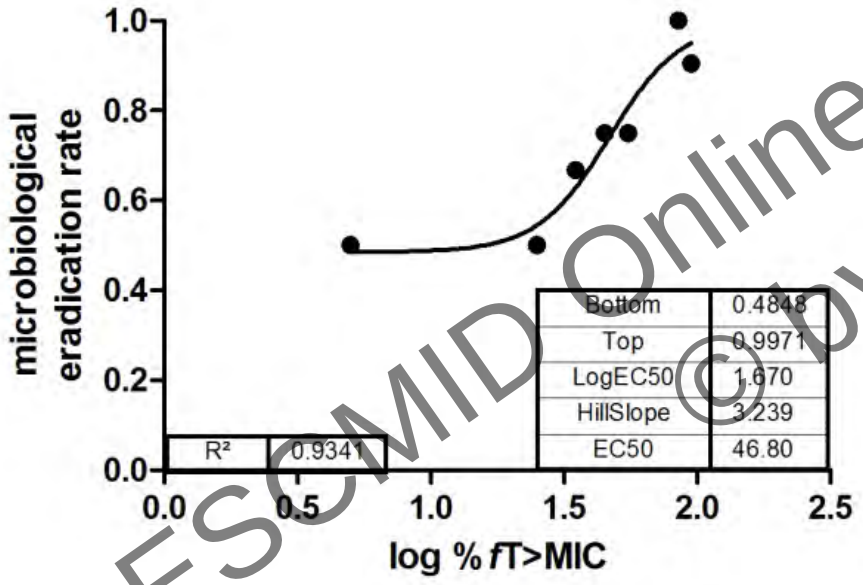
- randomized, double-blind phase 3 clinical trial (NCT00210964):
  - comparing the efficacy of ceftobiprole with the combination CAZ and linezolid
  - Ceftazidime 3dd 2 gr 2h infusion
  - Extensive and sparse sampling of ceftazidime



Muller et al, JAC 2013 68:900-906



Exposure-response Emax model

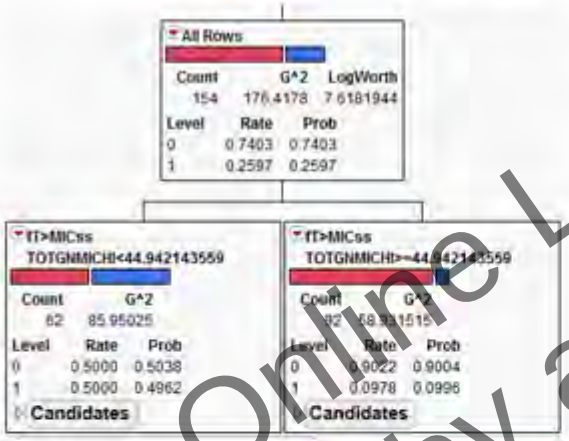


- Individual exposures to CAZ
- Categorised (%*f*T>MIC per 10%)
- Eradication rate per group
- 154 patients

Muller et al, JAC 2013 68:900-906

Ceftazidime in patients with nosocomial pneumonia

CART analysis



- to differentiate between lower and higher response rate

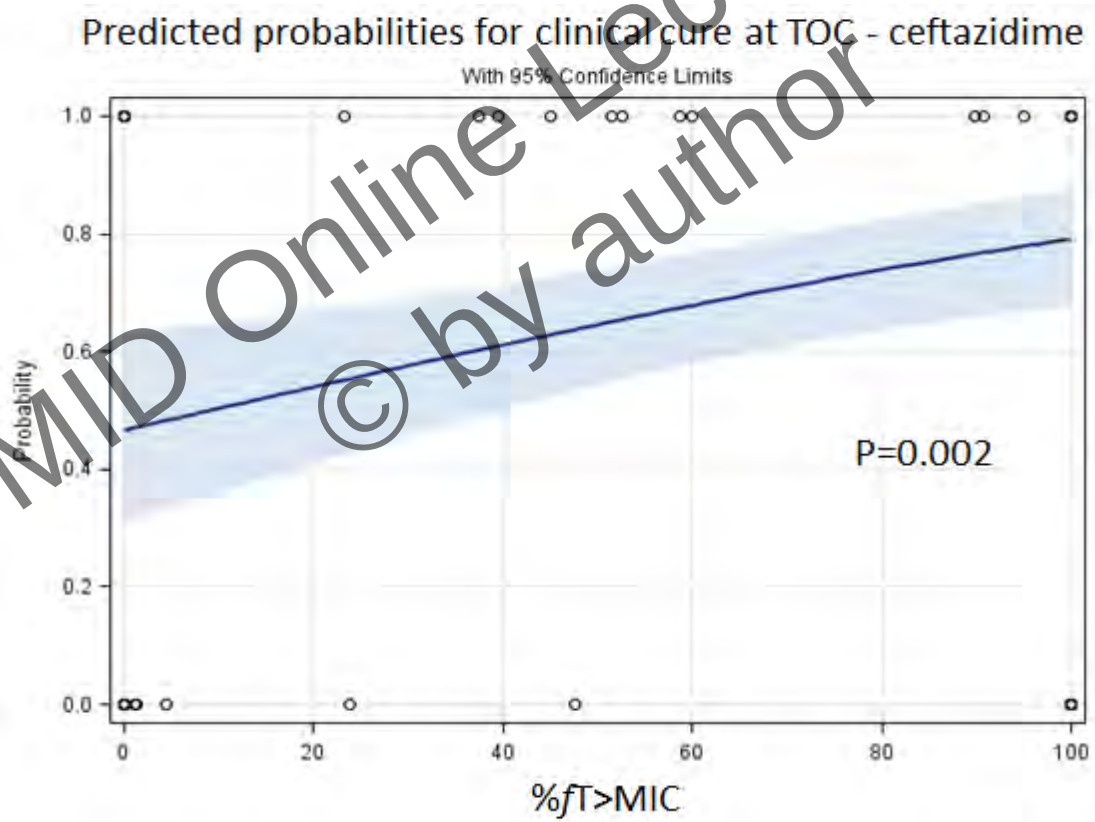
%*f*T>MIC breakpoint = 44.9 %

P< 0.0001

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

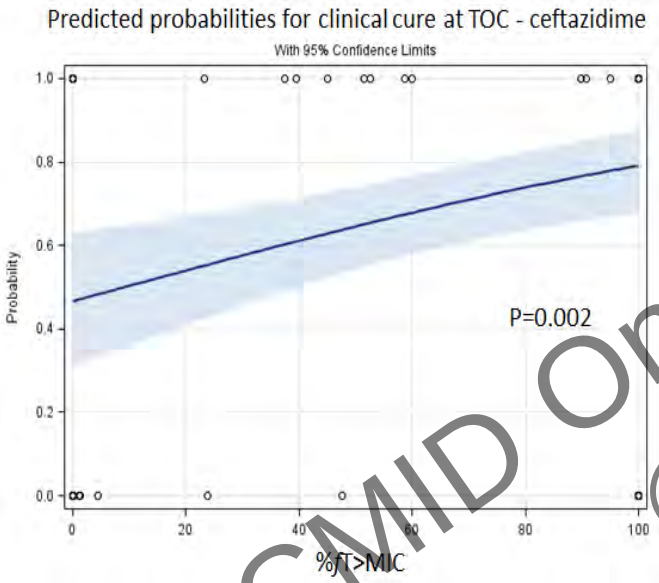
Muller et al, JAC 2013 68:900-906

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



Muller et al, JAC 2013 68:900-906

What does this tell us?



- Probability of cure increases if %*f*T>MIC increases

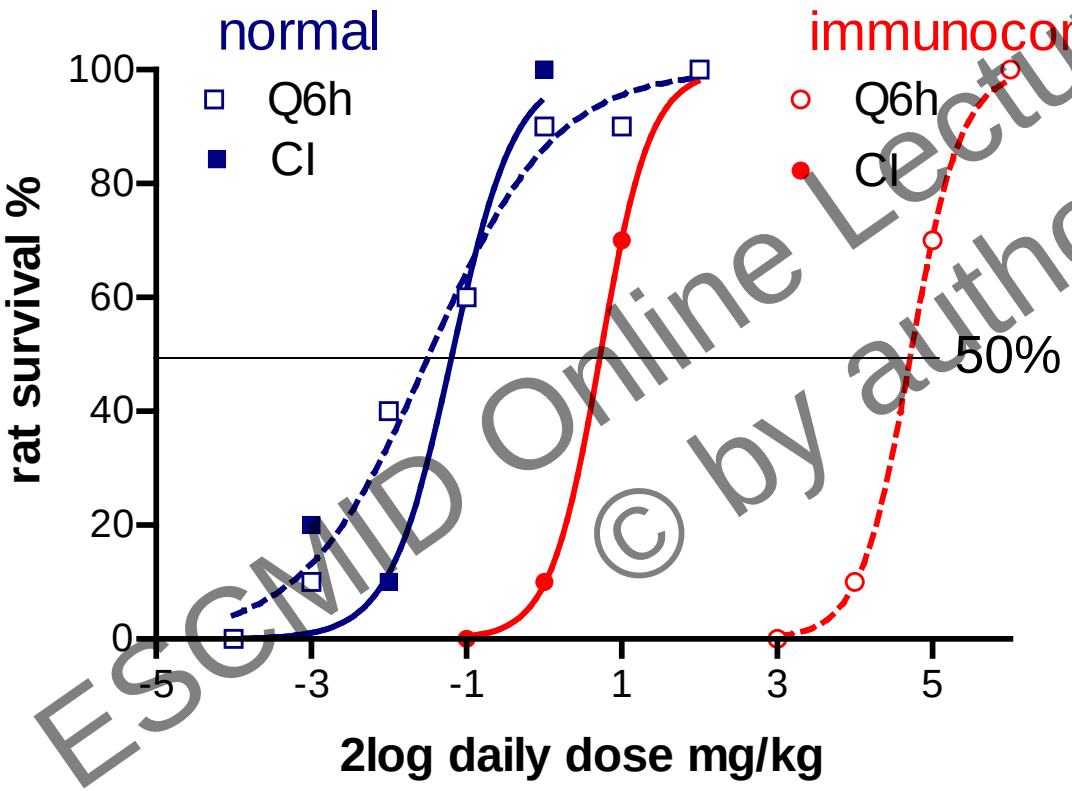
↓

- Increase %*f*T>MIC !

→ extended infusion

→ continuous infusion

Rat survival :
4 days Continuous Infusion vs Q6h



Regimen	PD50 mg/kg
CI	0.36
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Continuous Infusion
The ADDITIONAL EFFECT

- Theoretically , >4 x MIC would be optimal
  - More killing – absence of immune system
  - *EARLIER EFFECT - not measured in models*
  - *Is 24 h an adequate time to measure effect?*

So what are the arguments to use continuous infusion clinically?

- Pd arguments:
- Low maximum kill rate, small difference min and max kill
- Animal studies showing CI > II
- IVPM studies showing CI > II
- Anecdotal reports
- Cheaper!!
- Immunocompromised patients?
- ICU?
- Hometherapy?
- But…… Resistance issues not resolved

When is Individualized Therapy Useful?

- If the target of therapy is known
  - Mode of administration
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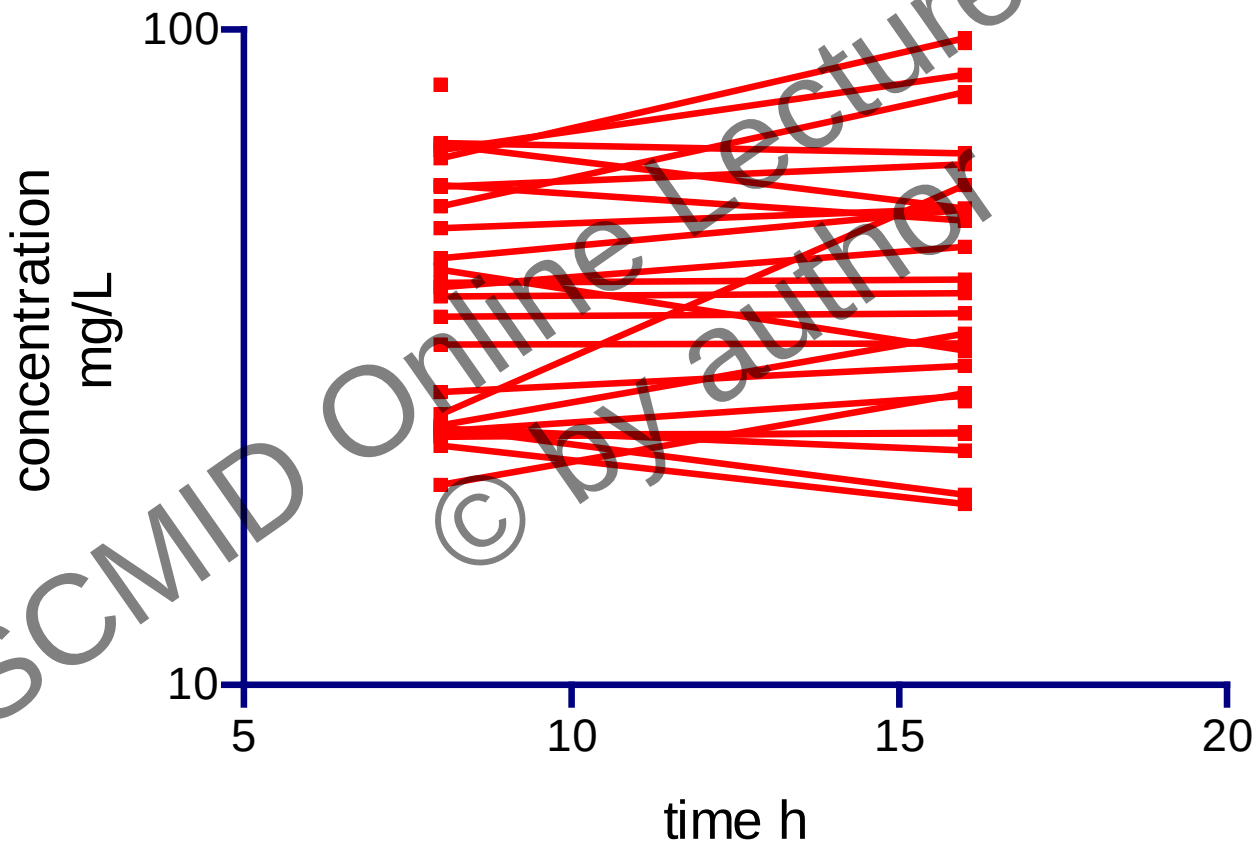
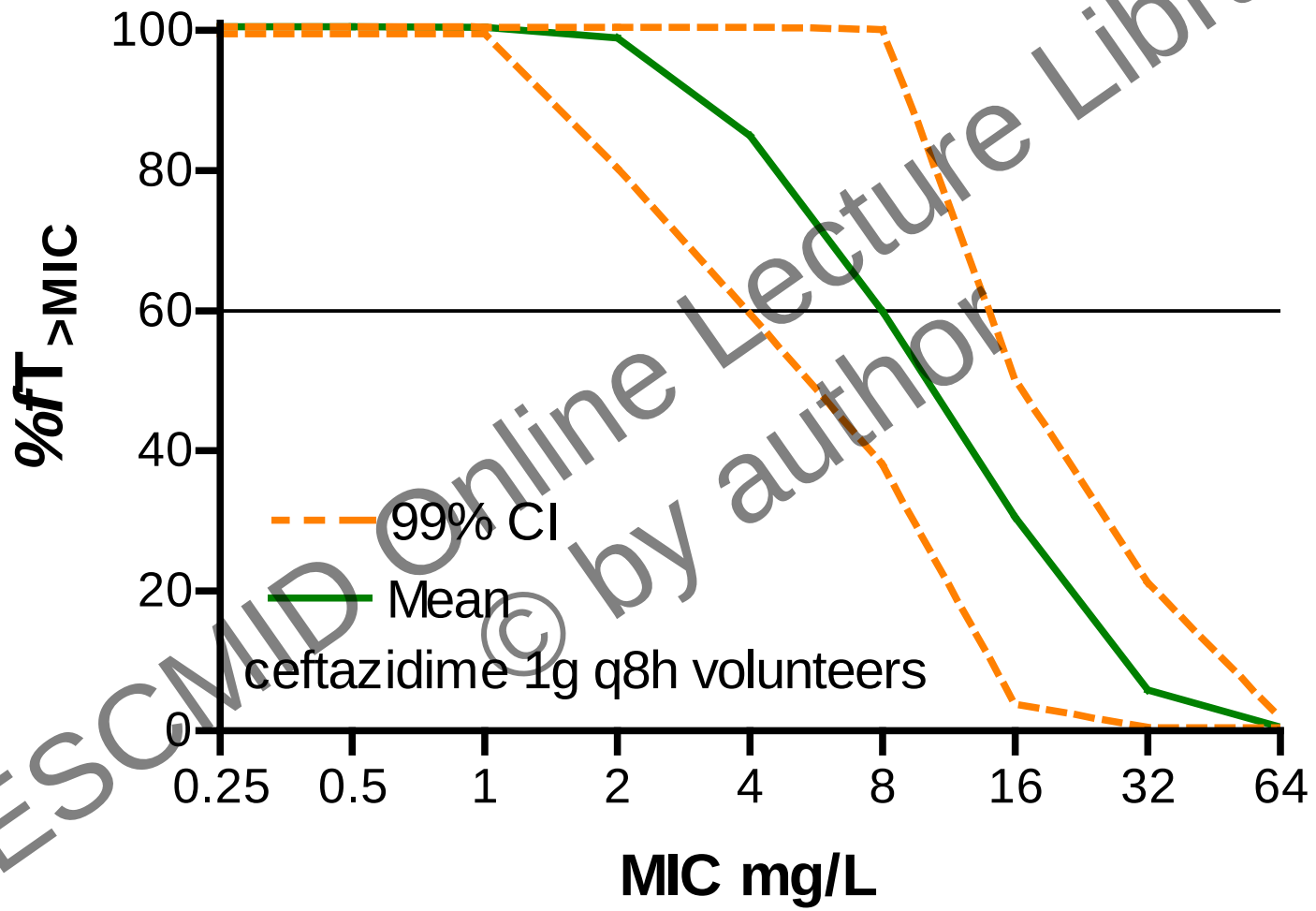
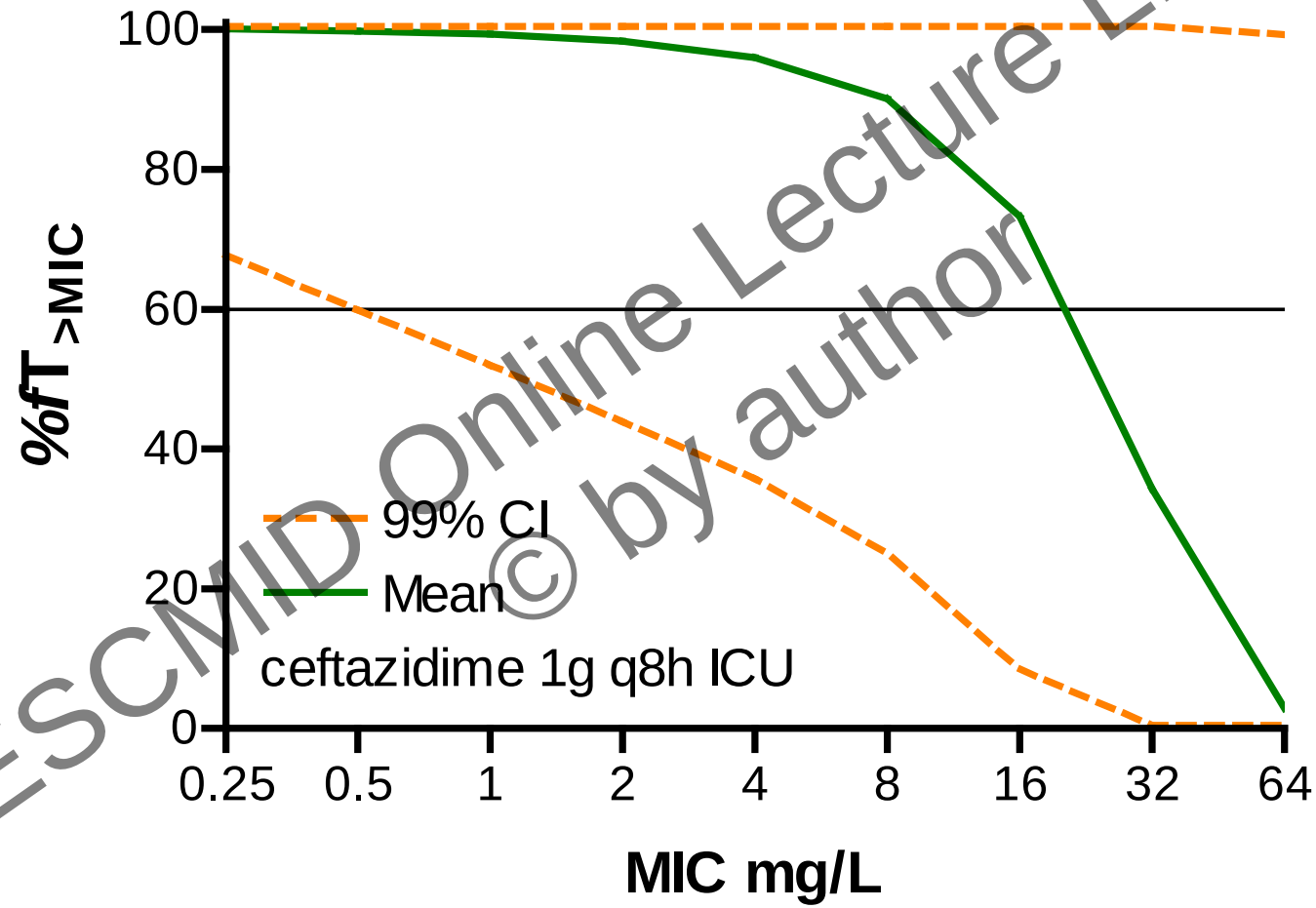
What is required to optimally dose in ICU patients?

Ceftazidim in ICU patients : observed variability

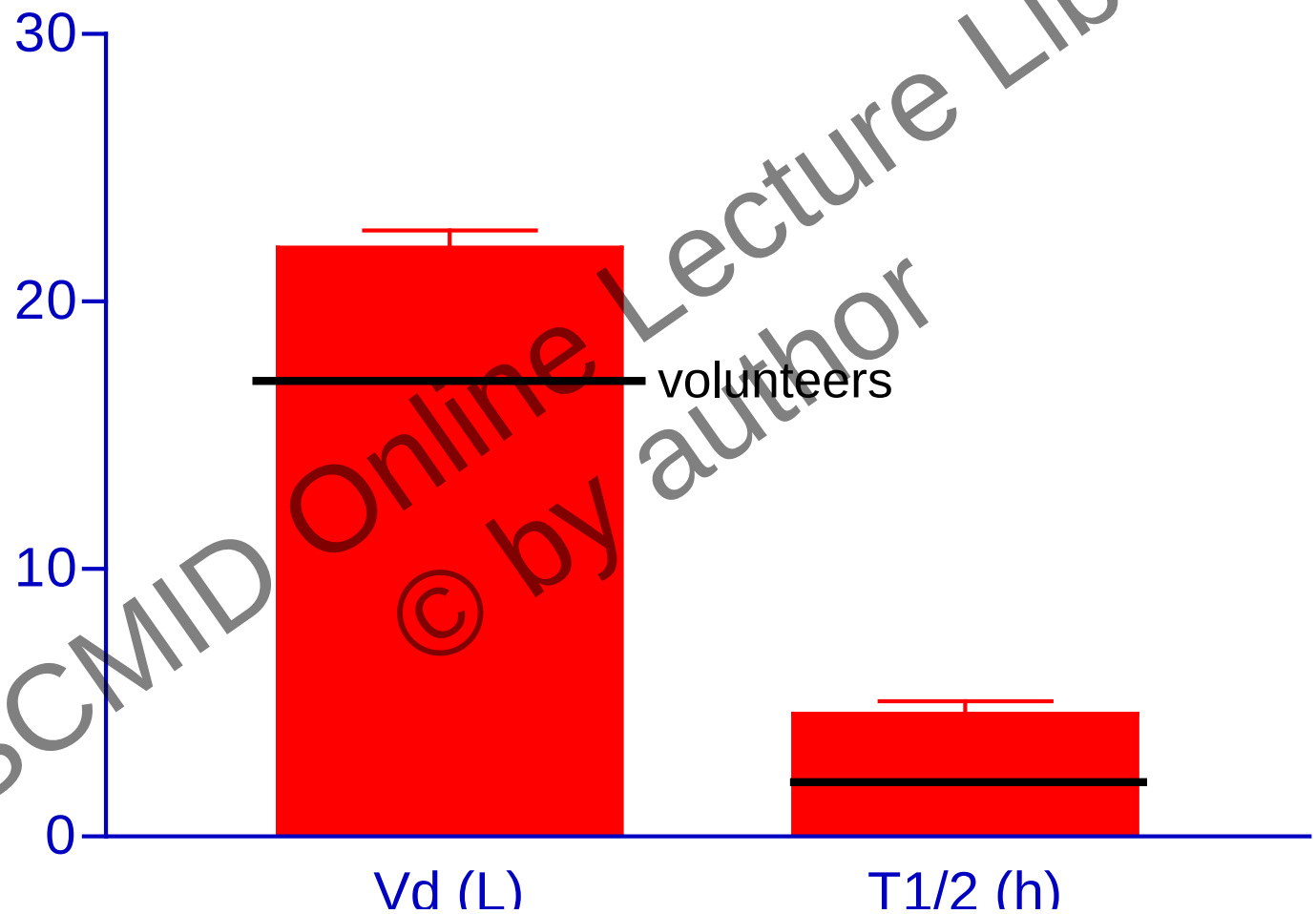




Mouton et al, Clin Ther 2005 27:762

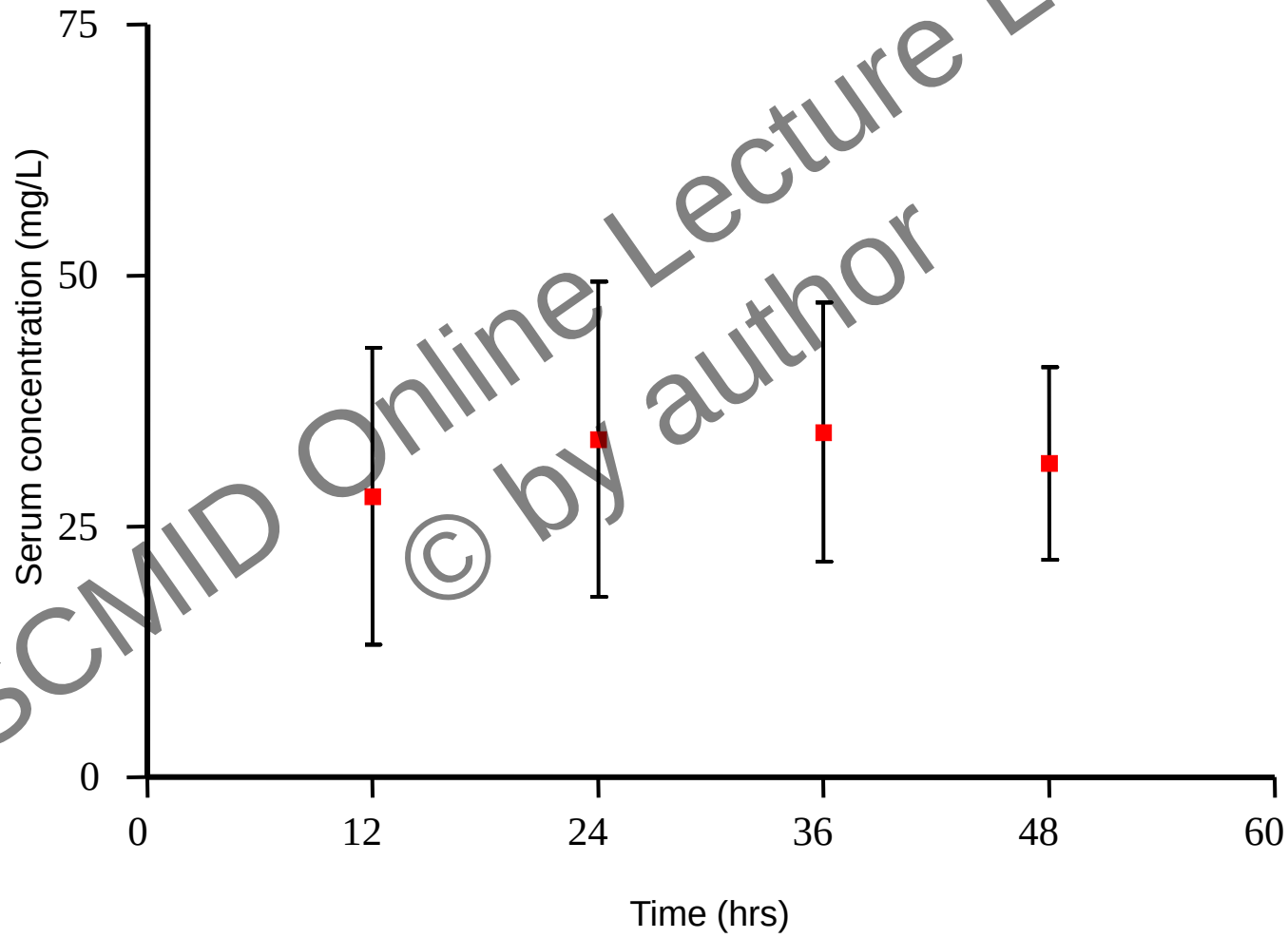


ICU patients, Vd and T1/2



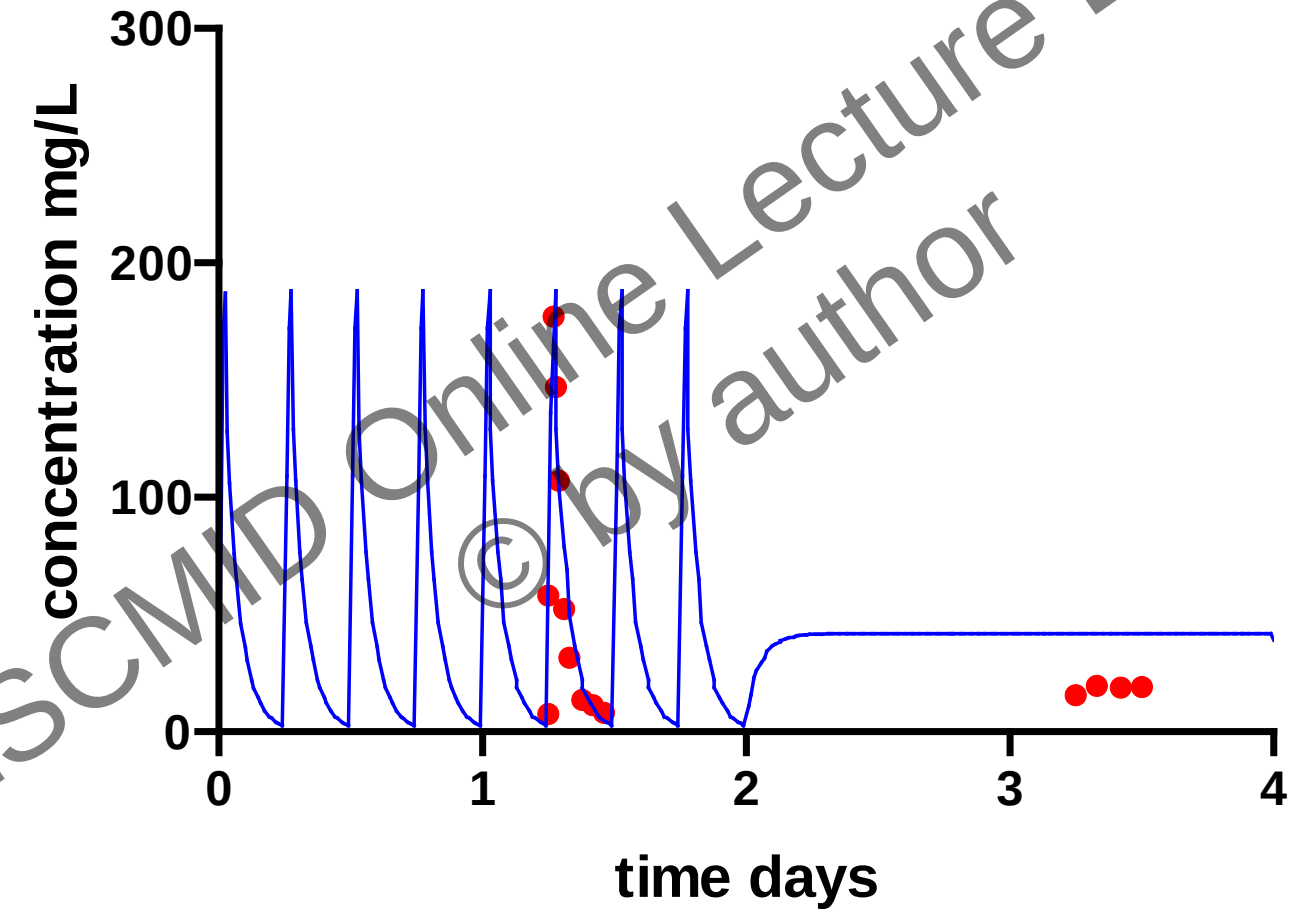
Buijk et al, ICAAC 1998, Mouton et al 1990

Cefotaxime concentrations liver transplants (n=12)



Buyk et al JAC 2003

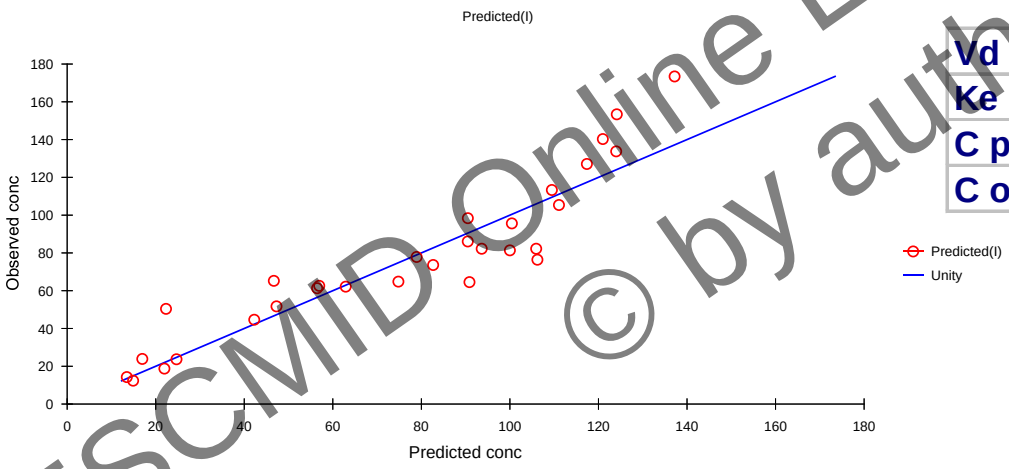
CI vs II of piperacillin in CF patients



Vinks et al, AAC 2003

Temocillin : CI vs II in ICU patients

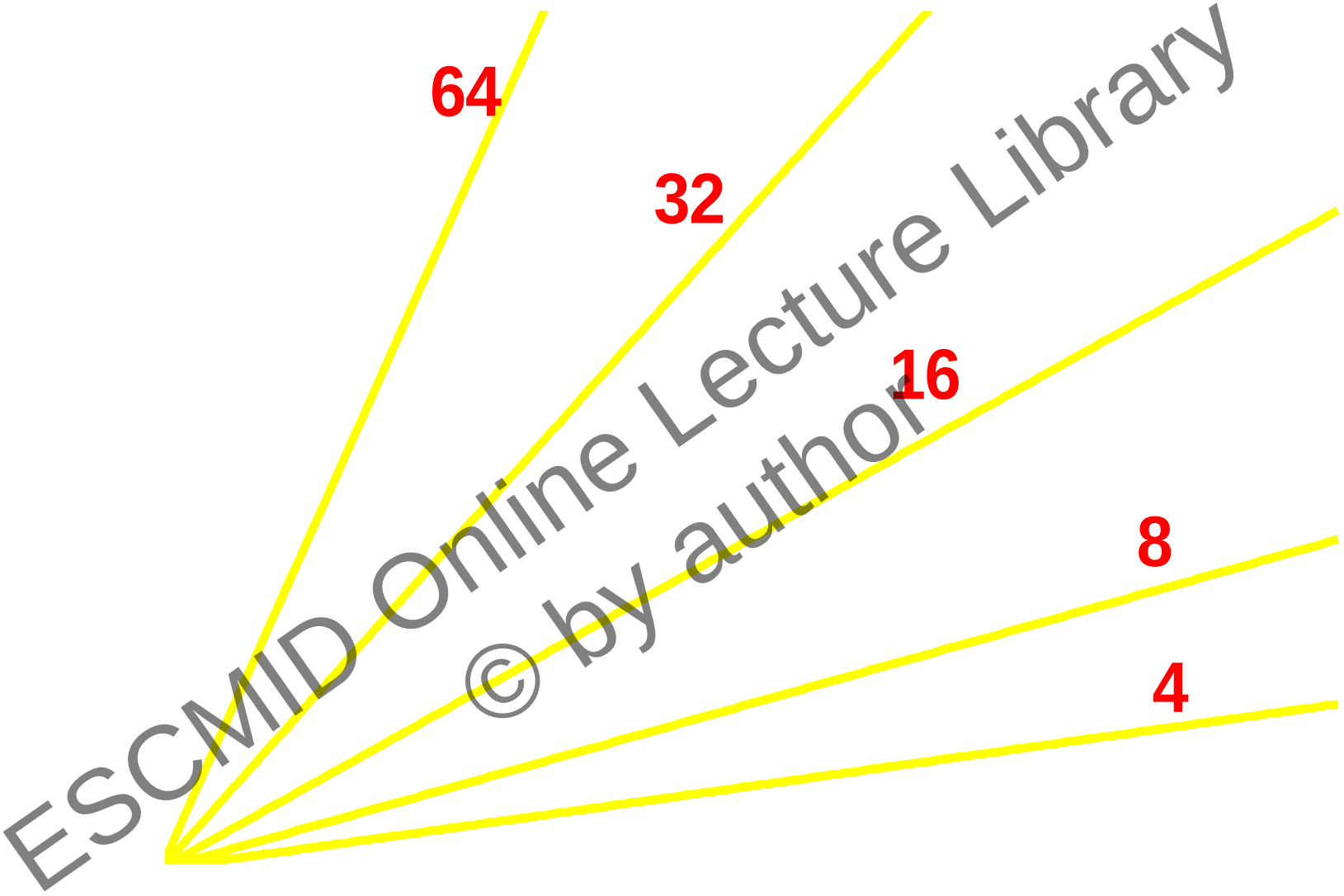
Pop PK model II (N=6)



Prediction CI

Vd	**14.3**	**L**
Ke	**0.172**	**1/h**
C pred	**16.9**	**mg/L**
C observed (n=6)	**17.0**	**mg/L**

De Jongh et al, JAC 2008



CI: Therapeutic drug monitoring

- Direct measurement
- Population pk models, clearance models

$$TBC = Ke \times Vd$$

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Conclusions

- Need PK/PD target (e.g. 4x MIC)
- Culture ! Need MICs to determine PK/PD target
- Estimate clearance! Population pk models, clearance models
- Determine daily dose