university of groningen

University Medical Center Groningen

TDM and dose optimisation of antibiotics and antifungals

Based on Pharmacokinetic and Pharmacodynamic Principles

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Disclosure

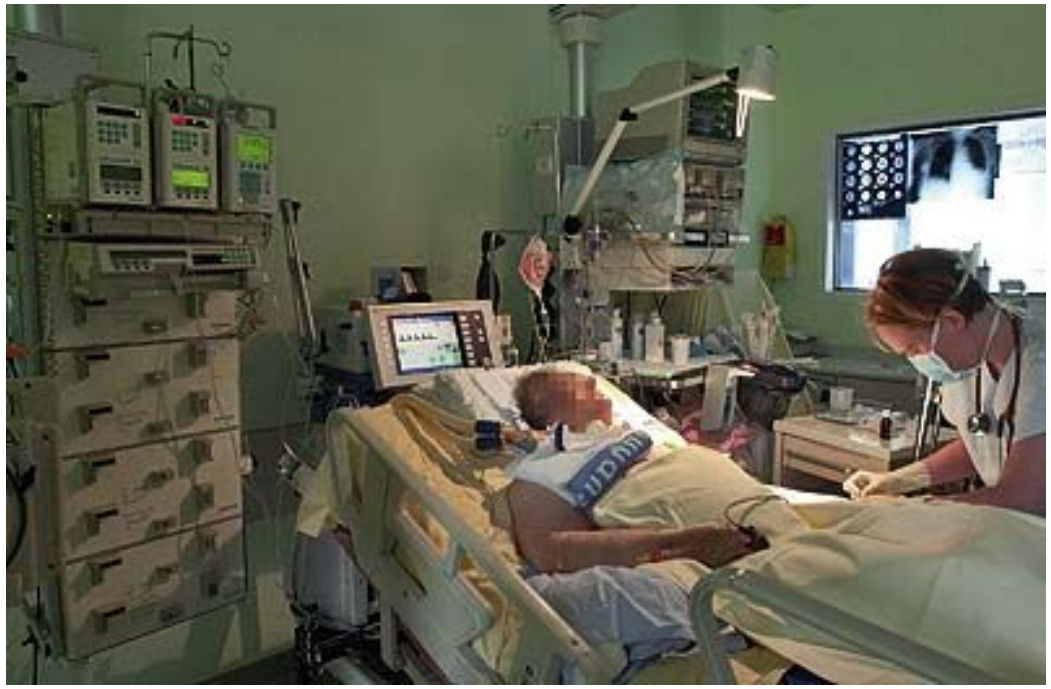
- Daan Touw reports grants of ZONMW, Astellas and Chiesi outside this topic
- Daan Touw is currently a Member of the Medical Advisory Board of Sanquin Blood Bank and Blood Products

UMCG

Outline presentation

- PK/PD principles of antibacterial drugs
- Population Pharmacokinetics
- Assay reliability
- Optimal sampling
- PK/PD principles of antifungal drugs

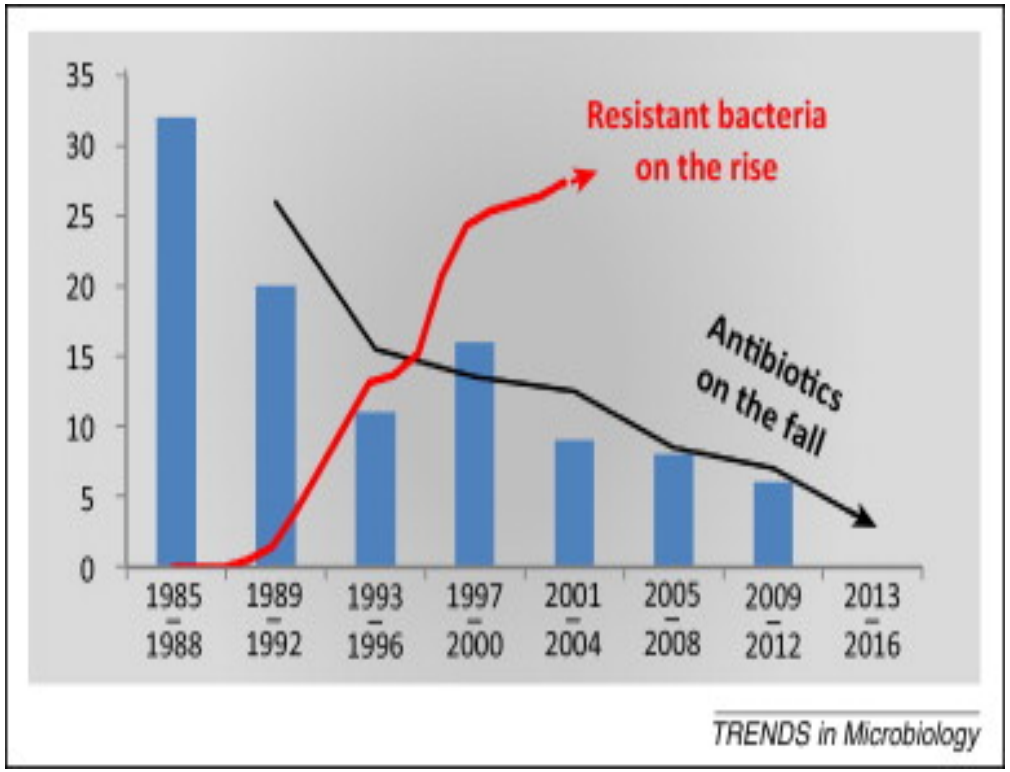
Empiric therapy (severe infections)



Mortality: increases with 10% for each hour delay.

Time is critical:
Get dose right from the beginning!

The Antibiotic Pipeline is Dry….

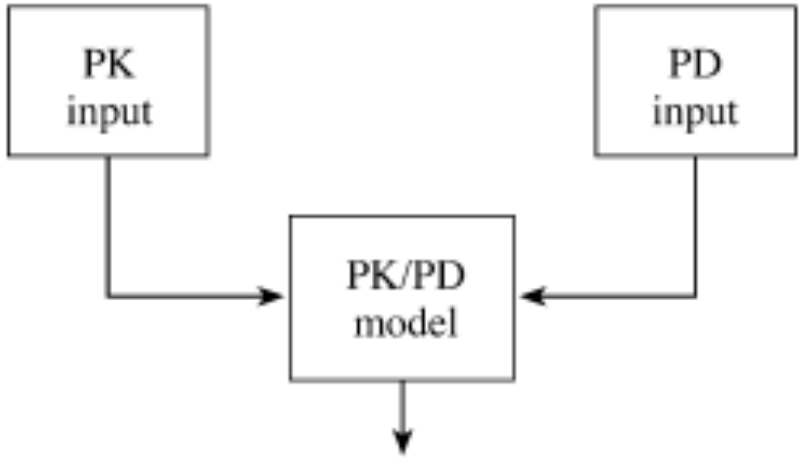


The solution

Modernise the use of our existing drugs!

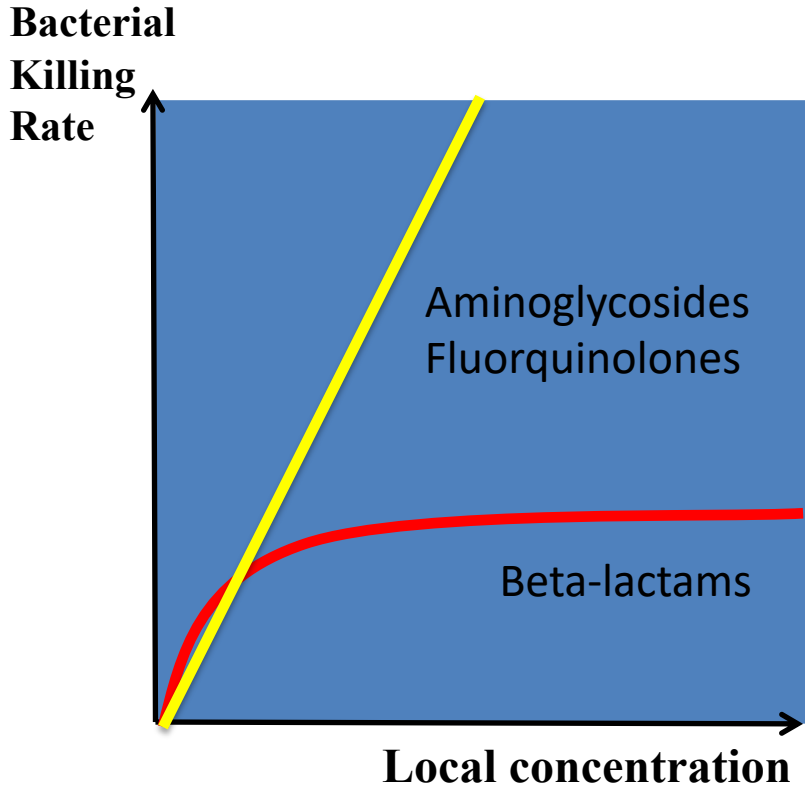
Therapeutic Drug Monitoring

- Goal: To better integrate pharmacodynamic and pharmacokinetic knowledge for optimal dosing:



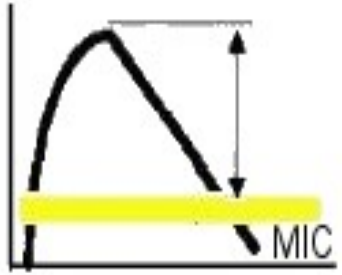
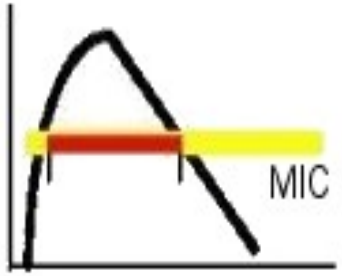
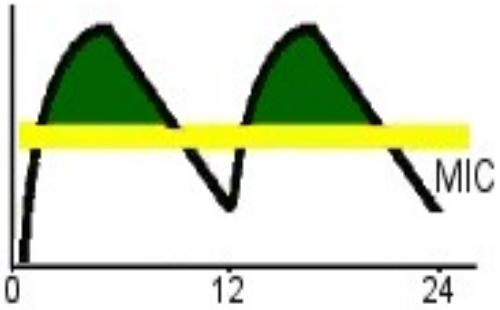
Basic PD principles of antibiotics

- Pharmacokinetic/ Pharmacodynamic (PK/PD) principles in the relevant dosing range:
  - Concentration dependent antibiotics: bacterial killing increases with increasing concentration
  - Time dependent antibiotics: bacterial killing is independent from concentration



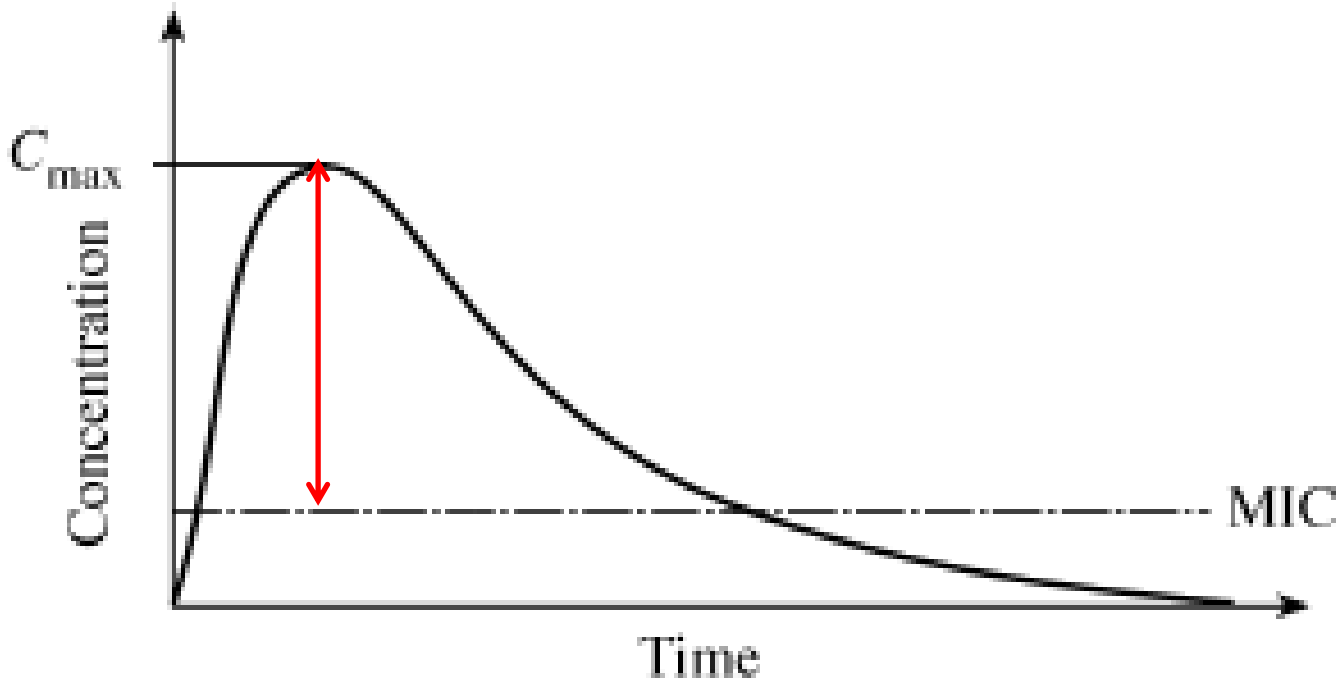
Pharmacodynamic principles:

Predictors of Bacterial Eradication: Pharmacokinetic/Pharmacodynamic Profiles

Peak/MIC	*T > MIC*	*24h-AUC/MIC*
		
- Aminoglycosides - Daptomycin - Fluoroquinolones	- Beta-lactams - Clindamycin - Erythromycin - Linezolid	- Azithromycin - Vancomycin

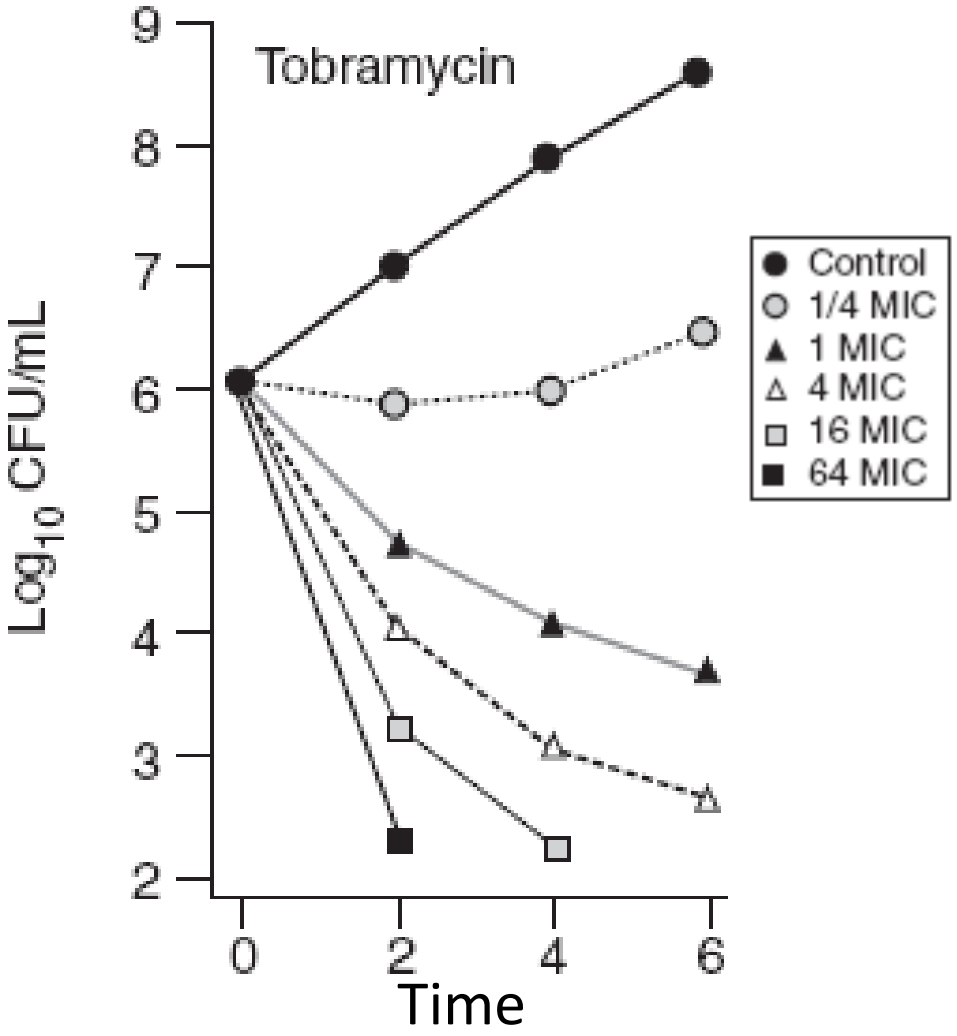
AMINOGLYCOSIDES

PK/PD principle: Cmax / MIC



Aminoglycosides, efficacy

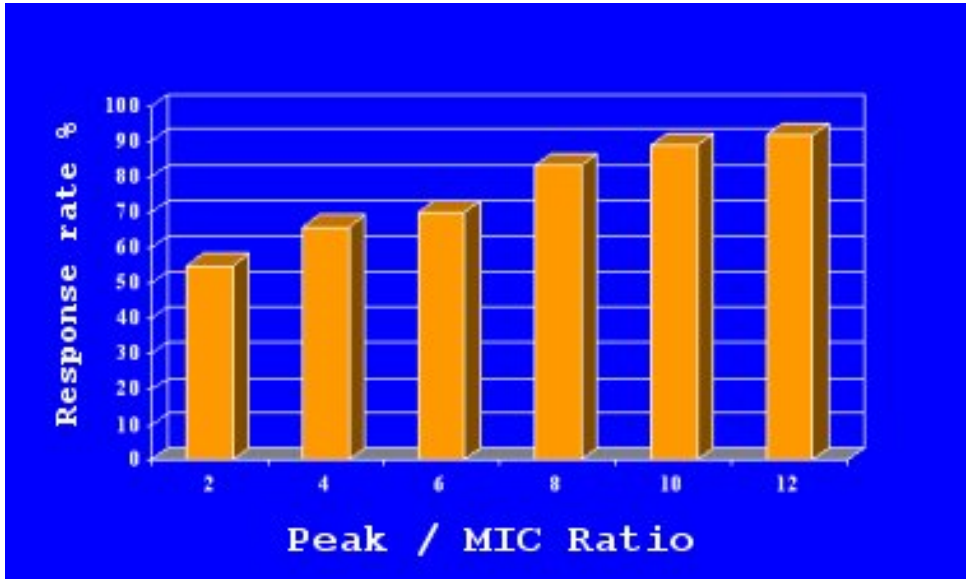
- Relationship between maximal concentration and bacterial killing over time in an **animal model of P aeruginosa infection**:



Craig, Scand J Inf Dis 1990

Aminoglycosides, efficacy

Initial serum peak level	Died (%)	Survived (%)
< 5mcg/ml	21	79
>= 5mcg/ml	2	98

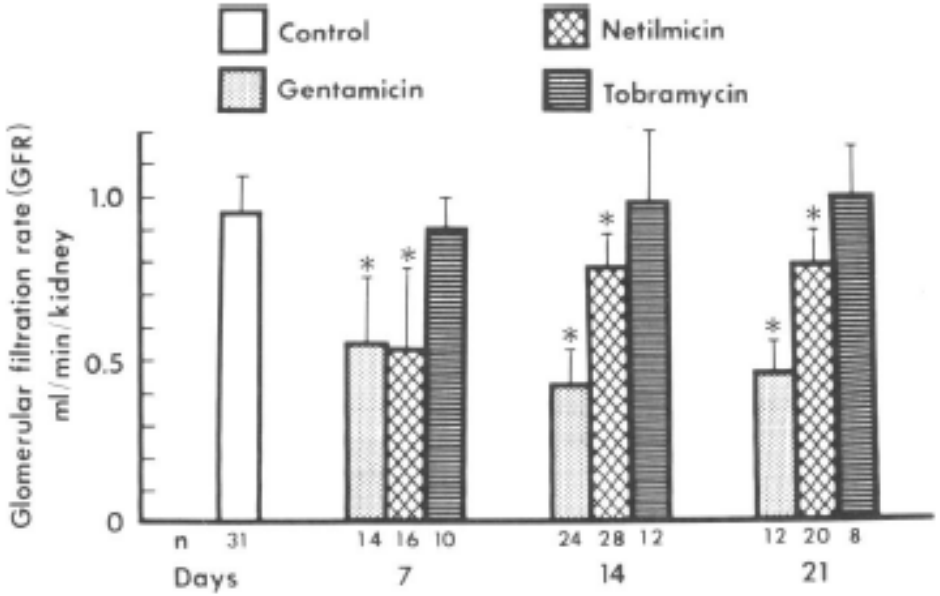


EUCAST: Ps aeruginosa MIC breakpoint = 4 mg/L

Moore, J Inf Dis 1984; Moore, J Inf Dis 1987

Aminoglycosides, toxicity

- GFR loss in animals related to drug and days of treatment



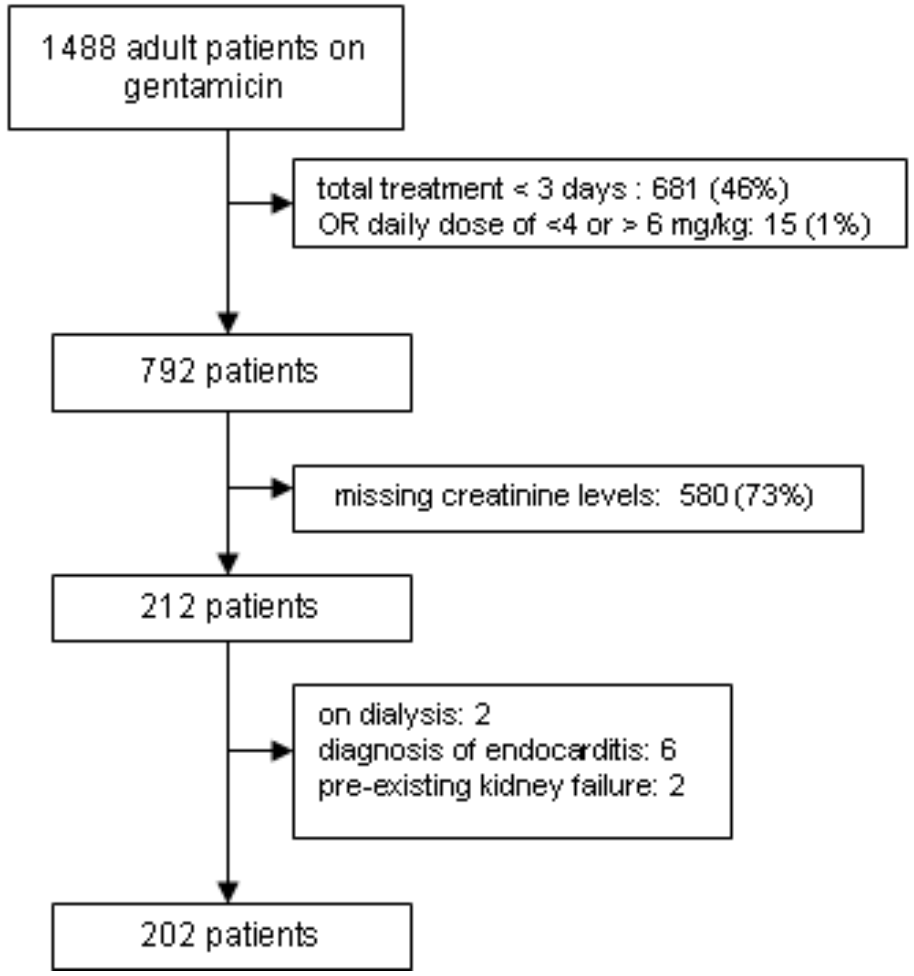
Cojocel 1984

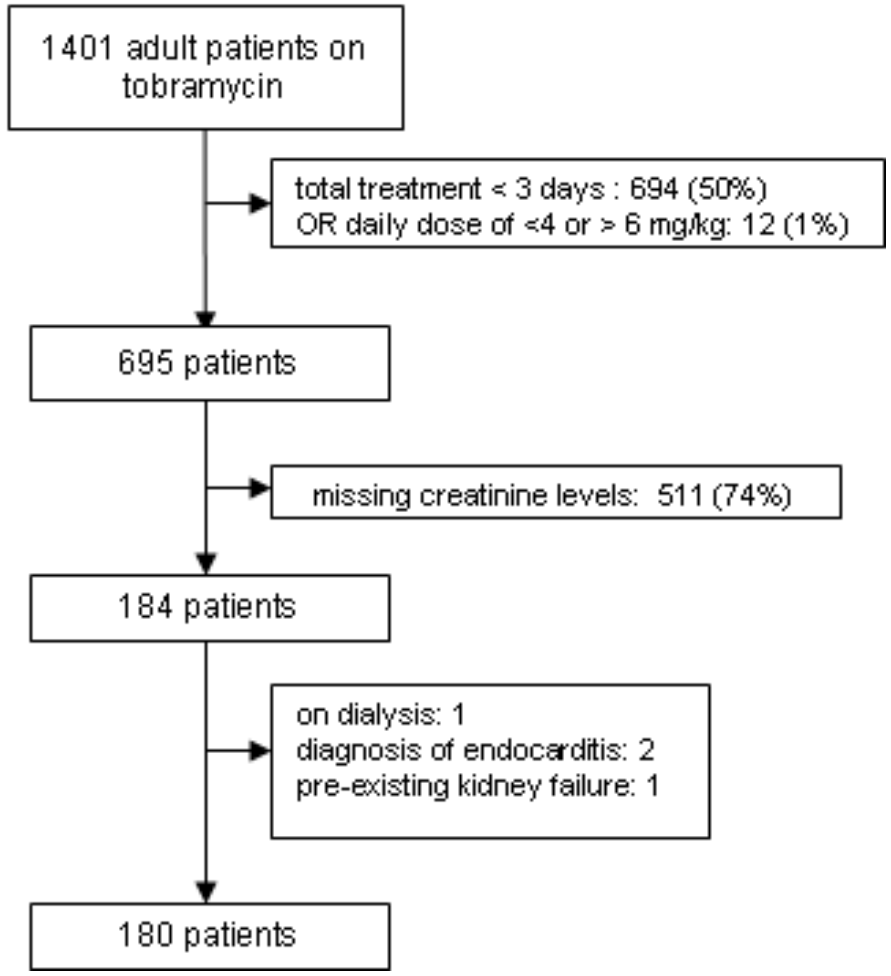
:h is more toxic, gentamicin or tobramycin?

- Study
  - Retrospective study general hospital
- Patients
  - Gentamicin group → may 2008 – december 2009
  - Tobramycin group → january 2010 – may 2012
  - No difference in treatment protocol: 1st dose kinetics
- Primary outcome
  - Difference in serum creat (end – start treatment)

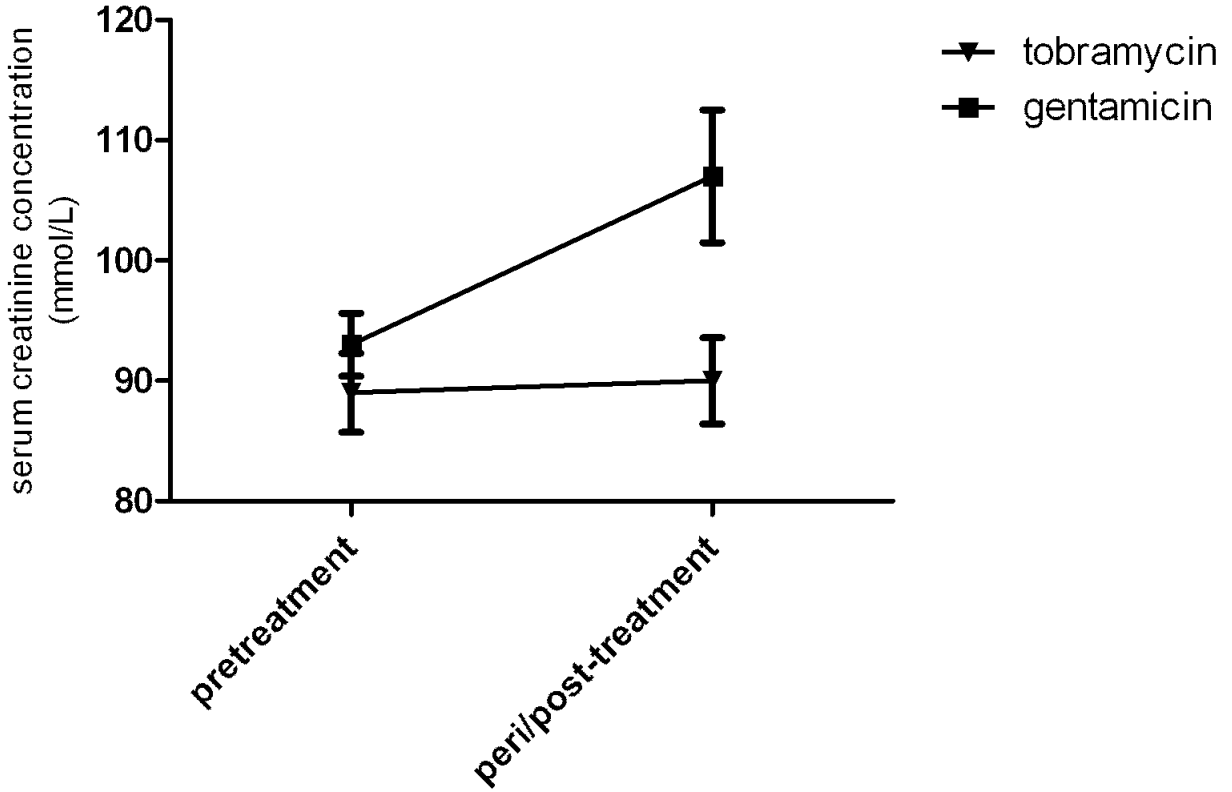
Van Maarseveen, JAC 2014

Study population





Results



RIFLE stage	gentamicin (n=202)	tobramycin (n=186)	OR	95%-CI	p-value
R	43	19	2.4	1.2-4.7	0.01
I	11	7	1.5	0.5-3.8	0.48
F	5	2	2.3	0.4-12.0	0.45

Post MIC effect

Time > MIC

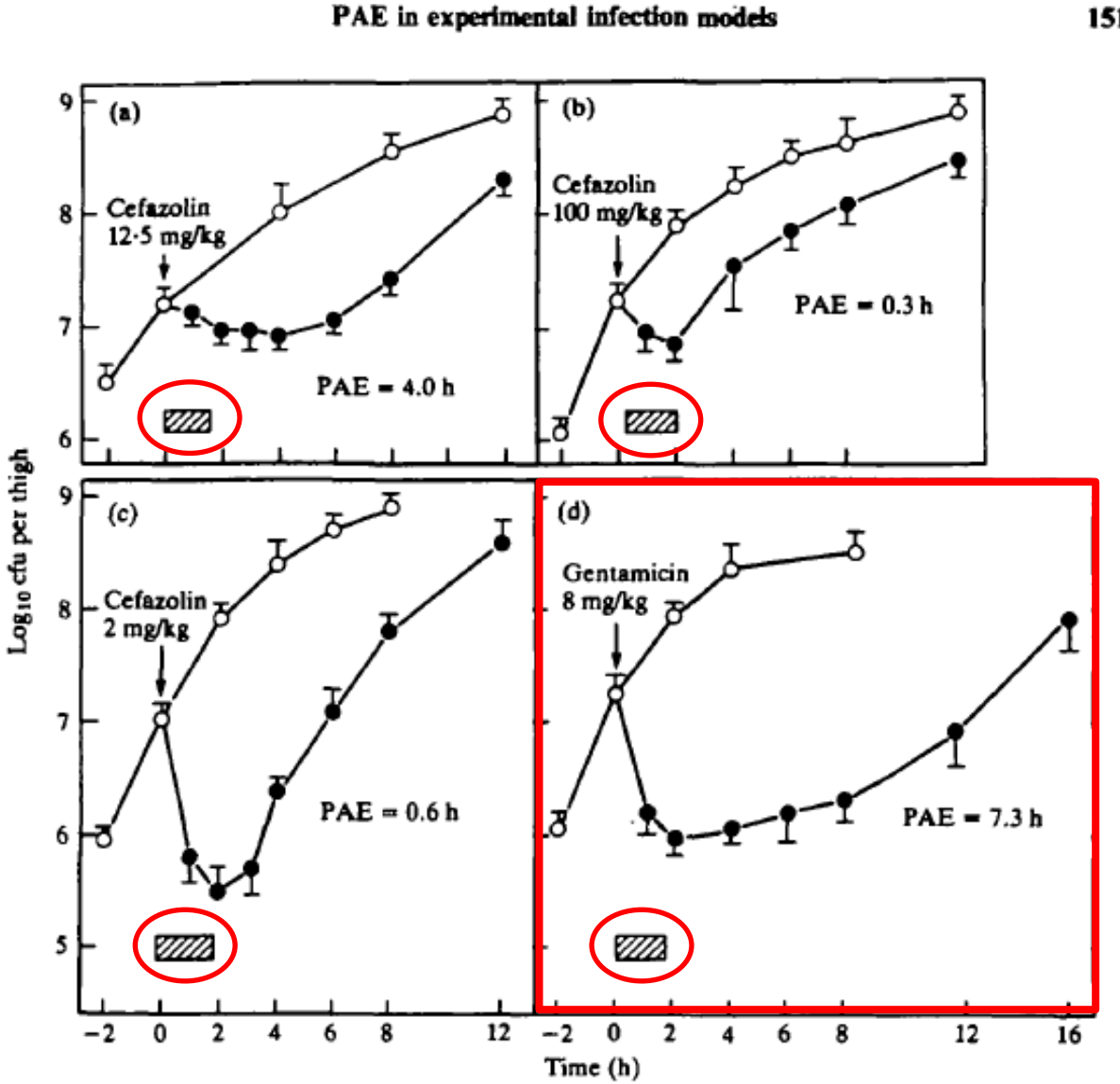


Figure 1. Growth curves in thighs of neutropenic mice with *S. aureus* ATCC 25923 (a) and *S. pneumoniae* ATCC 10813 (c) following a single 12·5 and 2 mg/kg doses of cefazolin, respectively, and with *K. pneumoniae* ATCC 43816 following a single 100 mg/kg dose of cefazolin (b) and 8 mg/kg of gentamicin (d). Each point represents the mean ± standard deviation (bars) of four to eight thighs. The width of each box with hatched lines represents the duration of time serum concentrations exceeded the MIC. The duration of in-vivo PAE is shown by each curve (○, control; ●, treated).

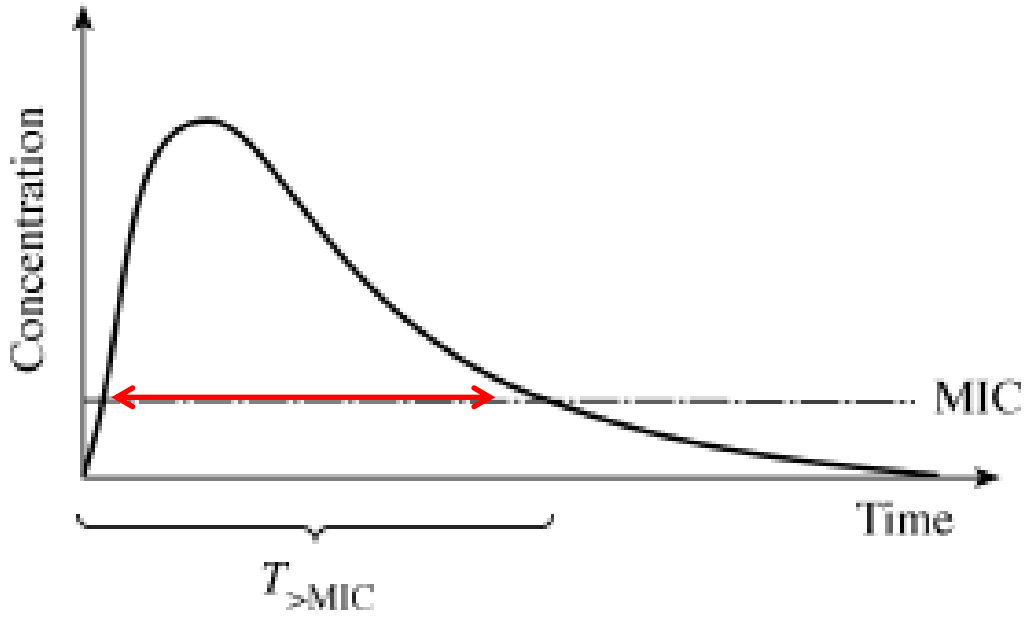
Craig, JAC 1993

Summary Aminoglycosides

- Concentration dependent killing of bacteria
- Peak/MIC ratio >8-10
- Post-MIC effect (7 hours)
- Increasing dosing interval decreases renal toxicity
- Tobramycin most probably less nephrotoxic than gentamicin

BETA LACTAM ANTIBIOTICS

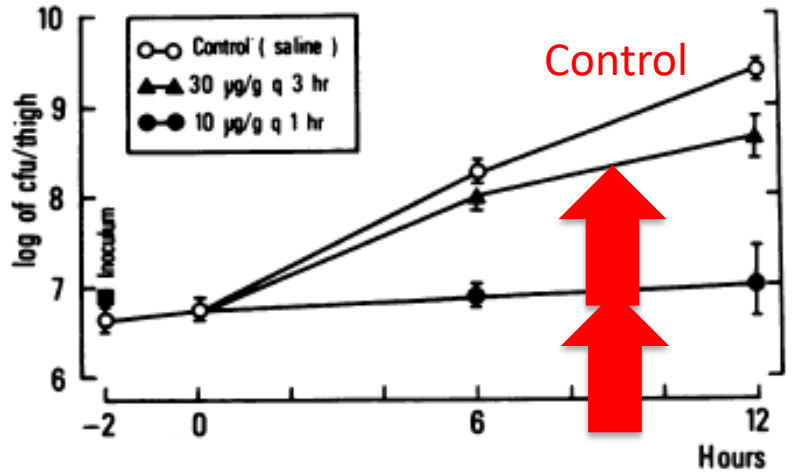
Time C > MIC

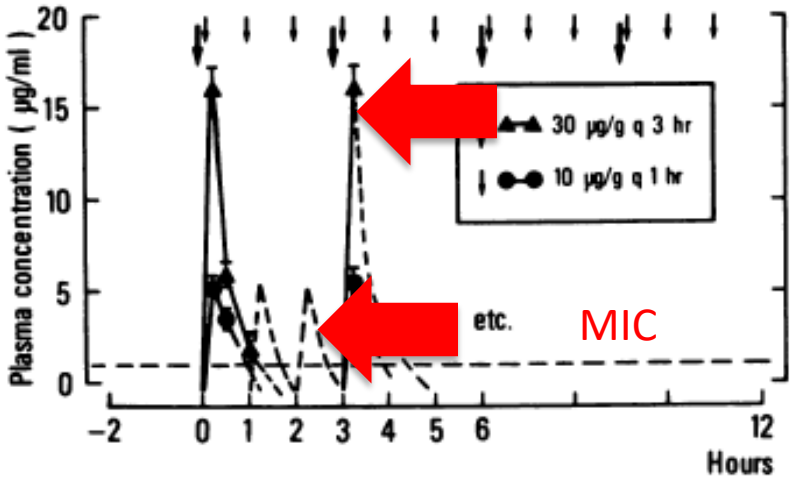


Beta-lactam antibiotics

- Bacterial growth with two dosing regimens of ticarcillin in neutropenic mouse P. aeruginosa infection models:

Dose	T>MIC	Outcome
30 mg/kg q 3hrs	35%	Growth
10mg/kg q 1h	60%	No growth





Gerber, J Inf Dis 1983

Time above MIC

- Neutropenic animal studies with penicillins, cephalosporins and carbapenems.

- Time > MIC:
  - At least 50%
  - Carb < Pen = Cef

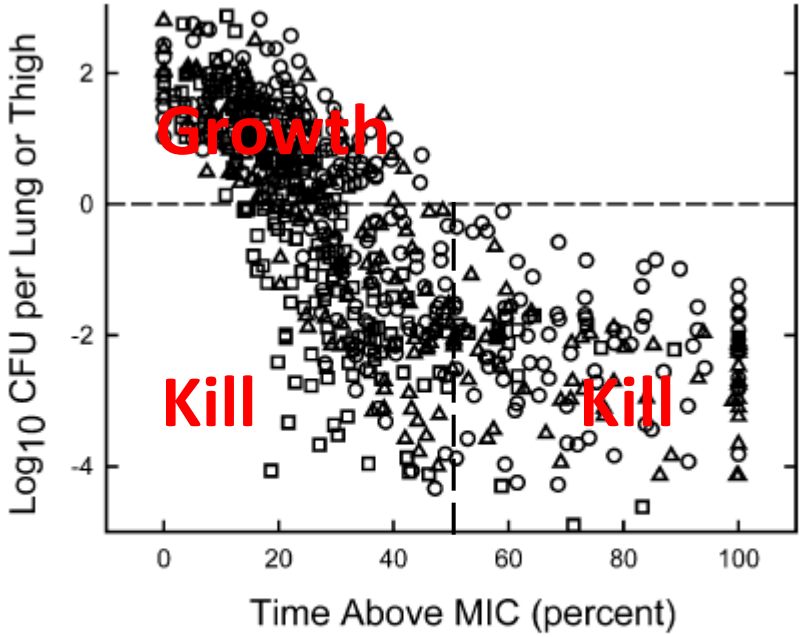


Fig. 7. Relationship between the change in $\log_{10}$ CFU per thigh or lung for various pathogens following 24 h of therapy with different doses of penicillins (△), cephalosporins (○), and carbapenems (□).

Andes and Craig, Int J Antimicrob Ag 2002

Continuous infusion

- P. aeruginosa exposed to ceftazidime c.i.
- Steady-state free concentrations studied:
  - 1x MIC (o - - o)
  - 4x MIC (+——+)
  - 16x MIC (Δ - - Δ)

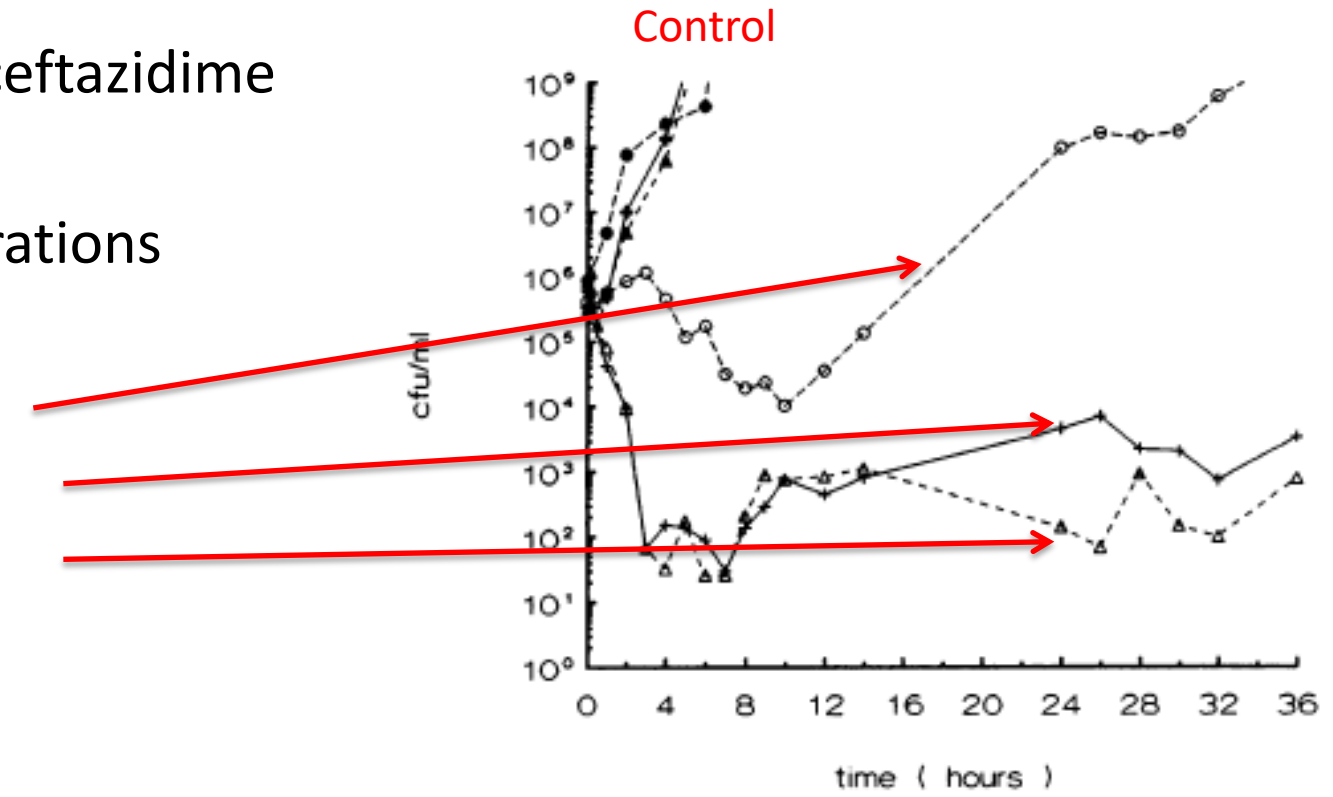


FIG. 5. Killing curves for *P. aeruginosa* AT1, CF4, and CF16 and growth controls during continuous infusion. Data shown are geometric means of at least two experiments. Symbols are as described for Fig. 4.

Mouton, AAC 1994

Clinical evidence in favor of c.i.?

Tamma *et al. BMC Infectious Diseases* 2011, **11**:181
http://www.biomedcentral.com/1471-2334/11/181

BMC Infectious Diseases

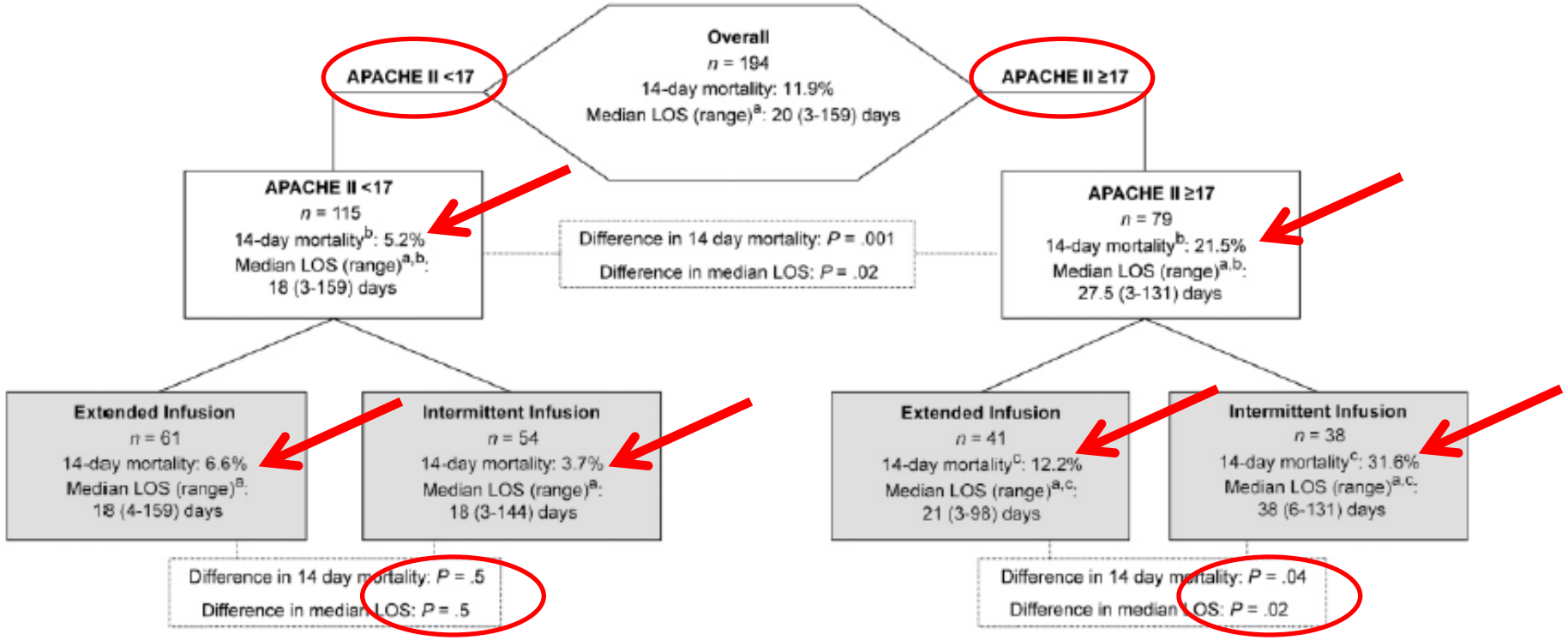
RESEARCH ARTICLE Open Access

Does prolonged β-lactam infusions improve clinical outcomes compared to intermittent infusions? A meta-analysis and systematic review of randomized, controlled trials

Pranita D Tamma[1*], Nirupama Putcha[2], Yong D Suh[3], Kyle J Van Arendonk[4] and Michael L Rinke[5]

Results: Fourteen randomized controlled trials (RCTs) were included. Prolonged infusion β-lactams were not associated with decreased mortality (n= 982; RR 0.92; 95% CI:0.61-1.37) or clinical cure (n = 1380; RR 1.00 95% CI:0.94-1.06) compared to intermittent infusions. Subgroup analysis for β-lactam subclasses and equivalent total daily β-lactam doses yielded similar results. Most studies had notable methodological flaws.

Clinical evidence for c.i.



Lodise, CID 2007

Protein binding

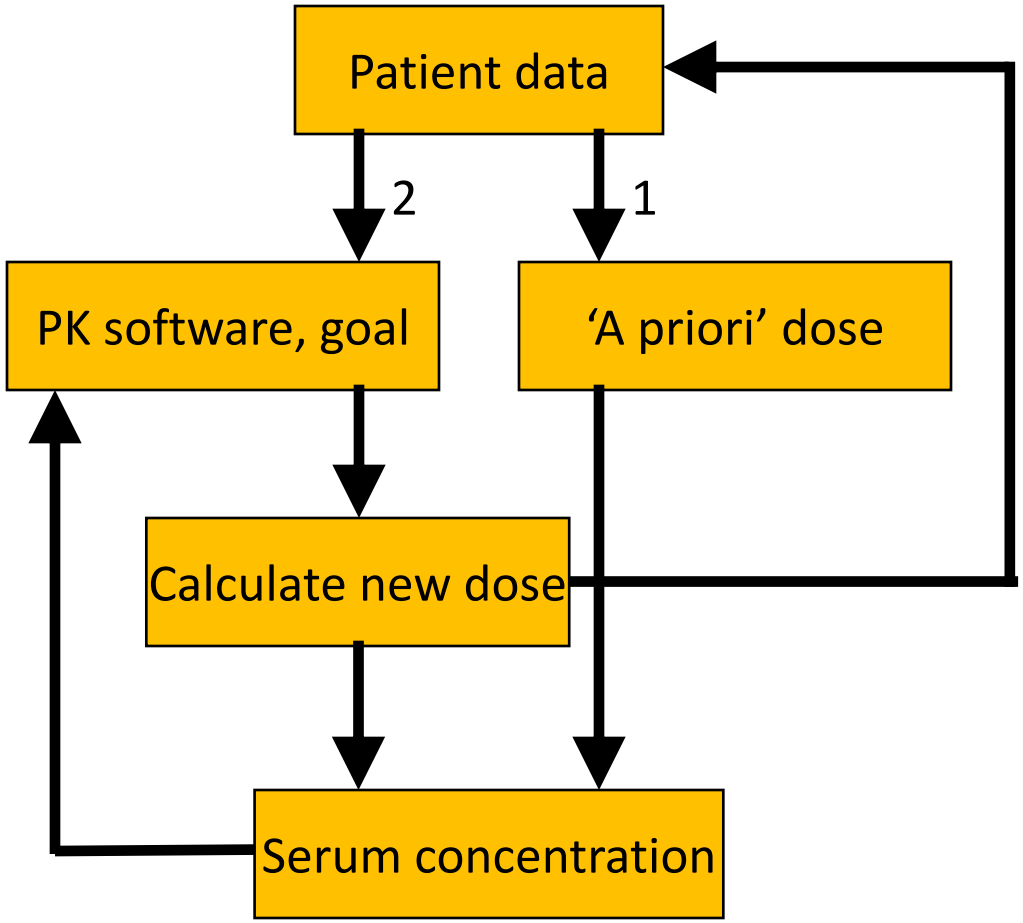
- Most beta-lactams are hardly bound to plasma proteins except:
  - Flucloxacillin: 95% protein bound
  - Ceftriaxone: 90-95% protein bound
- Free concentration is effective (flucloxacillin 5% of total)!
- Protein binding can get saturated at high levels
  - Increase of clearance: lower total concentrations
- Hypoalbuminemia can give saturation of protein binding at therapeutic levels or less
  - Increase of clearance: lower total concentration

HOW TO INTEGRATE THIS INTO TDM?

When TDM?

- With the present PK software equipped with a population PK model there is no need to wait for steady-state, besides, severely ill patients will never be in a steady-state.

P iple of Therapeutic Drug Monit g



- Goal-oriented, model-based dosing:
- Define the therapeutic goal.
- Start an optimal '*a priori*' dosing scheme based on a population PK model and patient data (gender, height, weight, renal function, …).
- Draw blood samples at one or more optimally chosen moments.
- Feed the data to the PK software.
- Calculate the new dose.
- Look at the response of the patient

TDM

- What you need for Therapeutic drug monitoring:
  - PK/PD targets
  - Population pharmacokinetic model for the '*a priori*' dose
  - Patient characteristics
  - Knowledge when to take sample(s)
  - Knowledge on the reliability of your assay results
  - Pharmacokinetic software (e.g. OPT, MWPharm)

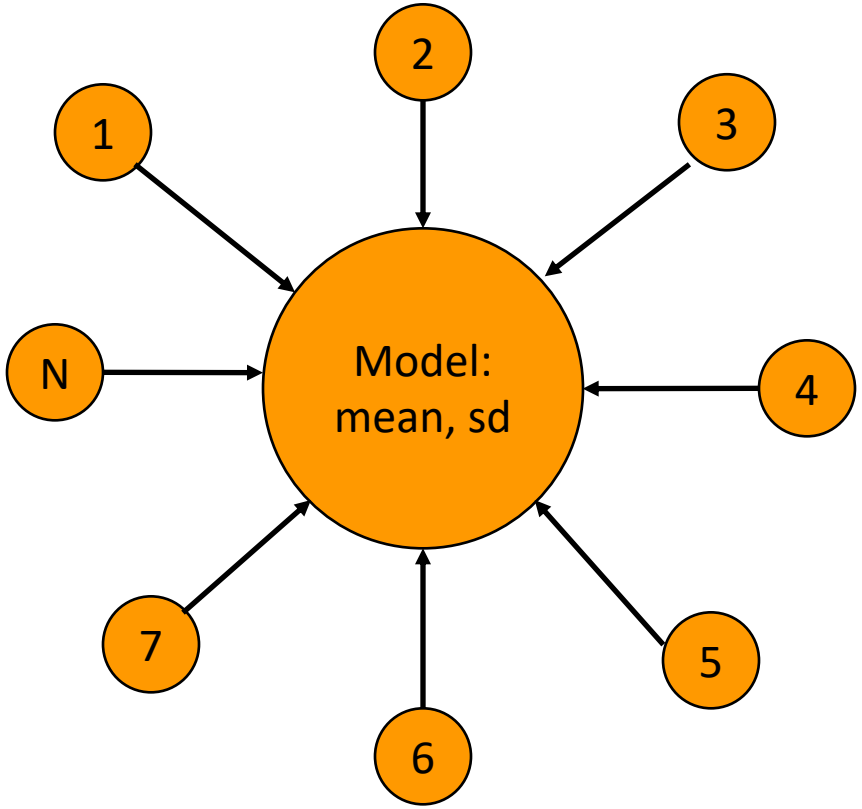
How do you know the PK in your patient to calculate the ‘a priori’ dose?

Individual PK parameters?

Population PK parameters

Individual PK parameters?

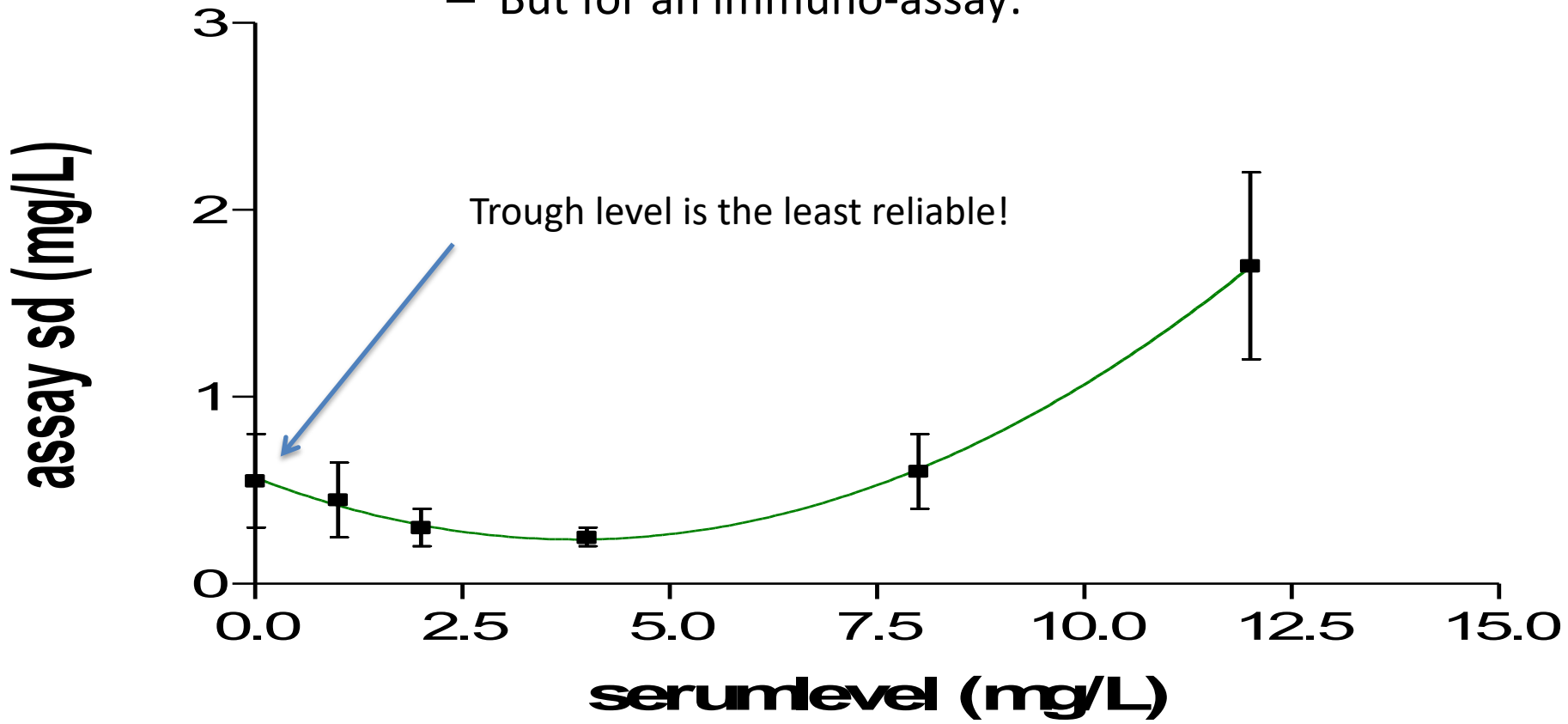
Population PK model:



Confounders: gender, height, body weight, renal function, ...

Reliability of the assay

- Description of the assay error:
  - E.g. for an HPLC assay: s.d. = LLOQ + 0.05 * C
  - But for an immuno-assay:

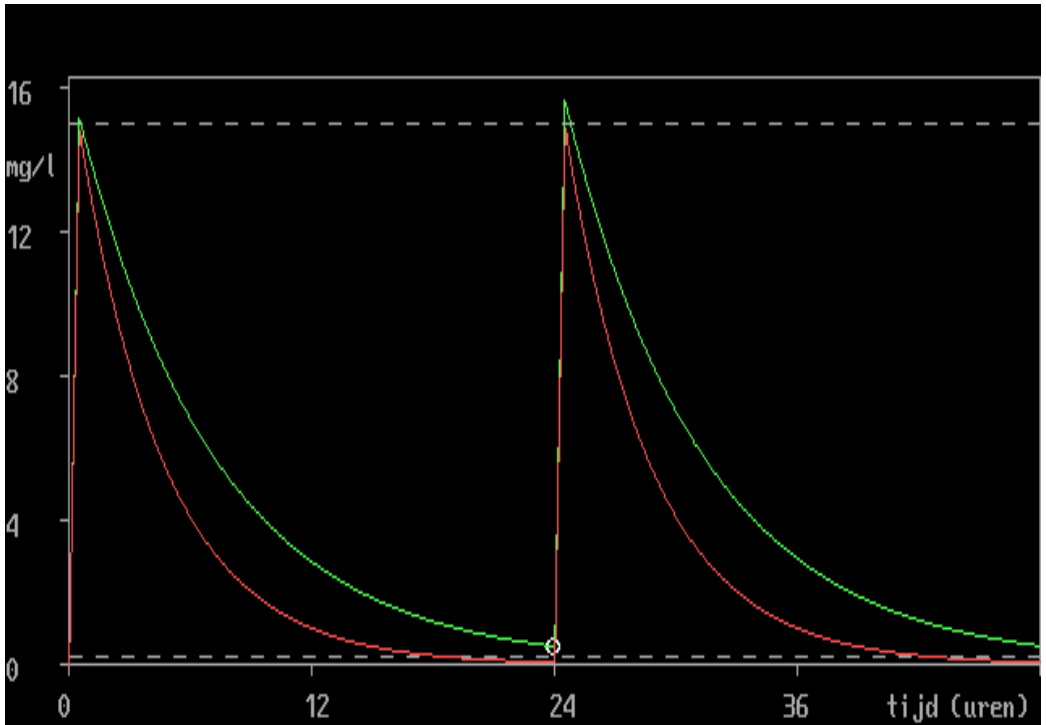


Trough level is the least reliable

- Suppose you only measure a trough level and the result is <0.5 mg/L. This means that the real result is somewhere between 0 and 1 mg/L.

– Red graph (trough = 0.1 mg/L): AUC=66

– Green graph (trough = 1 mg/L): AUC=104



Optimal sampling

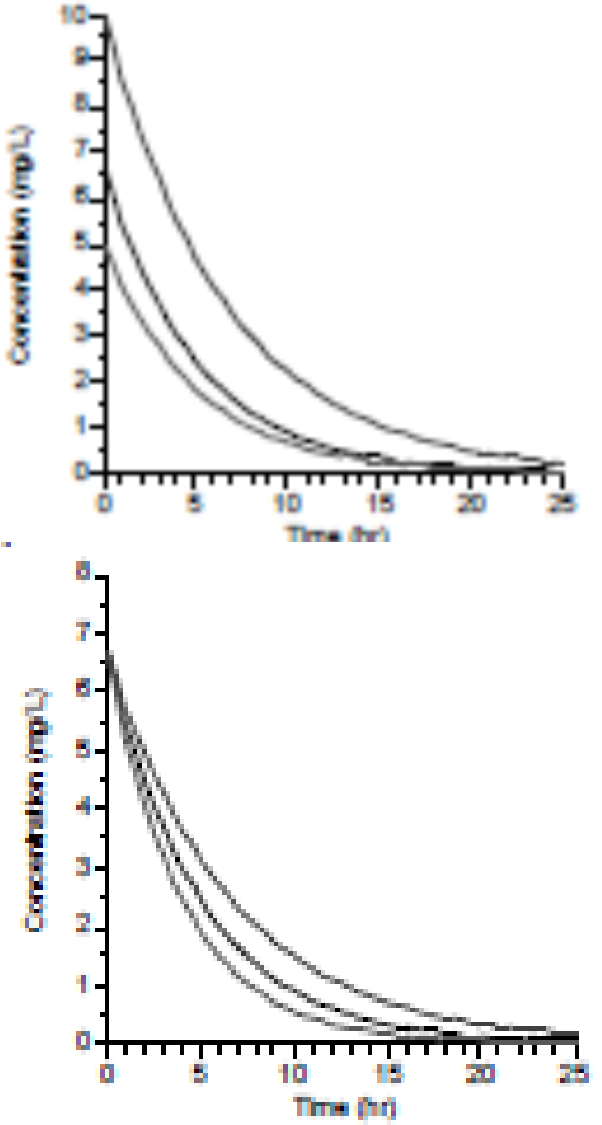
- Why optimal sampling?
  - You want the most of the information from a limited number of samples.
  - You want the best information from each sample.

D-Optimal sampling

PK described with Vd and Cl:
Every sample has different information:

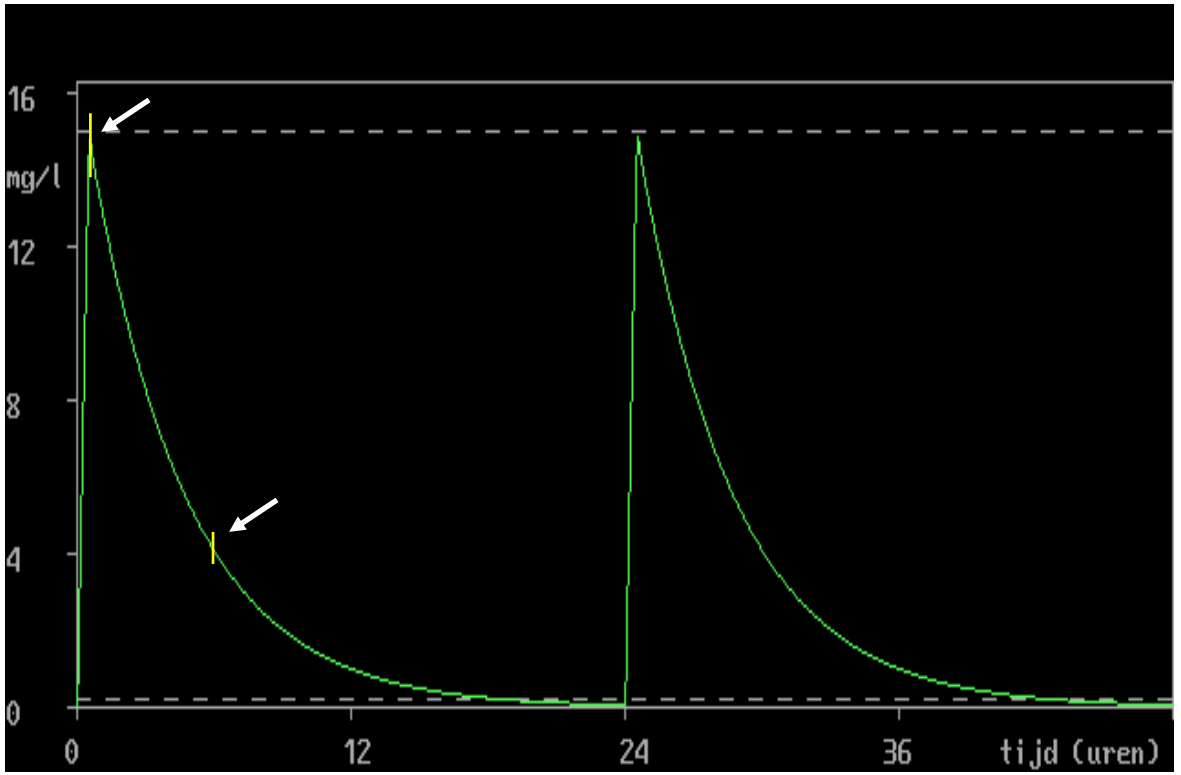
- Optimal sampling time for Vd:
  - differentiate dCp/dt = maximal:
  - t = end of administration

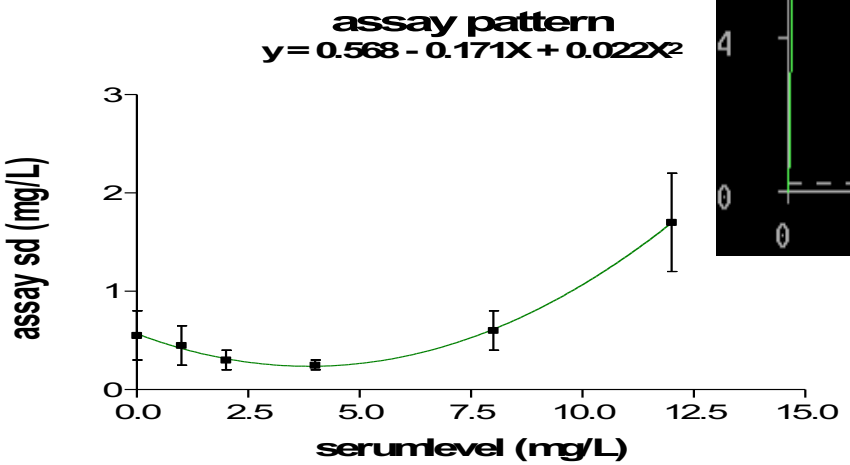
- Optimal sampling time for Cl:
  - differentiate dCp/dt = maximal:
  - t = 1/Kel (~1.5 x t1/2)



D-Optimal sampling

- Optimal sampling points:
  - 1. Cmax
  - 2. 1.5 x T1/2 later
- Opportunity to optimize the dose before the 2nd dose





Evidence for TDM?

- Efectiveness studies:
  - Van Lent Evers et al, 1999
  - Bartal et al, 2003

Outline TDM study

TDM Control group:

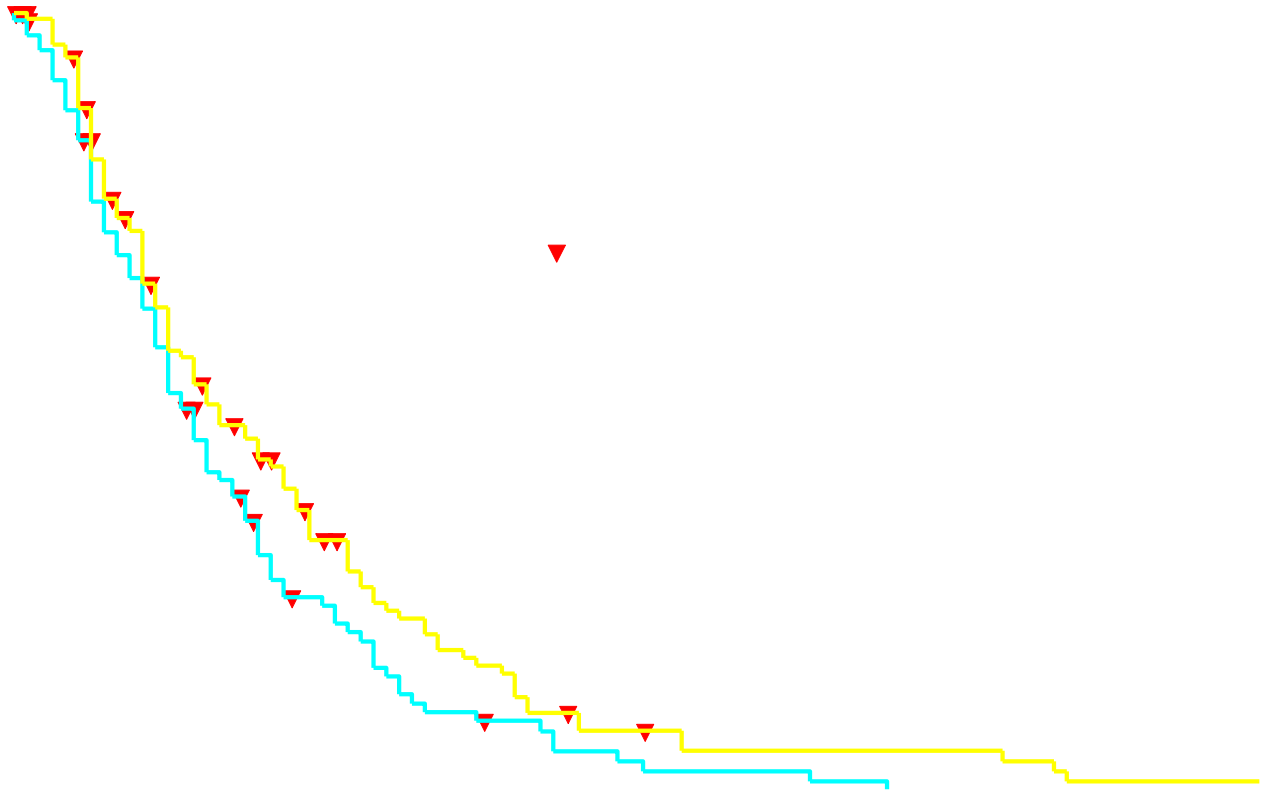
1. Aminoglycoside started as described in antibiotics protocol,
2. m.d. orders aminoglycoside levels,
3. Levels are measured and new dose is calculated by pharmacist.

Active TDM Intervention group:

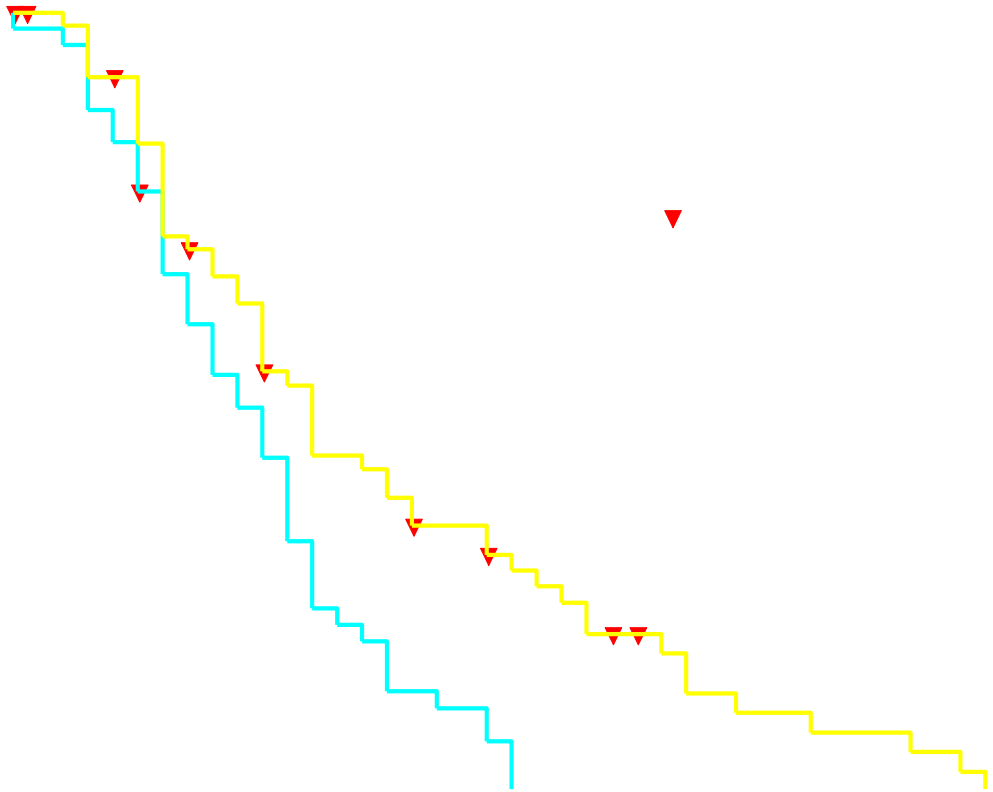
1. Pharmacist consulted **before** starting aminoglycoside for optimal dose,
2. Immediately **after first dose** 2 levels (D-optimal) are drawn,
3. Levels are measured and new dose is calculated by pharmacist **before 2nd dose**.

van Lent-Evers, Ther Drug Monit 1999

Patients with suspected or proven Gram(-) infection (All patients)



Patients with suspected or proven Gram(-) infection (Admitted patients)



Pharmacokinetic Dosing of Aminoglycosides: A Controlled Trial

Carmi Bartal, MD, Abraham Danon, MD, PhD, Francisc Schlaeffer, MD, Klaris Reisenberg, MD, Michael Alkan, MD, Rosa Smoliakov, MD, Aviel Sidi, MD, Yaniv Almog, MD

PURPOSE: To evaluate whether individualized pharmacokinetic dosing of aminoglycosides can reduce nephrotoxicity and improve the outcome of patients with gram-negative sepsis.

METHODS: We conducted a prospective controlled trial at a tertiary care university hospital. Eighty-one patients with suspected or documented gram-negative infections were enrolled. All were treated with either gentamicin or amikacin, according to clinical judgement. Patients were allocated to one of two groups based on the last digit (odd/even) of their identification number. In the study group (pharmacokinetic dosing) of 43 patients, plasma aminoglycoside levels were determined 1 hour after initiation of drug infusion and 8 to 16 hours later to estimate the elimination half-life and volume of distribution, from which the subsequent dosage schedule was calculated. Target peak plasma levels were 20 μg/mL for gentamicin and 60 μg/mL for amikacin. Target trough levels were <1 μg/mL for both drugs. The control group (fixed once-daily dosing) consisted of 38 patients who were prescribed single daily doses of gentamicin or amikacin. The primary endpoints were renal toxicity ($\geq$25% increase in serum creatinine level or a serum creatinine level $\geq$1.4 mg/dL) and 28-day mortality.

RESULTS: The two study groups were similar in age, sex, indications for therapy, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and clinical assessment at baseline. Although the pharmacokinetic group received significantly greater doses of aminoglycosides than did the once-daily group, the incidence of nephrotoxicity was significantly lower in the pharmacokinetic group (5% [2/43] vs. 21% [8/38], $P = 0.03$). There was no statistically significant difference in 28-day mortality (27% [12/43] vs. 22% [8/38], $P = 0.3$).

CONCLUSION: These results suggest that individualized pharmacokinetic dosing of aminoglycosides reduces the incidence of nephrotoxicity and allows the use of greater doses of aminoglycosides. **Am J Med. 2003;114:194–198.**

- Design:
  - Fixed dose (5 mg/kg) (N=38)
  - Peak/trough targeted dose (20/1 mg/L) (N=43)
- End points:
  - Nephrotoxicity (>25% rise of serum creat)
  - 28 days mortality
- Results:
  - No difference in mortality
    - 27% versus 22% (PK versus FD)
  - Significantly less nephrotoxicity
    - 5% versus 21% (PK versus FD)

Bartal, Am J Med 2003

Conclusions TDM studies

- TDM of aminoglycosides:
  - Improves patients outcomes,
  - Decreases morbidity (renal toxicity),
  - Reduces time spent in hospital,
  - Is cost-effective,
- … only if serum samples are drawn at the right moment and the right dose is calculated using goal oriented and model based

ANTIFUNGAL DRUGS

1991

TABLE I—RECOMMENDATIONS FOR LABORATORY MONITORING OF ANTIFUNGAL CHEMOTHERAPY

Antifungal drug	Sensitivity tests	Assays of serum concentration
Amphotericin B	Not required unless treatment failure or relapse	Not required
Flucytosine	Essential if drug used alone and for isolates recovered during treatment	Useful in all patients; essential if renal function impaired or if used in combination with amphotericin B
Ketoconazole	*Not required unless treatment failure or relapse	Useful if poor absorption suspected or treatment failure or relapse
Fluconazole	Not required unless treatment failure or relapse	Not required
Itraconazole	*Not required unless treatment failure or relapse	Essential if serious infection or poor absorption anticipated or treatment failure or relapse

*Measure serum concentrations of drug before doing sensitivity tests to ensure adequate levels are being achieved. For details of methods see text.

Lancet 1991:

‘in case of failure or relapse’

1997

Table IV. Recommendations for antifungal therapeutic drug monitoring[a]

Antifungal agent	Recommended concentration	Timing of sample	Targeted patient populations
Flucytosine	< 100 mg/L	peak level (2 h post-dose) after 24 h of therapy	decreased or changing renal status, current bone marrow suppression, suspected noncompliance
Ketoconazole	detectable	trough level (pre-dose) after 48 h of therapy	suspected malabsorption, concurrent acid-modifying agents, suspected noncompliance, inadequate response to therapy, potential drug interactions
Itraconazole	detectable	after 7–10 days of therapy[b], non-steady-state trough levels may be obtained earlier if needed	suspected malabsorption, concurrent acid-modifying agents, suspected noncompliance, inadequate response to therapy, potential drug interactions
Fluconazole	detectable	after 5–7 days of therapy[b], non-steady-state trough levels may be obtained earlier if needed	suspected noncompliance, inadequate response to therapy, potential drug interactions

[a]TDM for amphotericin B is not recommended.
[b]Based on the extended half-lives of itraconazole (~20–60 h) and fluconazole (~30 h), timing of the sample in relation to administration of the dose has little influence on the concentrations once steady state is reached.

Summers, JAC 1997

2008

Table 1. Summary of data supporting the application of serum concentration monitoring for newer antifungal agents

Medication	Serum concentration monitoring recommended	Peak	Trough	Comment
Amphotericin B	no	n/a	n/a	
Flucytosine	yes	2 h post-dose: 30–80 mg/L for cryptococcal infections; 40–60 mg/L for candidal meningitis	n/a	toxicity seen with 2 h post-dose concentrations >100 mg/L
Fluconazole	no	n/a	n/a	
Itraconazole	yes	n/a	>0.5 to 1 mg/L	to ensure adequate absorption
Voriconazole	yes[a]	<6 mg/L	>2 mg/L	to ensure efficacy, limit toxicity
Posaconazole	yes[a]	>1.48 mg/L[b]	n/a	limited data, average concentration of 1.25 mg/L associated with 75% response[b]
Caspofungin, micafungin and anidulafungin	no	n/a	n/a	

[a]Consider (when available) in 'non-responders', questionable medication compliance, significant drug–drug interactions, suspected toxicity.
[b]Data based on treatment of *Aspergillus* with posaconazole.

Goodwin, JAC 2008

2014

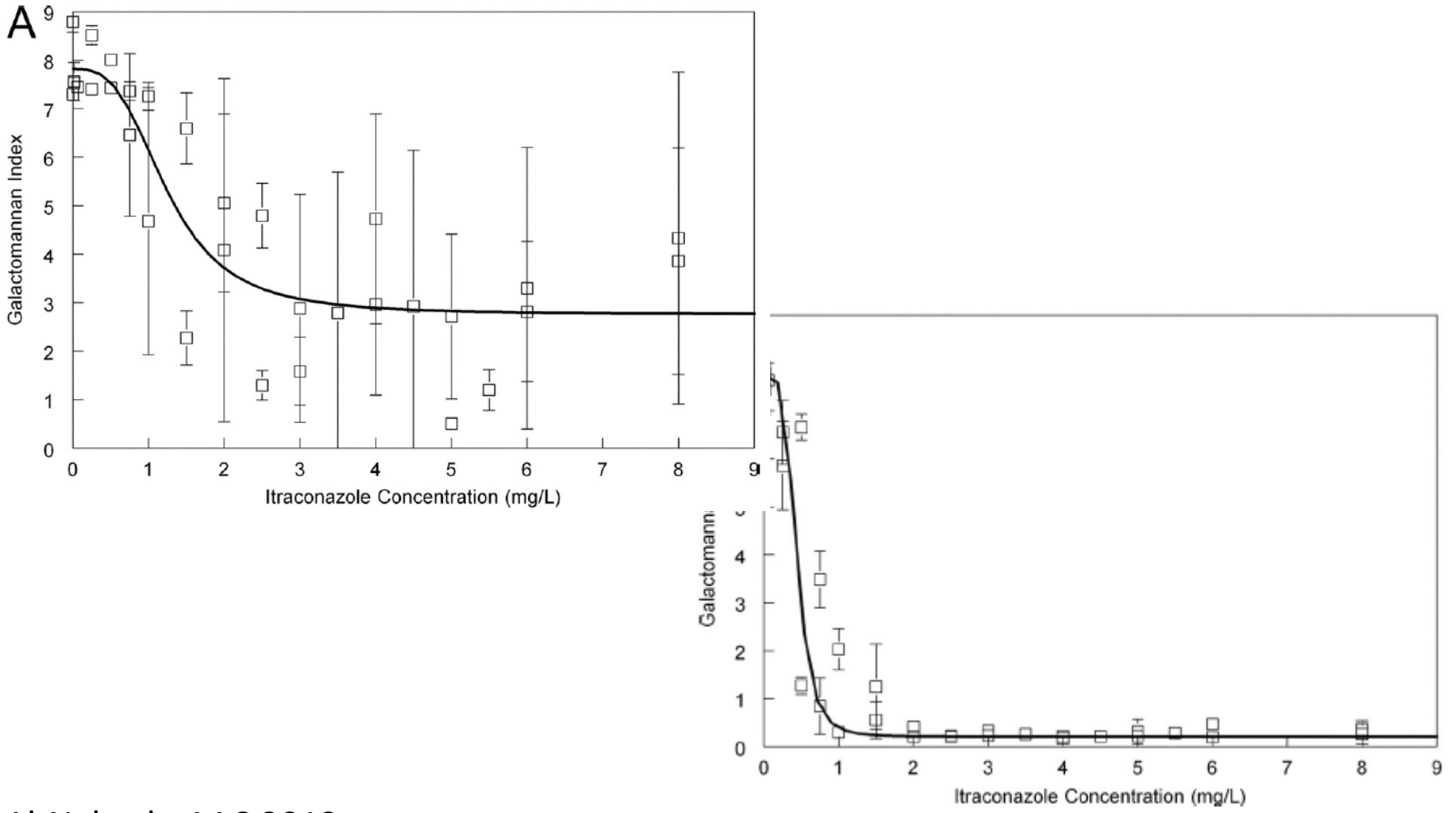
Table 5. Recommendations for TDM for itraconazole

Patient group	Specific indication	Quality of evidence	Strength of recommendation
Immunocompromised patients receiving itraconazole for prevention of invasive fungal infection	target trough concentration for prophylaxis is 0.5 mg/L	high	strong
	measurement of trough serum concentrations 5–7 days after initiation of therapy or dose adjustment	high	strong
	when interacting drugs start or stop (either inhibiting absorption or affecting metabolism)	high	strong
	uncertain compliance with oral therapy	high	strong
	concerns about gastrointestinal absorption	low	weak
	potential clinical or laboratory manifestations of toxicity occur	moderate	strong
Patients receiving itraconazole for established invasive and allergic fungal diseases	target trough concentration for treatment is >0.5 mg/L	moderate	strong[a]
	measurement of trough serum concentration 5–7 days after initiation of therapy or dose adjustment	high	strong
	when interacting drugs start or stop (either inhibiting absorption or affecting metabolism)	high	strong
	uncertain compliance for oral therapy	high	strong
	concerns about gastrointestinal absorption, especially for prolonged periods of time	low	weak
	potential clinical or laboratory manifestations of toxicity occur	low	weak

[a]The target concentration for treatment is inferred from prophylaxis data, although there are few treatment studies that have addressed this.

Ashbee, JAC 2014

PD marker: galactomannan

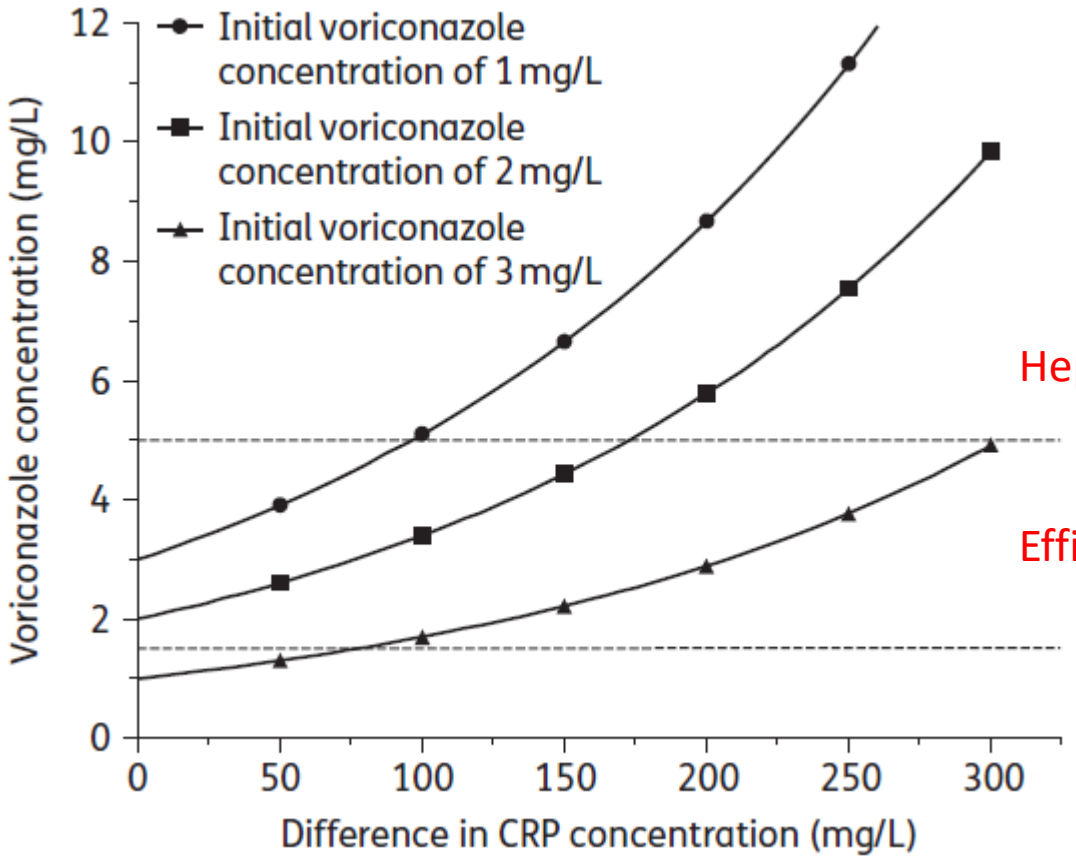


Al-Nakeeb, AAC 2012

Azole Target concentrations

- Fluconazole: C_{min} >10 mg/L
- Itraconazole: C_{min} >1.0 mg/L
- Voriconazole: C_{min} >1.5 mg/L, >5 mg/L hepatic damage
- Posaconazole: C_{min} > 1.5 mg/L
- Isavuconazole: ?

Voriconazole caveat



Hepatic toxicity

Efficacy

Veringa, JAC 2016

Voriconazole-N-oxide

Table 1. Voriconazole/voriconazole-*N*-oxide concentrations in relation to typical clinical situations

	Low voriconazole	High voriconazole
Low voriconazole-*N*-oxide	non-compliance malabsorption	poor metabolizer/ intermediate metabolizer hepatic impairment DDI: CYP450 inhibitor inflammation
High voriconazole-*N*-oxide	DDI: CYP450 inducer ultra-rapid metabolizer	overdose

DDI, drug–drug interaction.

Veringa, JAC 2016

TDM is like a nice but complex meal

pe I have sorted out all ingredie

Happy to answer your questions