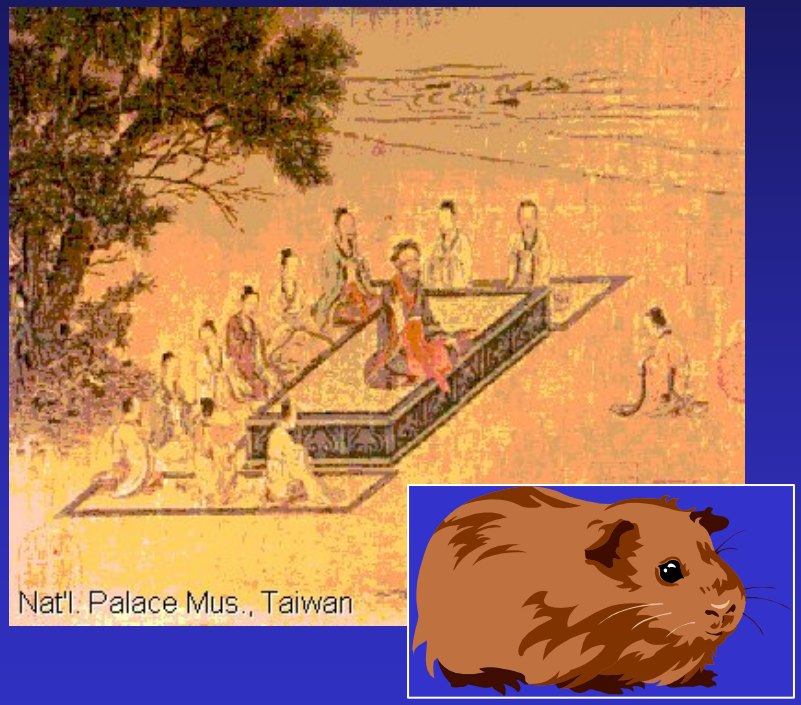
Asian PK/PD Educational Workshop

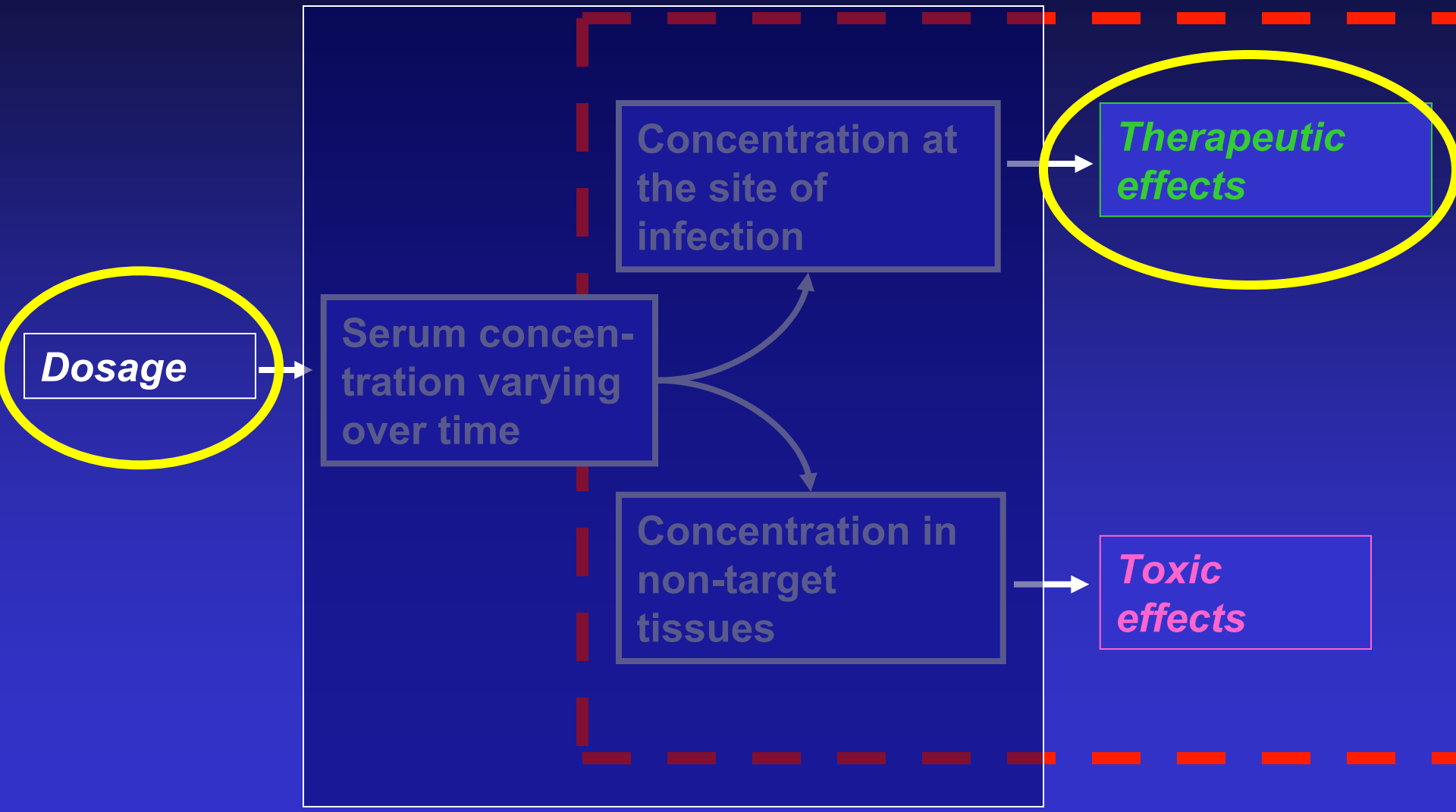


Pharmacodynamics as applied to animal models

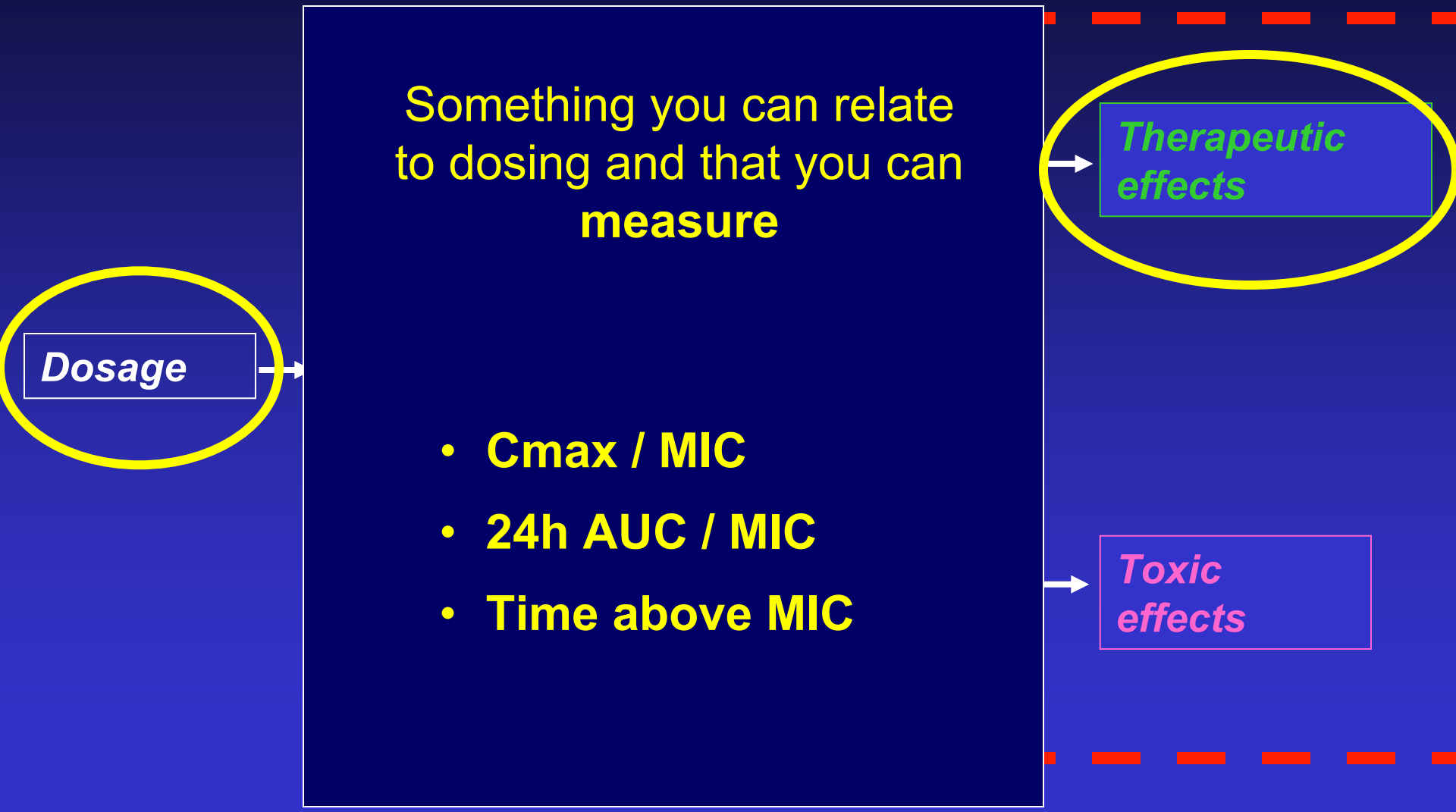
- how to uncover the PK/PD properties of antibiotics
- how to classify the main antibiotics

This part uses material from presentations of W.A. Craig (Madison, WI.) made at the 2000 and 2002 ISAP Educational Workshops

Pharmacokinetics Pharmacodynamics



Pharmacokinetics Pharmacodynamics



A reminder ...

Parameter	influenced by		
Cmax :	+ dose *	– clearance	– Vd
half-life:		– clearance	+ Vd
AUC:	+ dose **	– clearance	

this is what you do ...

\+ directly propoportional

– indirectly proportional

* unit dosis

** total dose for the period considered (usually 24h)

A reminder ...

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this is what you do ...

those are drug properties

\+ directly propoportional

– indirectly proportional

* unit dosis

** total dose for the period considered (usually 24h)

Why are animal models essentials

- Explore the conditions of success AND of failures
- Dissociate the pharmacokinetic co-variables

Why are animal models essentials

- Explore the conditions of success AND of failures

This is fairly obvious but often neglected by

- teachers (why bother ? …)
- regulators (viz. the design of clinical trials !!)
- and clinicians
  (who wants to fail too often ? … and to report it ????)

Why are animal models essentials ?

- Expl
of fa

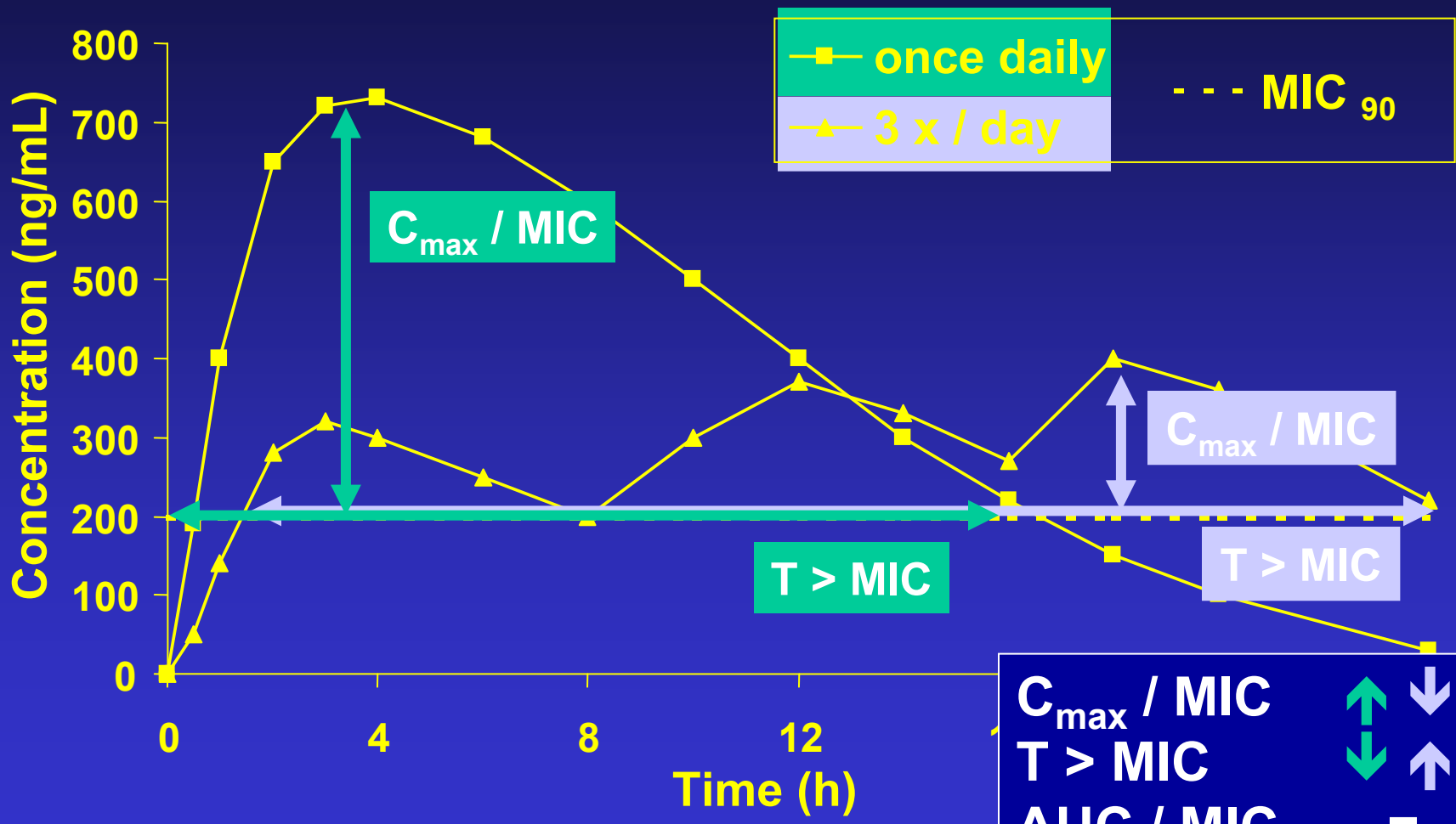
Ignoring this **IS** one of the biggest mistake made by

- regulators
- clinicians

who draw conclusions from clinical trials only !!

- Dissociate the pharmacokinetic co-variables

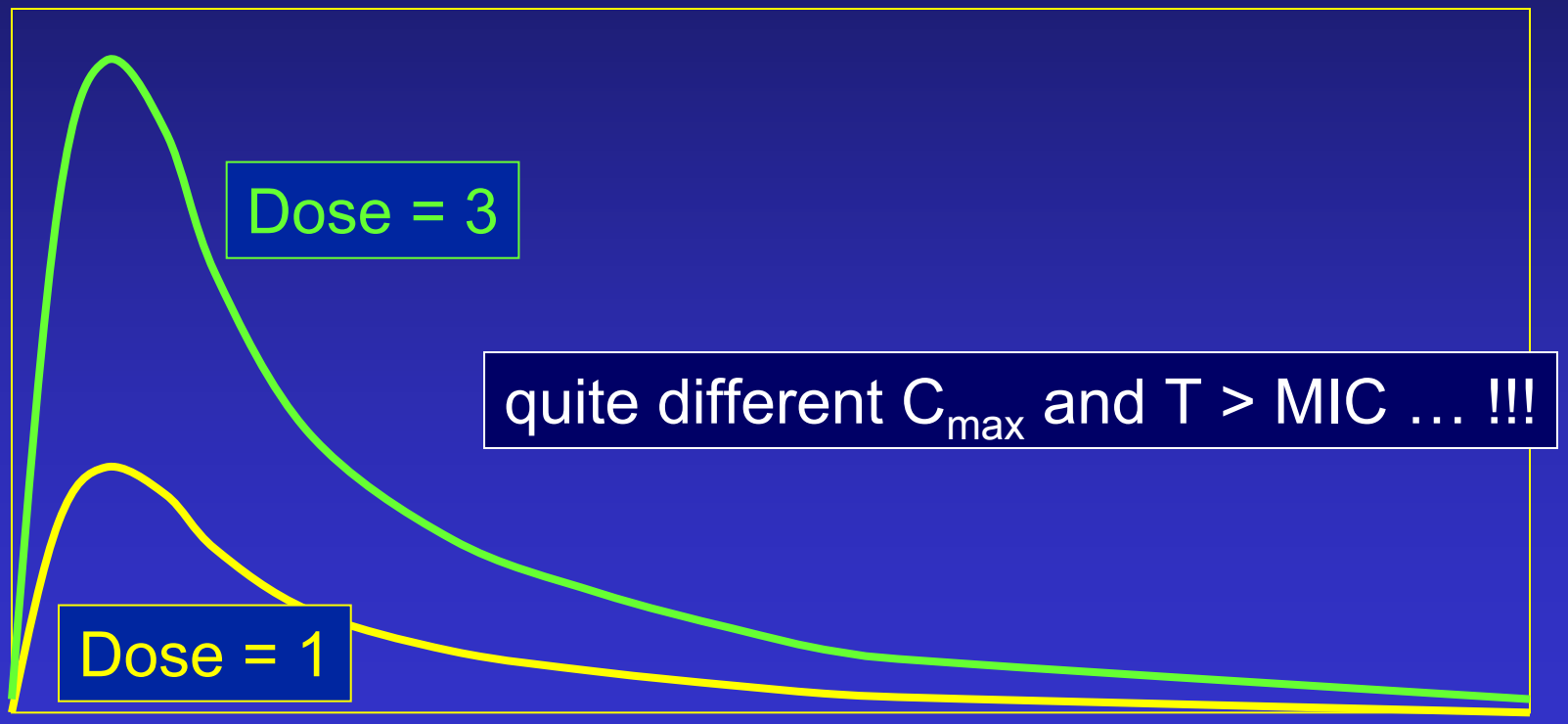
Dissociating the pharmacokinetic co-variables ...



Adapted from F. O. Ajayi, ISAP-FDA Workshop, 1999

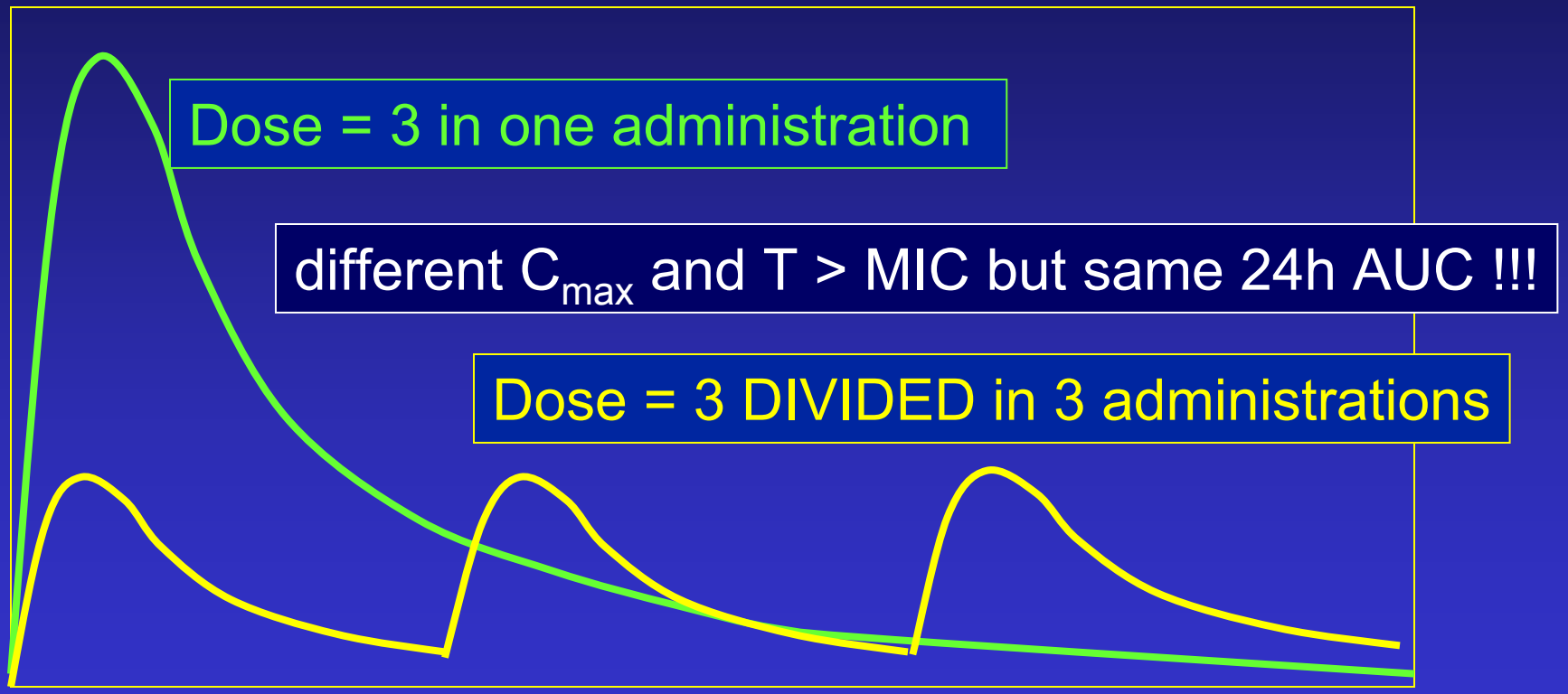
Do it again ...

C_{max} and "Time above a given value" are co-variables because they are both directly related to the unit dose

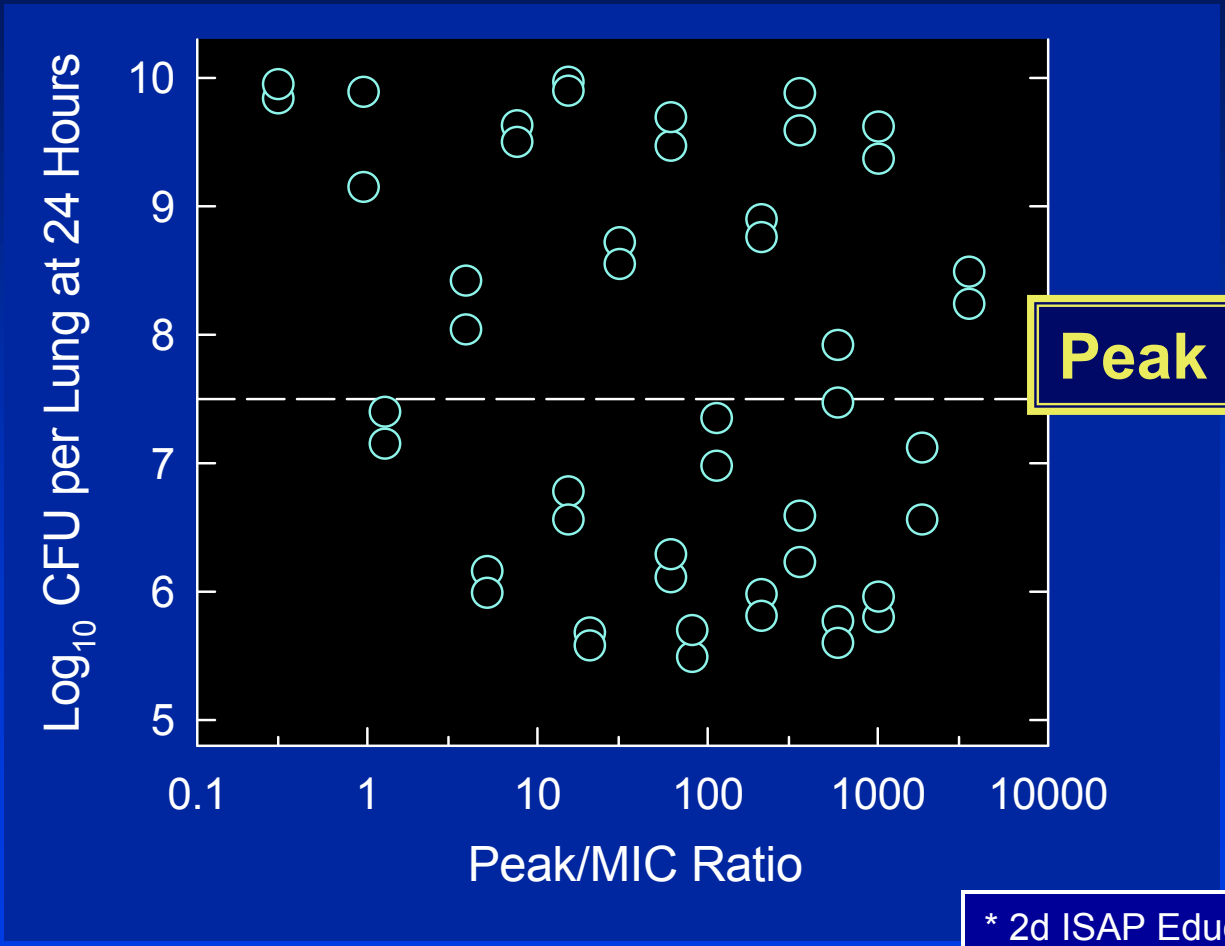


Do it again ...

24h AUC is only dependent of the total daily dose...



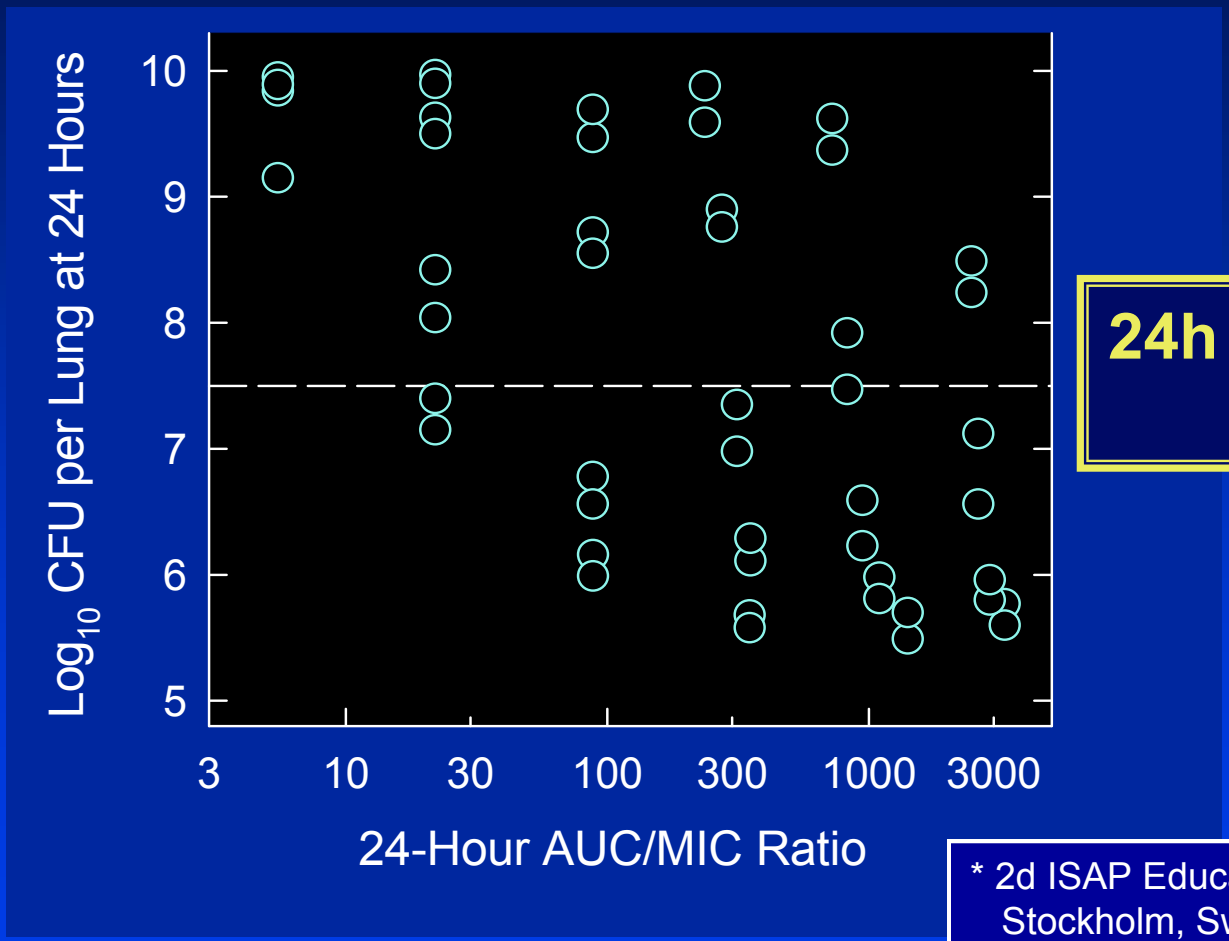
Looking for PK/PD parameters predictive of β-lactam activity (cefuroxime) in a model of murine pneumonia (*Klebsiella pneumoniae*) in neutropenic mice (after W.A. Craig *)



Peak / MIC ratio

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

Looking for PK/PD parameters predictive of β-lactam activity (cefuroxime) in a model of murine pneumonia (*Klebsiella pneumoniae*) in neutropenic mice (after W.A. Craig *)



24h AUC / MIC ratio

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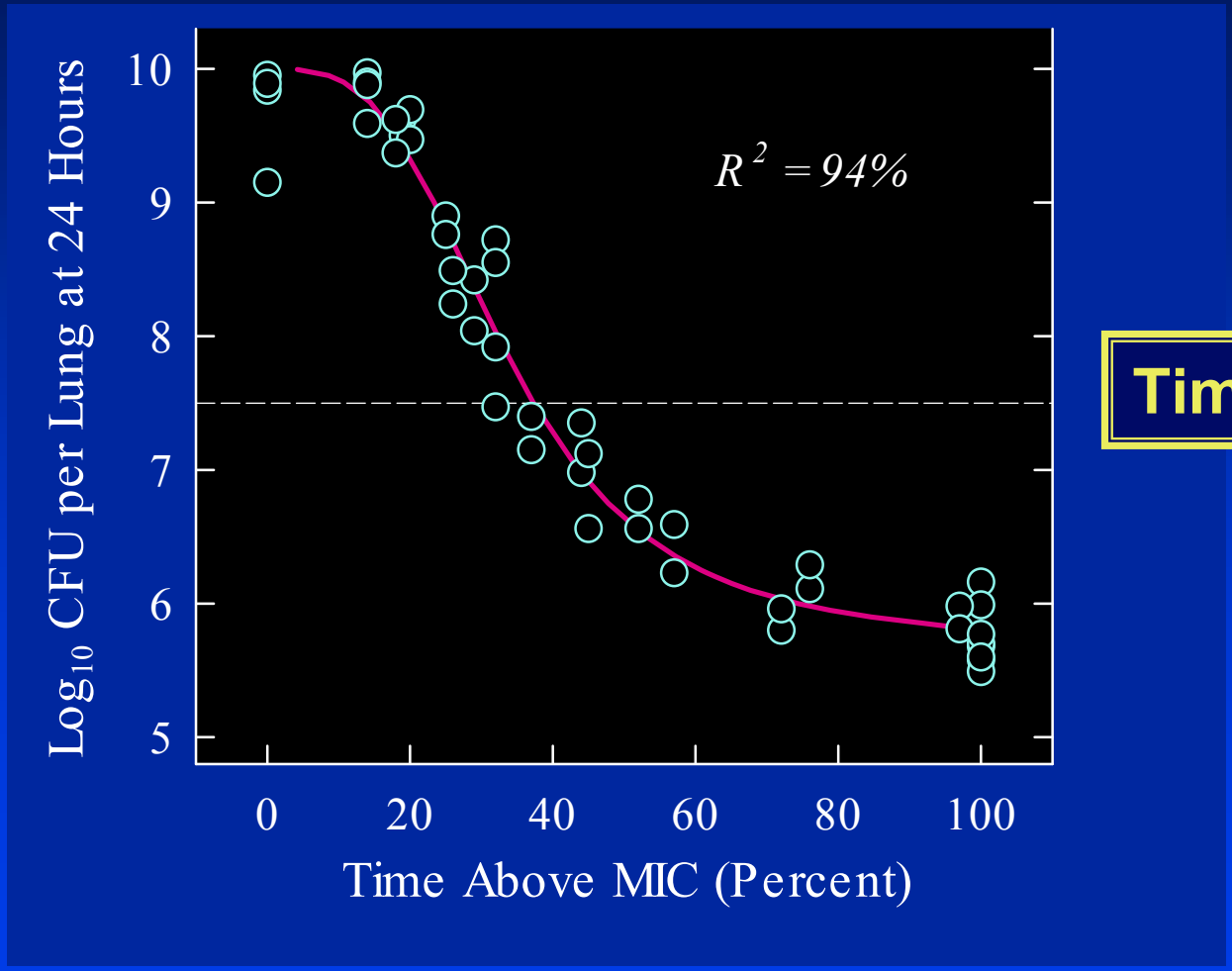
Looking for PK/PD parameters predictive of β-lactame activity (cefuroxime) in a model of murine pneumonia (*Klebsiella pneumoniae*) in neutropenic mice (after W.A. Craig *)



Time > MIC

Main PK/PD properties of antibiotics

Available antibiotic can be divided in 3 groups

- time - dependent (T > MIC)
- AUC / MIC - dependent
- both AUC / MIC AND peak / MIC - dependent

Antibiotics Group # 1
(after W.A. Craig, 2000; revised 2002)

1. Antibiotics with time-dependent effects and no or little persistent effects

AB	PK/PD parameter	Goal
β-lactams clindamycin oxazolidinones flucytosine	Time above MIC	Maximalize the exposure time

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000; revised accord. to Craig, et al. ICAAC 2002

Antibiotics Group # 2
(after W.A. Craig, 2000; revised 2002)

2. Antibiotics with time-dependent effects, with little or no influence of the concentration BUT with persistent effects

AB	PK/PD parameter	Goal
glycopeptides tétracyclines macrolides streptogramines fluconazole	24h AUC / MIC ratio	Optimize the quantity of AB administered

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000; revised accord. to Craig et al., ICAAC 2002

Antibiotics Group # 2
(after W.A. Craig, 2000; revised 2002)

3. Antibiotics with concentration-dependent activity and with persistant effects (PAE)

AB	PK/PD parameter	Goal
aminoglycosides fluoroquinolones daptomycin ketolides amphotericin	C_{max} / MIC **and** 24h AUC / MIC ratios	Optimize **both the peak** and the **quantity** of drug

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000; revised accord. to Craig ek al., ICAAC 2002

Are PK/PD Parameters universals ?

- Is the magnitude of the parameter required for efficacy the same in different animal species?
- Does the magnitude of the parameter vary markedly with:
    1. the dosing regimen?
    2. different drugs within the same class?
    3. different organisms ?
    4. different sites of infection (e.g. blood, lung, peritoneum, soft tissue) ?

From WA. Craig: 7th ISAP Educational Workshop, San Diego, CA, 2002

The 'saga' of the “Static Dose” ...

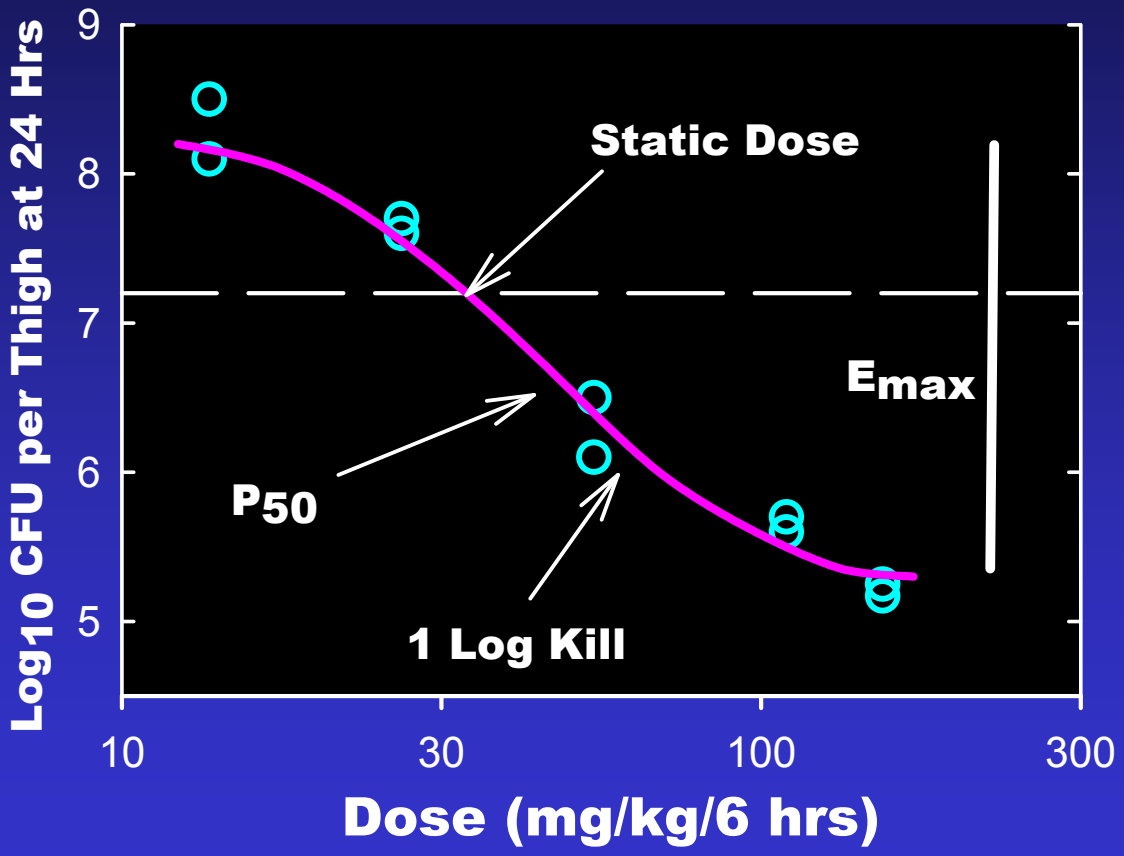
- Determine cfu/thing in untreated controls and mice treated with 4-5 different total doses
- Use nonlinear regression and modified Hill equation to estimate E_{max} (difference from untreated control), P_{50} (dose giving 50% of E_{max}) and slope (N) of dose-response relationship

$$\Delta CFU = (Emax)\ Dose^N / Dose^N + P_{50}^N$$

- Calculate the “static dose”

From WA. Craig: 7th ISAP Educational Workshop, San Diego, CA, 2002

Relationship Between 6-Hour Dose and Number of Klebsiella pneumoniae in Thighs of Neutropenic Mice



From WA. Craig: 7th ISAP Educational Workshop, San Diego, CA, 2002

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

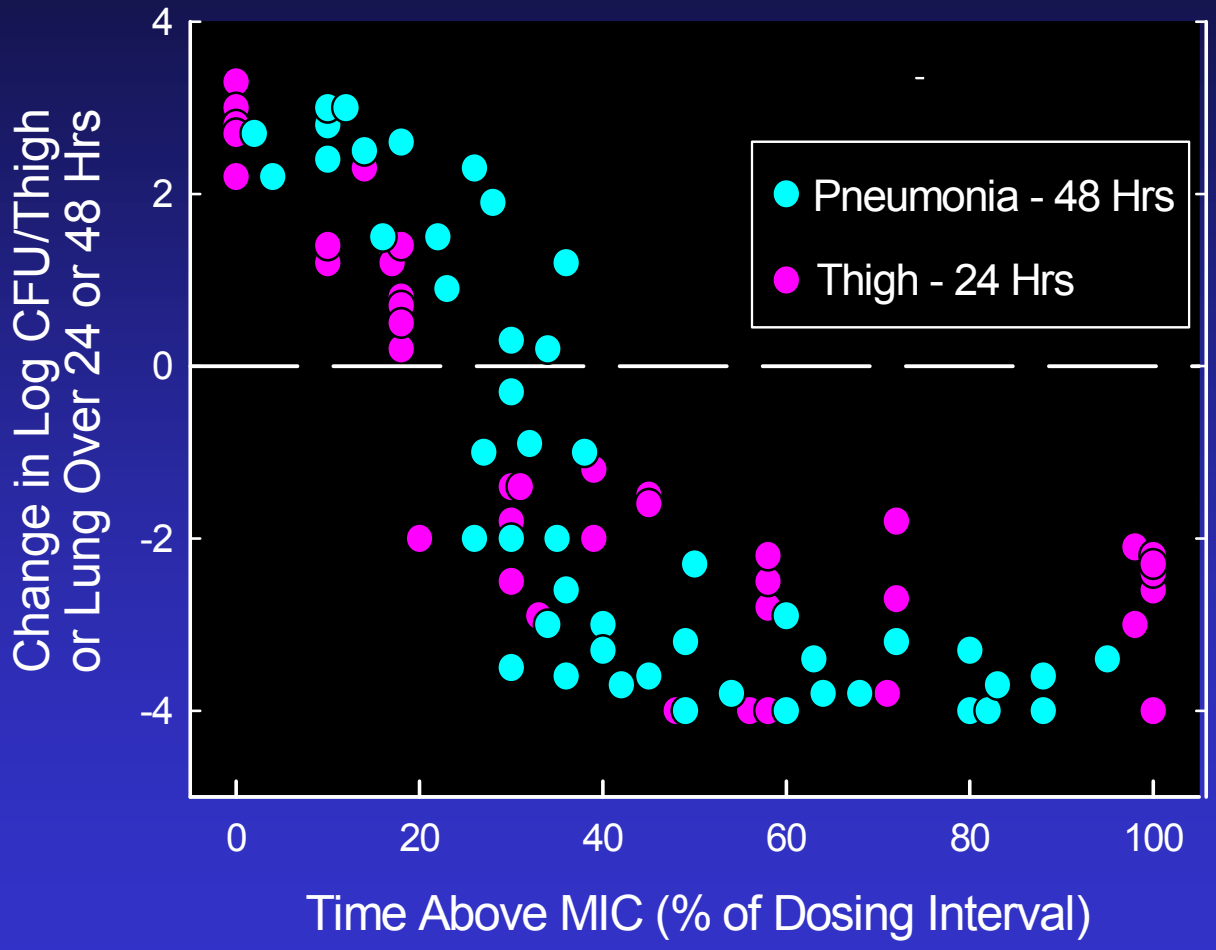
Time Above MIC (Percent of Dosing Interval)

Drug	Enterobacteriaceae	S. pneumoniae
Ceftriaxone (Total)	72 (66-79)	74 (69-78)
Ceftriaxone (Free)	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 is mean (95 % CI)

From WA. Craig: 7th ISAP Educational Workshop, San Diego, CA, 2002

Relationship Between T>MIC and Efficacy for Amoxicillin against *Streptococcus pneumoniae* in Rat Pneumonia and Murine Thigh-Infection Models

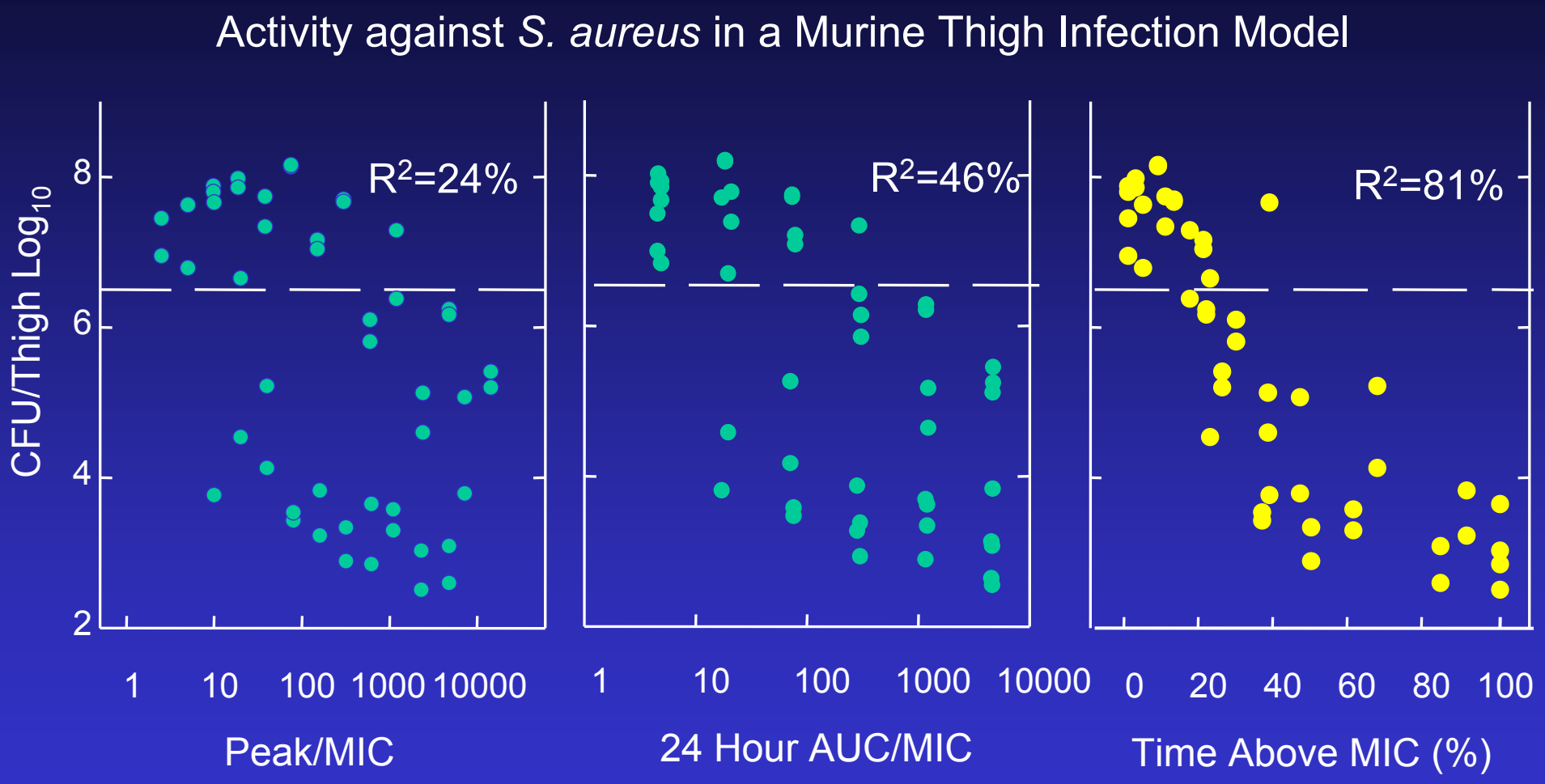


From WA. Craig: 7th ISAP Educational Workshop, San Diego, CA, 2002

Why have we sometimes hesitated ?

- Not enough experimental data
- Not enough separation of the covariables
- Specificities of the animal models

More experimental data with ertapenem ...



More experimental data with ertapenem ...

T > MIC ~ 6 % : bacteriostatic

T > MIC ~ 60 % : max. bactericidal

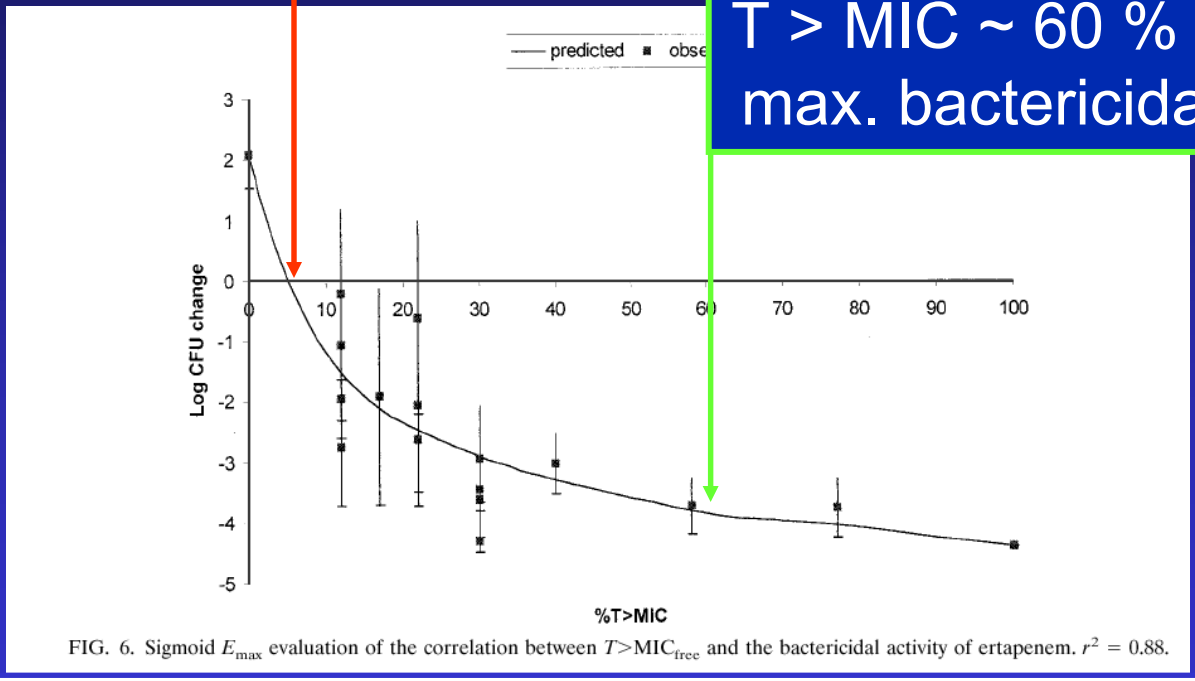


FIG. 6. Sigmoid E_{max} evaluation of the correlation between $T>MIC_{free}$ and the bactericidal activity of ertapenem. $r^2 = 0.88$.

S. pneumoniae in a murine neutropenic thigh infection model

Xuan *et al*, AAC 1998, 46: 2990-2995

More experimental data with penicillins, cephalosporins and carbapenems ...

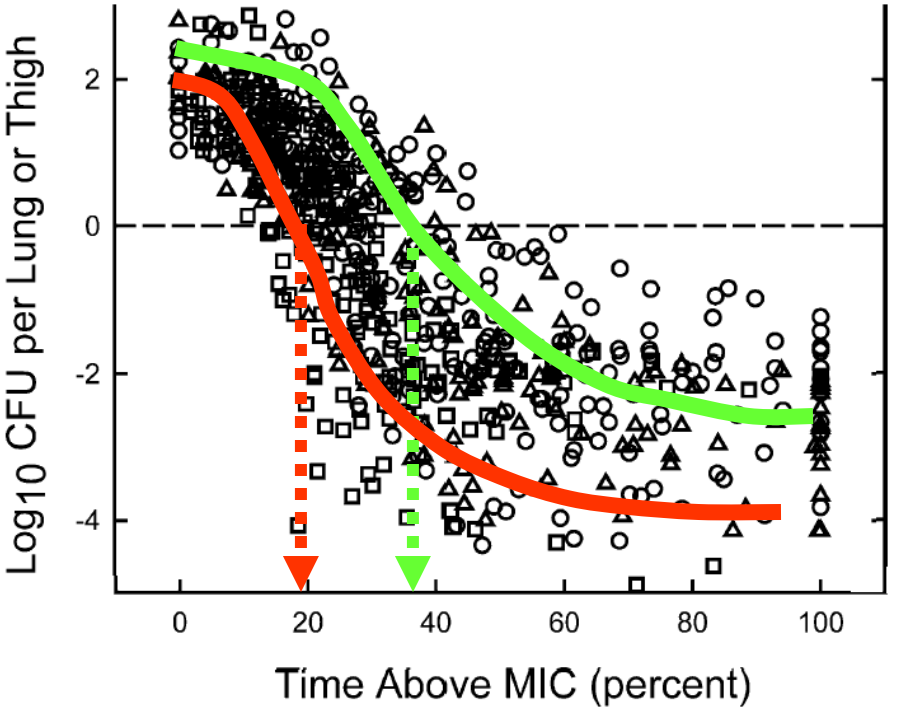


Fig. 7. Relationship between the change in $\log_{10}$ CFU per thigh or lung for various pathogens following 24 h of therapy with different doses of penicillins (△), cephalosporins (○), and carbapenems (□).

different pathogens

- same shape of dose response
- diff. In **T > MIC** for a static effect (penicill. > carbap.)
- diff **E_{max}** (penicill. < carbap.)

Andes & Craig Int. J. Antimicrob. Agents 2002, 19: 261-268

Why have we sometimes hesitated ?

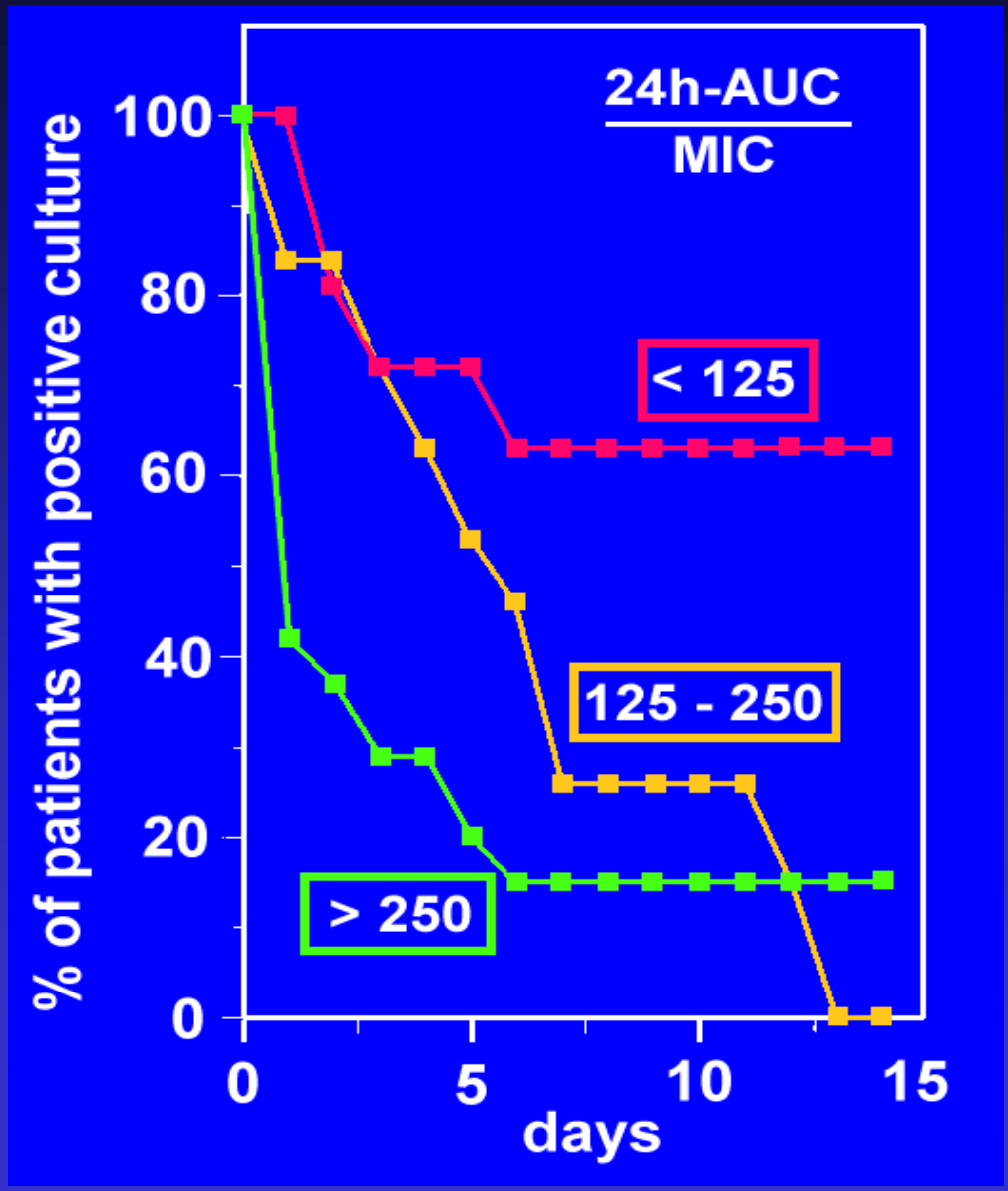
- Not enough experimental data
- Not enough separation of the covariables
- Specificities of the animal models

Lack of separation of the PK co-variables ...

- As already stated, this is a common problem in all clinical trials
  - which are not specifically designed to test for one PK variable independetly from the other
  - have not enough PK-related failures to unambigously assess success or failures to one PK variable...

The saga of the AUC / MIC vs C_{max} / MIC ratio for fluoroquinolones ...

AUC / MIC is the parameter ...



Forrest et al., AAC, 1993

24h-AUC/MIC : actual data ...

Parameter	No. pat.	% microb. cure		% clin. cure
MIC (mg/L)				
<0.125	28	82		79
0.125-0.25	13	75	success	69
0.5	14	54		79
1	9	33	failure	44
2	2	0		0

Forrest et al., AAC, 1993

24h-AUC/MIC : actual data ...

Parameter	No. pat.	% microb. cure		% clin. cure
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<0.125	28	82		79
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0.5	14	54		79
1	9	33	failure	44
2	2	0		0
24h AUC / MIC				
0-125	19	32	failure	42
125-250	16	81	success	88
250-1000	14	79		71
1000-5541	15	87		80

Forrest et al., AAC, 1993

Is 24h AUC/MIC the only parameter for fluoroquinolones...

- All patients in the Forrest et al's study received ciprofloxacin on a bid or tid schedule

➔ the study was, therefore, not powerful enough to assess C_{max} independently from the total daily dose

➔ since success was linked mostly to a low MIC, and the only independent variable was the total daily dose, only 24h AUC / MIC could emerge as a predictive PK/PD parameter

Fq PK/PD : a study demonstrating the role of peak to MIC ratio in the clinic (1/2)

Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. Preston et al., J.A.M.A., 1998 Jan 14;279(2):125-9

OBJECTIVE:
To prospectively quantitate the relationship between plasma levels of levofloxacin and successful clinical and/or microbiological outcomes and occurrence of adverse events in infected patients.

PATIENTS: 313 with clinical signs and symptoms of bacterial infections of the respiratory tract, skin, or urinary tract.

MAIN OUTCOME MEASURES: Clinical response and microbiological eradication of pathogenic organisms.

Fq PK/PD : a study demonstrating the role of peak to MIC ratio in the clinic (1/2)

Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. Preston et al., J.A.M.A., 1998 Jan 14;279(2):125-9

RESULTS (as presented by the authors):

- 134 / 313 had both PK and MIC
- **clinical AND bacterial outcomes were related to peak/MIC**
  (logistic regression; $p < 0.001$)
- **results were favourable if peak / MIC > 12.2**

Is Cmax / MIC ratio truly the only parameter for predicting fluoroquinolones efficacy ?

- most patients in the Preston *et al*'s study received levofloxacin at a fairly large dose (for the MIC of *S. pneumoniae* at that time…; 500 mg) and with only one administration scheme (once-a-day) ...
- this very design caused most patients to have a C_{max}/MIC ratio > 10 ...
- there were very few failures ...

Is Cmax / MIC ratio truly the only parameter for predicting fluoroquinolones efficacy ?

- the data, actually, showed that both C_{max}/MIC and 24h AUC/MIC were linked to clinical sucess

" Peak/MIC ratio, AUC/MIC ratio, and Time>MIC were virtually indistinguishable in their ability to alter the probability of a successful outcome (Table 2). This is understandable as, when examined, Peak/MIC and AUC/MIC ratios were highly correlated, with an r value of 0.942 (Spearman rank correlation). "

➔ The authors decided to select C_{max}/MIC as the critical parameter… but could have use 24h AUC/MIC rr even time > MIC since these three parameters are true co-variables when only one schedule is used...

Fluoroquinolones: the role of the peak for efficacy: demonstrations in animal models

Increase in bactericidal activity

- **peak/MIC ratio becomes predictive at ratios > 10**
  AUC / MIC is more predictive at peak/MIC < 10
  no influence of time > MIC when tested specifically
  Drusano et al., Antimicrob Agents Chemother 1993 Mar;37(3):483-90)

- **Dose-dependency (= AUC) in vivo**
  Dalhoff, J Antimicrob Chemother 1999 May;43 Suppl B:51-9)

- **Penetration in inflammatory fluids and interstitial fuids, and rapid equilibration between compartments (= AUC)**
  - Wise et al., Antimicrob Agents Chemother 1999 Jun;43(6):1508-10)
  - Muller et al., Antimicrob Agents Chemother 1999 Oct;43(10):2345-9)
  - Stass et al., Antimicrob Agents Chemother 1998 Aug;42(8):2060-5)

FQ are dependent of both the peak /MIC and the AUC/ MIC ratios ...

Why have we sometimes hesitated ?

- Not enough experimental data
- Not enough separation of the covariables
- Specificities of the animal models
  - non-neutropenic *vs.* neutropenic animals
  - differences in PK parameters between rodents and man
  - timing of the infection / treatment schedule

Difficulties of animal models

- Most models need to use neutropenic animals as many pathogens for man (incl. *S. pneumoniae* and *H. influenzae*) are relatively avirulent to small rodents
- Small rodents need also to be made renally-impaired in order to obtain drug pharmacokinetic parameters similar to those observed in humans
- Most studies start treatment quite soon after the infection, which is not what one does in humans ...

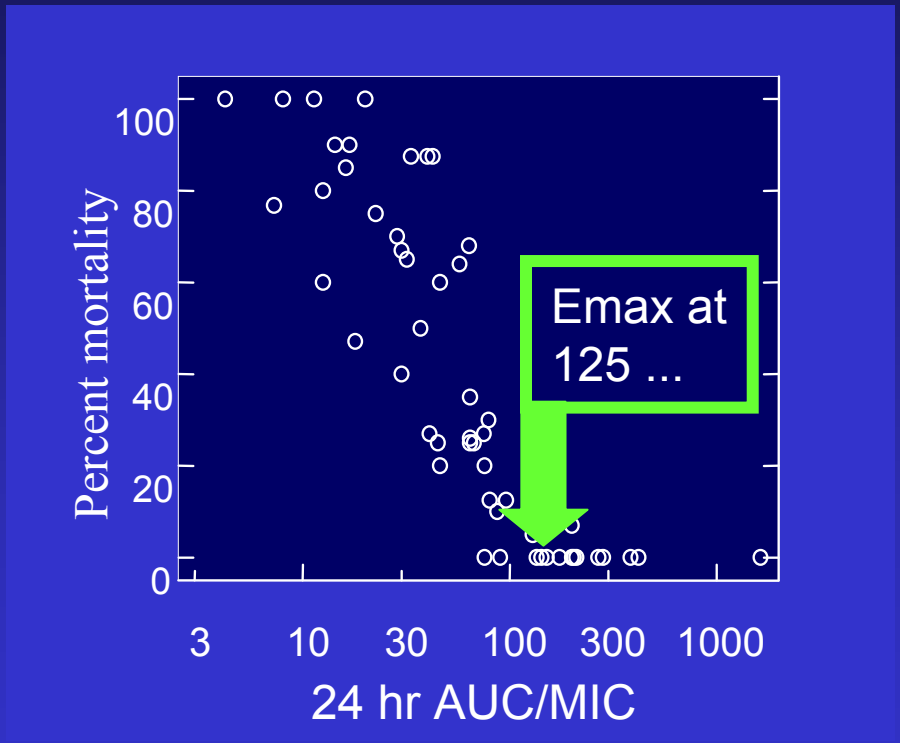
Why do we (often) use neutropenic animals ?

In order to be able to kill them rapidly …

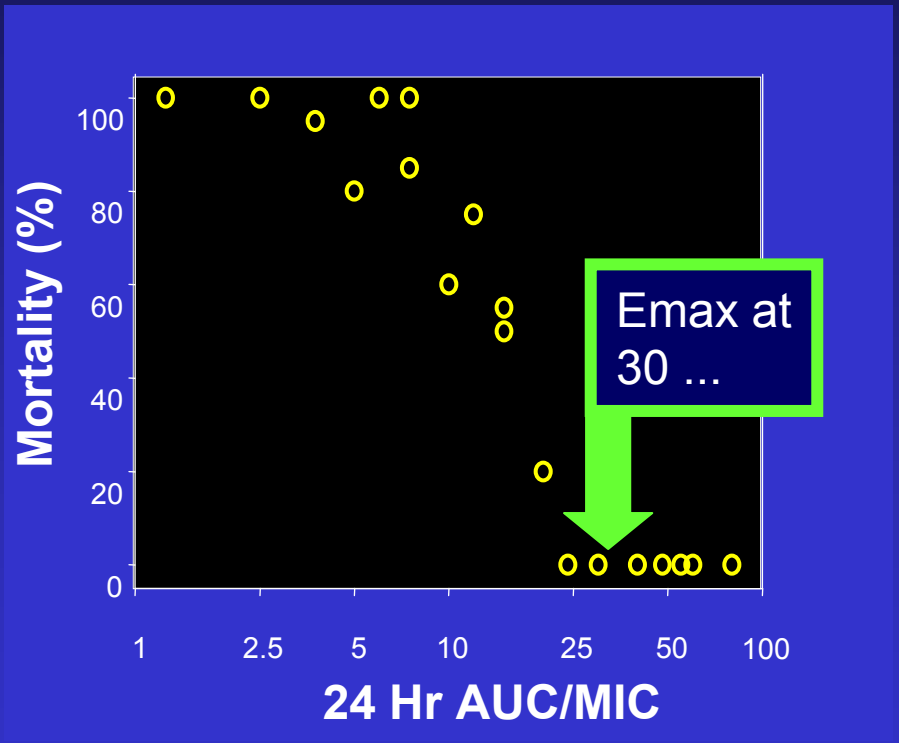
- if animals are not rapidly killed, you start having problems …
  - lack of clear-cut endpoint
  - building up of humoral and tissular means of defense ...
  - cost, nursing, etc…
- Many interesting pathogens for man (incl. *S. pneumoniae* and *H. influenzae*) are relatively inocuous to small rodents and animals eventually never die ..

But using neutropenic animals may modify the dose / effect response ...

Relationship Between 24 Hr AUC/MIC and Mortality
for Fluoroquinolones against *S. pneumoniae* in Immunocompetent vs. Immunocompromised animal Models



neutropenic



non-neutropenic

Adapted from W.A. Craig : 7th ISAP Educational Workshop, San Diego, CA, 2002

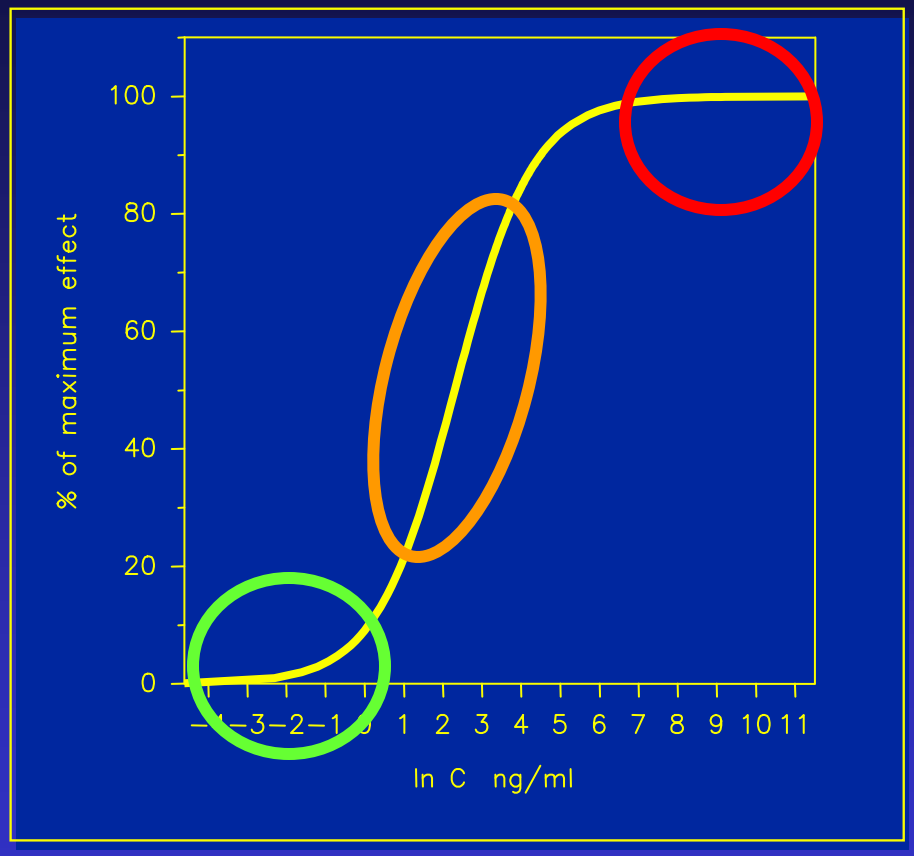
But beyond the difficulties, there is now a consensus for ...

to be predictive of the activity of

- C_{max} / MIC → fluoroquinolones aminoglycosides
- AUC / MIC → macrolides tetracyclines
- time > MIC → β-lactams oxazolidinones vancomycin

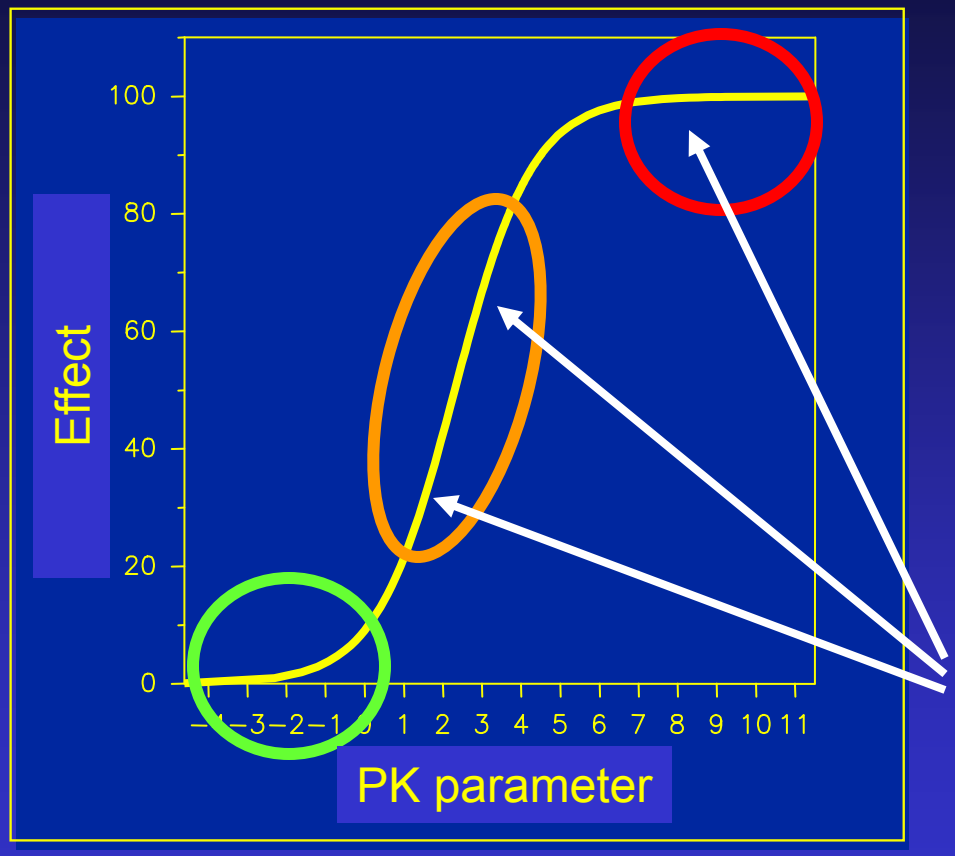
The difficulty remains to determine which is the minimal acceptable value for these parameters

So, please, remember pharmacodynamics...



- Emax
- steepness
- point of initial response

And now, decide ...



- Emax
- steepness
- point of initial response

Which effect would you like to obtain ?

This is where we are now ...

The black box is ...

- **Cmax / MIC**
- **24h AUC / MIC**
- **Time above MIC**

Dosage

Therapeutic effects

Toxic effects