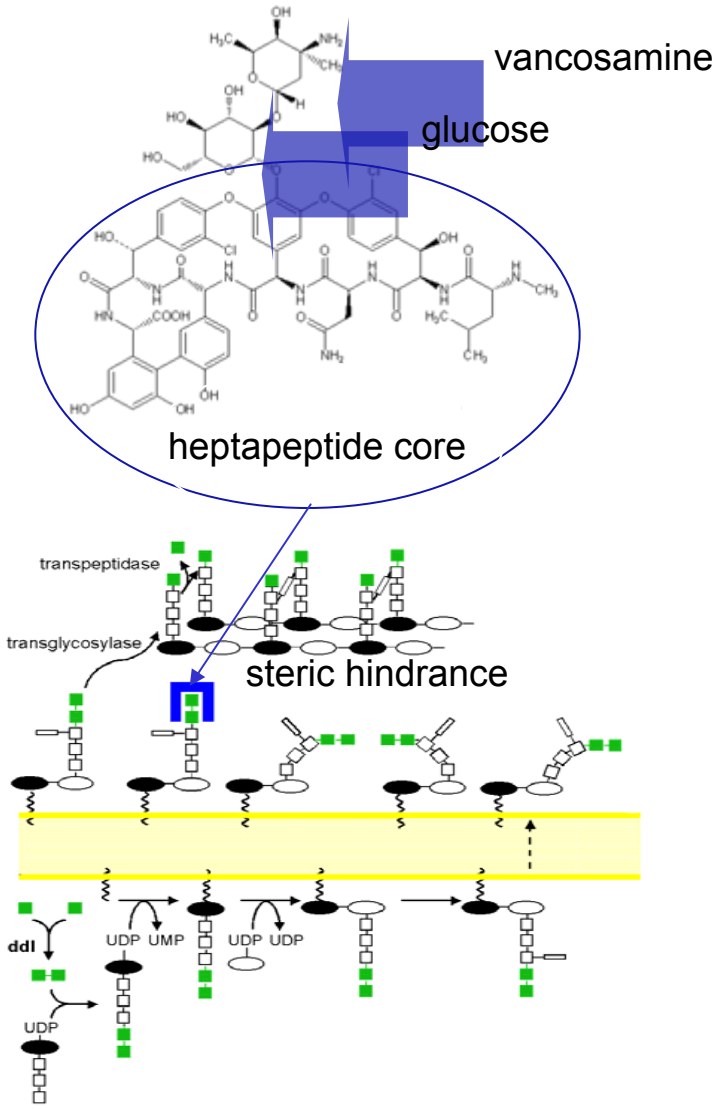
Continuous Infusion of Vancomycin in non-ICU Patients

Why, How and What's the Benefit?

Els Ampe, Pharm.

September 2nd 2013

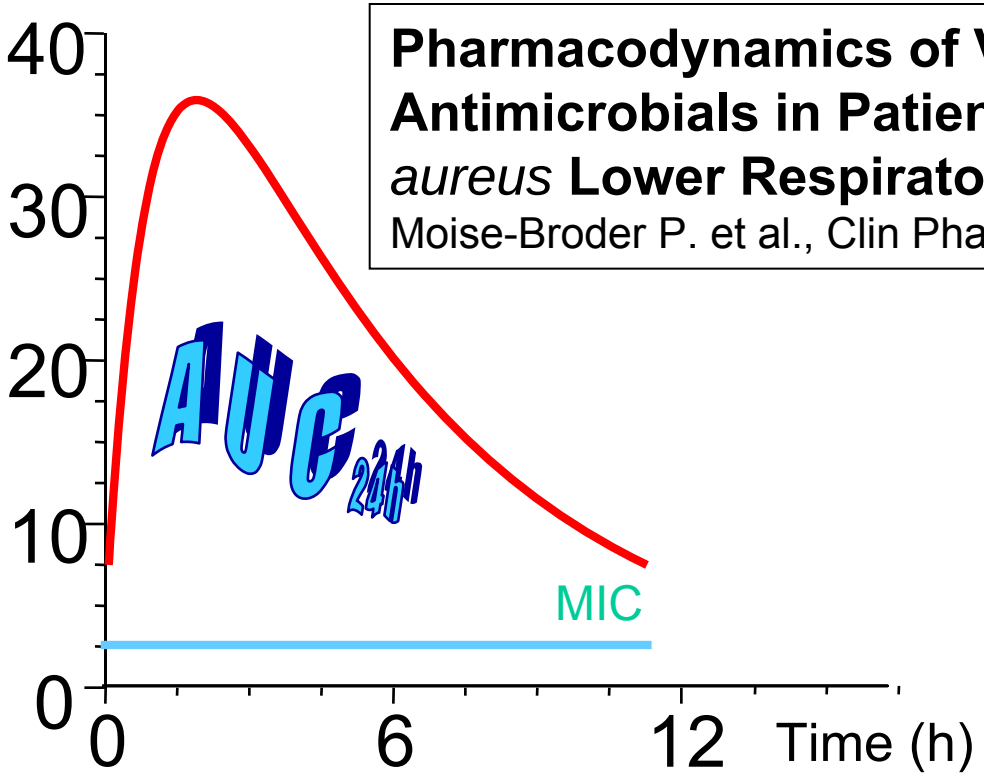
General introduction:



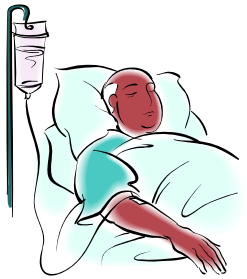
- glycopeptide AB isolated from a soil sample from Borneo containing *Amycolatopsis Orientalis* (1950's)
- inhibits bacterial cell wall synthesis
- limitations
  - slow killing rate
  - limited tissue penetration
  - organisms with decreased susceptibility
  - higher doses lead to increased toxicity
- still 1st line treatment of most methicillin-resistant Gram-positive infections

General introduction
how to optimize vancomycin treatment

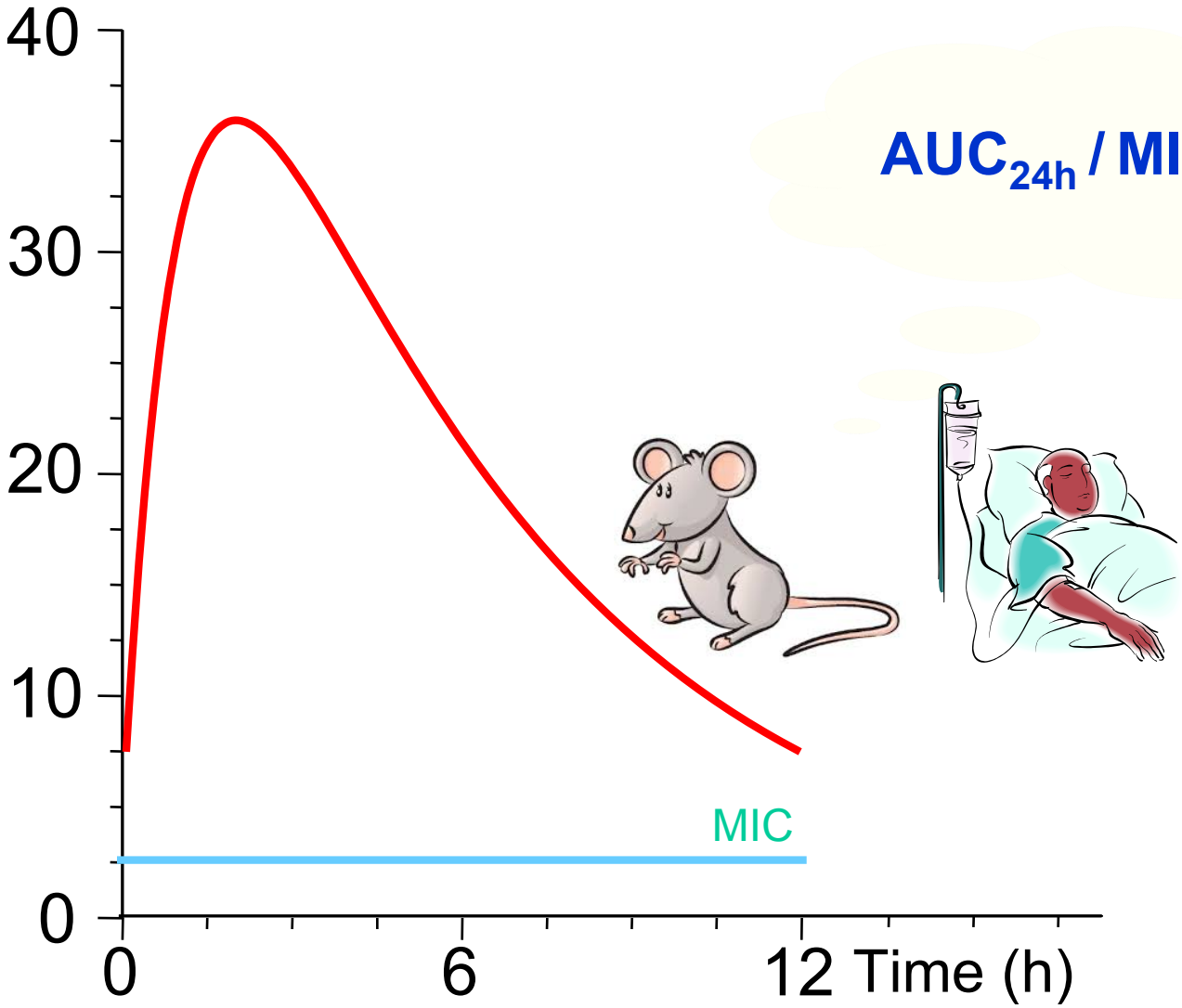
Basic pharmacodynamics of antibacterials with clinical applications to the use of β-lactams, glycopeptides, and linezolid. Craig W. et al., Infect Dis Clin N Am 17 (2003)



Pharmacodynamics of Vancomycin and Other Antimicrobials in Patients with *Staphylococcus aureus* Lower Respiratory Tract Infections
Moise-Broder P. et al., Clin Pharmacokinet 2004; 43 (13)



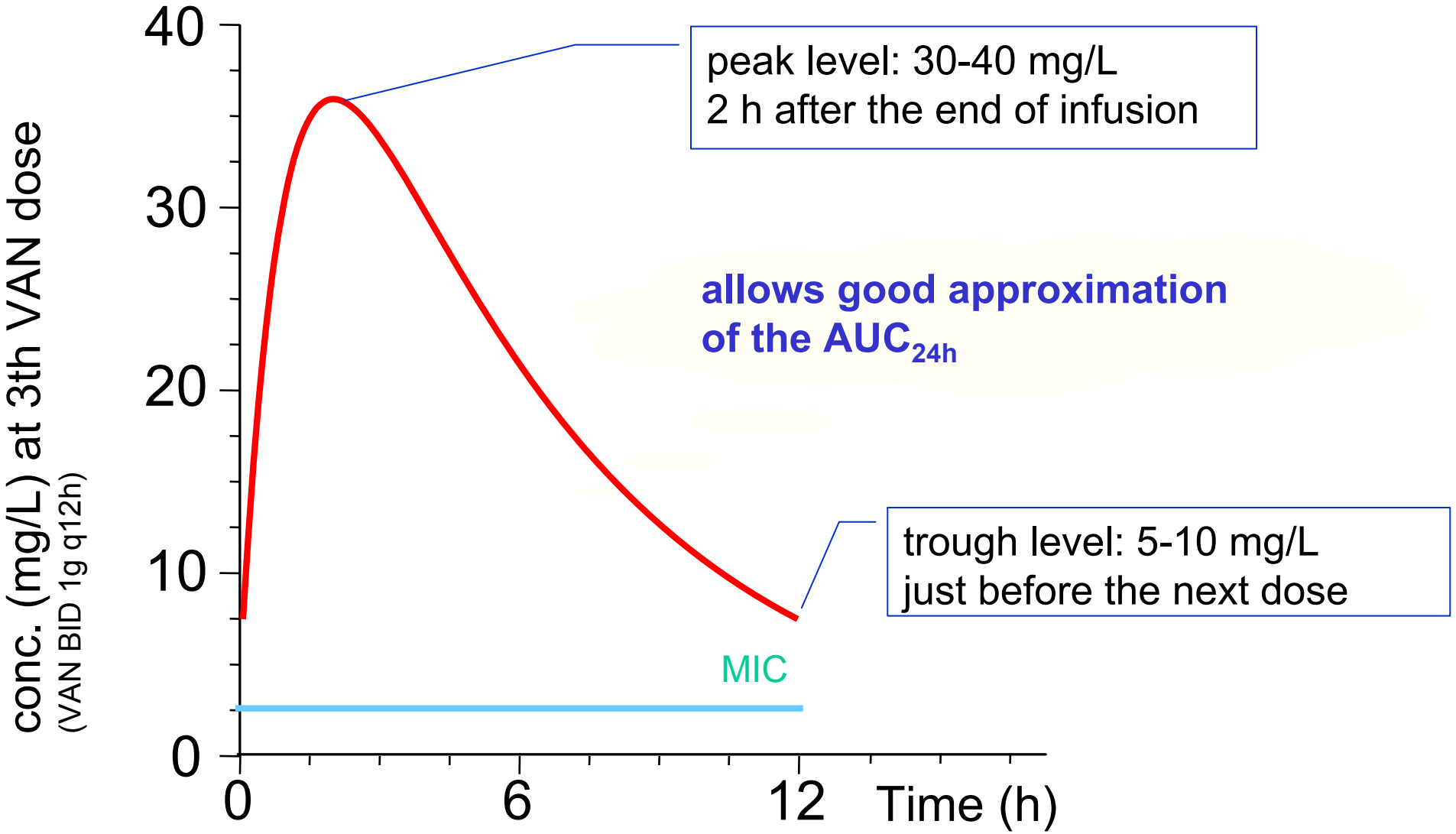
General introduction
how to optimize vancomycin treatment



AUC_{24h} / MIC = 400

General introduction

Vancomycin TDM at CHU Mont-Godinne at the start of the project



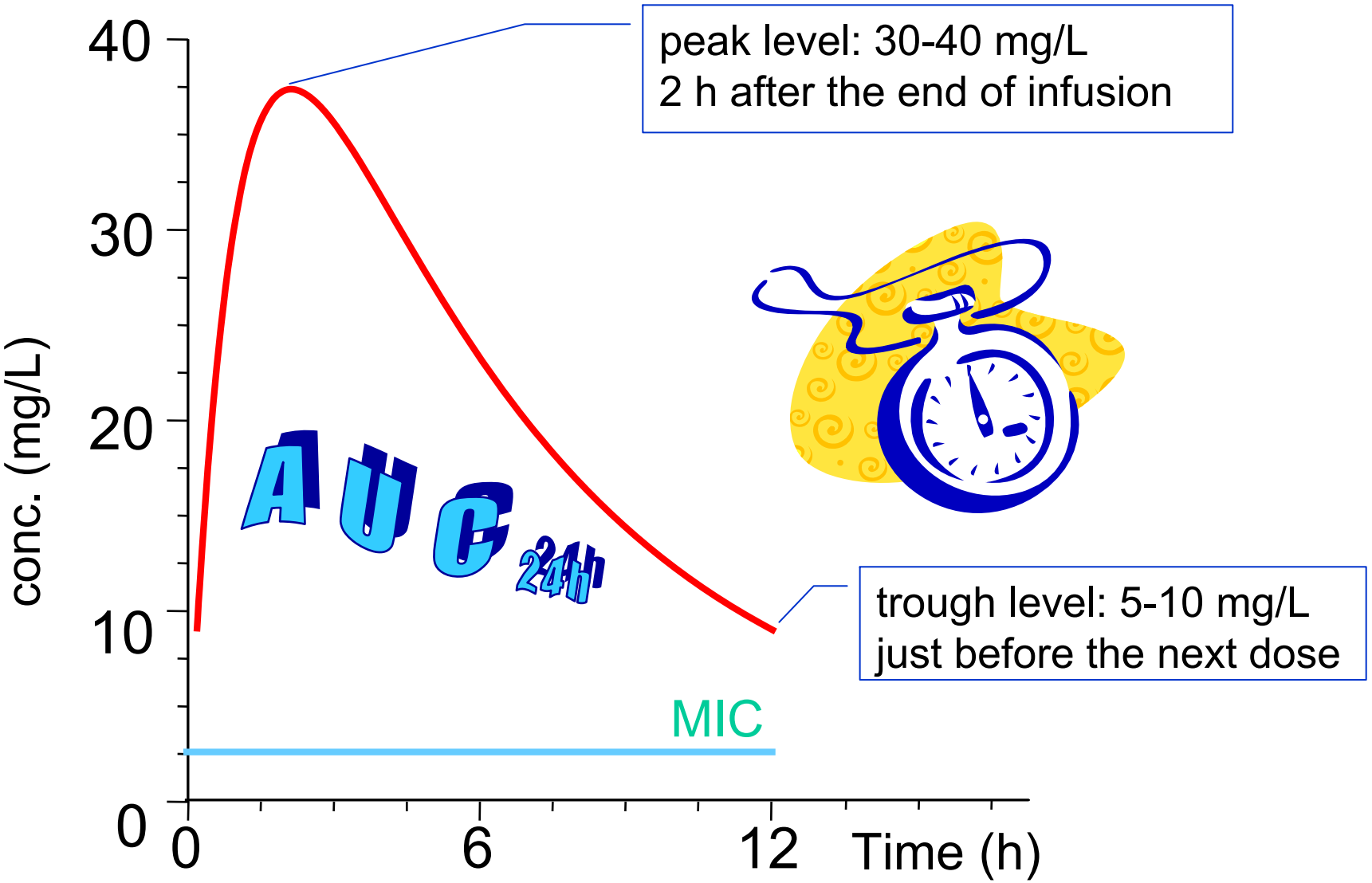
Vancomycin administration and therapeutic drug monitoring (TDM) from a quality of care perspective

Overcoming Insufficiencies in Therapeutic Drug Monitoring of Vancomycin in a European Setting by Switching from Intermittent Administration to Continuous Infusion: a Combined Observational and Qualitative Study.*

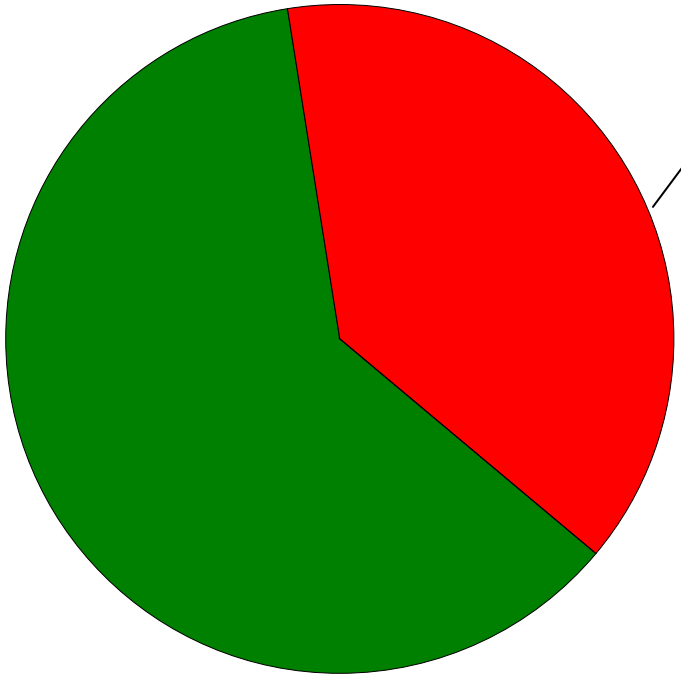
Els Ampe, PharmD; Bénédicte Delaere, MD; Anne Spinewine, PharmD, PhD; Julien Pierart, PhD; Catherine Bouland, PhD; Jean-Daniel Hecq, PharmD, PhD; Paul M. Tulkens, MD, PhD and Youri Glupczynski, MD

* Submitted

Vancomycin TDM at CHU Mont-Godinne at the start of the project



Observational study – results

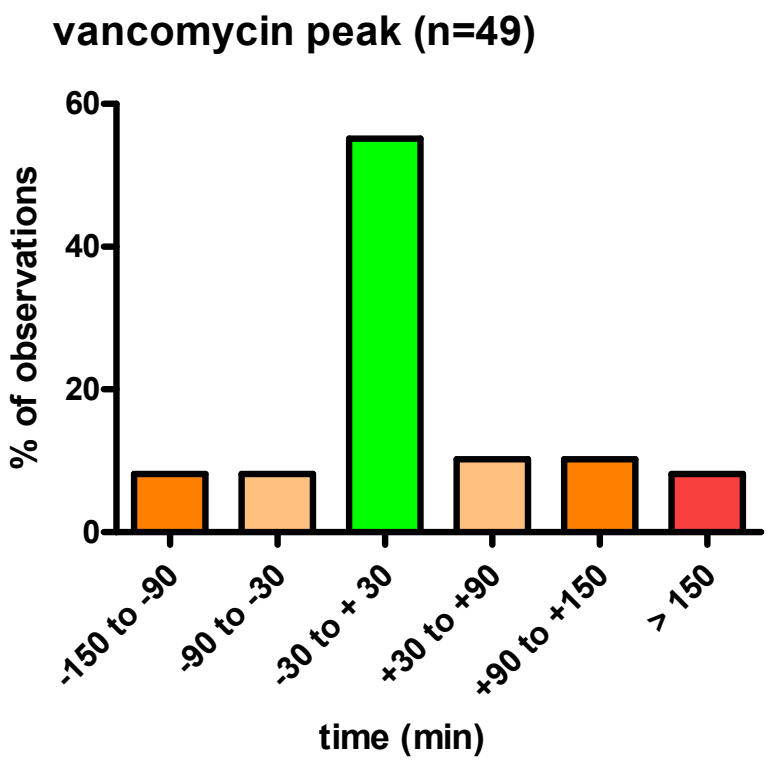


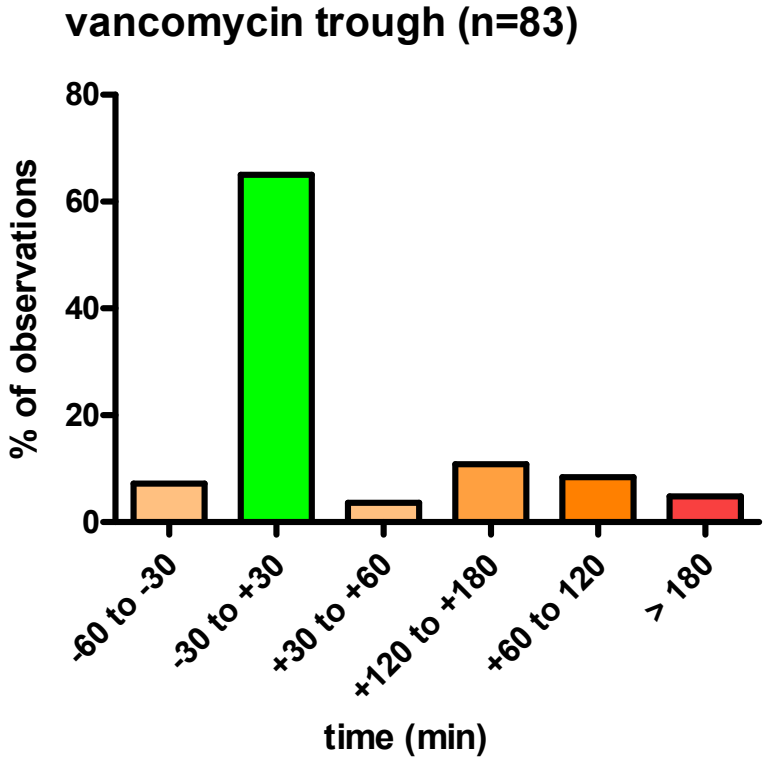
40% incorrect sample timing

*within 30 min. of recommended sample timing: peak 2h after the end of infusion, trough: just before the next dose

Observational study – results

Observed deviations (in min) from recommended sampling times at baseline.





*within 30 min. of recommended sample timing: peak 2h after the end of infusion, trough: just before the next dose

Observational study – results

TDM process measures for twice daily (BID; baseline) mode of administration of vancomycin

Criterium	BID
Sample timing within 30 min. from scheduled time	61.3% [81/132] [a]
Implementation of TDM dose recommendations	32 % [21/66]
Prescribed daily dose in accordance with hospital guidelines	17% [95/560]
% of serum levels in the recommended ranges	33.3% [37/112] [b]

[a] number of total observations (see Table 1 for the number of patients)
[b] most deviations were towards lower than expected values (average: 20 %)

Qualitative methods in healthcare

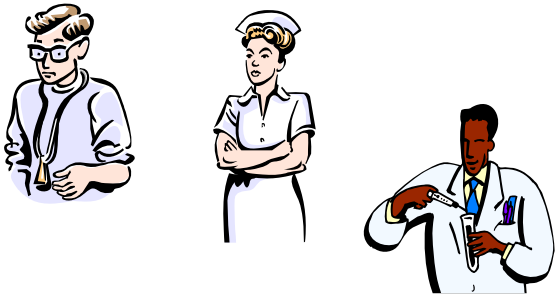
Quantitative methods (clinical trials)	**Qualitative methods (interviews, observations, notes)**
'how many'?	'why?' and 'how?' (hypothesis generating)
what is the % of inappropriate TDM? *what is the impact of x on this %?*	*why/how does inappropriate TDM occur?*
large, random samples	small, purposive samples

Qualitative study – results

Emerging themes identified during the analysis of the transcripts of the focus groups and related to low TDM performance and deviations from local TDM guidelines during the baseline phase (BID).

Socio-cultural and structural elements	-inertia of practice
	-lack of motivation and personal involvement
	-insufficient interdisciplinary collaboration
	-unclear definition of responsibilities
	-ill-adapted techniques
Training and information	-insufficient (post-) graduate education
	-'teacher-centred' learning approach
	-incomplete and/or difficult to apply local guidelines
	-conflict between local guidelines and external guidelines
harm-benefit ratio of TDM	-patient too frail
	-unnecessary samplings for the information gained

Qualitative study – results



M2: "I'm convinced that there are pharmacokinetic calculations on which we will base [our next dosing] and which are erroneous because the sample drawing and the timing of the administration have not been made correctly, it is completely random, I mean… "

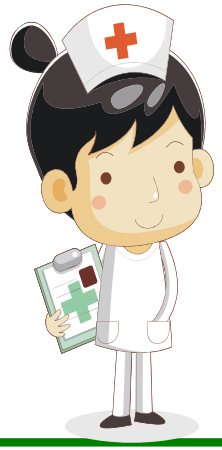
M1: "It is forbidden, on my ward, to follow the therapeutic recommendations of the laboratory, what the lab proposes."

N2: *"It represents a lot of additional samples for frail patients. Sometimes, I ask myself whether all these samples are necessary."*

Discussion

- combined observational and qualitative approach
  - identify factors related to poor performance.
- only “process measures”, no “outcome measures”
  - limited number of patients in the observational study (could not be extended for ethical reasons)
- studies performed in one single hospital prevents from generalization but the results can be decontextualized, this applies to:
  - similar baseline TDM scores have recently been observed in other European hospitals (Bailie GR *et al* Therapeutic Drug Monitoring 1988; vol: 10 p292-p295, Roustit M *et al* Scand J Infect Dis 2010; vol 42:177-184)
  - organisational and structural issues and aspects related to training including passive attitude towards learning have been identified elsewhere
- “Hawthorn effect”

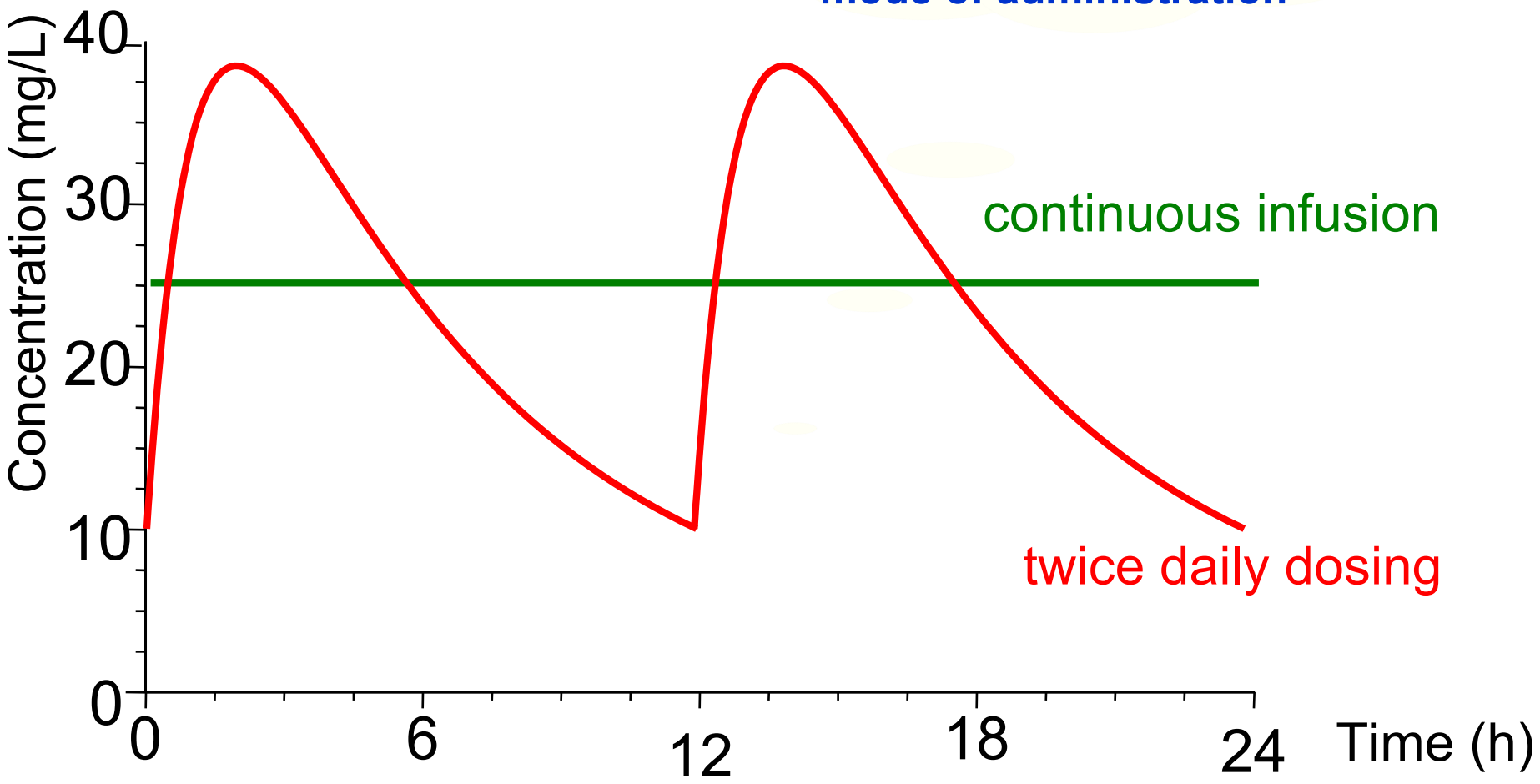
how to optimize vancomycin treatment



"Continuous infusion is easier because it allows to control the duration of administration and samples can be taken at any time"

TDM of vancomycin by continuous infusion

AUC24h /MIC independent of the mode of administration



Vancomycin administration and therapeutic drug monitoring from a PK/PD perspective

Implementation of a Protocol for Administration of Vancomycin by Continuous Infusion: Pharmacokinetic, Pharmacodynamic and Toxicological aspects

E. Ampe, PharmD; B. Delaere, MD; J.D. Hecq, PharmD, PhD; P.M. Tulkens, MD, PhD; Y. Glupczynski, MD

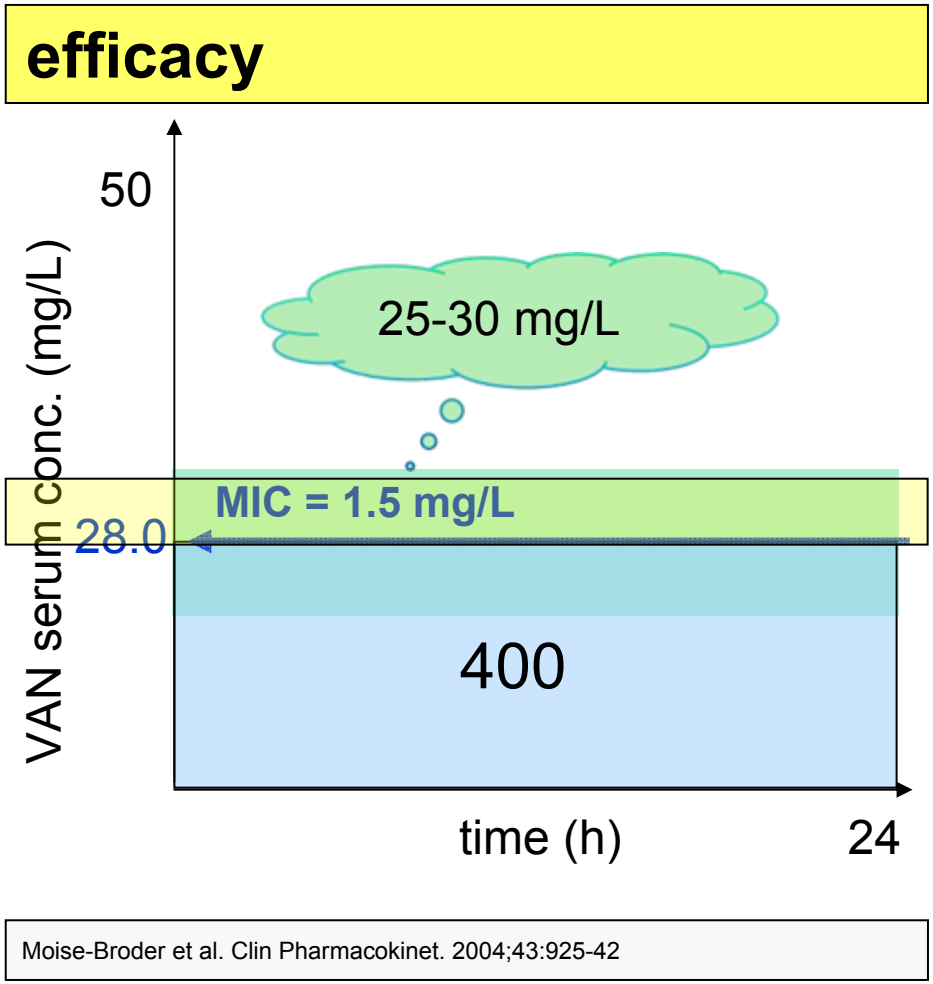
Int J Antimicrob Agents. 2013 May;41(5):439-46

vancomycin CI: which serum concentration should we target?

Data from a recent study point at a vancomycin AUC_{24h}/MIC of at least 400 to obtain optimal clinical outcome in patients with *S. aureus* lower respiratory tract infections (Moise-Broder et al., Clin Pharmacokinet. 2004;43(13):925-42)

MIC (mg/L)	minimal AUC ($mg*L^{-1}*h$)	target Css (mg/L)
1	400	16.6
2	800	33.3
4	1600	66.6

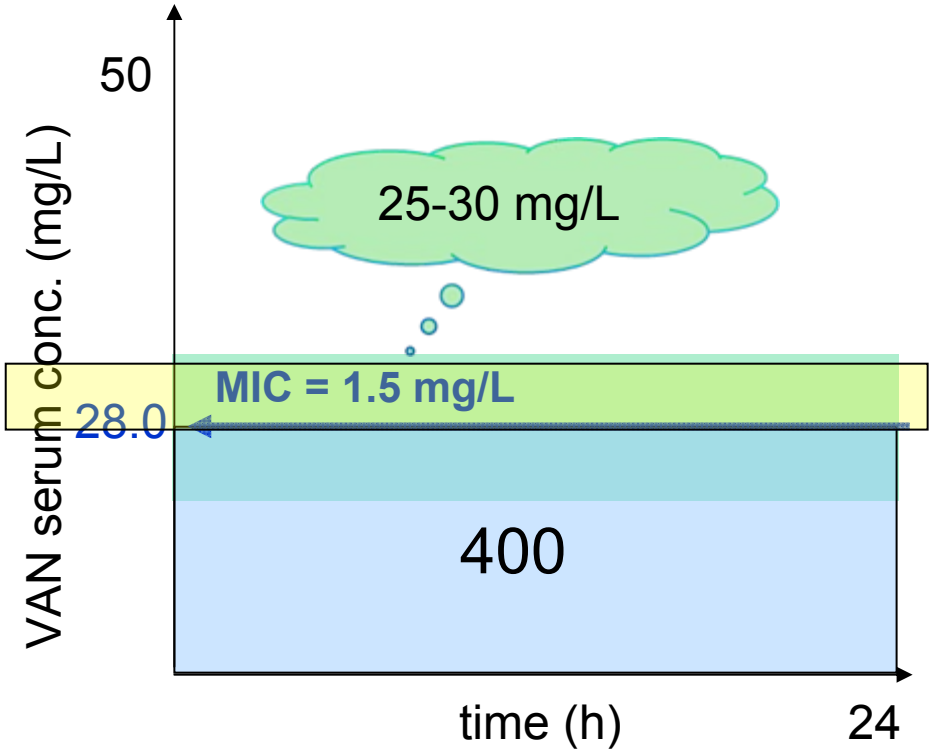
vancomycin CI: which serum concentration should we target?



Moise-Broder et al. Clin Pharmacokinet. 2004;43:925-42

vancomycin CI: which serum concentration should we target?

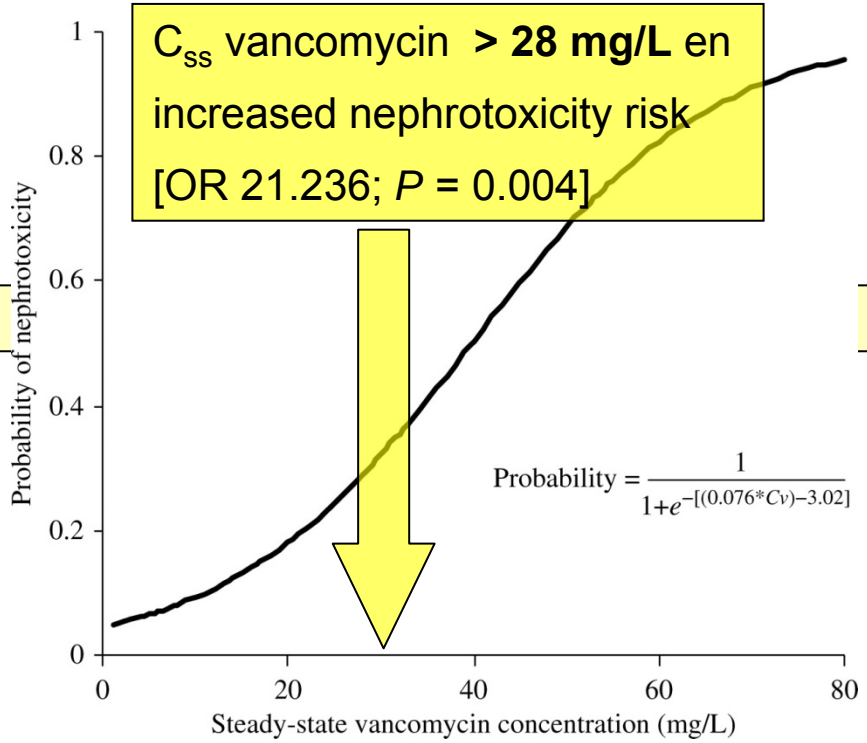
efficacy



Moise-Broder et al. Clin Pharmacokinet. 2004;43:925-42

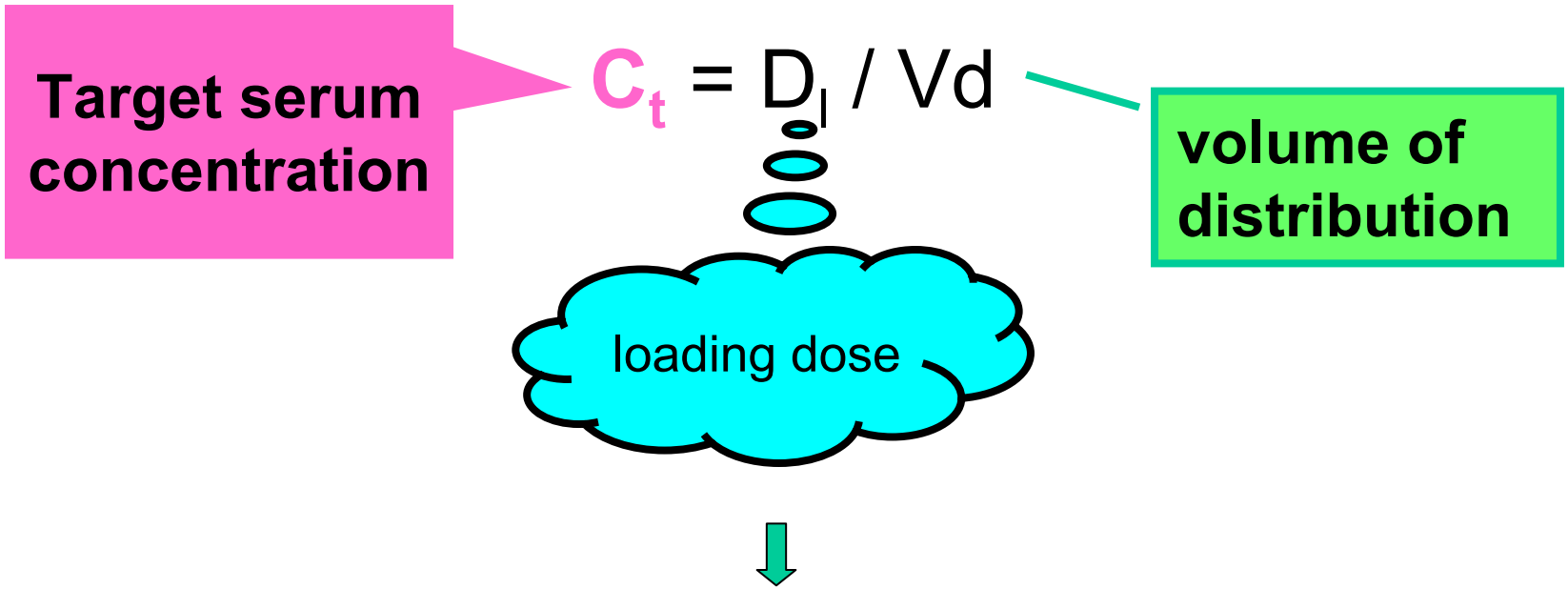
toxicity

C_{ss} vancomycin **> 28 mg/L** en increased nephrotoxicity risk [OR 21.236; *P* = 0.004]



Ingram, P. R. et al. J. Antimicrob. Chemother. 2008 Jul;62 (1): 168-71.

How to reach the serum target concentration target with CI?
1. loading dose: the correct scheme *

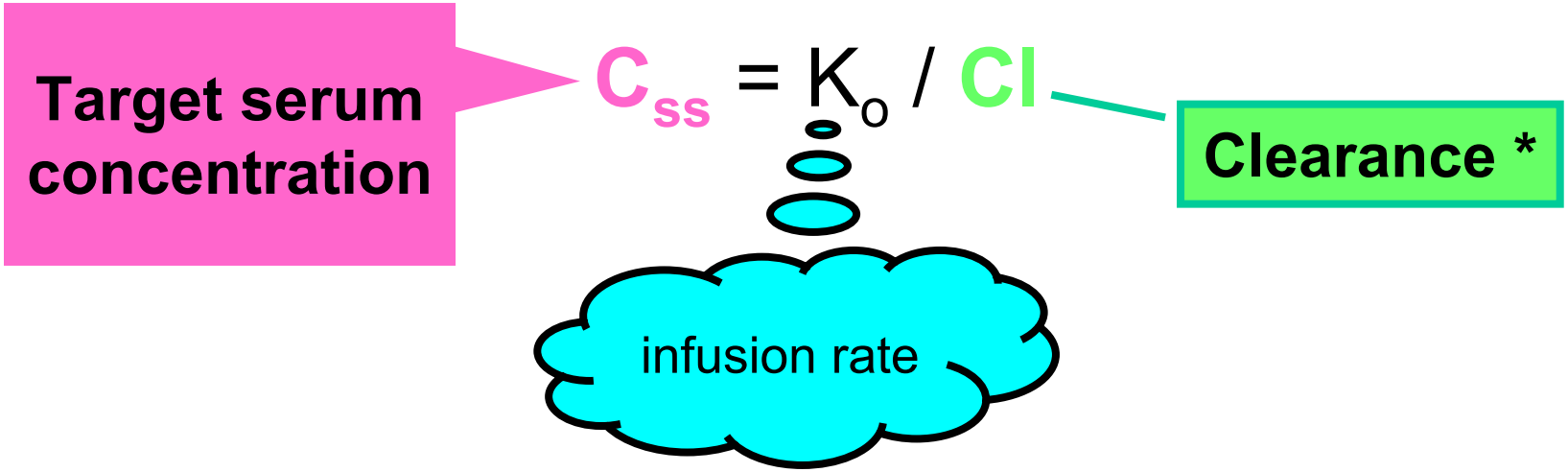


loading dose (in mg/kg) = C_t (mg/L) x **Vd** (L/kg)

loading dose (in mg/kg) = 20 mg/kg = **25** (mg/L) x **0.8** (L/kg)

* assuming linear pharmacokinetics

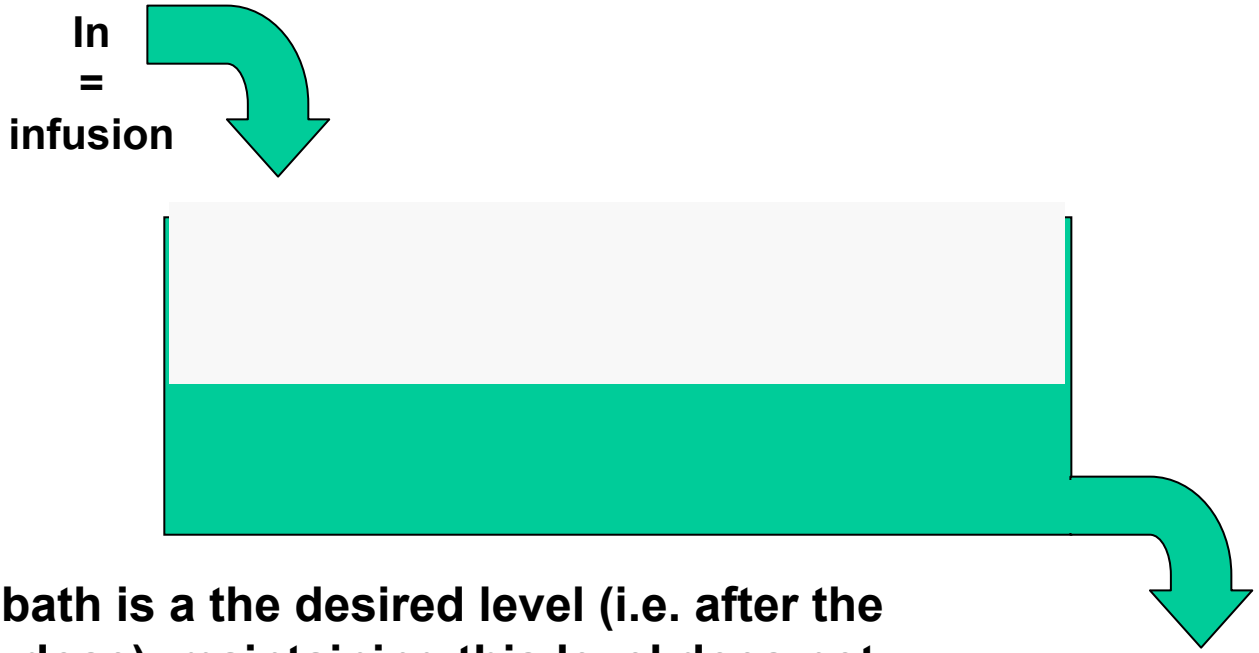
How to reach the serum target concentration target with Cl? 2: infusion *



daily dose (in mg) = 24 x **clearance** (L/h) x **Css**

* assuming linear pharmacokinetics

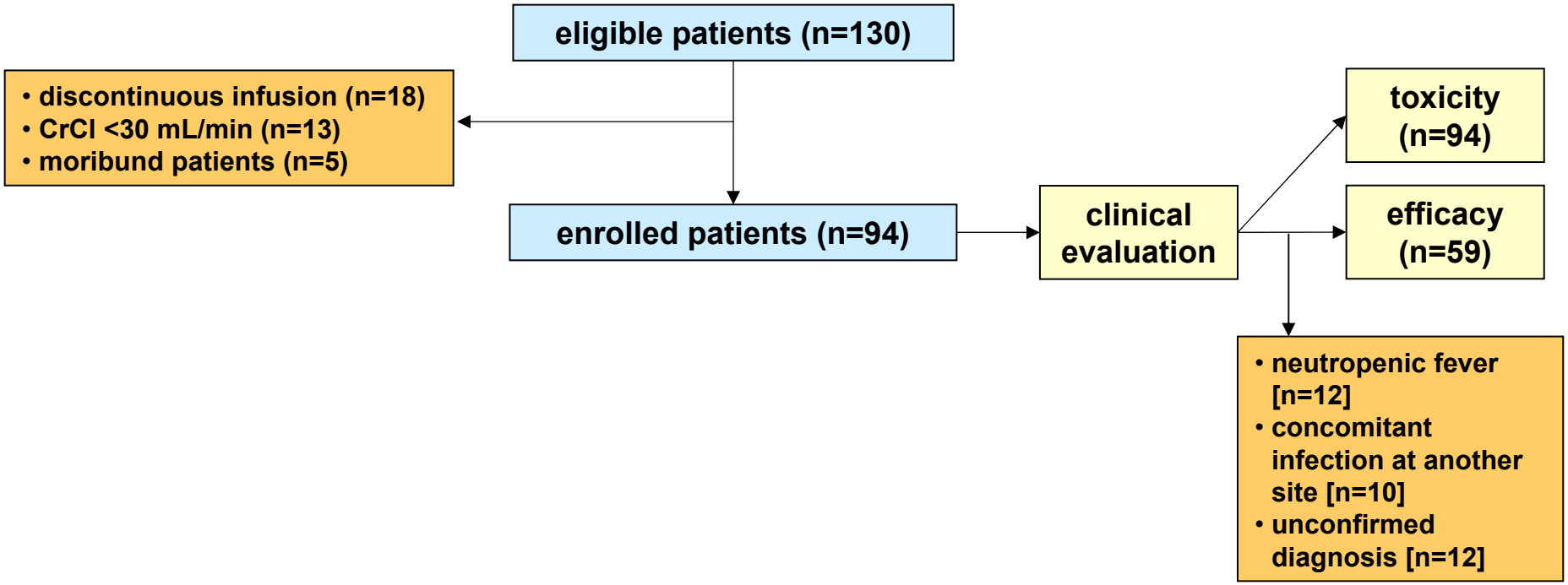
How to reach the serum target concentration target with CI?
2: infusion *



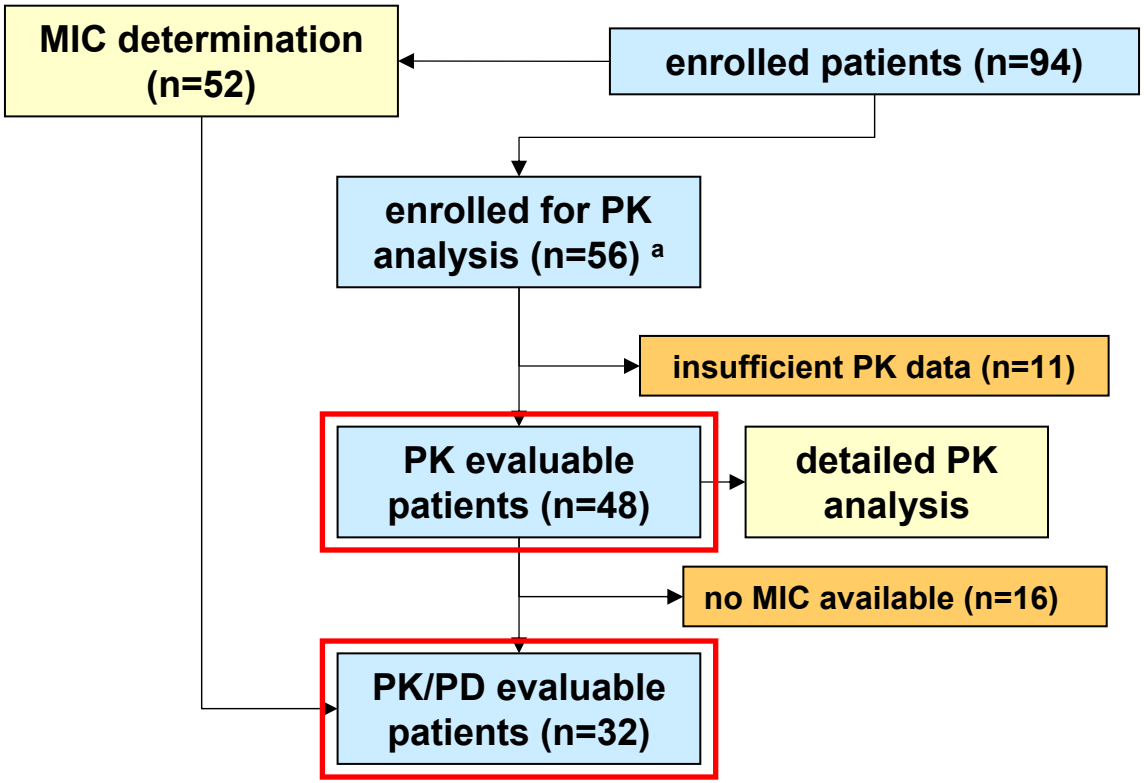
once a bath is a the desired level (i.e. after the loading dose), maintaining this level does not depend upon its volume but of the ratio of tap and drain flows (which musts be equal: in = out…)

*** during the infusion, the necessary dose (in 24h or per min) is only dependent upon the clearance**

2. Clinical evaluation: study outline

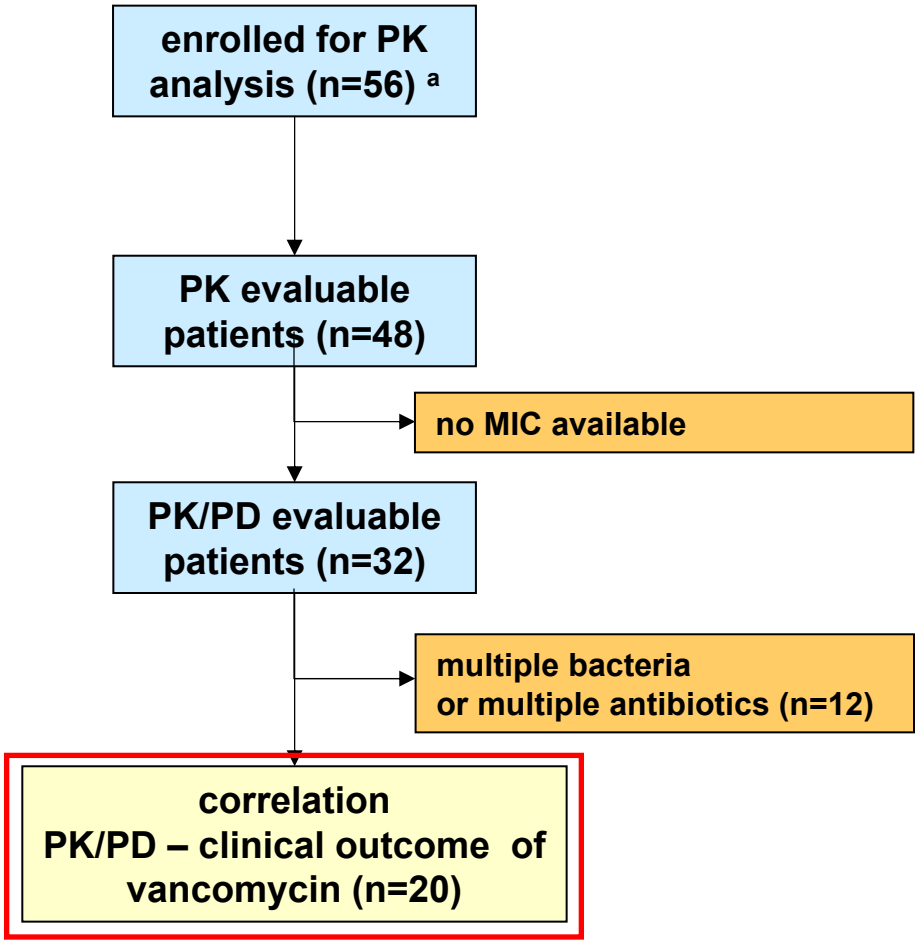


2. Pharmacokinetic evaluation: study outline



[a] signed informed consent for additional blood sampling
[b] standard of care only

2. Relationship between AUC_{24h}/MIC and clinical efficacy: outline



[a] signed informed consent for additional blood sampling
[b] standard of care only

4. Efficacy in clinically evaluable patients (n=59)

- clinical cure:

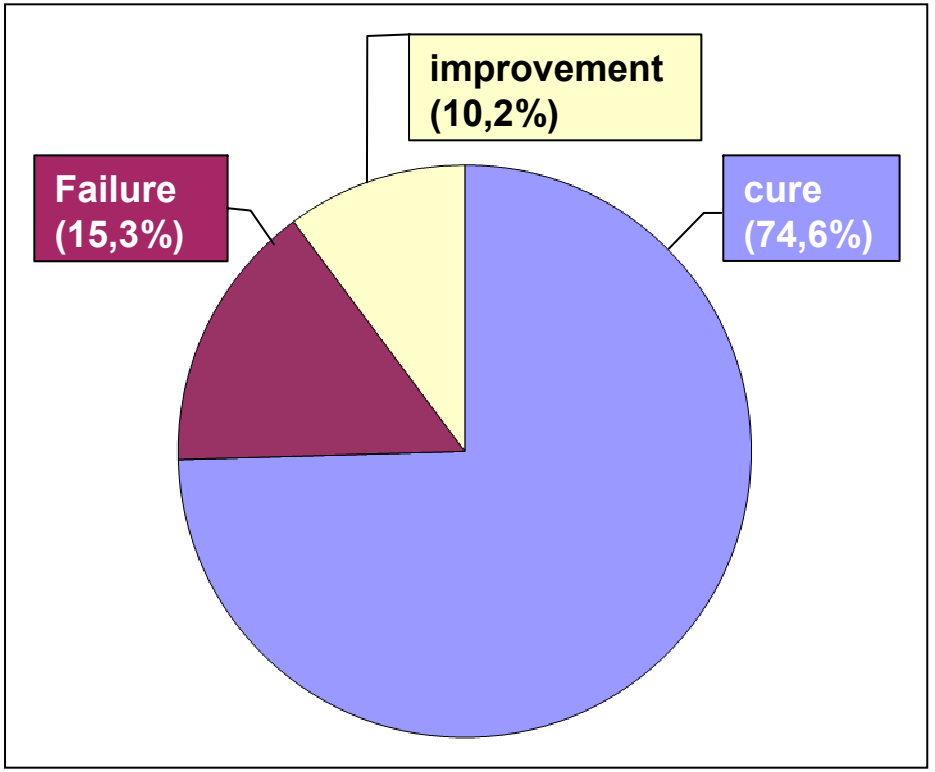
  (i) disappearance of all major signs of infection;

  (ii) normalization of body temperature;

  (iii) marked decrease of CRP.

- at EOT and at 6 months
- assessment retrospectively validated

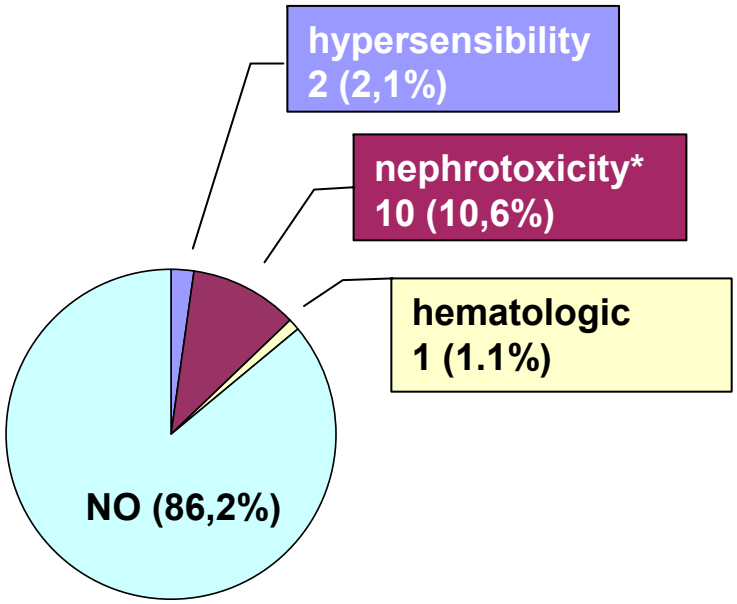
  by 2 ID physicians



3. Toxicity

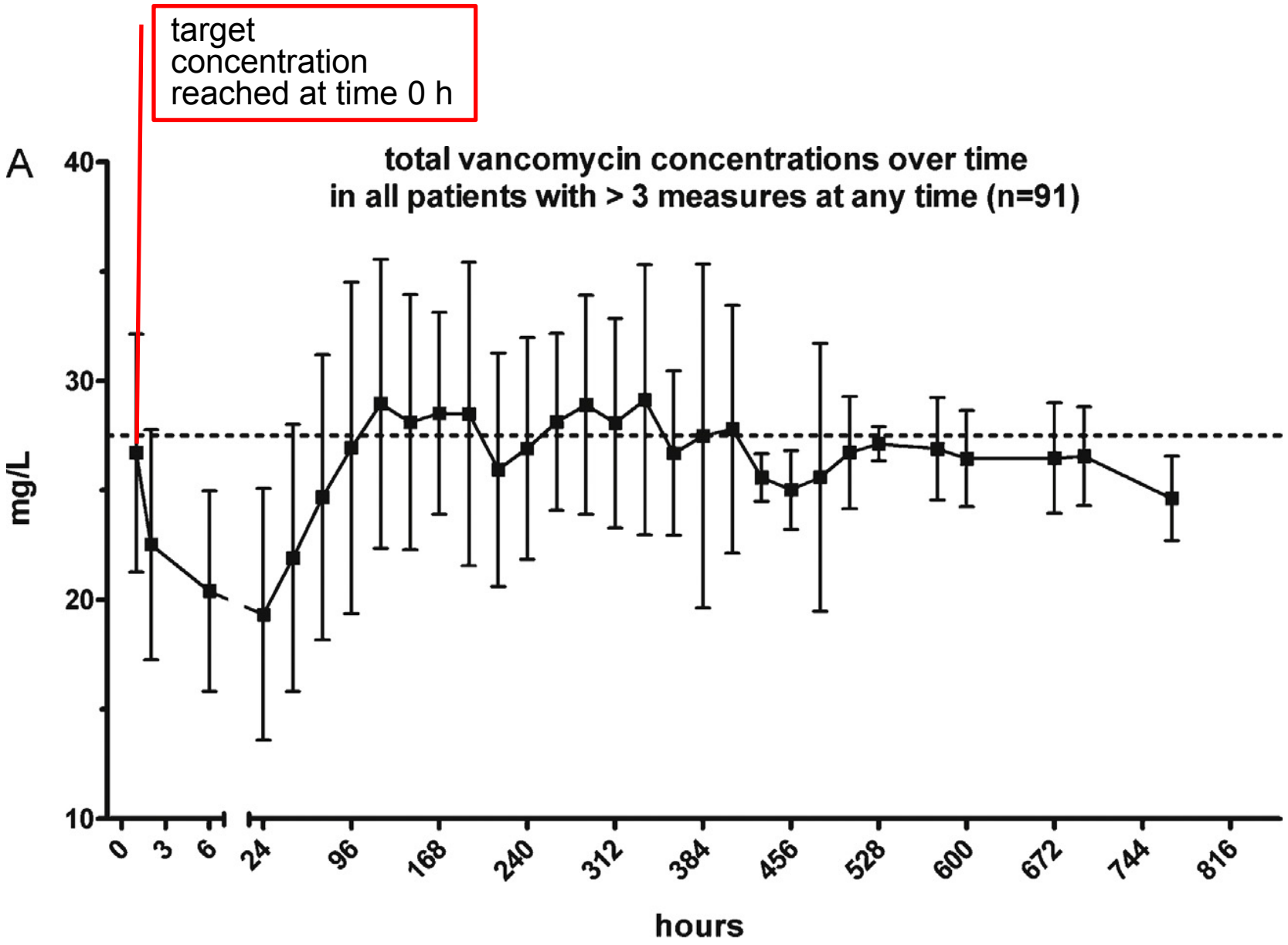
Adverse events observed in all enrolled patients (n = 94).

- at least 1 adverse event: 13.8%
- nephrotoxicity 'possible' ADE multiple RF
- treatment discontinuation in only 2 cases



*IDSA consensus statement def. of vancomycin nephrotoxicity (Rybak et al. Am J Health-Syst Pharm 2009):
2 or 3 documented increases in serum creatinine level; increase of 0.5 mg/dL OR ≥ 50% increase from baseline after several days of vancomycin therapy.

7. Total vancomycin serum concentrations



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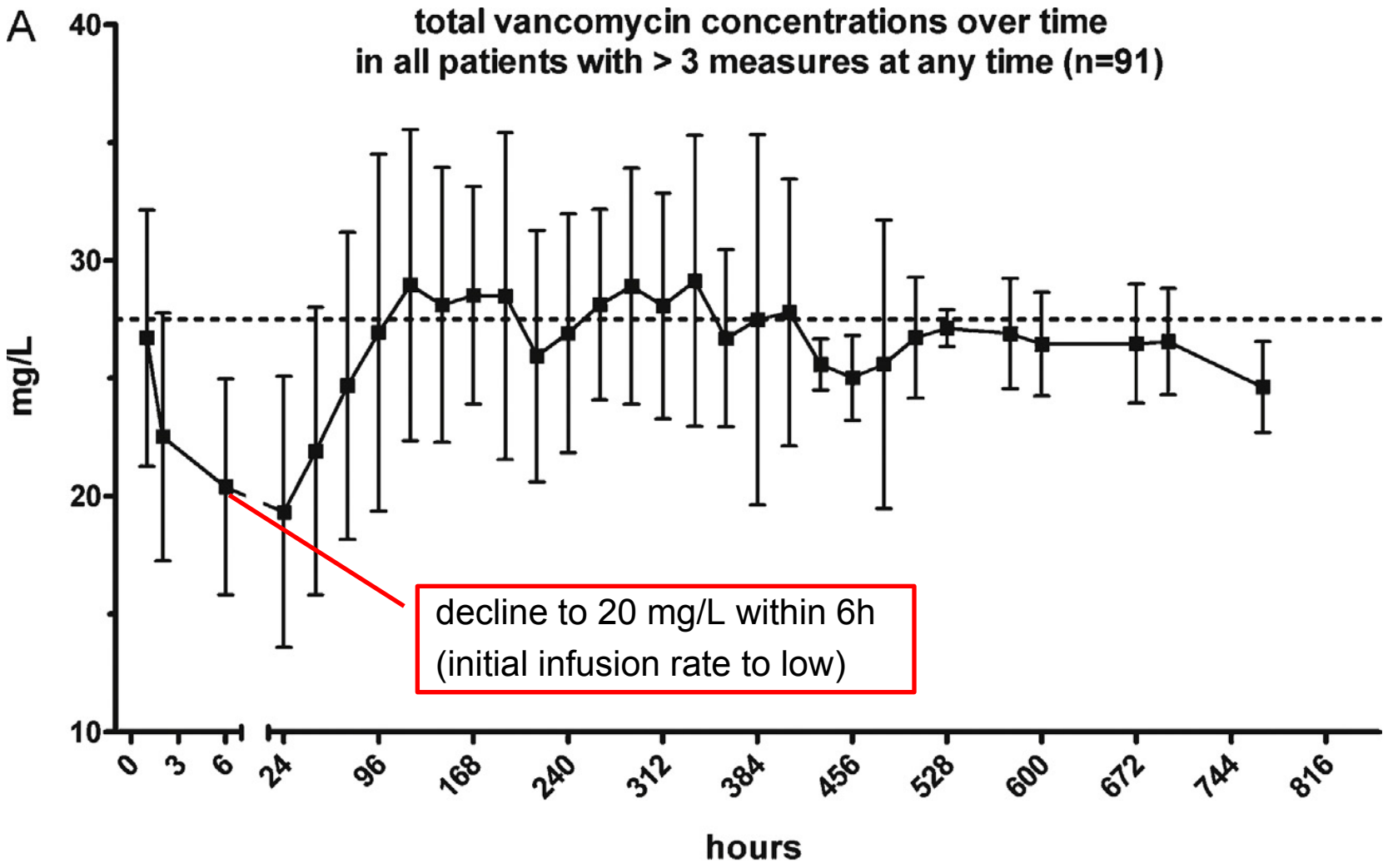

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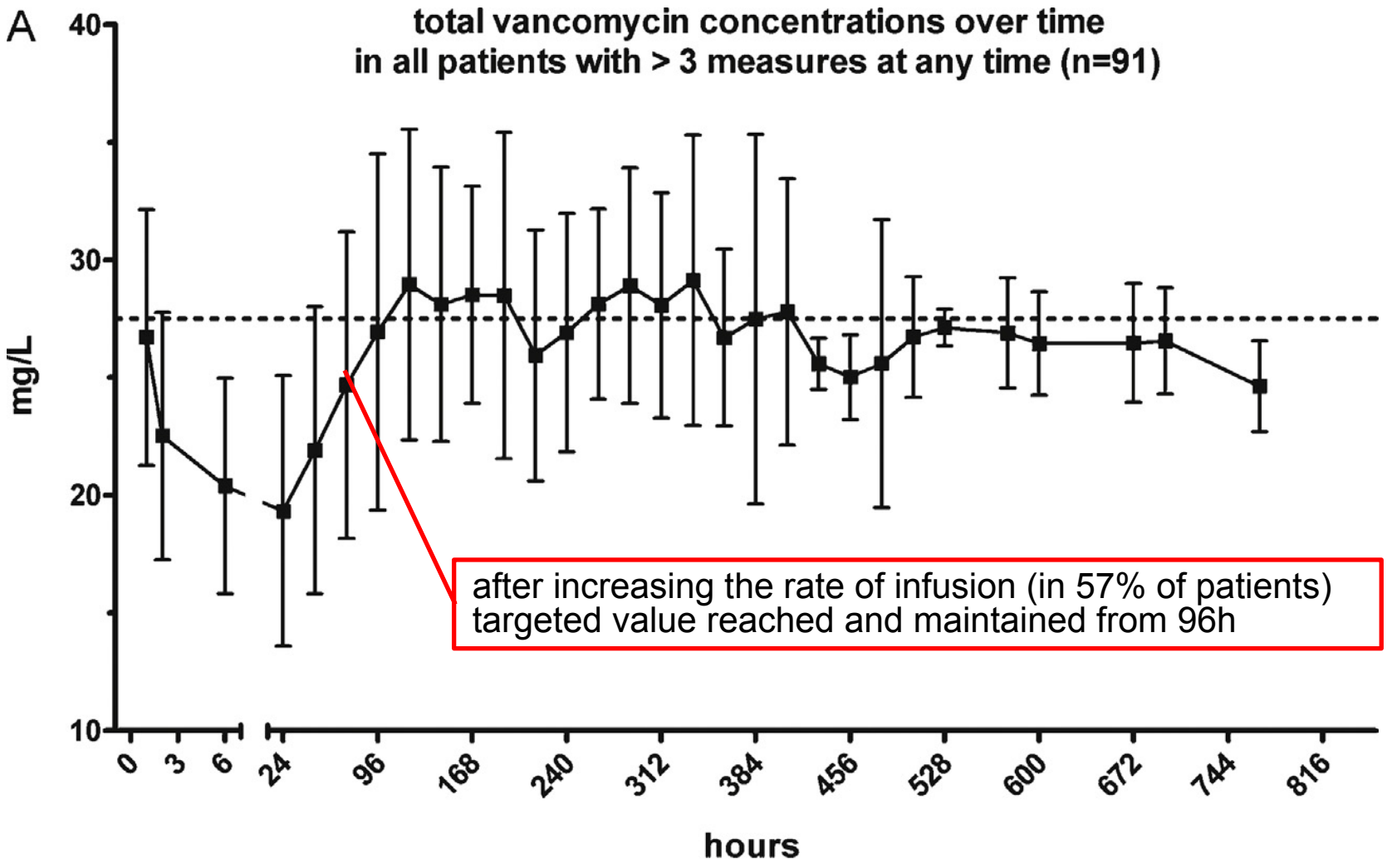
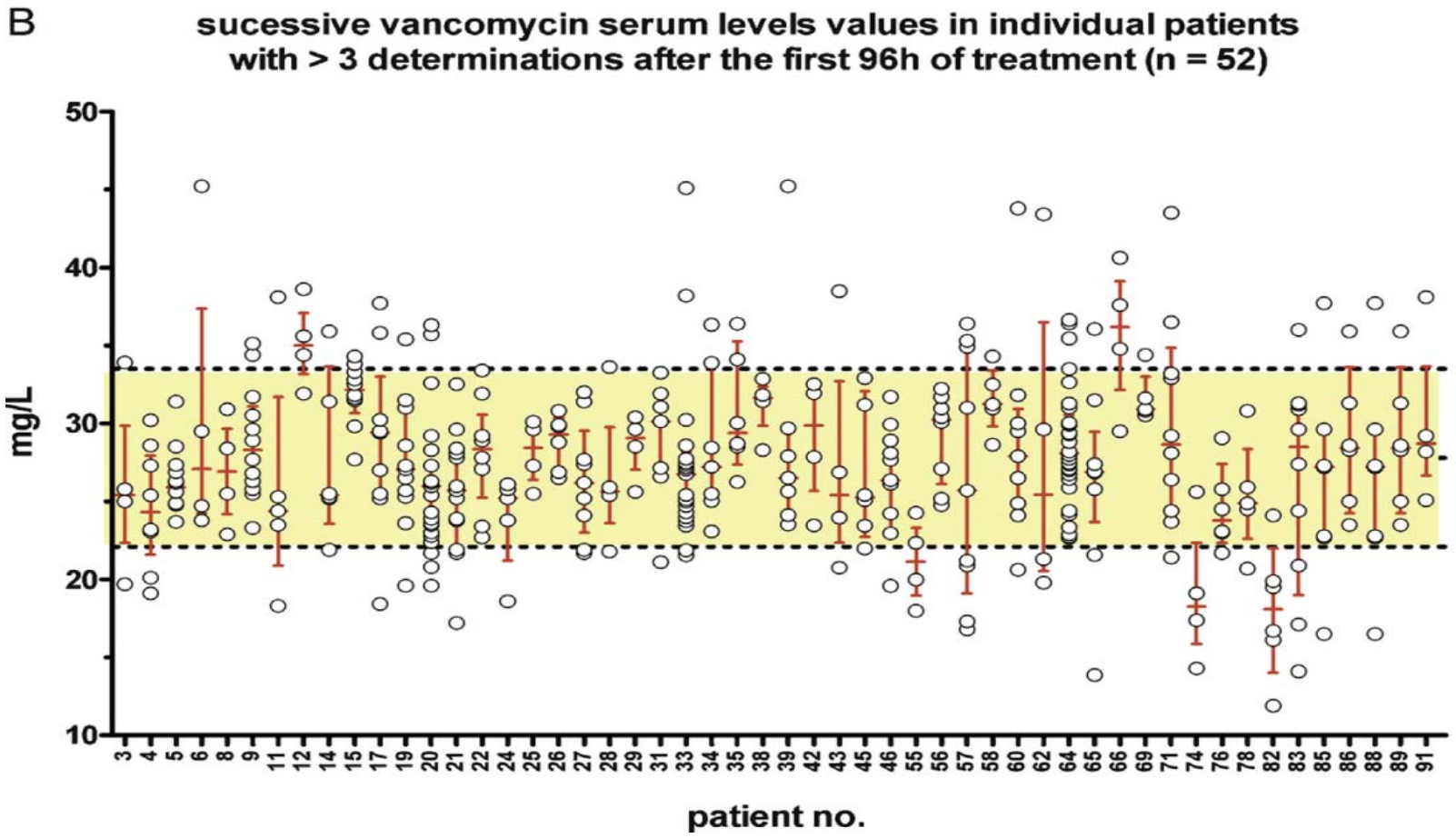
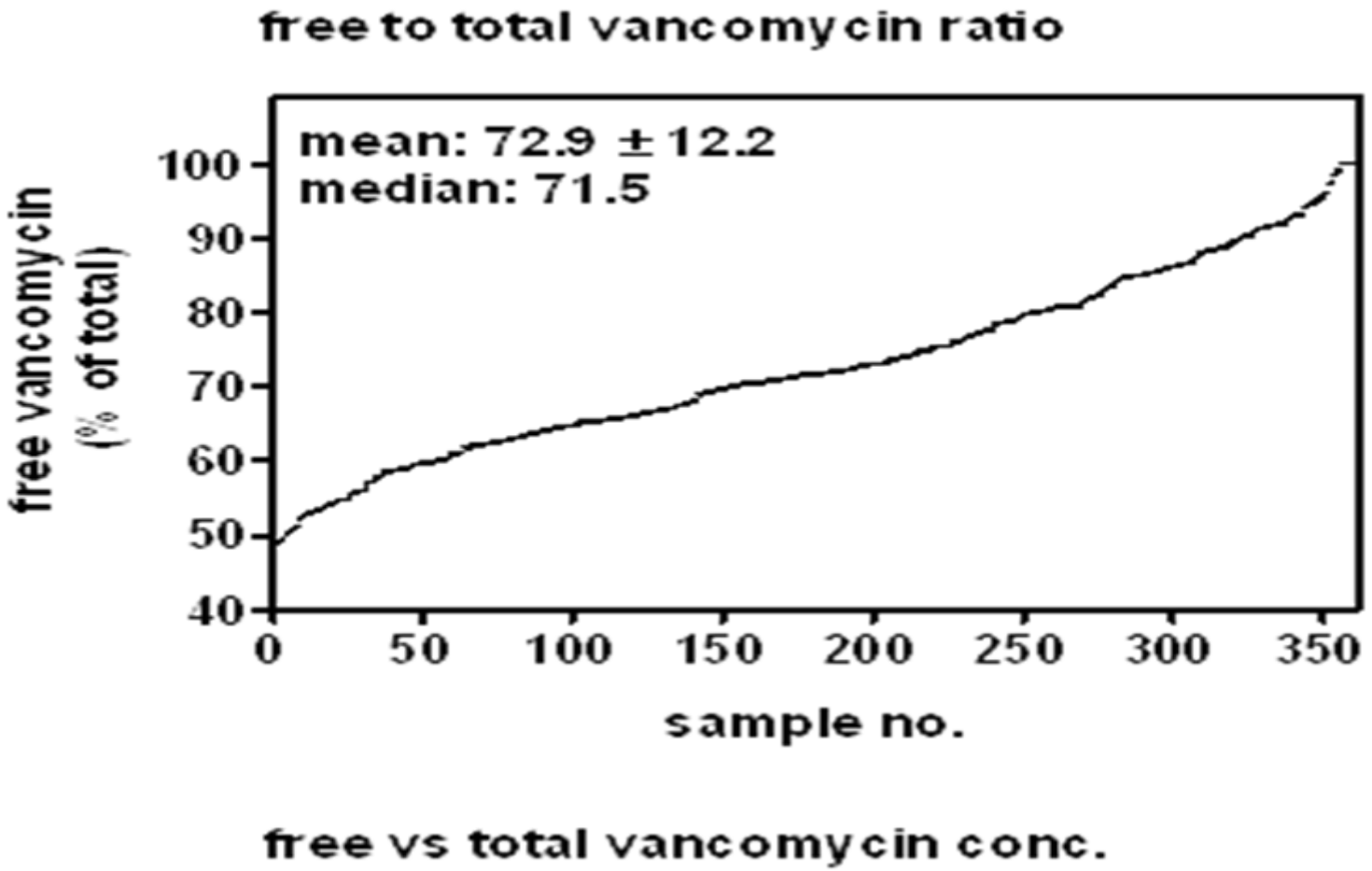


7. Total vancomycin serum concentrations



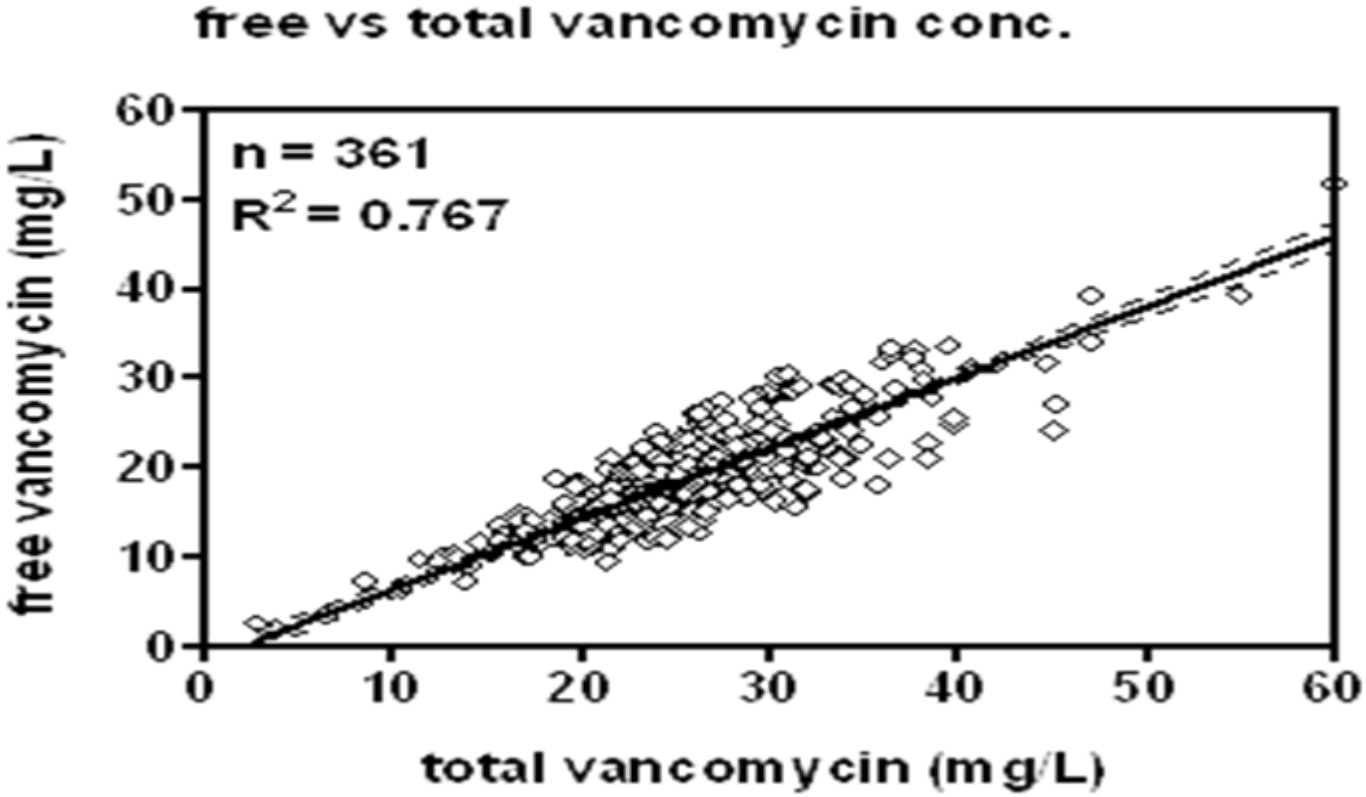
- deviations of >10 mg/L according to the recommended range
  - ↘ if increased CCrCl (threshold at >104 mL/min)
  - ↗ if concomitant use of diuretics

8. Free (unbound) vancomycin serum concentrations (n=30)



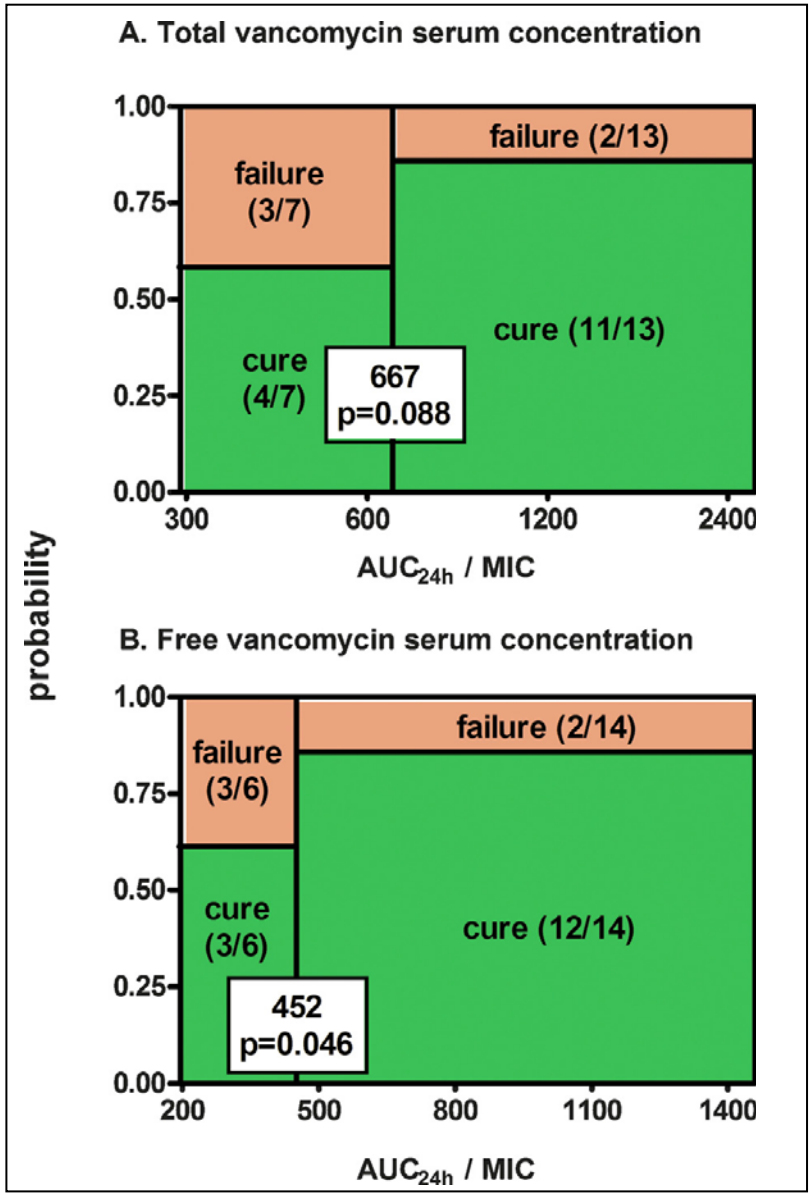
large variation in the free/total concentration ratio among individual samples

8. Free (unbound) vancomycin serum concentrations (n=30)



correlation between free and total concentrations was satisfactory at the population level (r^2=0.77)

9. AUC_{24h}/MIC predictive of clinical success/failure (n=20)



- Recursive partitioning analysis
- best AUC/MIC split value separating failure from success:
  - 667 (total serum concentration)
  - 452 (free serum concentration)

Discussion

- Steady state target concentration reached and maintained
- Efficacy comparable to other studies
- Acceptable safety profile despite higher target range (25-30 mg/L)
- High inter- and intra-patient variability => need for TDM
- Limited number of patients, heterogeneous patient population, no prospective control group
- Re-evaluation of initial infusion rate
- Higher AUC_{24h}/MIC-ratio of 667 necessary for optimal efficacy in our context … MIC of 1 mg/L is probably the limit for vancomycin…

Observational study – results after implementation of CI

TDM process measures for twice daily (BID; baseline) mode of administration of vancomycin

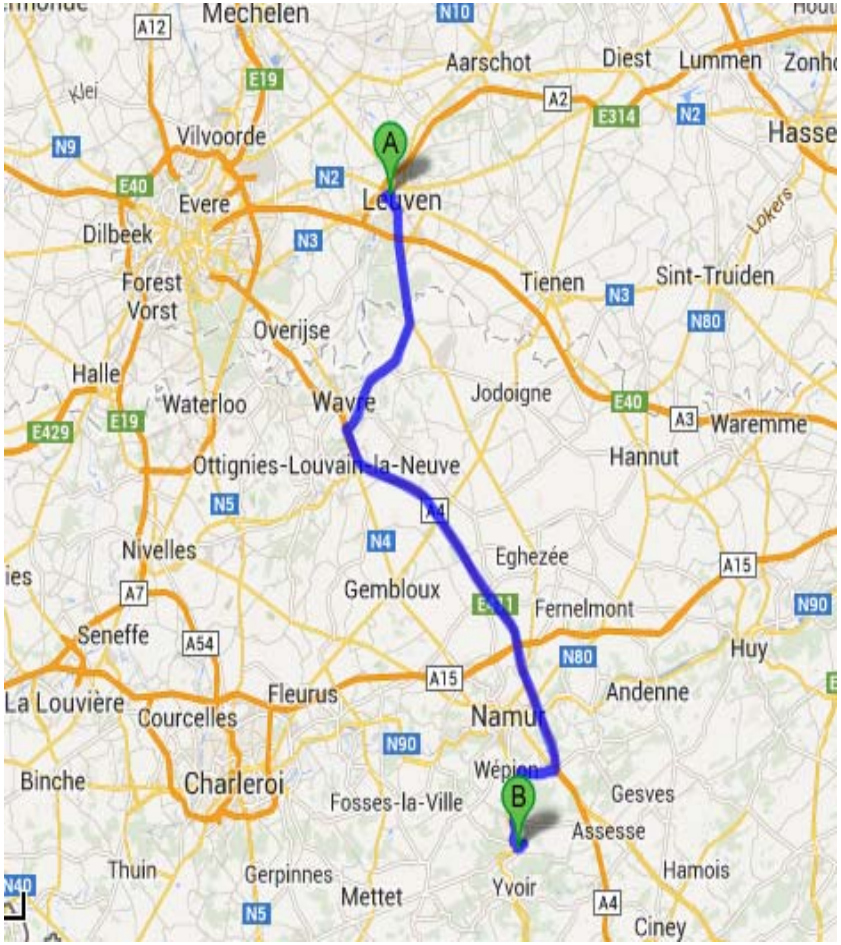
Criterium	BID	continuous infusion	p-value
Sample timing within 30 min. from scheduled time	61.3% [81/132] [a]	97.0% [217/224]	p<0.0001*
Implementation of TDM dose recommendations	32 % [21/66]	94.4% [205/218]	p<0.0001*
Prescribed daily dose in accordance with hospital guidelines	17% [95/560]	86% [1395/1622]	p<0.0001 **
% of serum levels in the recommended ranges	33.3% [37/112] [b]	66.8% [159/238]	p<0.0001*

* Fisher exact test two sided
** Chi-square two sided (because of the large number of observations)
[a] number of total observations (see Table 1 for the number of patients)
[b] most deviations were towards lower than expected values (average: 20 %)

qualitative study – results one year after the end of the study

Implementation of CI by physicians

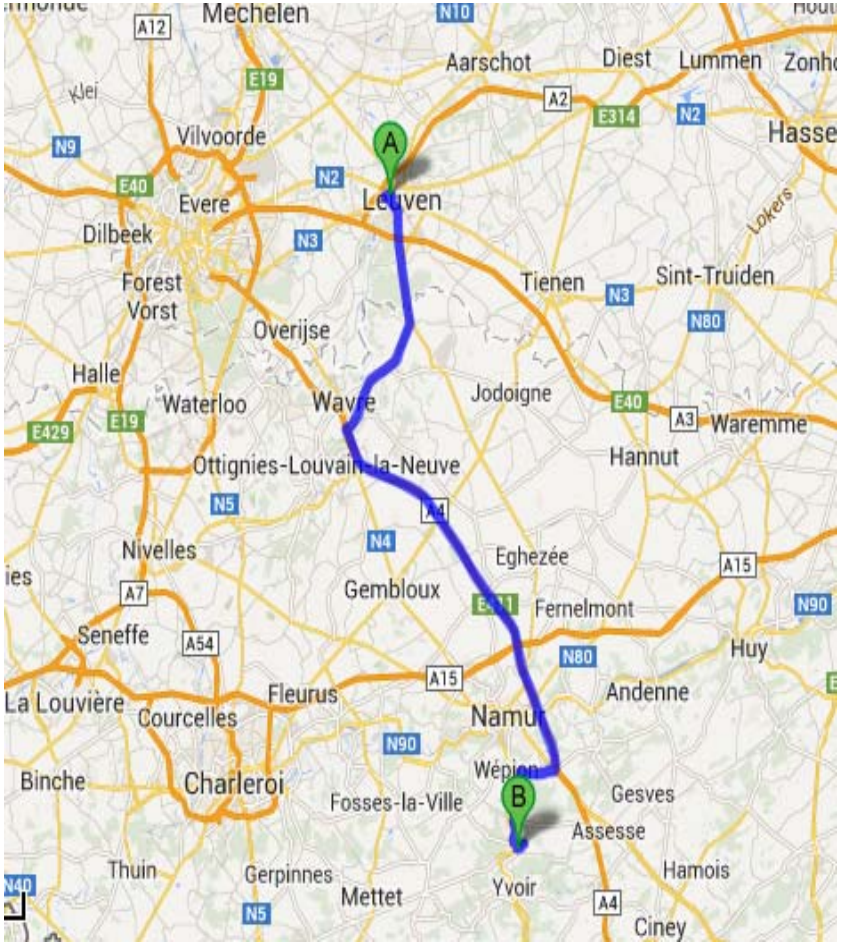
	mean (%)	min-max
Frequency of CI	99	95-100
Follow-up TDM recommendations	96	95-100



qualitative study – results one year after the end of the study

global satisfaction of HCP with CI

	global satisfaction score* (/5)	min-max
Physicians** (n=7)	4.5	4-5
nurses (n=10)	4.3	3.5-5
laboratory personnel (n=8)	4.4	4-5



Qualitative study – results after implementation of CI

M7: "Before even trough samples were obtained incorrectly. They were often just performed together with the other blood sampling without taking care of correct sample timing. Now with CI, samples are always performed correctly."

M7: "We follow dose recommendations. In my opinion treatment follow up is better now and I feel patients are treated correctly."

N1: "We perform just one sampling in the morning for all the scheduled blood analysis. We hardly ever perform additional samples for TDM only anymore."

Final conclusions

- Hospital-wide implementation of CI is feasible and well accepted by health care professionals.
- Centralized preparation facilitated nursing and was perceived as contributing to the quality of care
- Clinical Pharmacists can play an important role in the development and implementation of transversal quality improvement strategies
- CI may help optimizing vancomycin usage in the absence of pharmacokinetic services and may improve the quality of these services if available

Perspectives

- application to other area's of pharmacotherapy?
  - from a 'quality of care' perspective:
    - factors underlying inappropriateness identified in other area's of drug therapy
    - intervention proved positive impact on quality of administration and TDM
  - from a PK/PD perspective:
    - special patient populations (hyperclearance, morbidly obese patients, patients infected with a certain type of organism…)
    - Other AUC or time-dependent drugs (e.g. β-lactams, antifungals…)
    - 'On line' monitoring
  - from a clinical/hospital pharmacist perspective:
    - standardization of drug preparation/administration
    - opportunities for clinical pharmacy services (TDM recommendations, drug incompatibilities…)
  - from a hospital administrator perspective
    - cost-effective?

Thank you for your attention!!