

Vancomycin: from old Mississipi mud to modern use by continuous infusion

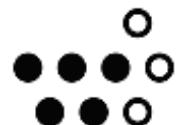
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<http://www.facm.ucl.ac.be>

With the support of *Wallonie-Bruxelles-International*



Disclosures and slides availability

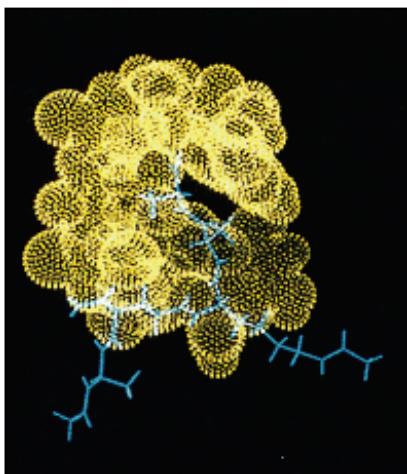
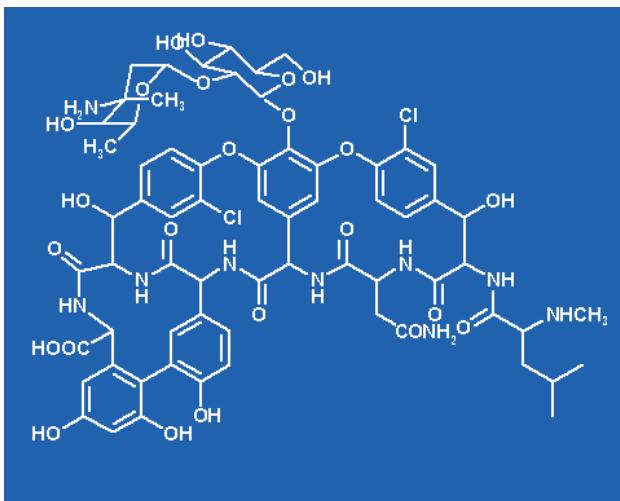
- Research grants
 - Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica, Debiopharm
 - Belgian Science Foundation (*F.R.S.-FNRS*), Ministry of Health (*SPF*), Walloon and Brussels Regions, European Union (*FP7 programme*)
- Decision-making and consultation bodies
 - European Committee for Antimicrobial Susceptibility Testing [EUCAST] (General Assembly and steering committee (2010-2012))
 - European Medicines Agency (external ad-hoc expert)
 - US National Institutes of Health (grant reviewing)
 - Drive-AB [*Driving reinvestment in R&D and responsible use for antibiotics*] (governance)
- This presentation: *Wallonie-Bruxelles International*

<http://www.facm.ucl.ac.be/cooperation>

Contents of the presentation

- Vancomycin
 - short summary of its history and general properties
 - how to measure MICs and heteroresistance
 - vancomycin PK/PD and minimal AUC_{24h}/MIC
 - high doses in America ... and the risks
 - continuous infusion of vancomycin:
 - why
 - how we do it...
 - do the others do the same

Vancomycin History



binding of vancomycin
to D-Ala-D-Ala

- first isolated in 1953 by Edmund Kornfeld at Eli Lilly & Co.¹ from a soil sample collected in Borneo and produced by *Amycolatopsis orientalis*.
- active against Gram-positive organisms only (size !) and most notably against penicillin-resistant *S. aureus* and *Enterococci* (naturally poorly susceptible to penicillins) by binding to the D-Ala-D-Ala motif in nascent peptidoglycan
- remained for long a rarely used antibiotic because
 - poor oral bioavailability (must be given intravenously for most infections)
 - development of β-lactamase-resistant semi-synthetic penicillins (methicillin and derivatives) that solved the problem of β-lactamase-producing *S. aureus*
 - originally impure forms ("Mississippi mud") causing oto- and nephrotoxicity
- regained increasingly large usage from the mid-80's because of the widespread emergence of MRSA (methicillin-resistant *S. aureus*) that are resistant to all conventional β-lactams (incl. carbapenems)

¹ first company to mass-produce penicillin in the 1940's

Vancomycin: spectrum and resistance

- Broad activity against Gram-positive microorganisms.
 - *Staphylococci* (*S. aureus*, *S. epidermidis*, *S. saprophyticus*, *S. haemolyticus*, *S. hominis*, *S. warneri*, and other coagulase-negative staphylococci)
 - most *Enterococcus faecalis* (variable for *E. faecium*)
 - *Streptococcus pneumoniae* and *S. pyogenes*; *S. agalactiae*, group C and group G streptococci,
 - *Listeria monocytogenes*
 - *Bacillus anthracis*, *B. cereus*, and other *Bacillus* spp.,
 - *Corynebacterium* spp.
 - anaerobes: *Peptostreptococcus* spp., *Actinomyces* spp., *Propionibacterium* spp., *Clostridium* spp. (including *Clostridium difficile* (not *Clostridium ramosum*)
- *Lactobacillus* spp., intrinsically vancomycin resistant.
- Clinically important resistance:
 - *S. aureus*: thickening of the cell wall (VISA): MICs increase from 2 to 8-16 mg/L (heteroresistance)
 - *Enterococci* (VRE): acquisition of gene(s) causing a change from D-Ala-D-Ala to D-Ala-D-Lac or D-Ala-D-Ser (usually high MICs)

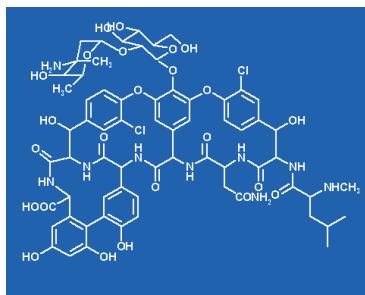
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How to measure vancomycin MIC: 2 main problems

- vancomycin diffuses poorly in agar → diffusion tests give abnormally large values



MW:1449.253 g/mol

- vancomycin MICs are not homogenous in a given high inoc

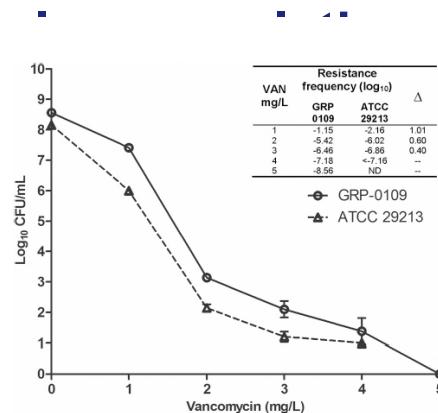
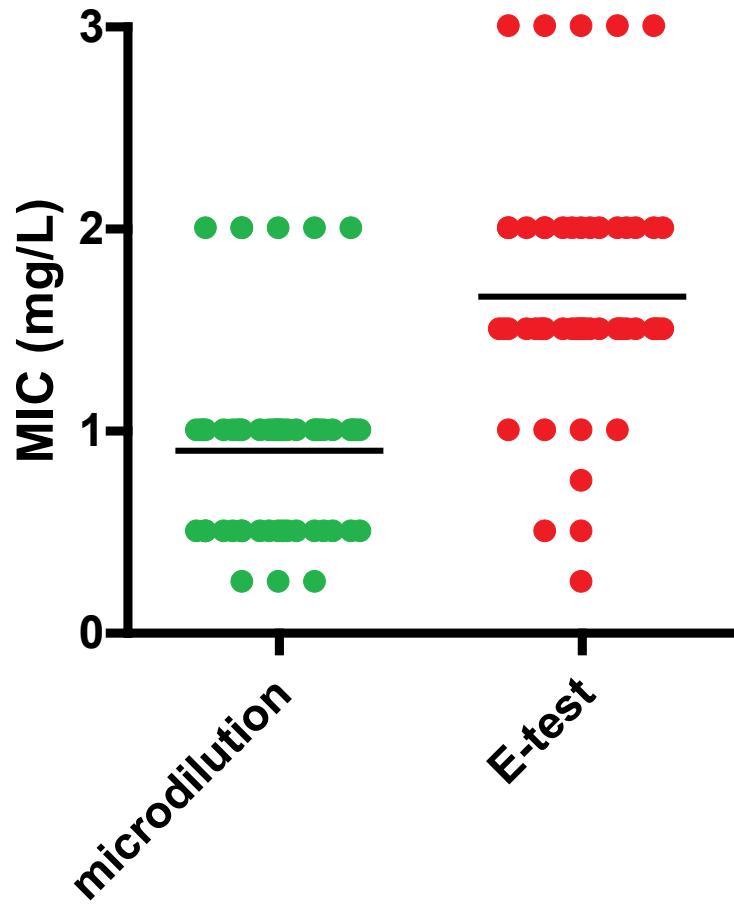


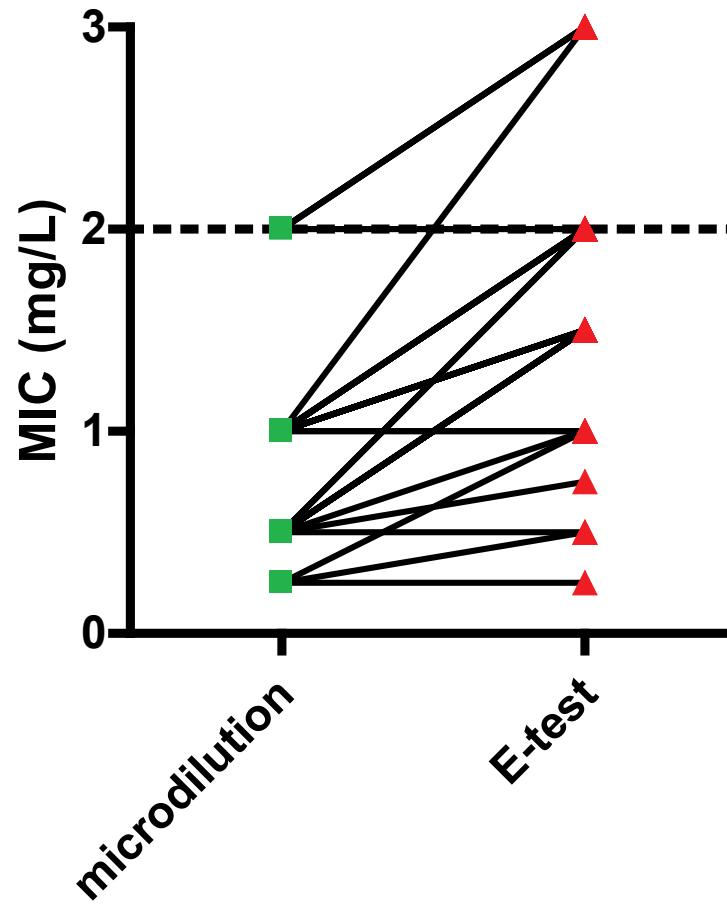
FIG 1 Vancomycin population analysis profile of *S. aureus* GRP-0109 after being isolated from a patient with persistent bacteremia and unsuccessful generic treatment, indicating altered susceptibility in comparison with strain ATCC 29213: 10 times more cells were able to grow at 1 mg/liter of vancomycin, 4 times more grew at 2 mg/liter, and 2.5 times more grew at 3 mg/liter (resistance frequency data at right).

A comparison between broth microdilution and E-test

microdilution vs E-test

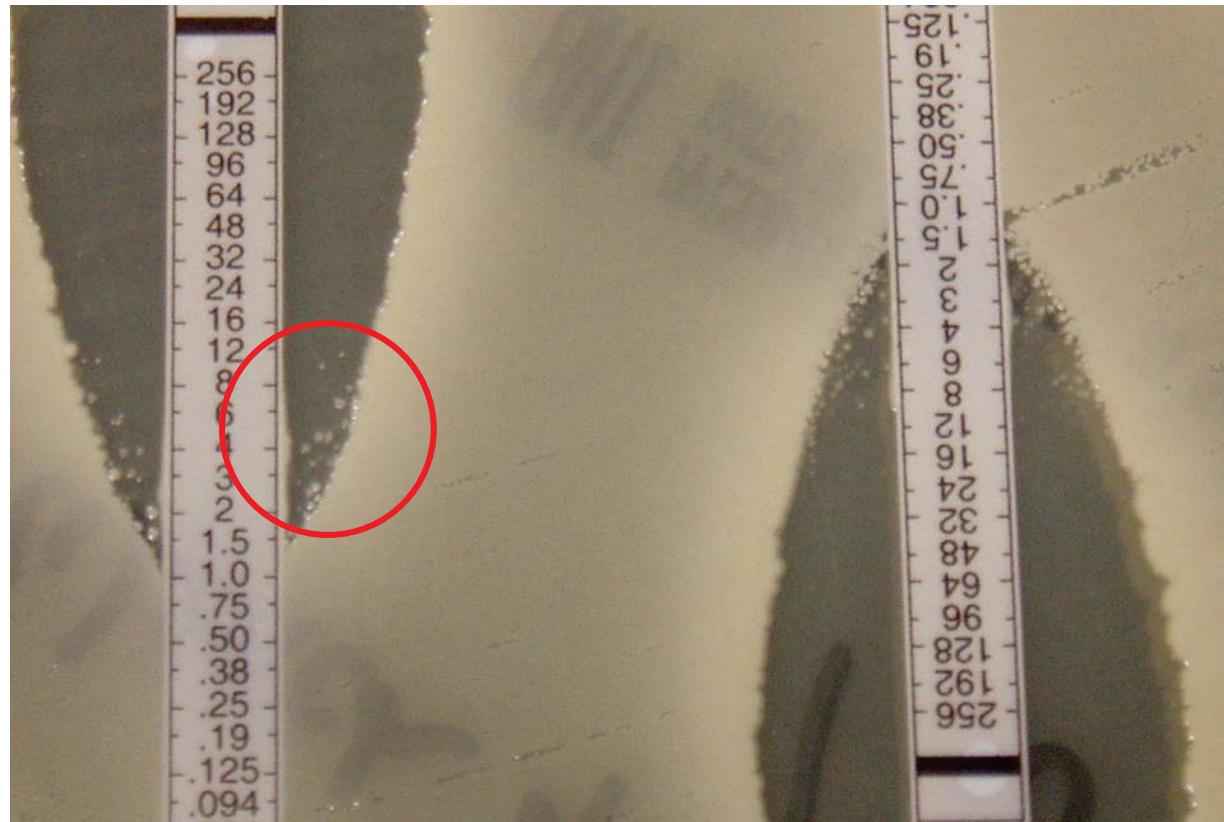


microdilution vs E-test



54 strains (MSSA, MRSA and CNS) – Ampe et al. IJAA 2013 41(5):439-46 – Suppl. Mat.

Hetero-resistance: how to see it ...



This slide borrowed from Dr M. Dryden, Royal Hampshire Hospital, Winchester, UK

Heteroresistance: development during treatment..

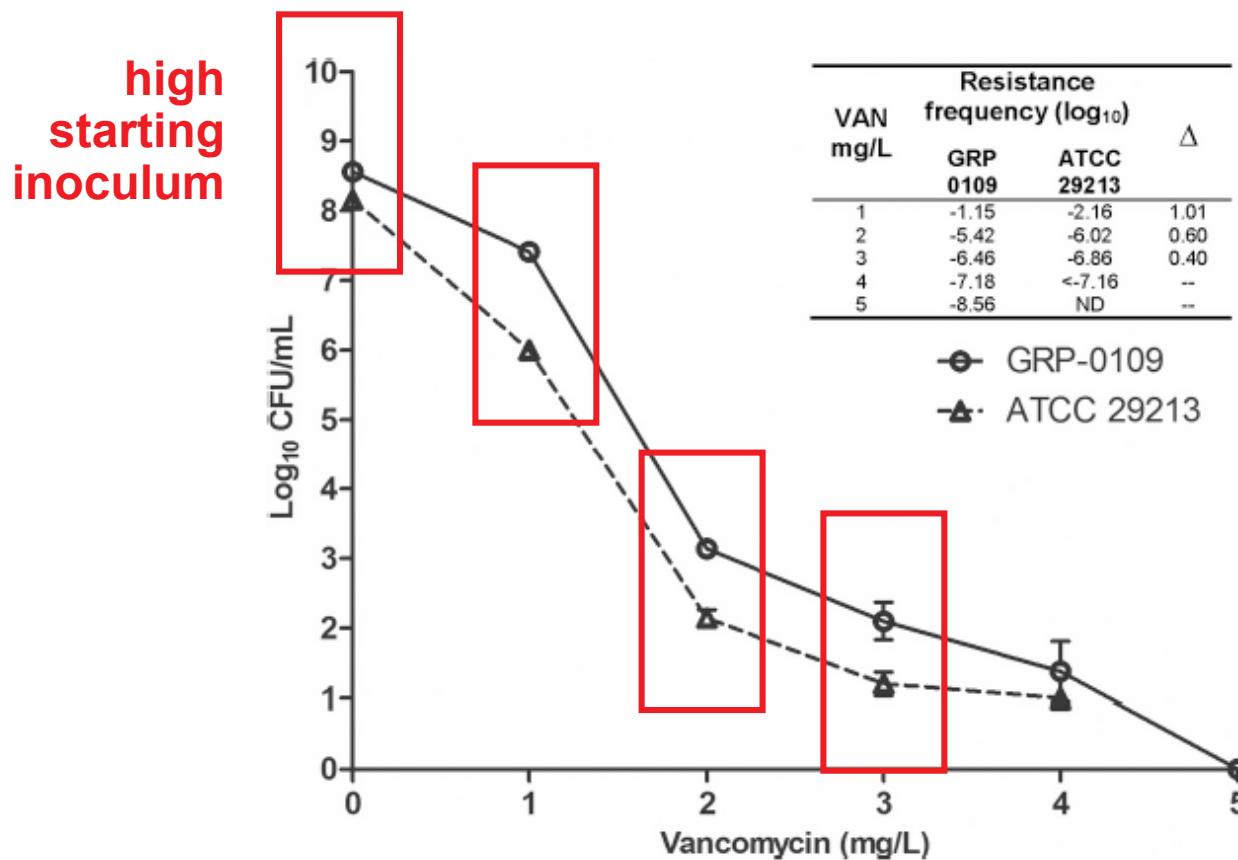


FIG 1 Vancomycin population analysis profile of *S. aureus* GRP-0109 after being isolated from a patient with persistent bacteremia and unsuccessful generic treatment, indicating altered susceptibility in comparison with strain ATCC 29213: 10 times more cells were able to grow at 1 mg/liter of vancomycin, 4 times more grew at 2 mg/liter, and 2.5 times more grew at 3 mg/liter (resistance frequency data at right).

Rodriguez et al. Antimicrob Agents Chemother. 2012; 56:243–247

How to measure vancomycin MIC

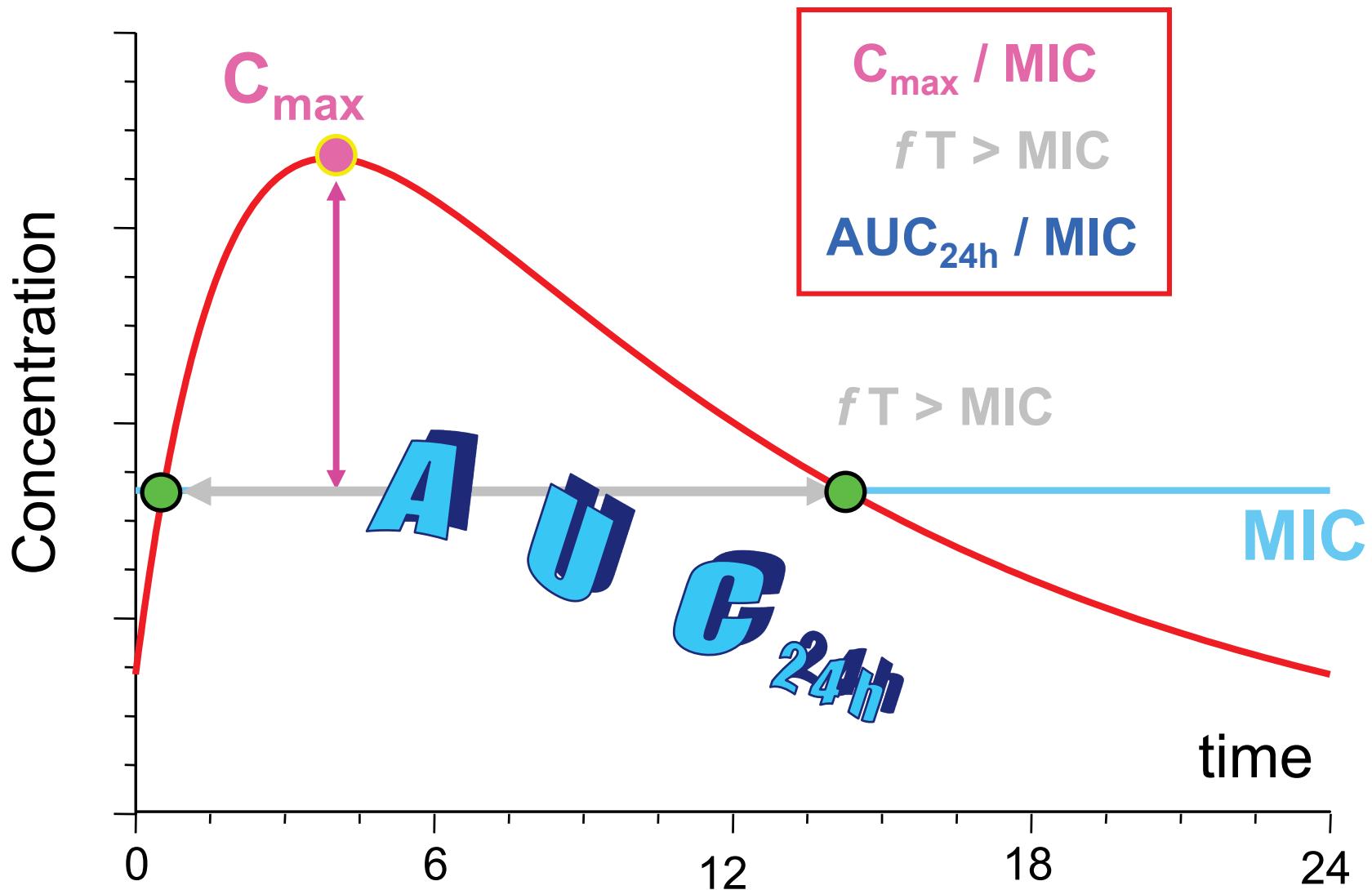
- **broth microdilution is the only ISO standard**
 - by definition, correct values
 - BUT does not inform about heteroresistance...
- **disks or E-test**
 - tend to give abnormally higher values (poor diffusion of vancomycin)
 - BUT shows heteroresistance (colonies within the inhibition zone)
- **plating on agar with 4 mg/L vancomycin**
 - shows heteroresistance and gives warinng for failures
- **gradient techniques (1-10 mg/L)**
 - shows the presence and quantifies to which level heteroresistance is observed.

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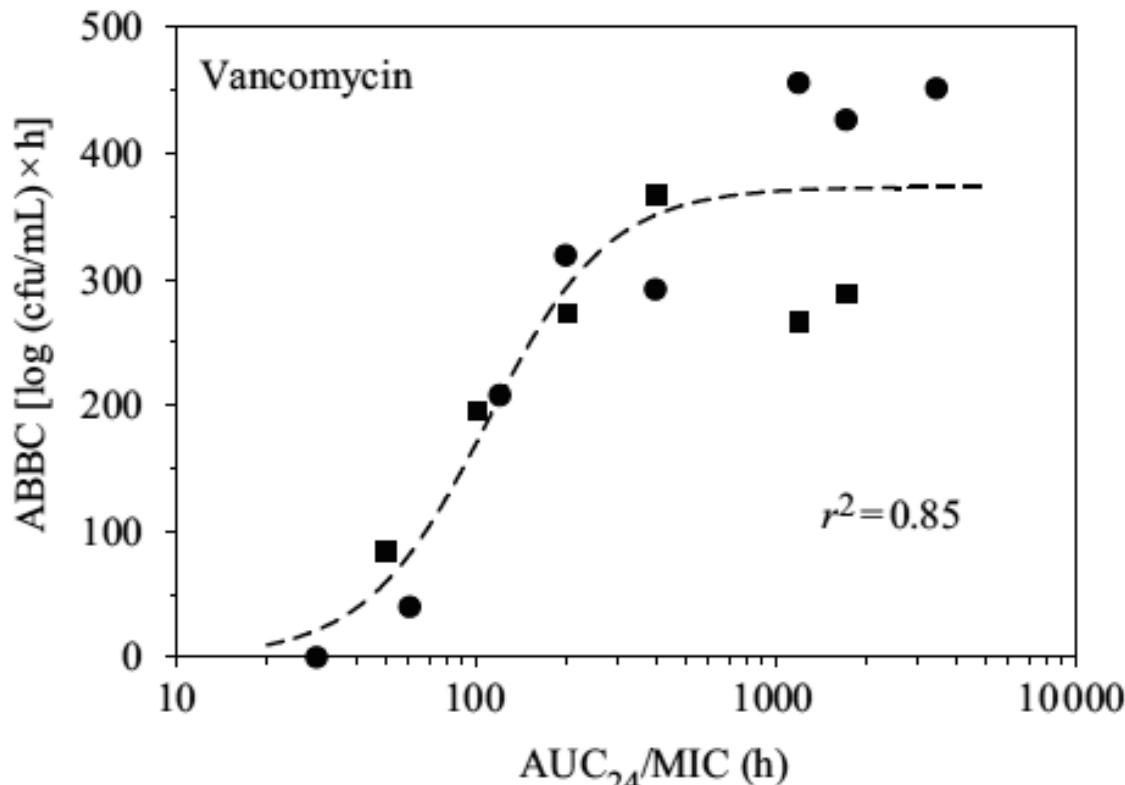
Vancomycin and Pharmacodynamics

- Vancomycin is an AUC_{24h} -MIC dependent antibiotic



Vancomycin – AUC_{24h} and efficacy

1. In vitro model mimicking the human PK

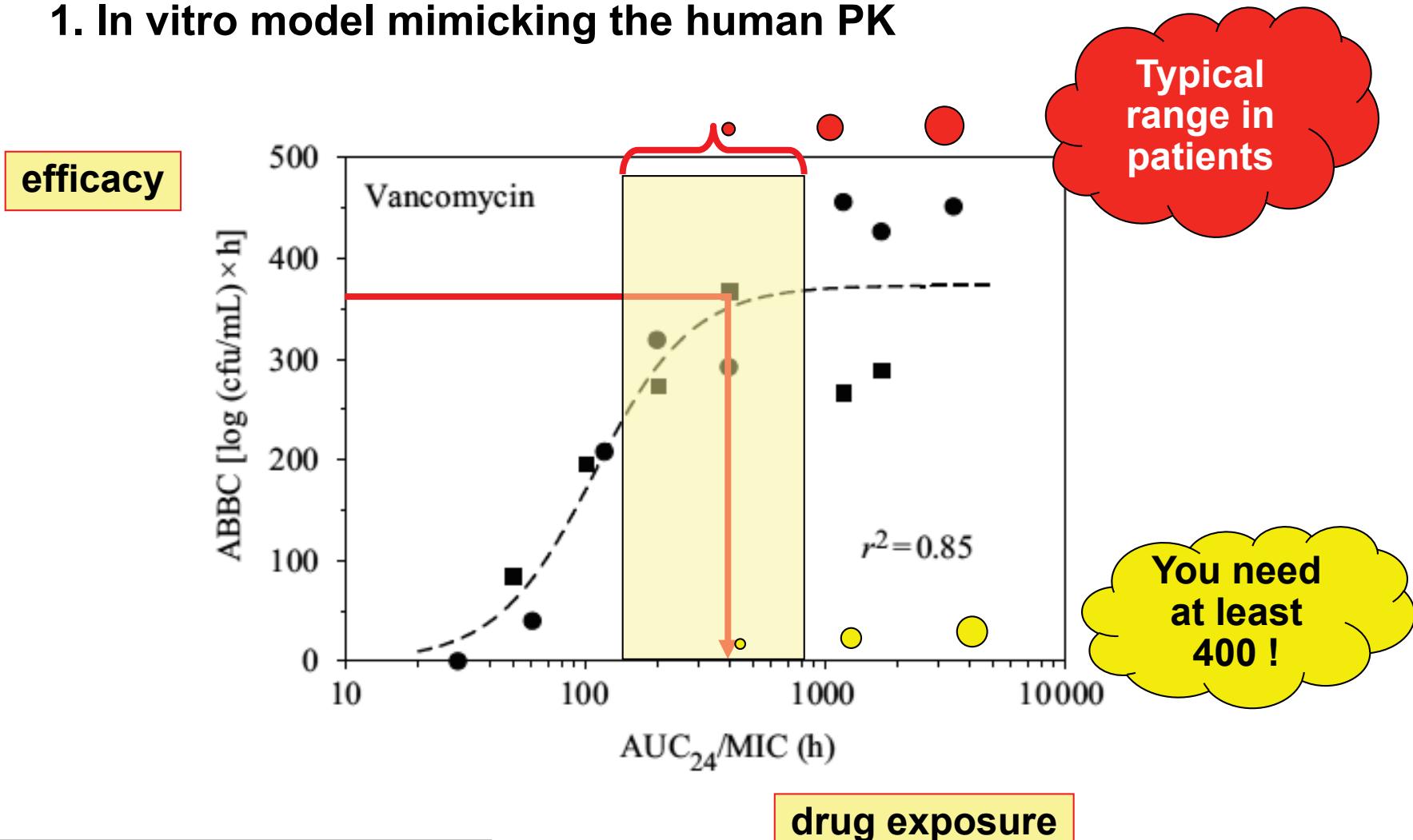


Lubenko et al. J Antimicrob Chemother. 2008; 62:1065-9.

drug exposure

Vancomycin – AUC_{24h} and efficacy

1. In vitro model mimicking the human PK



Lubenko et al. J Antimicrob Chemother. 2008; 62:1065-9.

drug exposure

Vancomycin – AUC_{24h} and efficacy

ORIGINAL RESEARCH ARTICLE

Clin Pharmacokinet 2004; 43 (13): 925-942
0312-5963/04/0013-0925/\$1.00/0

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Pharmacodynamics of Vancomycin and Other Antimicrobials in Patients with *Staphylococcus aureus* Lower Respiratory Tract Infections

Pamela A. Moise-Broder,¹ Alan Forrest,^{1,2} Mary C. Birmingham¹ and Jerome J. Schentag^{1,2}

1 CPL Associates, LLC, Amherst, New York, USA

2 University at Buffalo School of Pharmacy and Pharmaceutical Sciences, Buffalo, New York, USA

Moise-Broder et al. Clin. Pharmacokinet. 2004; 43:925-942

Vancomycin – AUC_{24h} and efficacy

2. In vivo (clinical study) – clinical success

Table IV. Odds ratios for clinical success

Characteristic	Odds ratio	95% CI	p-Value
Vancomycin AUC ₂₄ /MIC value ≥ 350	7.19	1.91, 27.3	0.0036
MSSA as pathogen	3.88	1.10, 14.8	0.0359
Single lobe involvement	6.32	1.56, 25.6	0.0099
Baseline serum albumin (per 1 g/dL)	3.73	1.09, 12.8	0.0364
Baseline CLCR (per 1 mL/min)	1.04	1.01, 1.07	0.0154

AUC₂₄/MIC = steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration; CLCR = creatinine clearance; MSSA = methicillin-susceptible *Staphylococcus aureus*.

Moise-Broder et al. Clin. Pharmacokinet. 2004; 43:925-942

Vancomycin – AUC_{24h} and efficacy

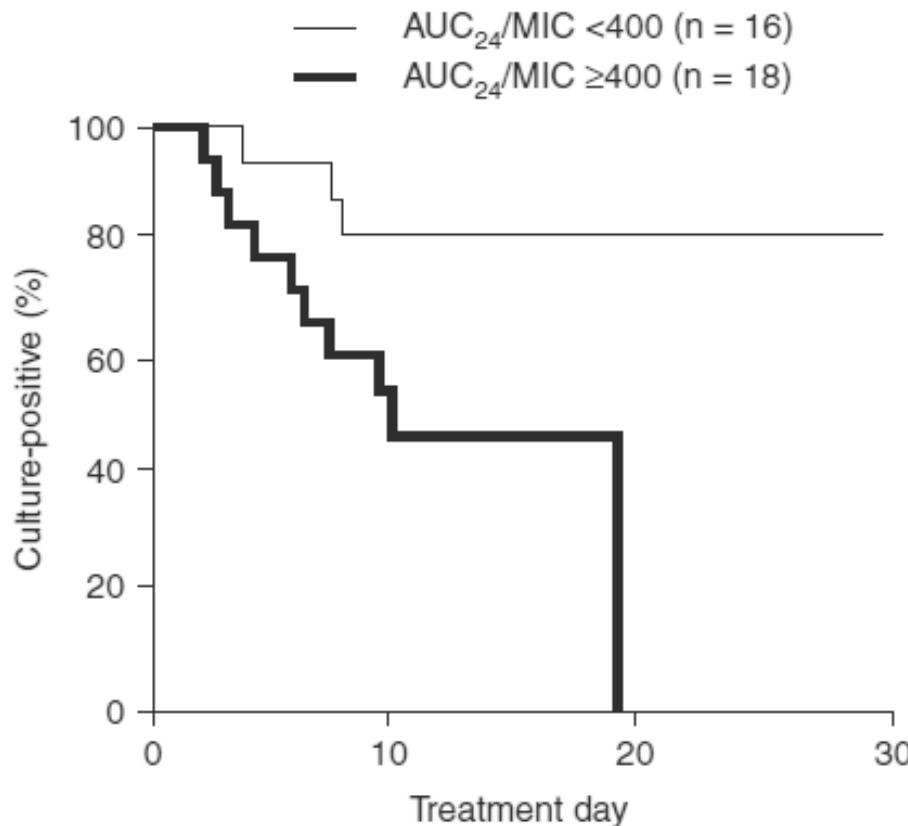
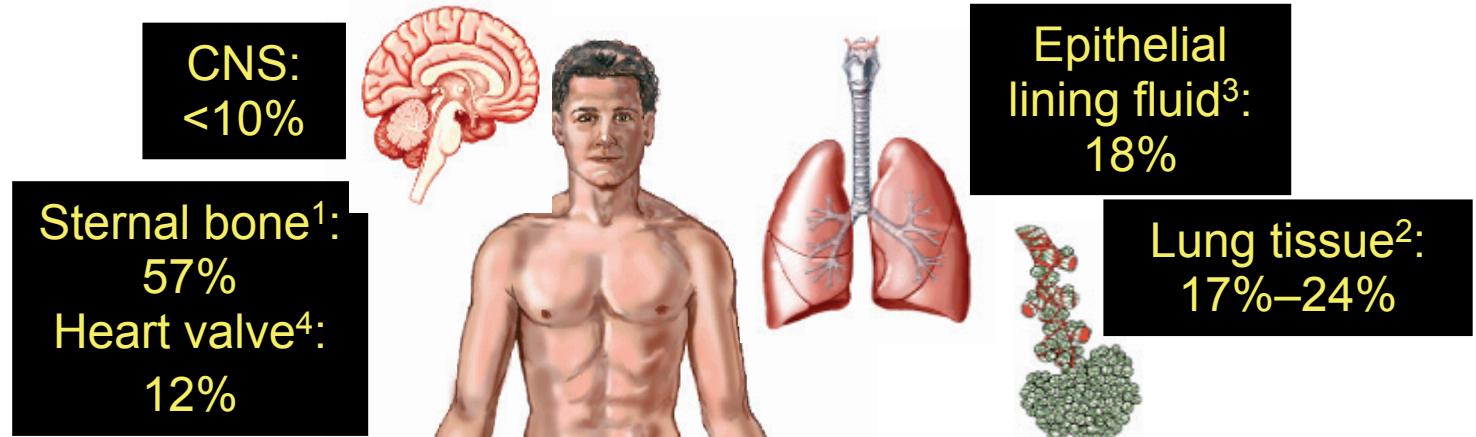


Fig. 4. Time (days of therapy) to bacterial eradication vs vancomycin $\text{AUC}_{24}/\text{MIC} < 400$ and $\text{AUC}_{24}/\text{MIC} \geq 400$ illustrated by a Kaplan-Meier survival plot of day of therapy vs the percentage of patients remaining culture-positive on that day. The two $\text{AUC}_{24}/\text{MIC}$ groups differed significantly ($p = 0.0402$). AUC_{24} = steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration.

Moise-Broder et al. Clin. Pharmacokinet. 2004; 43:925-942

Why is a so large AUC_{24h}/MIC needed ?



Vancomycin Tissular Penetration is poor

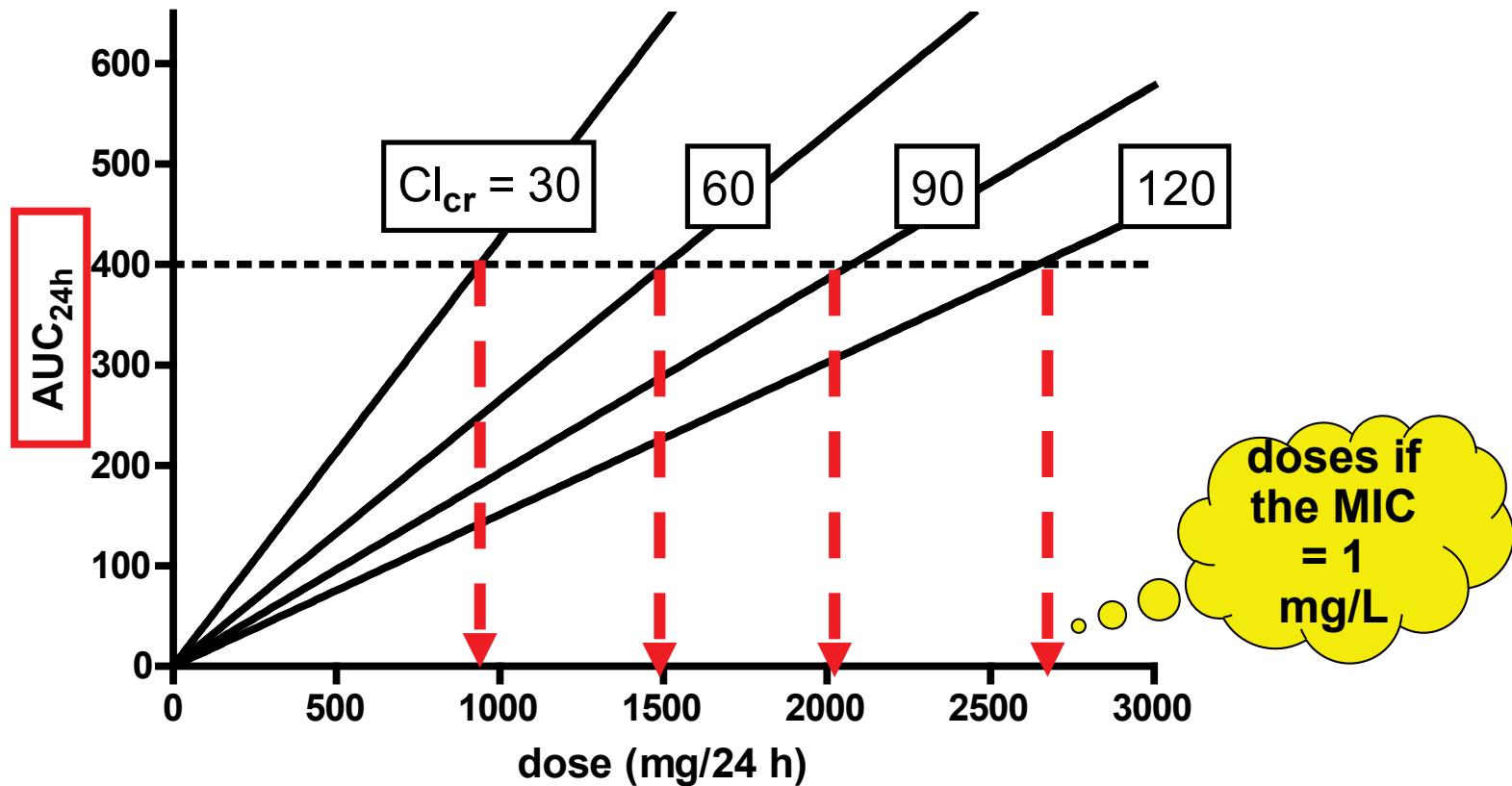


1. Massias L et al. *Antimicrob Agents Chemother*. 1992;36:2539-2541. 2. Cruciani M et al. *J Antimicrob Chemother*. 1996;38:865-869. 3. Lamer C et al. *Antimicrob Agents Chemother*. 1993;37:281-286. 4. Daschner FD et al. *J Antimicrob Chemother*. 1987;19:359-362. 5. Graziani AL et al. *Antimicrob Agents Chemother*. 1988;32:1320-1322.

This slide borrowed from Dr M. Dryden, Royal Hampshire Hospital, Winchester, UK

How to calculate the AUC_{24h} with the conventional BID schedule ?

AUC vs. dose for diff. CL_{cr}

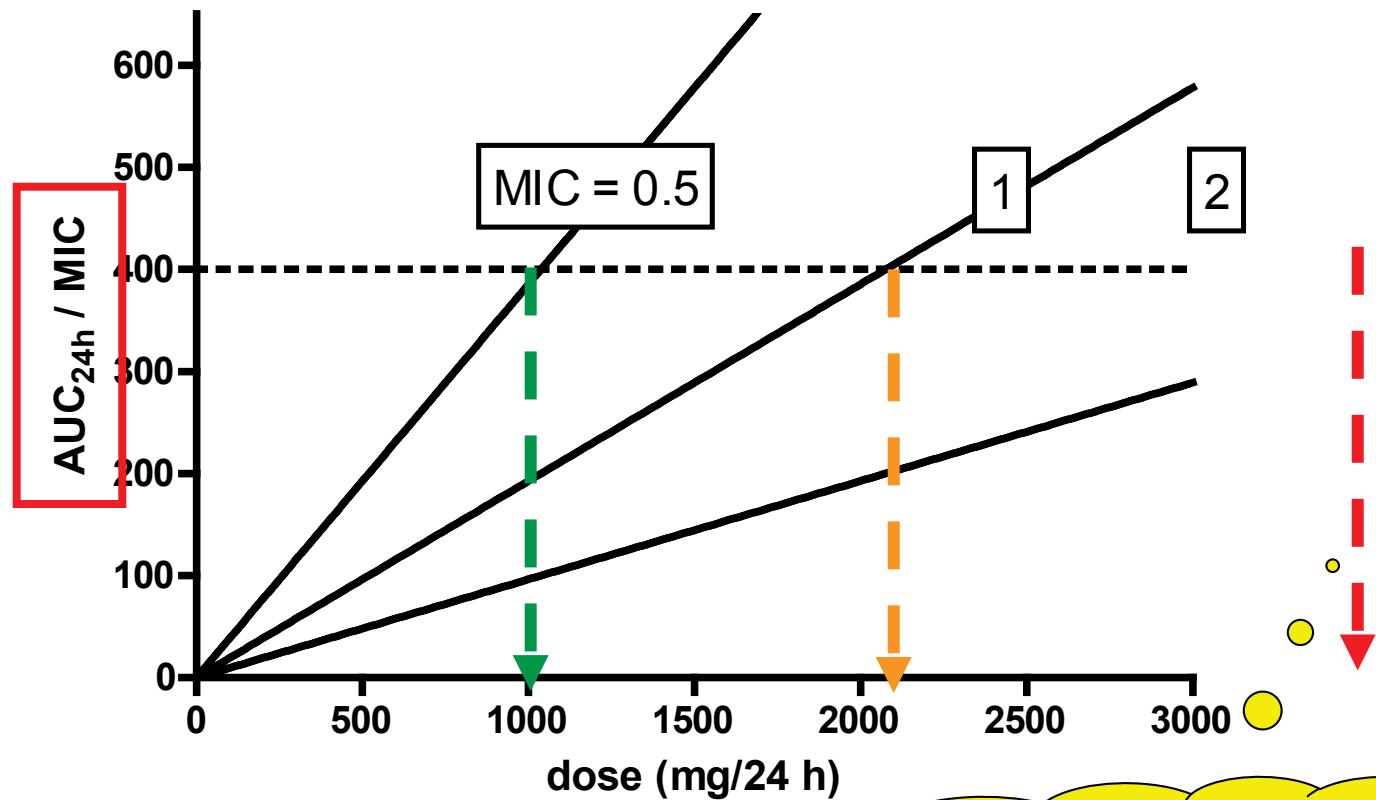


$$AUC_{24} = \frac{D}{[(CL_{CR} \times 0.79) + 15.4] \times 0.06}$$

Moise-Broder et al. Clin. Pharmacokinet. 2004; 43:925-942

How to calculate the AUC_{24h} with the conventional BID schedule ?

AUC_{24h} / MIC vs. dose for diff. MIC and $CL_{cr}=90$ mL/min

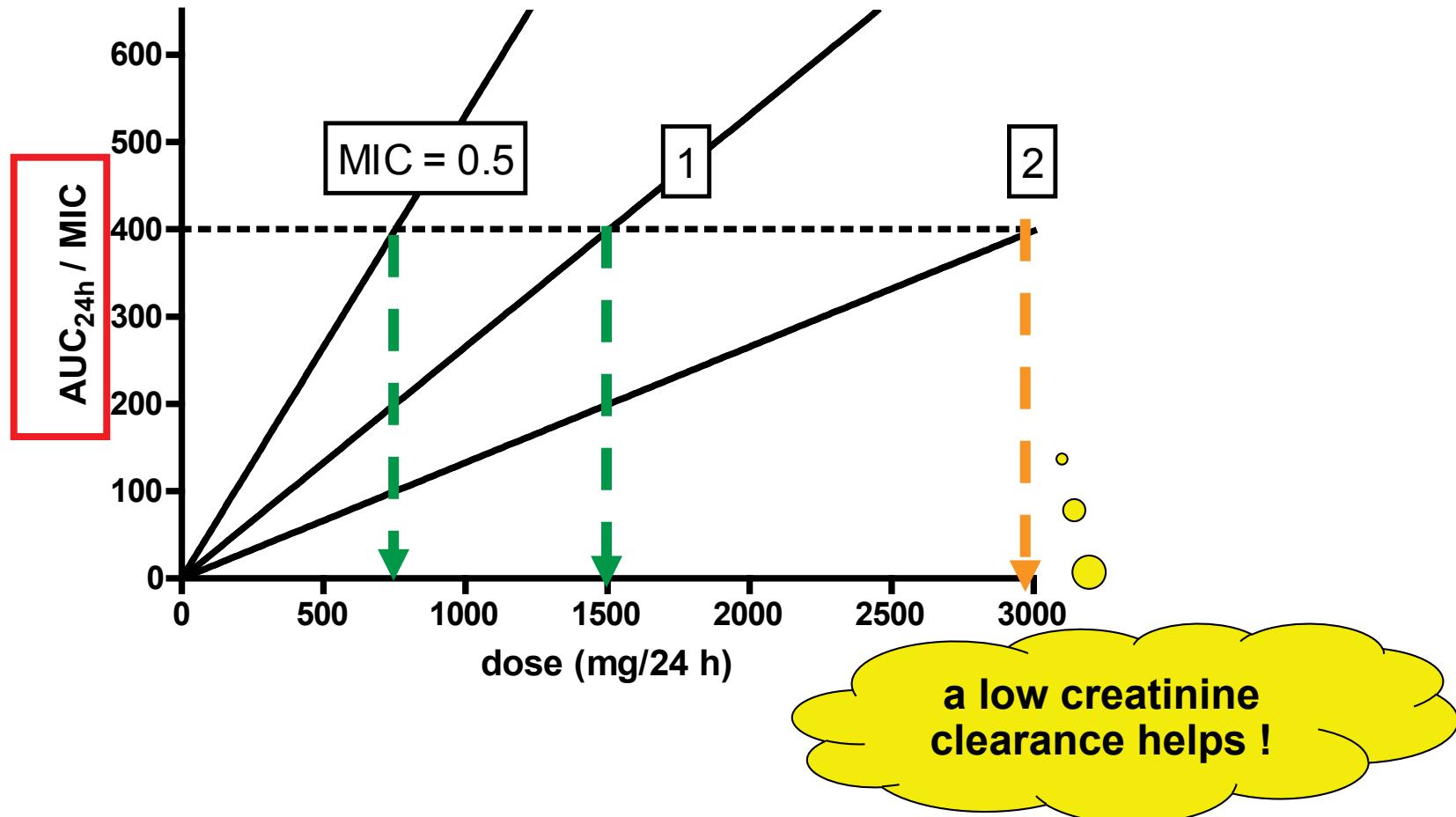


if the MIC is 2, you may have problems

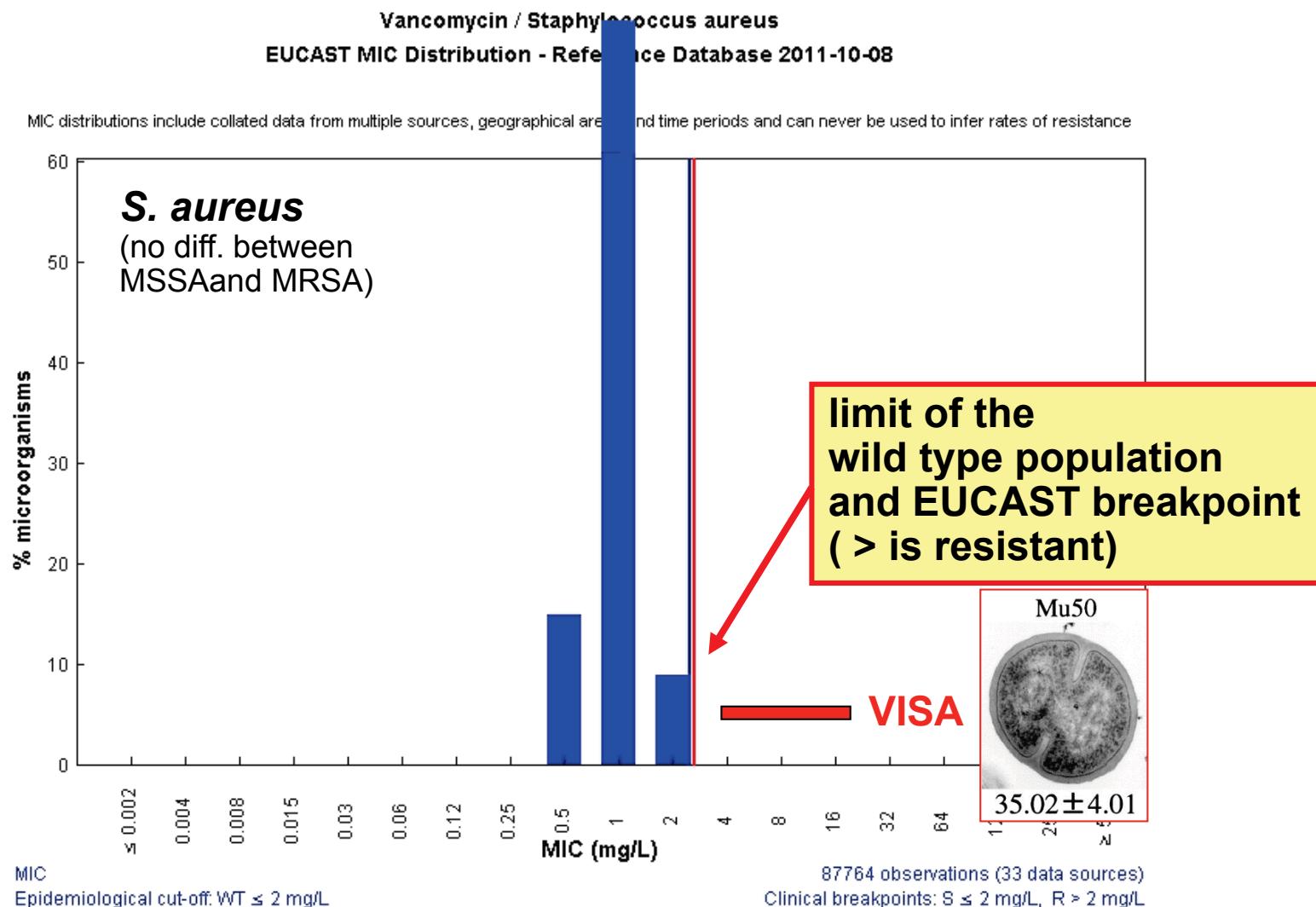
Moise-Broder et al. Clin. Pharmacokinet. 2004; 43:925-942

How to calculate the AUC_{24h} with the conventional BID schedule ?

AUC_{24h} / MIC vs. dose for diff. MIC and $CL_{cr}=60 \text{ mL/min}$



Vancomycin and MIC (EUCAST distributions)



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What if you do not know your MIC ?

- assume a MIC of 2 mg/L (breakpoint) and check at the level of the population ...
- monitor serum concentrations with
 - peak and trough (best to calculate AUC, but ...see next slide)
 - through only (and **ensure trough values of 15-20 mg/L !**)
→ this will (probably) ensure an AUC/MIC ~ 400
- use a loading dose (25-30 mg/kg)
 - obtain rapidly the peak and the necessary AUC/MIC
- organisms with an MIC \geq 2 mg/L will be difficult ...

See details in: Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists.

Rybak et al. Am J Health-Syst Pharm. 2009; 66:82-98

What if you target a "high" trough level ?

Pharmacotherapy. 2012 Jan 31. doi: 10.1002/PHAR.1017. [Epub ahead of print]

Effects of Targeting Higher Vancomycin Trough Levels on Clinical Outcomes and Costs in a Matched Patient Cohort.

Kullar R, Davis SL, Taylor TN, Kaye KS, Rybak MJ.

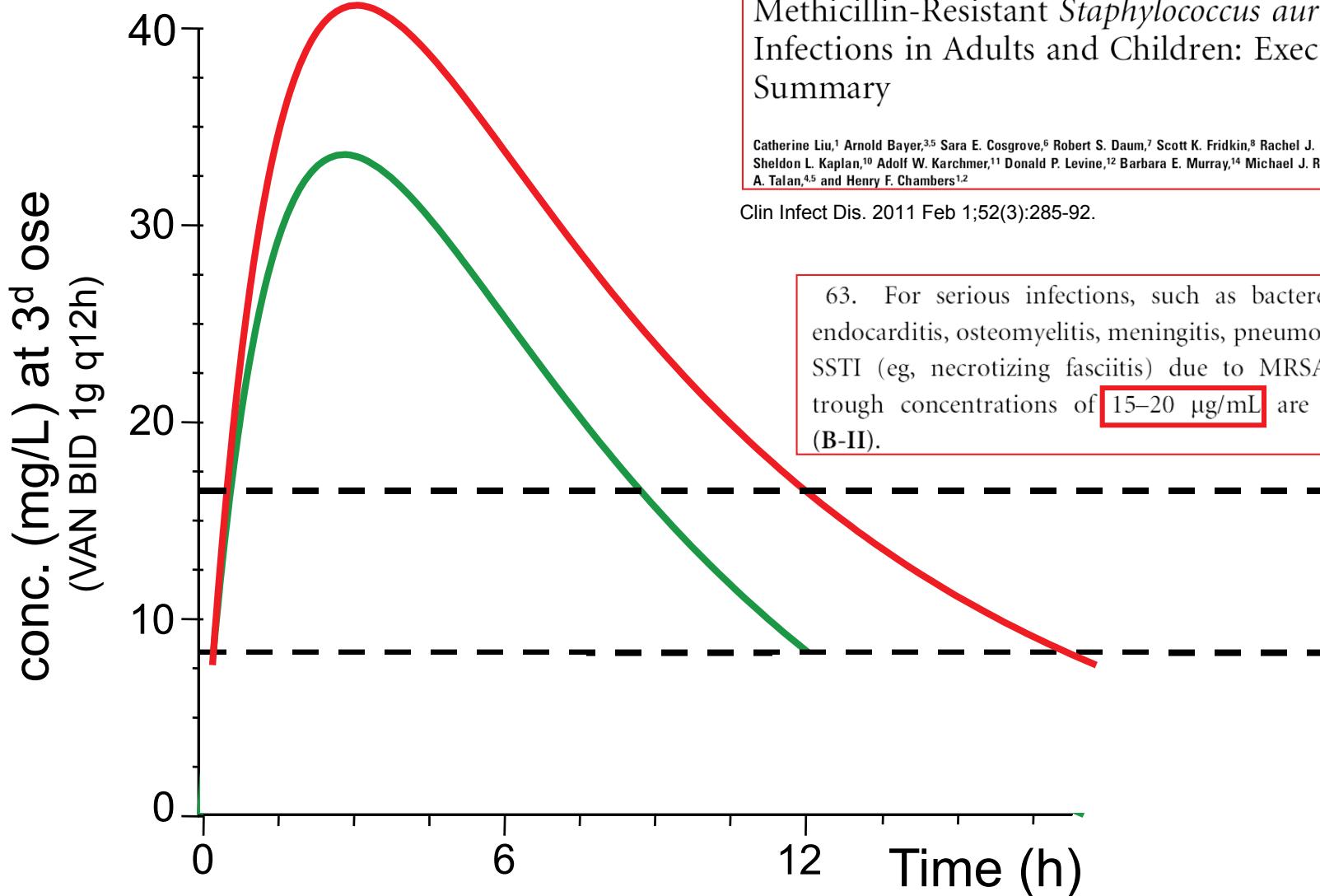
Anti-Infective Research Laboratory.

- STUDY OBJECTIVE: To compare clinical outcomes and costs in patients treated with the new vancomycin guidelines recommending goal serum **trough concentrations of 15-20 mg/L** versus patients treated with vancomycin doses targeting trough concentrations 5-20 mg/L prior to the new guidelines.
- PATIENTS: 200 with confirmed, complicated methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia
 - 100 before implementation (preperiod)
 - 100 after implementation (postperiod)
 - matched for diagnosis, any concomitant nephrotoxic agents (e.g., aminoglycosides, colistin, acyclovir), and age \pm 5 years.

What if you target a "high" trough level ?

- MEASUREMENTS AND MAIN RESULTS :
- Patients in the post-period
 - higher success rates (60% vs 45%, p=0.034).
 - similar length of stay (13.5 days vs 15 days; p=0.28)
 - shorter median treatment (8.5 days vs 13 days; p<0.001).
 - no difference was in total hospital costs (\$ 27,709 vs \$ 32,754 p=0.147)
 - higher drug and monitoring costs
 - initial vancomycin trough levels were significantly higher (15.8 mg/L vs 12.3 mg/L, p=0.02).
 - higher rates of nephrotoxicity (18% vs 15%; p=0.85)
 - higher costs if developing nephrotoxicity.

IDSA guidelines in 2011



IDSA GUIDELINES

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children: Executive Summary

Catherine Liu,¹ Arnold Bayer,^{3,5} Sara E. Cosgrove,⁶ Robert S. Daum,⁷ Scott K. Fridkin,⁸ Rachel J. Gorwitz,⁹ Sheldon L. Kaplan,¹⁰ Adolf W. Karchmer,¹¹ Donald P. Levine,¹² Barbara E. Murray,¹⁴ Michael J. Rybak,^{12,13} David A. Talan,^{4,5} and Henry F. Chambers^{1,2}

Clin Infect Dis. 2011 Feb 1;52(3):285-92.

63. For serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI (eg, necrotizing fasciitis) due to MRSA, vancomycin trough concentrations of **15–20 µg/mL** are recommended (B-II).

But risks in 2013 ...

Hall et al. BMC Pharmacology and Toxicology 2013, 14:12
<http://www.biomedcentral.com/2050-6511/14/12>



RESEARCH ARTICLE

Open Access

Empiric guideline-recommended weight-based vancomycin dosing and nephrotoxicity rates in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: a retrospective cohort study

Ronald G Hall II^{1,2*}, Kathleen A Hazlewood^{1,7}, Sara D Brouse^{1,8}, Christopher A Giuliano^{3,9}, Krystal K Haase³, Christopher R Frei⁴, Nicolas A Forcade^{4,10}, Todd Bell⁵, Roger J Bedimo⁶ and Carlos A Alvarez^{1,2}

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Nephrotoxicity occurred in 78 patients (23%), occurring in 56%, 11%, and 33% of patients at Hospitals A, B, and C, respectively. The median (interquartile range) increase from baseline to peak serum creatinine was 0.0 mg/dL (0.0, 0.2) for patients who did not develop nephrotoxicity versus 1.0 mg/dL (0.6, 2.1) for patients who developed nephrotoxicity. Fifteen percent of patients had a vancomycin trough concentration greater than 20 mcg/ml. Concurrent nephrotoxins included contrast dye (34%), aminoglycosides (19%), and vasopressors (12%). Concomitant antimicrobials active against MRSA were used in 23% of patients.

But be aware of the risk of underdosing

- Patients in continuous infusion and with increased renal clearance



International Journal of Antimicrobial Agents

Available online 3 March 2012

In Press, Corrected Proof — Note to users



Augmented renal clearance in septic patients and implications for vancomycin optimisation

João Pedro Baptista  , Eduardo Sousa, Paulo J. Martins, Jorge M. Pimentel

Serviço de Medicina Intensiva, Hospitais da Universidade de Coimbra, Praceta Professor Mota Pinto 3000-075, Coimbra,
Portugal

Dosing adjustment...

loading dose (1h):

- 1000 mg if ≤ 70 kg
- 1500 mg if > 70 kg)

over 1 h

infusion: 30 mg/kg/day

this was
the
mistake !

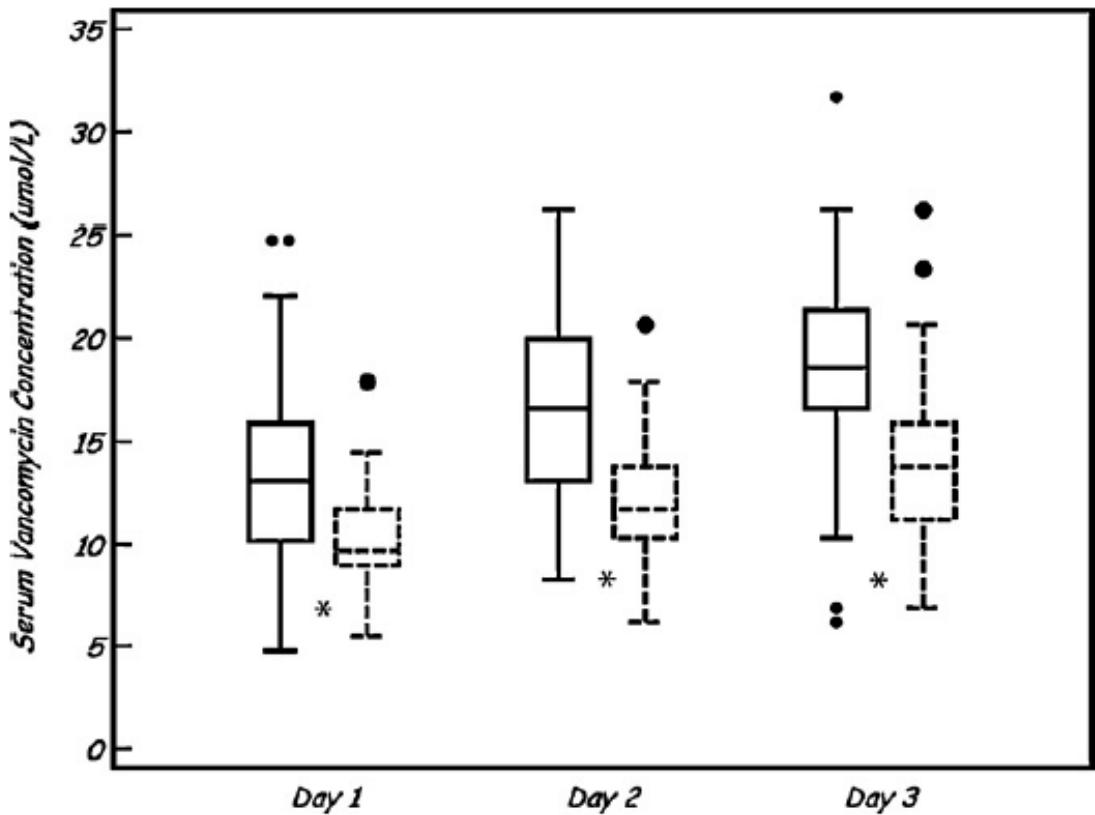
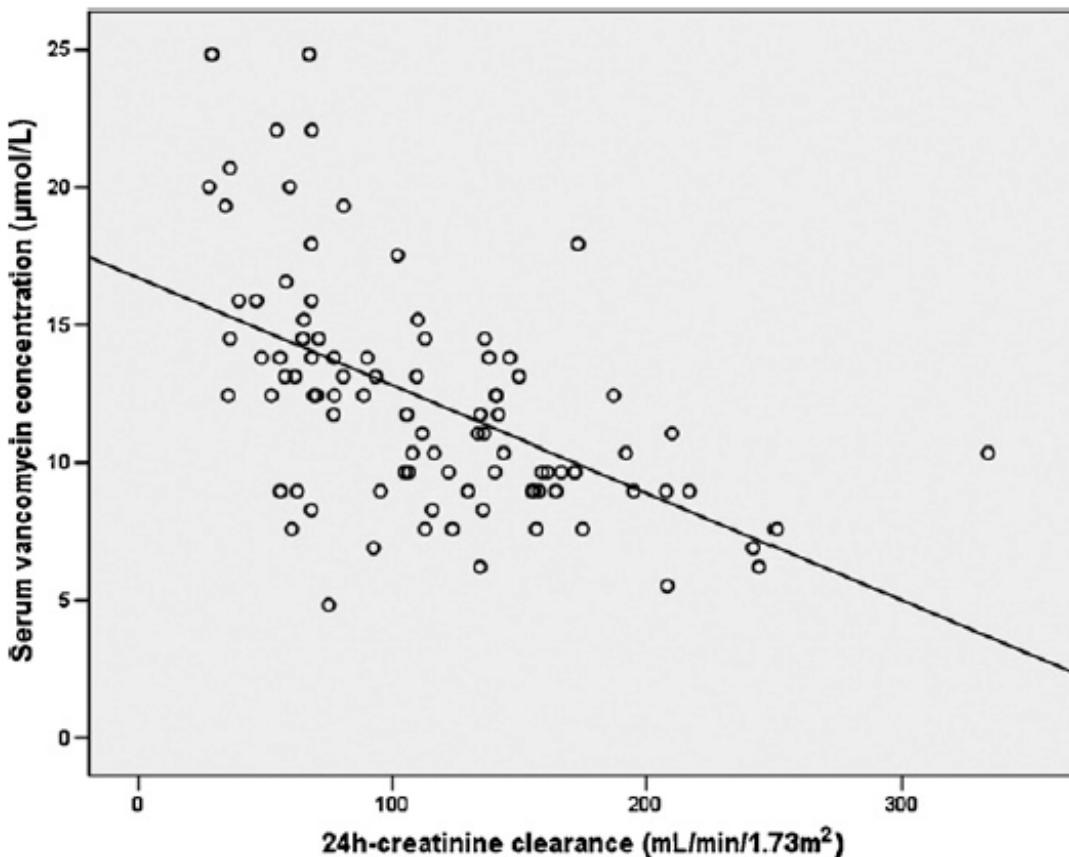


Fig. 1. Box and whisker plots showing the evolution of median (interquartile range) serum vancomycin concentrations on the studied days (Days 1–3) and comparison between Group A [control group without augmented renal clearance (ARC); continuous line] and Group B (study group with ARC; dashed line). * Indicates statistical significance for median differences ($P < 0.01$).

ARC was defined as $\text{CLCr} > 130 \text{ mL/min}/1.73 \text{ m}^2$

Dosing adjustment...



Vancomycin concentration in continuous infusion (at equilibrium) is dependent from its clearance

Fig. 2. Linear correlation between 24-h creatinine clearance (CL_{Cr}) and serum vancomycin concentration on Day 1. The serum vancomycin concentration displayed a significant direct correlation with CL_{Cr} in 93 septic critically ill patients ($r_S = -0.57$; $P < 0.01$).

Vancomycin: provisional conclusions

1. an old drug put back into service
2. will work for organisms with an MIC up to 2 mg/L but probably not higher (beware of CLSI !)
3. You must
 - use a loading dose
 - optimize the maintenance dose
 - if using continuous infusion, you MUST base your infusion rate on clearance, NOT body weight
 - if possible, monitor blood levels AND compare with the MIC
4. use combined therapy for organisms with $\text{MIC} > 2 \text{ mg/L}$
5. do not forget to detect heteroresistance... (use E-test)

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Vancomycin: continuous infusion



International Journal of Antimicrobial Agents 41 (2013) 439–446

International Journal of Antimicrobial Agents

journal homepage: <http://www.elsevier.com/locate/ijantimicag>



Implementation of a protocol for administration of vancomycin by continuous infusion: pharmacokinetic, pharmacodynamic and toxicological aspects



Els Ampe^{a,b,1}, Bénédicte Delaere^b, Jean-Daniel Hecq^b, Paul M. Tulkens^{a,*},
Youri Glupczynski^b

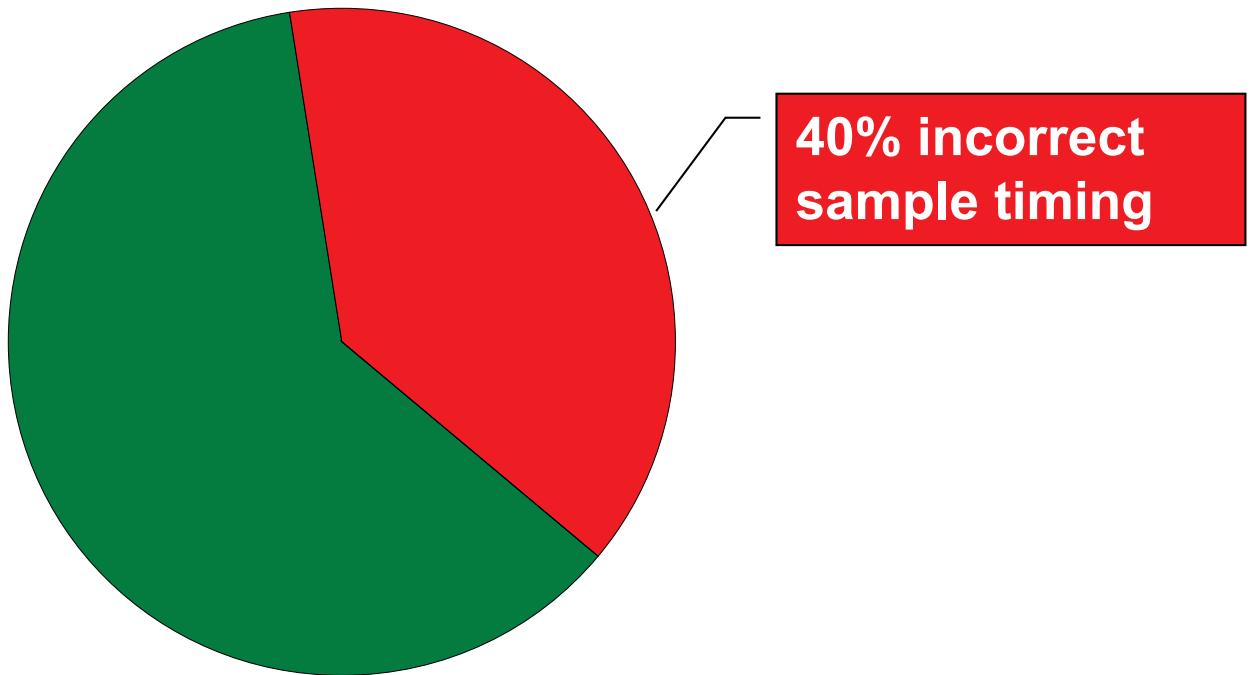
^a Pharmacologie cellulaire et moléculaire et Centre de pharmacie clinique, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium

^b Laboratoire de microbiologie, Service d'infectiologie et Département de pharmacie, CHU Mont-Godinne, Yvoir, Belgium

Vancomycin: continuous infusion

- Why → monitoring serum levels with the conventional mode is impossible...
- How
- Do the others do the same ?

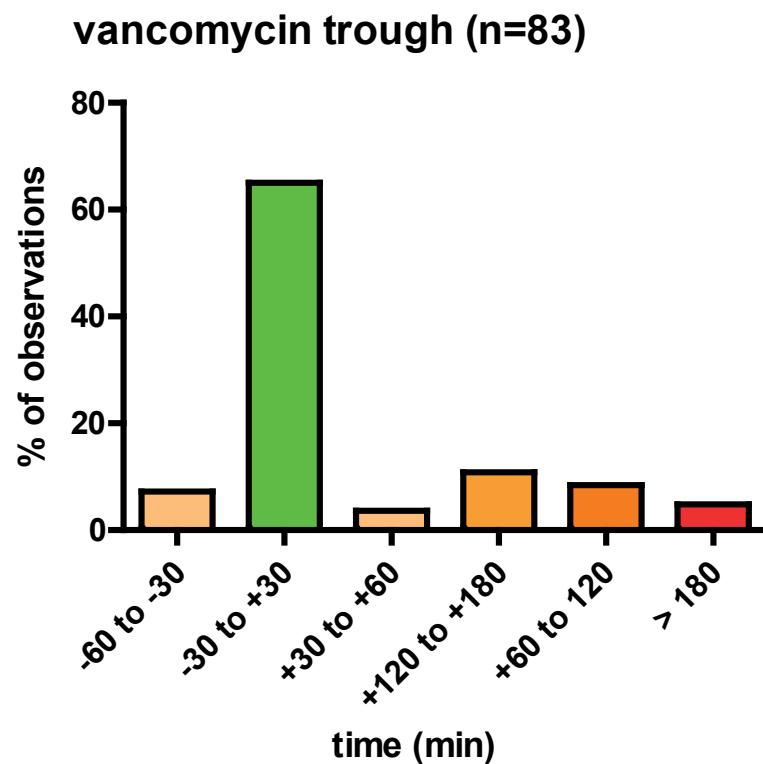
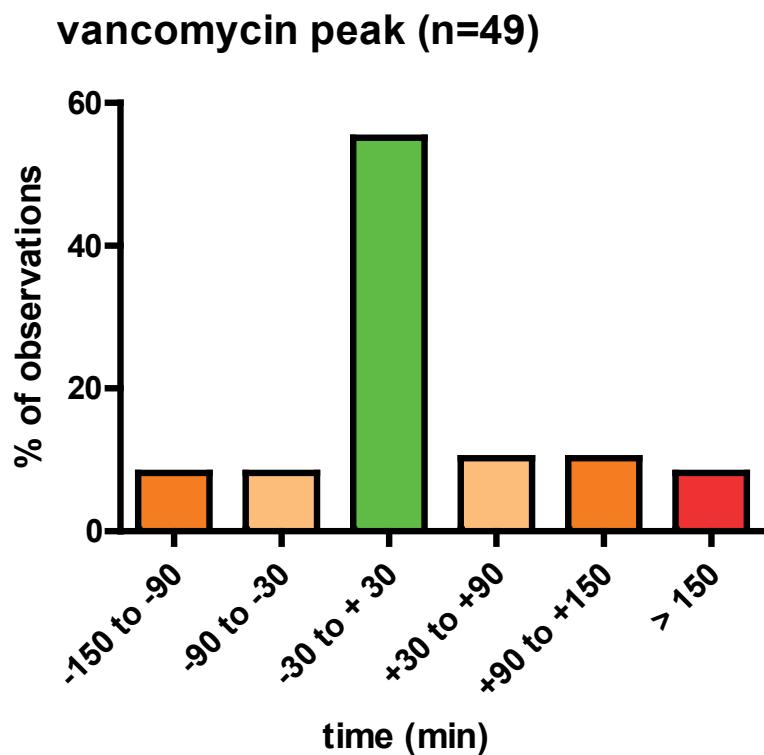
Observational study – results



*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



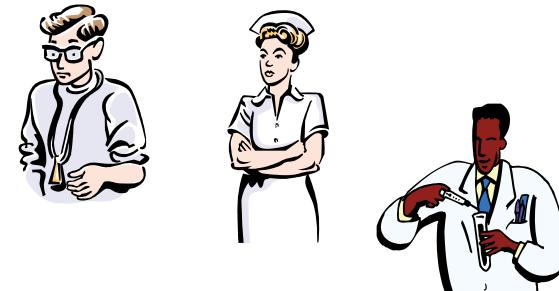
Quantitative methods (clinical trials)	Qualitative methods (interviews, observations, notes)
'how many'?	'why?' and 'how?' (hypothesis generating)
<i>what is the % of inappropriate TDM? what is the impact of x on this %?</i>	<i>why/how does inappropriate TDM occur?</i>
large, random samples	small, purposive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

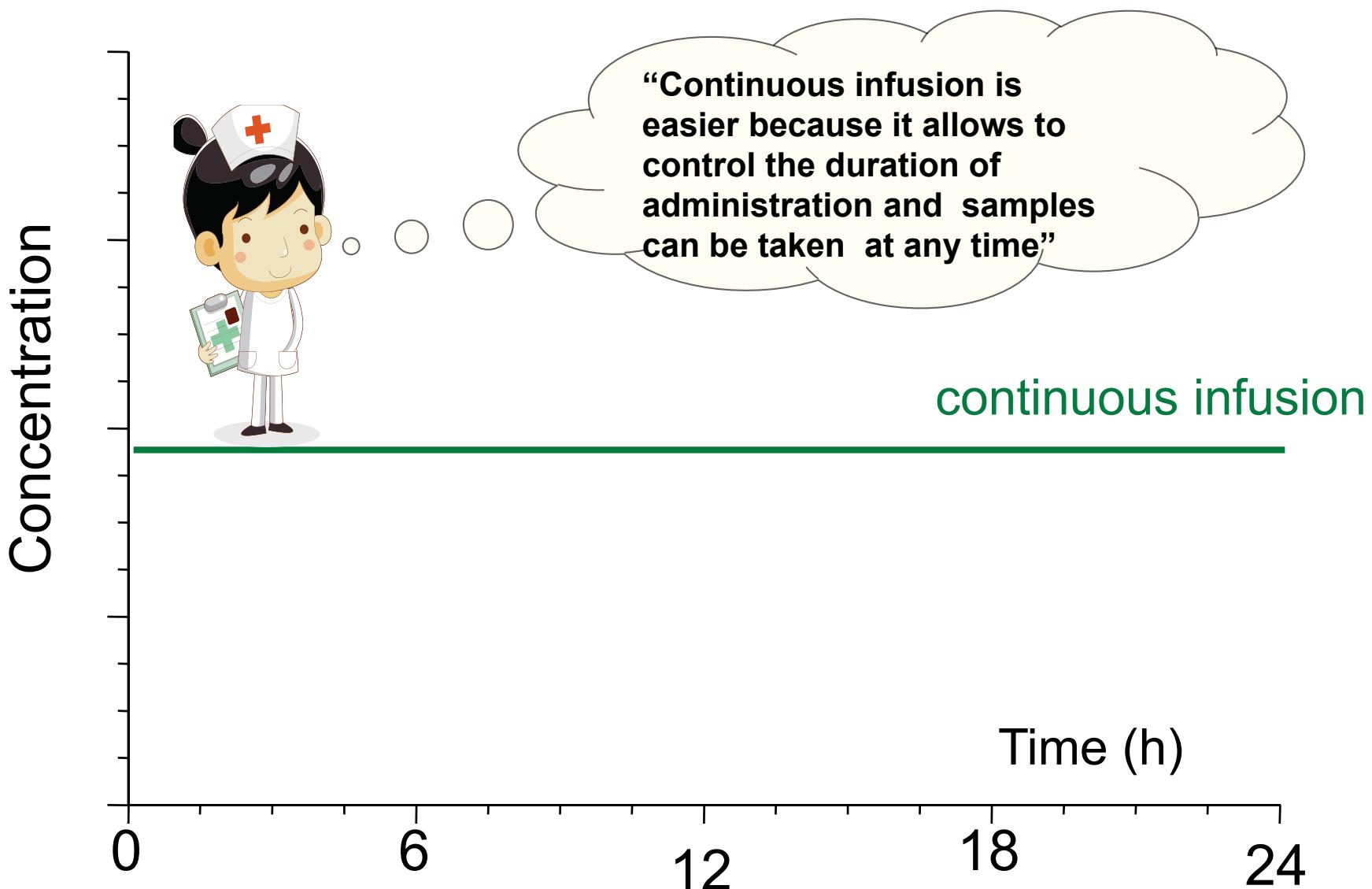


M2: “I'm convinced that there are pharmacokinetic calculations on which we will base [our next dosing] and which are erroneous because the sample drawing and the timing of the administration have not been made correctly, it is completely random, I mean...”

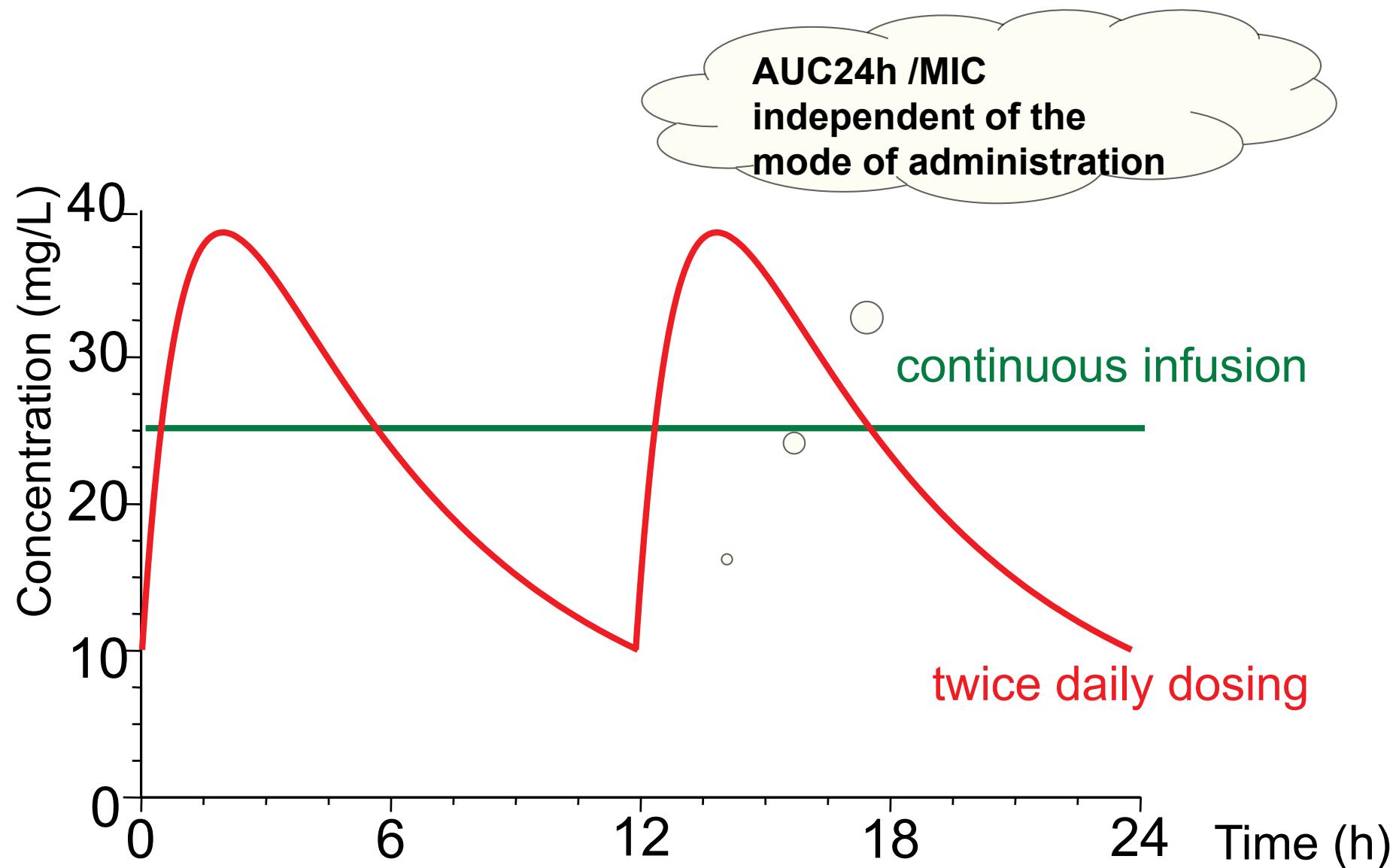
M1: “It is forbidden, on my ward, to follow the therapeutic recommendations of the laboratory, what the lab proposes.”

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

how to optimize vancomycin treatment



TDM of vancomycin by continuous infusion



Vancomycin: continuous infusion

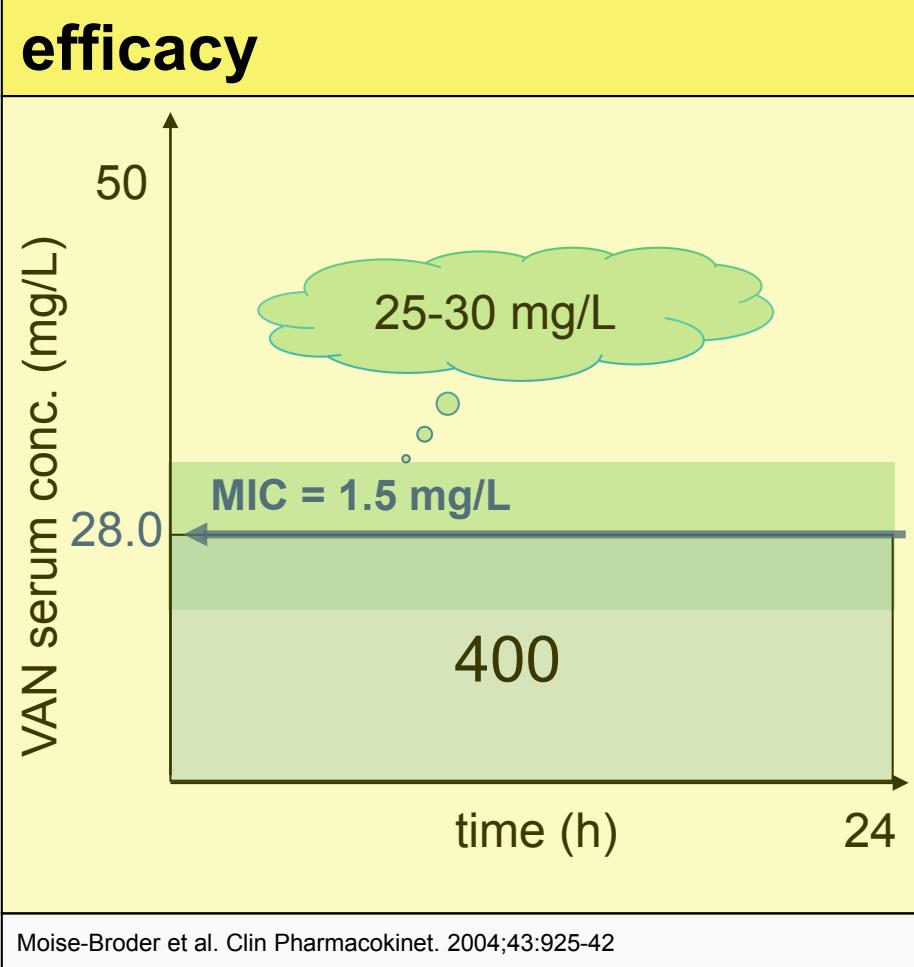
- Why → monitoring serum levels with the conventional mode is impossible...
- How: **the details of what we did**
- Do the others do the same ?

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)

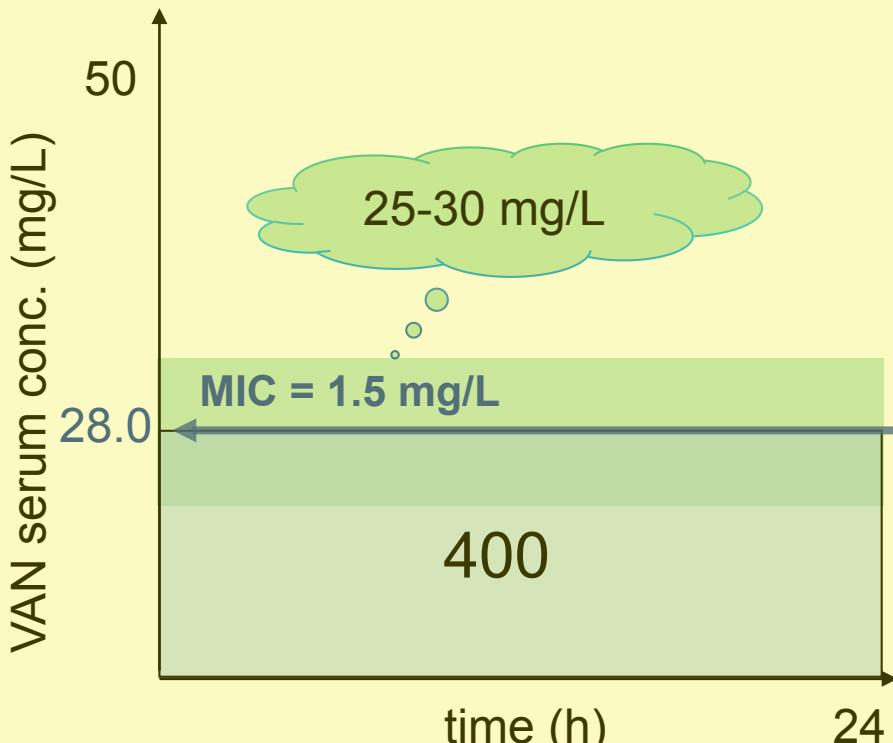
MIC (mg/L)	minimal AUC (mg*L ⁻¹ *h)	target Css (mg/L)
1	400	16.6
2	800	33.3
4	1600	66.6

vancomycin CI: which serum concentration should we target?



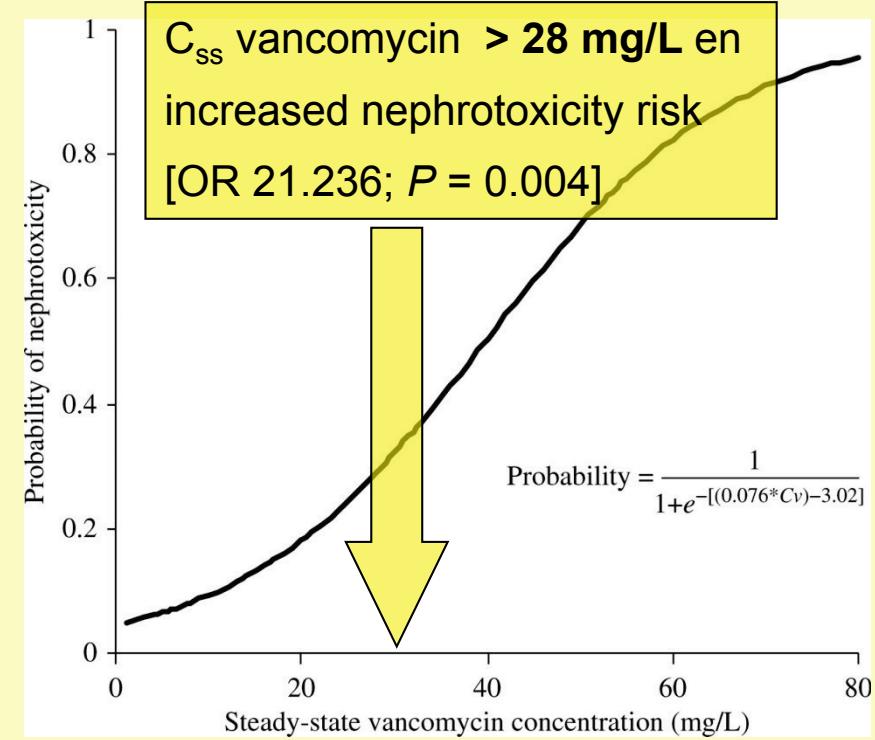
vancomycin CI: which serum concentration should we target?

efficacy



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

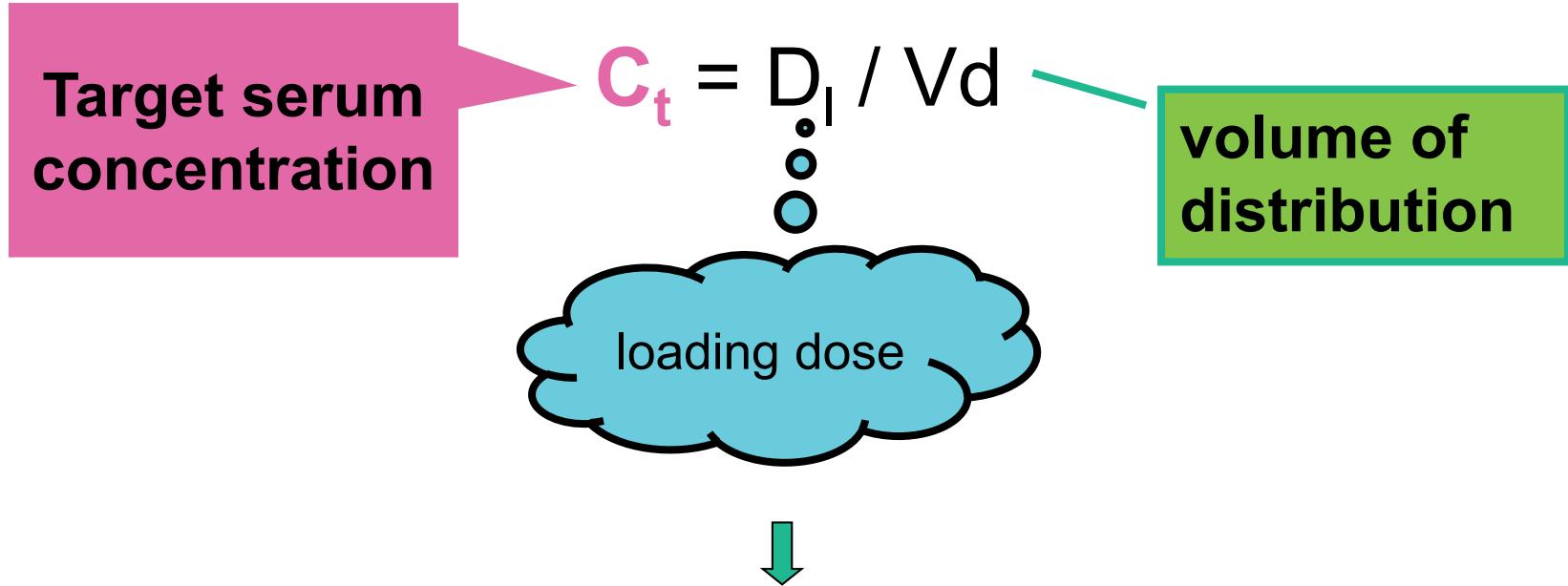
toxicity



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 *

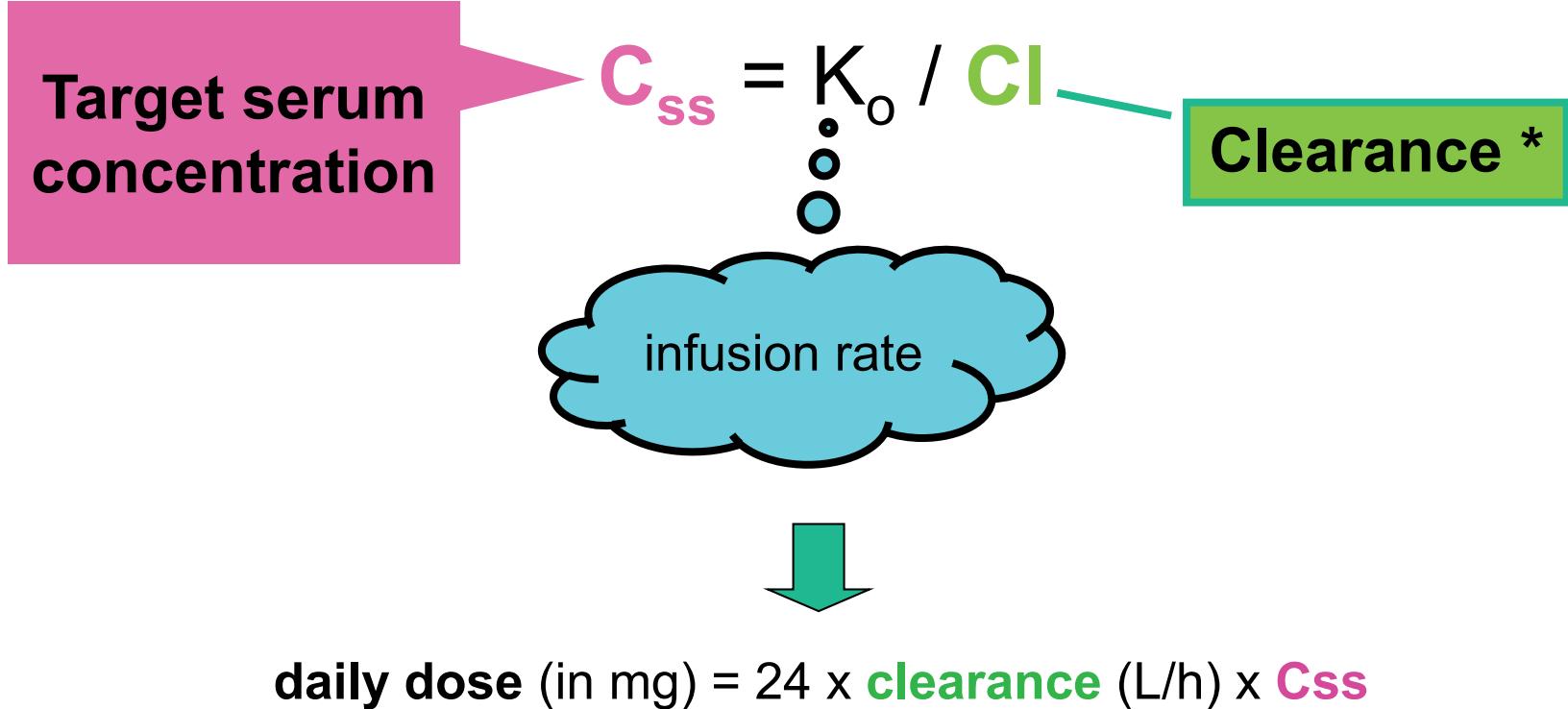


$$\text{loading dose (in mg/kg)} = 20 \text{ mg/kg} = 25 \text{ (mg/L)} \times 0.8 \text{ (L/kg)}$$

* assuming linear pharmacokinetics

How to reach the serum target concentration target with CI?

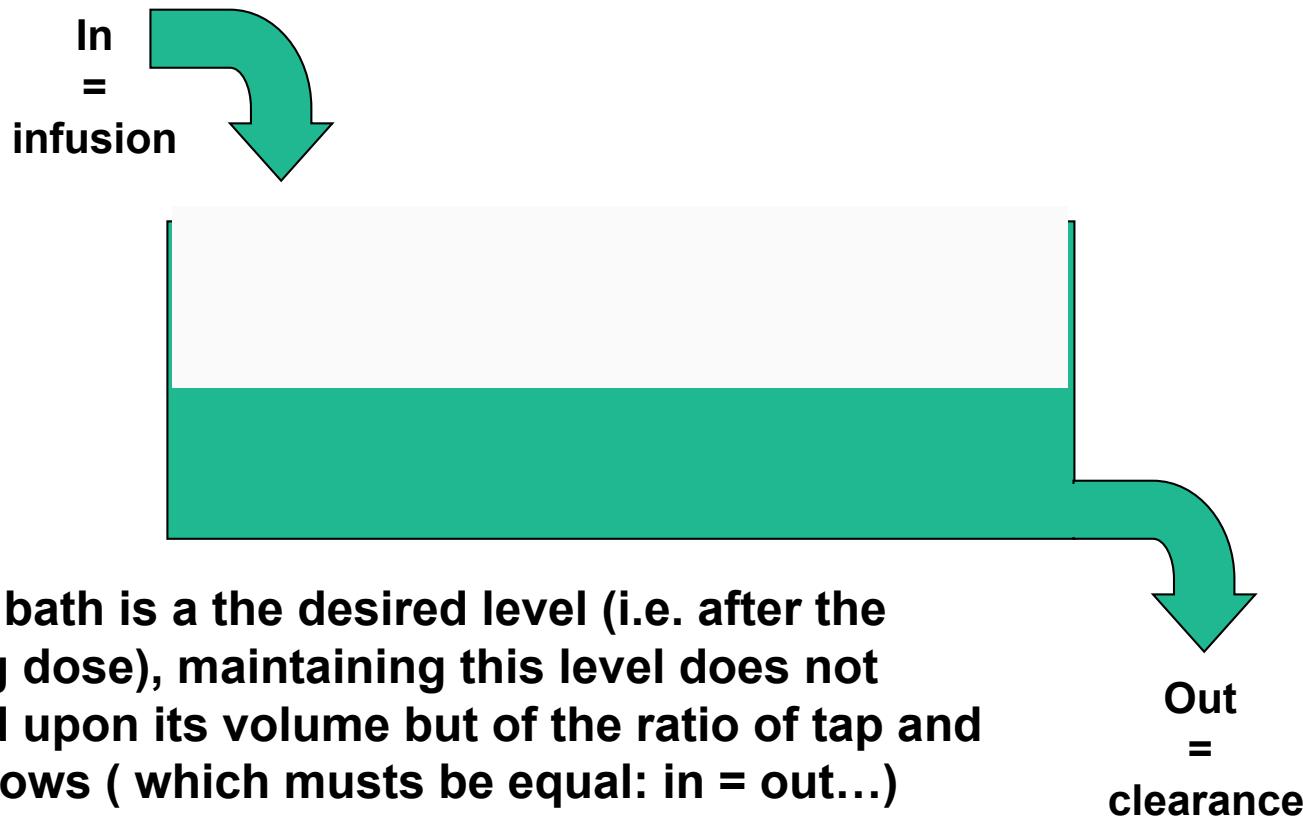
2: infusion *



* assuming linear pharmacokinetics

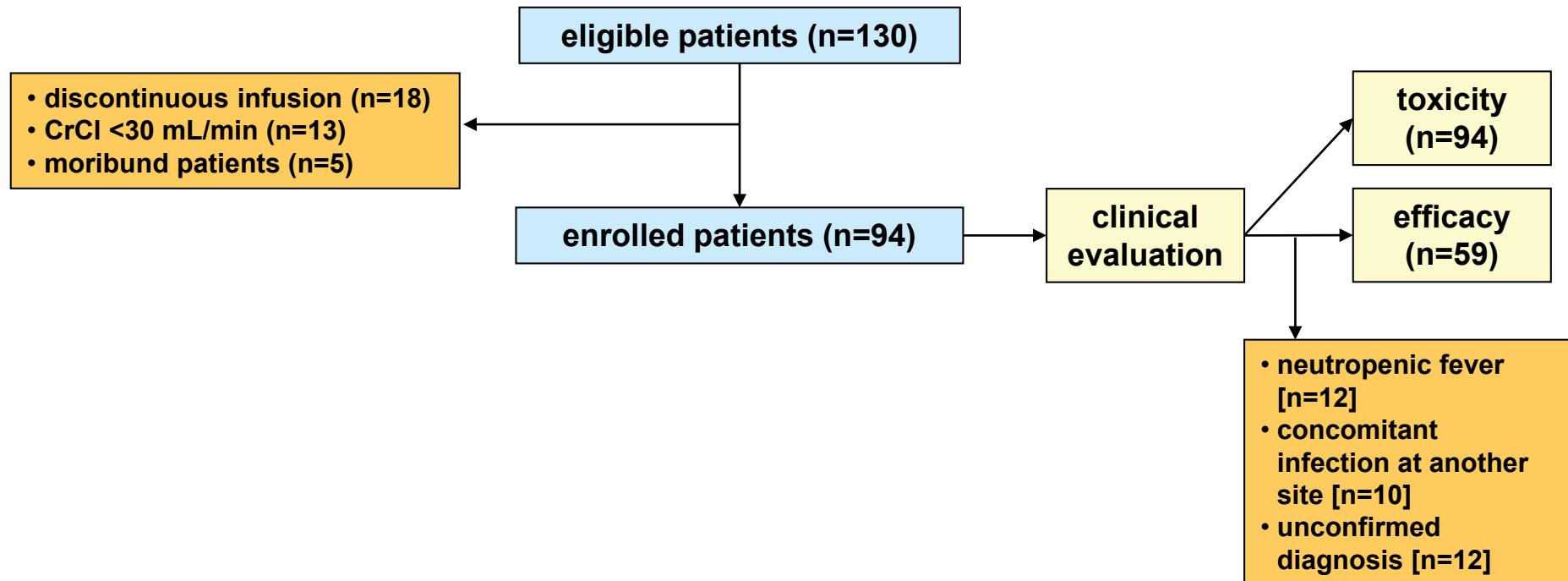
How to reach the serum target concentration target with CI?

2: infusion *

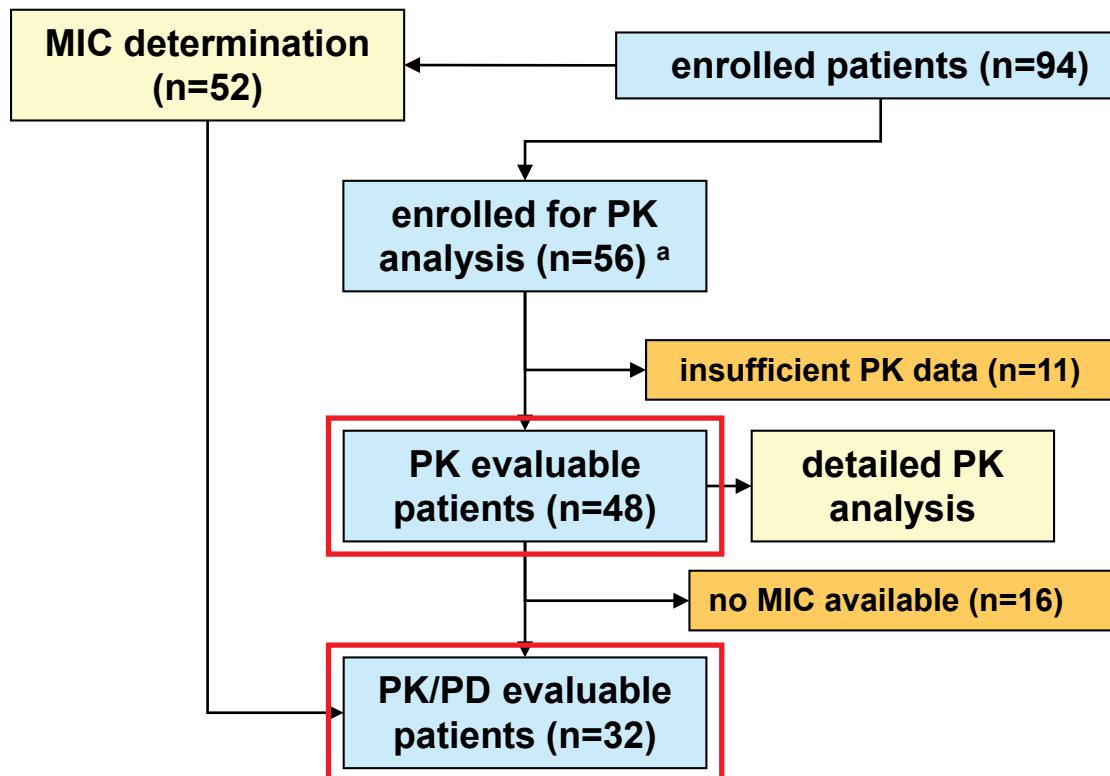


* during the infusion, the necessary dose (in 24h or per min) is only dependent upon the clearance

2. Clinical evaluation: study outline



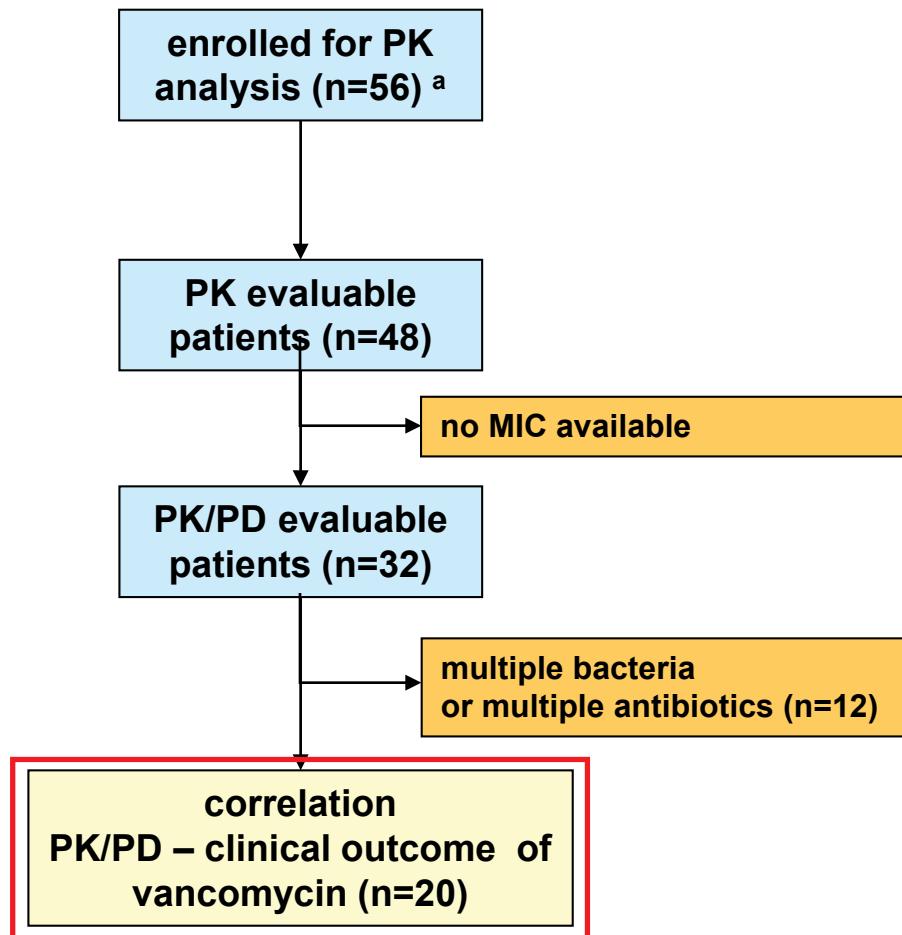
2. Pharmacokinetic evaluation: study outline



^a signed informed consent for additional blood sampling

^b standard of care only

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

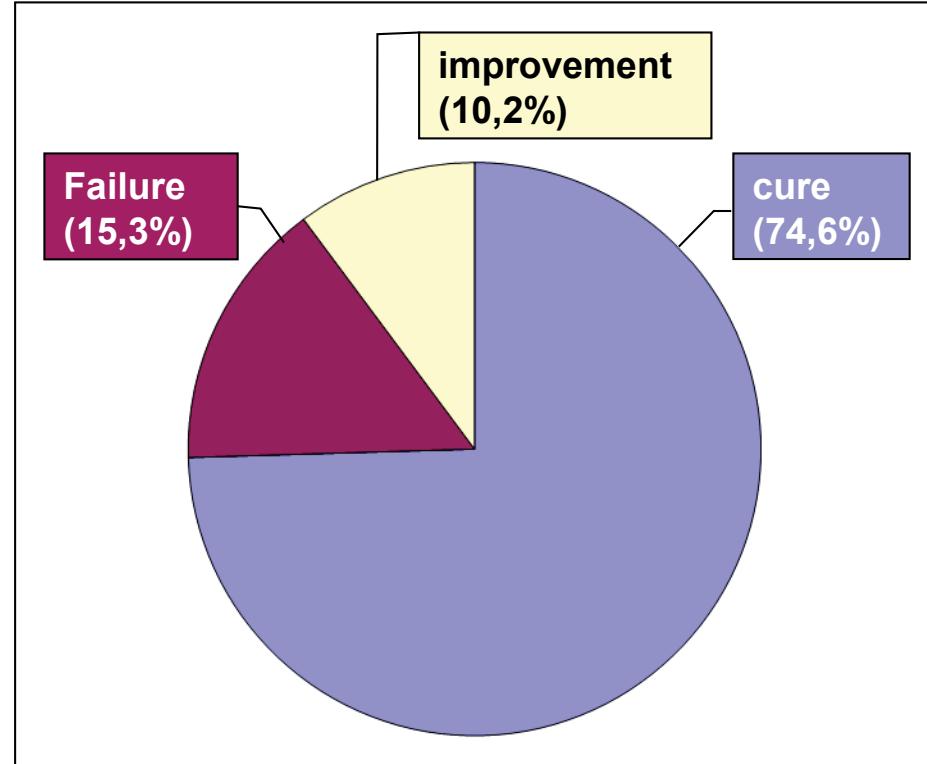


^a signed informed consent for additional blood sampling

^b standard of care only

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

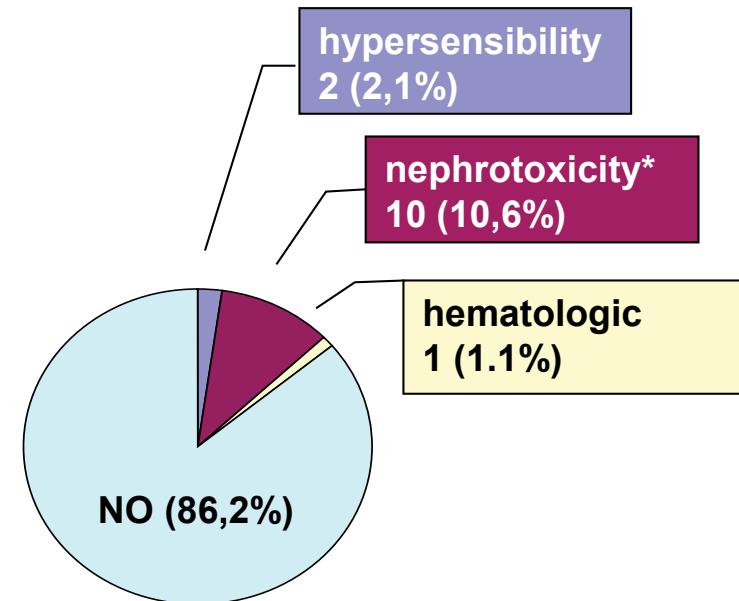
- clinical cure:
 - (i) disappearance of all major signs of infection;
 - (ii) normalization of body temperature;
 - (iii) marked decrease of CRP.
- at EOT and at 6 months
- assessment retrospectively validated by 2 ID physicians



3. Toxicity

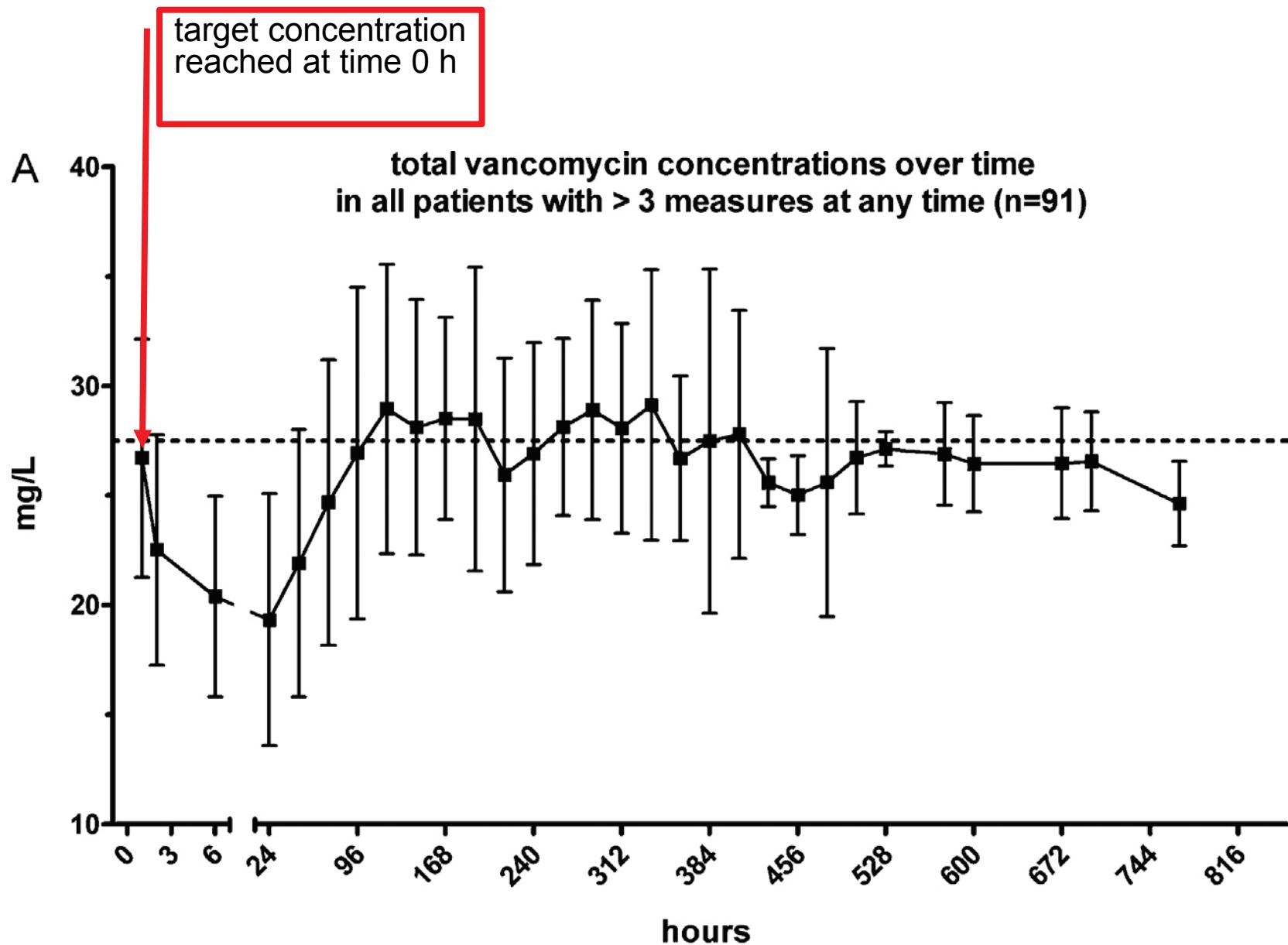
Adverse events observed in all enrolled patients (n = 94).

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

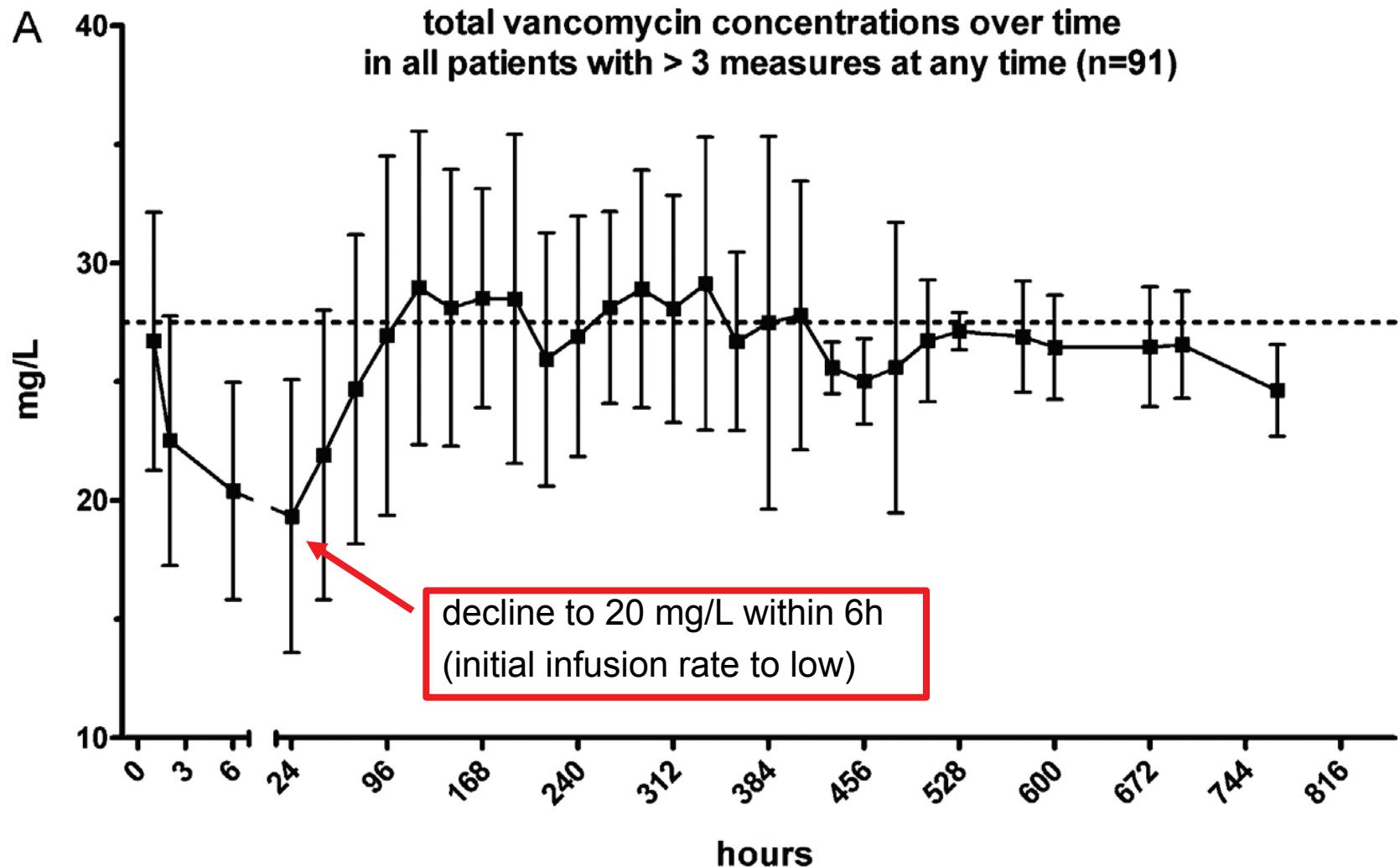


*IDSA consensus statement def. of vancomycin nephrotoxicity (Rybak et al. Am J Health-Syst Pharm 2009):
2 or 3 documented increases in serum creatinine level; increase of 0.5 mg/dL OR $\geq 50\%$ increase from baseline after several days of vancomycin therapy.

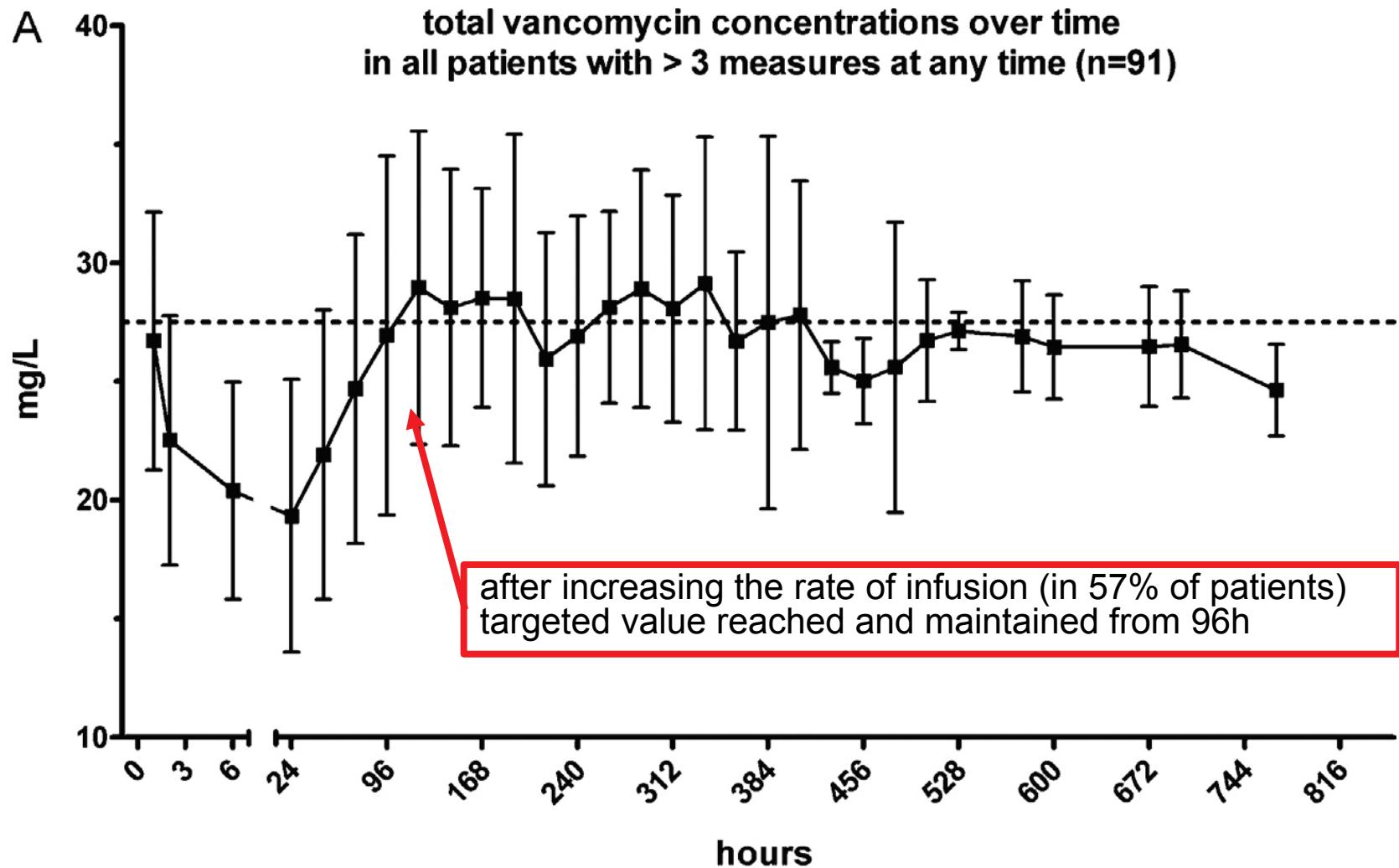
7. Total vancomycin serum concentrations



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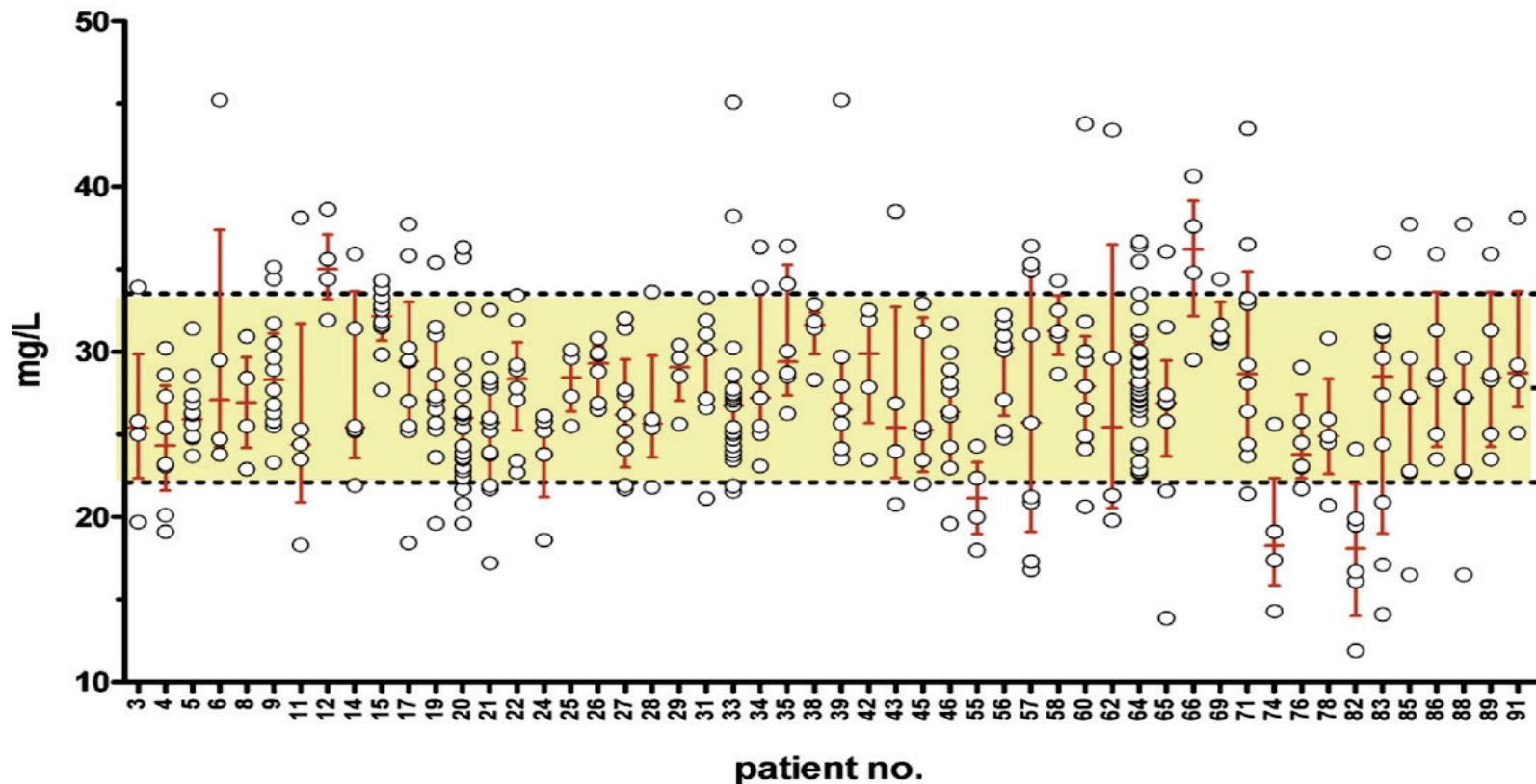


7. Total vancomycin serum concentrations



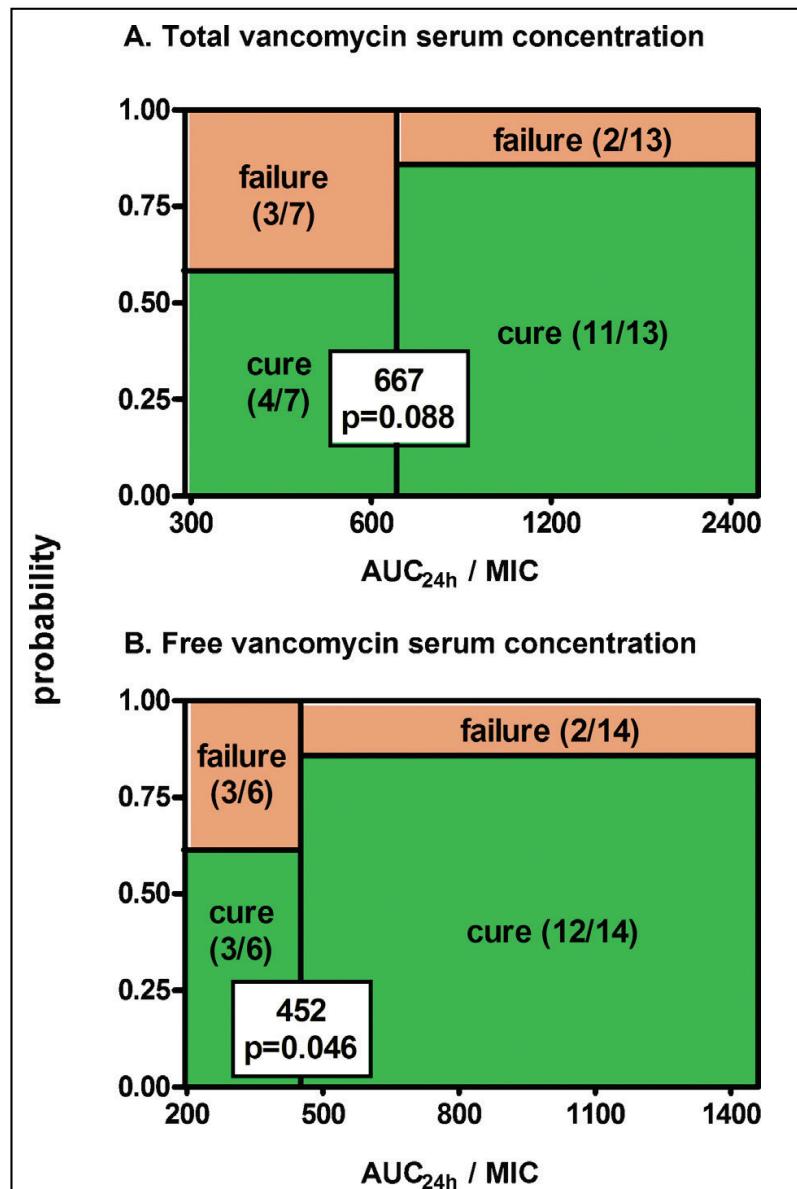
7. Total vancomycin serum concentrations

B successive vancomycin serum levels values in individual patients with > 3 determinations after the first 96h of treatment (n = 52)



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

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)

Vancomycin continuous infusion: dose adaptation

Table SP1: Dose adaptations for deviations of the targeted serum level

Target level: 25-30 mg/L

Actual concentration (measured)	Dose adaptation
0-5 mg/L	<ul style="list-style-type: none">• Add a loading dose (20 mg/kg)• Increase of the rate of infusion (+ 8 mL/h)^a
6-10 mg/L	<ul style="list-style-type: none">• Add a loading dose (15 mg/kg)• Increase of the rate of infusion (+ 6 mL/h)^a
11-15 mg/L	<ul style="list-style-type: none">• Add a loading dose (10 mg/kg)• Increase of the rate of infusion (+ 4 mL/h)^a
16-25 mg/L	<ul style="list-style-type: none">• Increase of the rate of infusion (+ 2 mL/h)^a
26-30 mg/L	<ul style="list-style-type: none">• No change
31-35 mg/L	<ul style="list-style-type: none">• Decrease of the rate of infusion (- 2 mL/h)^a
> 35 mg/L	<ul style="list-style-type: none">• STOP infusion for 6 h• Decrease of the rate of infusion (- 4 mL/h)^a• Control serum level the next day

^a standard infusion solution at 10 mg/mL

Vancomycin continuous infusion: how does it work

- **Loading dose**
 - 20 mg/kg (based on actual body weight and an estimated distribution volume of 0.7 L/kg [10-12]) administered over 1 h for doses < 2 g or over 2 h for larger doses.
- **Infusion:**
 - "bags" are prepared in the Central pharmacy at 10 g/L in 5% glucose solution for infusion and transferred to the wards
 - the preparation is infused with volumetric infusion pump (Volumed 7000®; Arcomed AG, Regensdorf, Switzerland).

Note: vancomycin is stable at 37°C for at least 3 days...

(Raverdy V, Ampe E, Hecq JD, Tulkens PM. Stability and compatibility of vancomycin for administration by continuous infusion. J Antimicrob Chemother. 2013 May;68(5):1179-82).

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...

Are clinicians happy ?



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."

Continuous infusion in Mont-Godinne



- 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

Vancomycin: continuous infusion

- Why → monitoring serum levels with the conventional mode is impossible...
- How: the details of what we did
- **Do the others do the same ?**

Does it work elsewhere ?

The screenshot shows the PubMed search interface. The search term 'vancomycin AND continuous infusion' is highlighted with a red box. Below the search bar, there are links for 'Create RSS', 'Create alert', and 'Advanced'. On the left, there's a sidebar with filters for 'Article types' (Summary, Clinical Trial, Review, Customize ...), 'Text availability' (Abstract), and a 'Search results' section stating 'Items: 1 to 20 of 195'. On the right, there's a 'Filter your results:' section with a yellow arrow pointing to 'All (195)', and two items highlighted with red boxes: 'Clinical Trial (25)' and 'Free Full Text (62)'.

NCBI Resources How To ptulkens

PubMed vancomycin AND continuous infusion

Create RSS Create alert Advanced

Article types

Clinical Trial

Review

Customize ...

Text availability

Abstract

Search results

Items: 1 to 20 of 195

Send to: Filter your results:

All (195)

Clinical Trial (25)

Free Full Text (62)

To help you if you are interested...

[Eur J Clin Pharmacol](#). 2014 Nov;70(11):1353-9. doi: 10.1007/s00228-014-1742-6. Epub 2014 Aug 30.

Design and prospective validation of a dosing instrument for continuous infusion of vancomycin: a within-population approach.

[van Maarseveen EM¹, Bouma A, Touw DJ, Neef C, van Zanten AR](#).

[Author information](#)

¹Department of Clinical Pharmacy, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands,
E.M.vanmaarseveen@UMCUtrecht.nl.

[Crit Care](#). 2014 May 15;18(3):R99. doi: 10.1186/cc13874.

Does contemporary vancomycin dosing achieve therapeutic targets in a heterogeneous clinical cohort of critically ill patients? Data from the multinational DALI study.

[Blot S, Koulenti D, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Kaukonen KM, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Lipman J, Roberts JA](#).

[J Crit Care](#). 2014 Jun;29(3):351-5. doi: 10.1016/j.jcrc.2013.12.007. Epub 2013 Dec 21.

Evaluation of a dosing regimen for continuous vancomycin infusion in critically ill patients: an observational study in intensive care unit patients.

[Saukel B¹, Gramm C², Wagner JY³, Messer M², Lahmer T², Meidert AS², Schmid RM², Huber W²](#).

[Author information](#)

¹II. Medizinische Klinik und Poliklinik, Klinikum rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, 81675 München, Germany. Electronic address: bernd.saukel@gmx.de.

²II. Medizinische Klinik und Poliklinik, Klinikum rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, 81675 München, Germany.

³III. Medizinische Klinik, Klinikum rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, 81675 München, Germany.

So, you asked about vancomycin...

- Vancomycin
 - short summary of its history and general properties
 - how to measure MICs and heteroresistance
 - vancomycin PK/PD and minimal AUC_{24h}/MIC
 - high doses in America ... and the risks
 - continuous infusion of vancomycin:
 - why
 - how we do it...
 - do the others do the same

But why do you wish to use vancomycin and can you use it ?

- Do you have MRSE or MRSA ?
- Can you obtain MIC's
- Can you monitor blood levels ?

This is the end (for the time being) !

But ask questions

