# Vancomycin:
# from old Mississipi mud to modern use by continuous infusion (an update)

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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*)

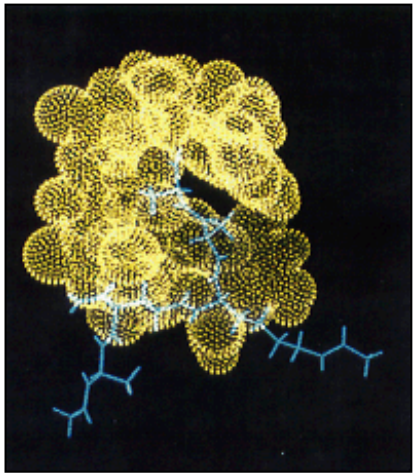
- Decision-making and consultation bodies
  - European Committee for Antimicrobial Susceptibility Testing [EUCAST] (General Assembly and steering committee (2010-2012))
  - European Medicines Agency (external ad-hoc expert)
  - US National Institutes of Health (grant reviewing)
  - Drive-AB [*Driving 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 did it …
    - do the others do the same ?
  - unconventional uses of vancomycin (a few words)

# 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 nephtotoxicity
- 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 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*: tickening 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)

# But when do you really need vancomycin ?

- Do you have these Infections ?
  - Sepsis
  - Endocarditis
  - Skin and soft tissue infections
  - Osteomyelitis
  - Lower respiratory tract infections
  - Diarrhea associated with Clostridium difficile
  - Nosocomial intravascular catheter infections (prophylaxis and treatment)

- Are they caused by these organsisms ?
  - Staphylococci (*S. aureus, S. epidermidis)* resistant to β-lactasm (so called methicillin-resistant → MRSA / MRSE)
  - *Enterococcus faecalis*
  - *Clostridium difficile* (oral form)

# But when do you really need vancomycin ?

- In
  - 
  - 
  - 
  - 
  - 
  - 
  - and

**Do NOT use vancomycin without suspicion or evidence that these organisms cause these infection(s) !**

- if caused by
  - Staphylococci (*S. aureus, S. epidermidis)* resistant to β-lactasm (so called methicillin-resistant → MRSA / MRSE)
  - *Enterococcus faecalis*
  - *Clostridium difficile* (oral form)

# Empiric treatments with vancomycin ?

Sandford guide (2012-2013)

# Skin infections, abscesses

| Infection | Pathogen | Treatment |
|---|---|---|
| Arthritis, bursitis, osteomyelitis | **risk factors for MRSA** | vancomycin |
| Abscess, mastitis | **risk factors for MRSA** | vancomycin |
| Diabetic foot grade 4 | **Recent exposure to AB** | Piperacillin-tazobactam or meropenem, + vancomycin if Gram(+) |
| Established burn wound infection | Staphylococci, Pseudomonas | vancomycin + (ceftazidime, cefepime or piperacillin-tazobactam) |
| Decubitus ulcer with sepsis | **Risk factor for MRSA** | vancomycin + pieracillin-tazobactam |
| Necrotizing soft tissue infection | **Risk factor for MRSA** | Vancomycin + clindamycin |
| Catheter related infections | **Severe or risk factors** | vancomycin + (ceftazidime, cefepime, piperacillin-tazobactam or meropenem) |
| | **MRSA** | vancomycin |

# Cardio-vascular infections

| Infection | Pathogen | Treatment |
|---|---|---|
| Cardiovascular device related infection | **Staphylococci** | Vancomycin + rifampicin |
| endocarditis | **Risk factor for MRSA or coag. neg. Staph** | Vancomycin + gentamicin + rifampicin |
| Mediastinitis after cardiac surgery | Staphylococci, enterobacteriaceae | Vancomycin + (ceftazidime or cefepime) |
| Catheter related thrombophlebitis | Staphylococci, enterococci, enterobacteriaceae, Pseudomonas | Vancomycin + (ceftazidime or cefepime or piepracillin-tazobactam) |
| | Intracranial vein | Vancomycin + metronidazole +ceftriaxone |

# Respiratory tract infections

| Infection | Pathogen/ population | Treatment |
|---|---|---|
| Pneumonia in immunocompetent neonates | Late onset in neonates > 7 days | Cefotaxime + vancomycin |
| HAP/VAP | **Risk of MRSA** | Amoxi-clav or cefuroxime + vancomycin |

# CNS infections

| Infection | Pathogen/ population | Treatment |
|---|---|---|
| Brain abscess | **risk factors for MRSA** | cephalo III + vancomycin |
| Meningitis | neonate | vancomycin + (cefotaxime of ceftazidime) |
| | Child, postsurgery | vancomycin + (ceftazidime or meropenem) |
| | S. pneumoniae, MIC peni > 0.06 | Vanco + cephalo III |
| Ventriculitis | **MRSA** | Vancomycin +/- rifampicin |

# Other type of infections

| Infection | Pathogen | Treatment |
|---|---|---|
| colitis | **Clostridium difficile;**<br>**- allergy to metronidazole**<br>**- severe** | - Vancomycin PO<br>- Vancomycin PO + metronidazole IV |
| Renal abscess | **risk factors for MRSA** | vancomycin |
| Toxic shock syndrome | **Risk factor for MRSA** | Vancomycin + clindamycin |
| Suppurative parotitis | **risk factors for MRSA** | vancomycin |

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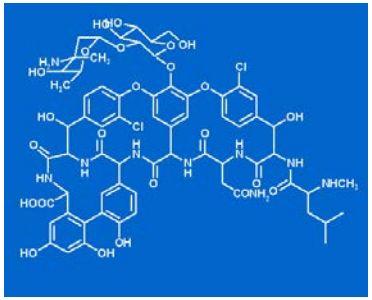
# How to measure vancomycin MIC: 2 main problems

- **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**

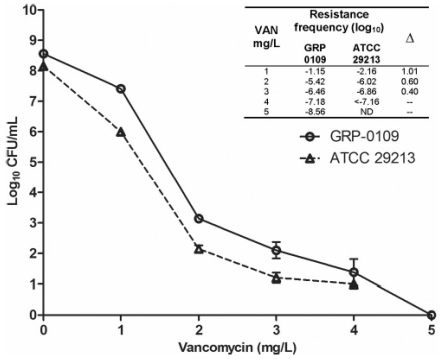
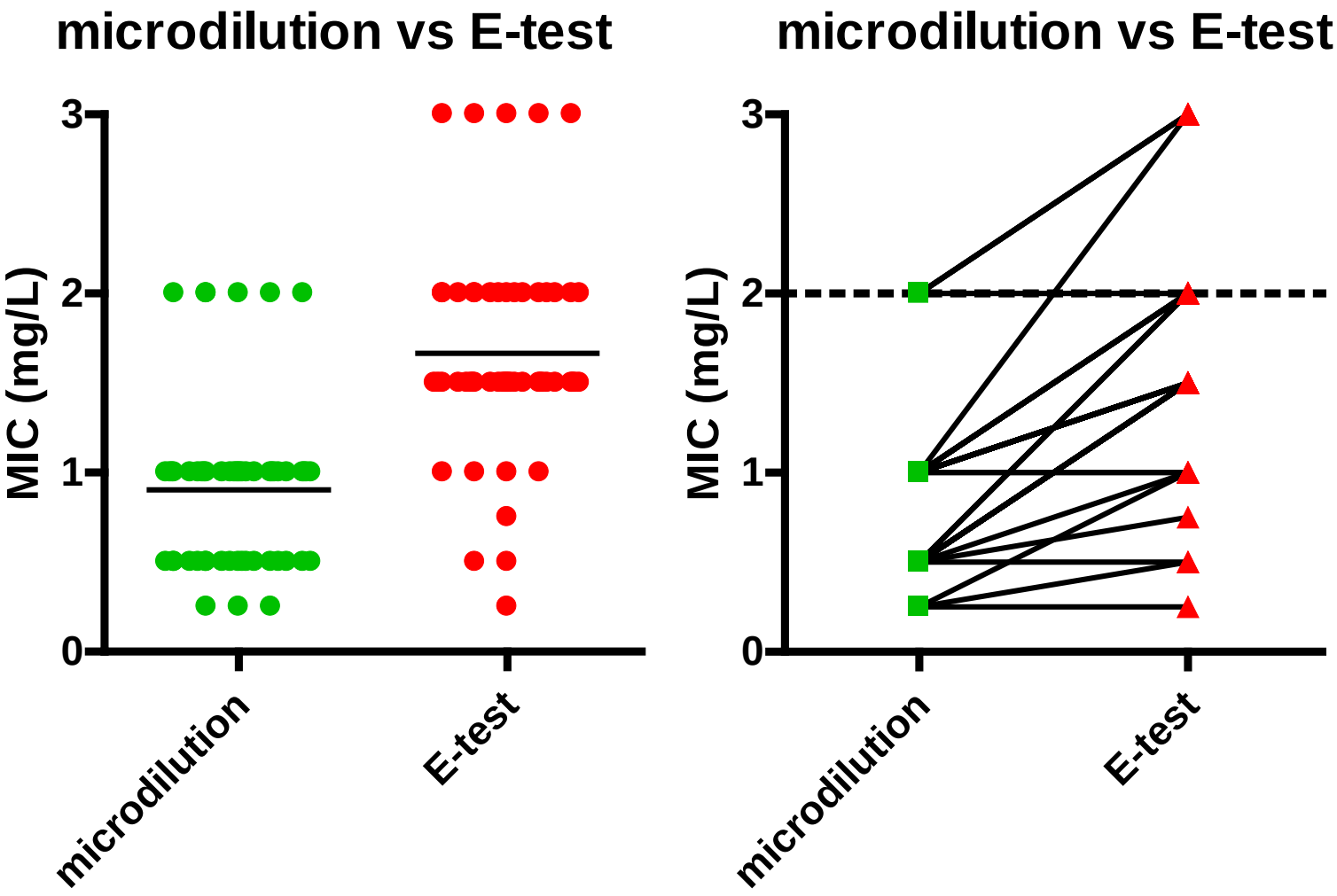


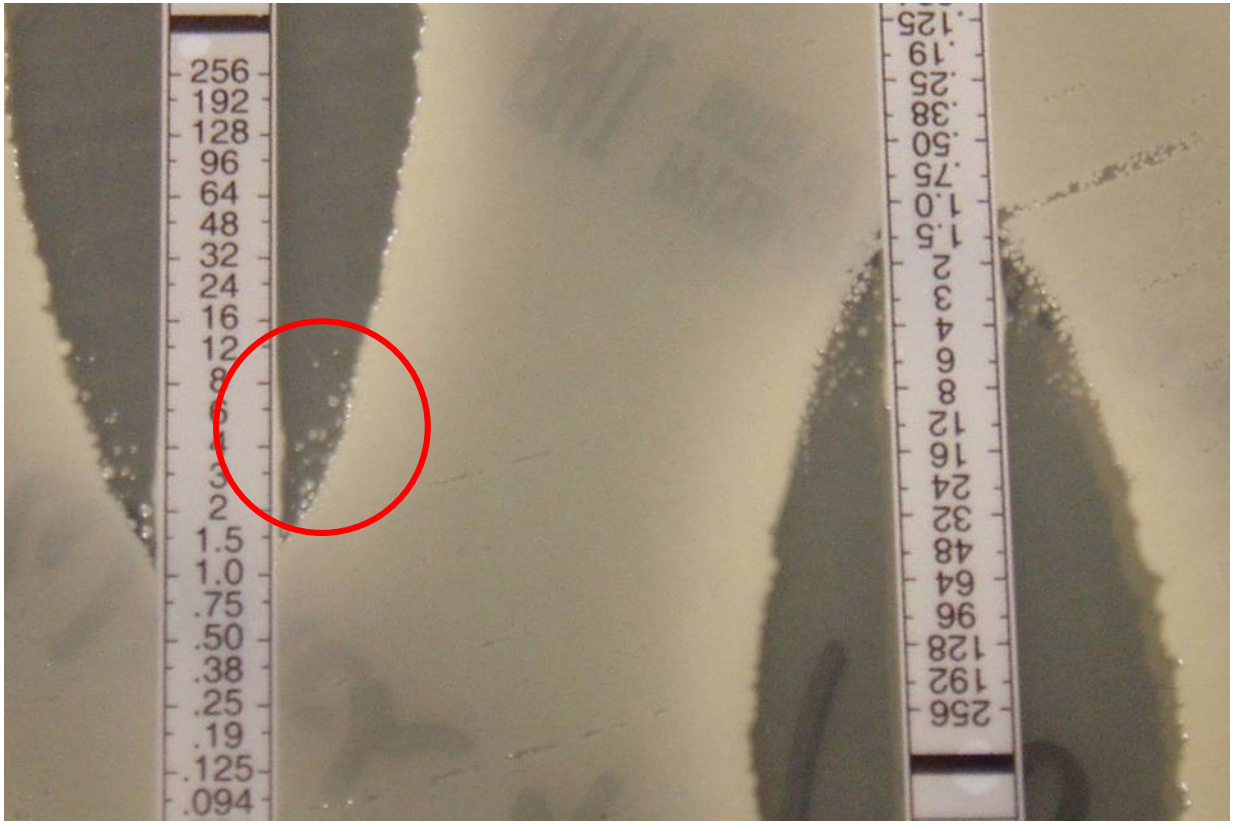

FIG 1 Vancomycin population analysis profile of *S. aureus* GRP-0109 after being isolated from a patient with persistent bacteremia and unsuccessful generic treatment, indicating altered susceptibility in comparison with strain ATCC 29213: 10 times more cells were able to grow at 1 mg/liter of vancomycin,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




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

# Hetero-resistance: how to see it …

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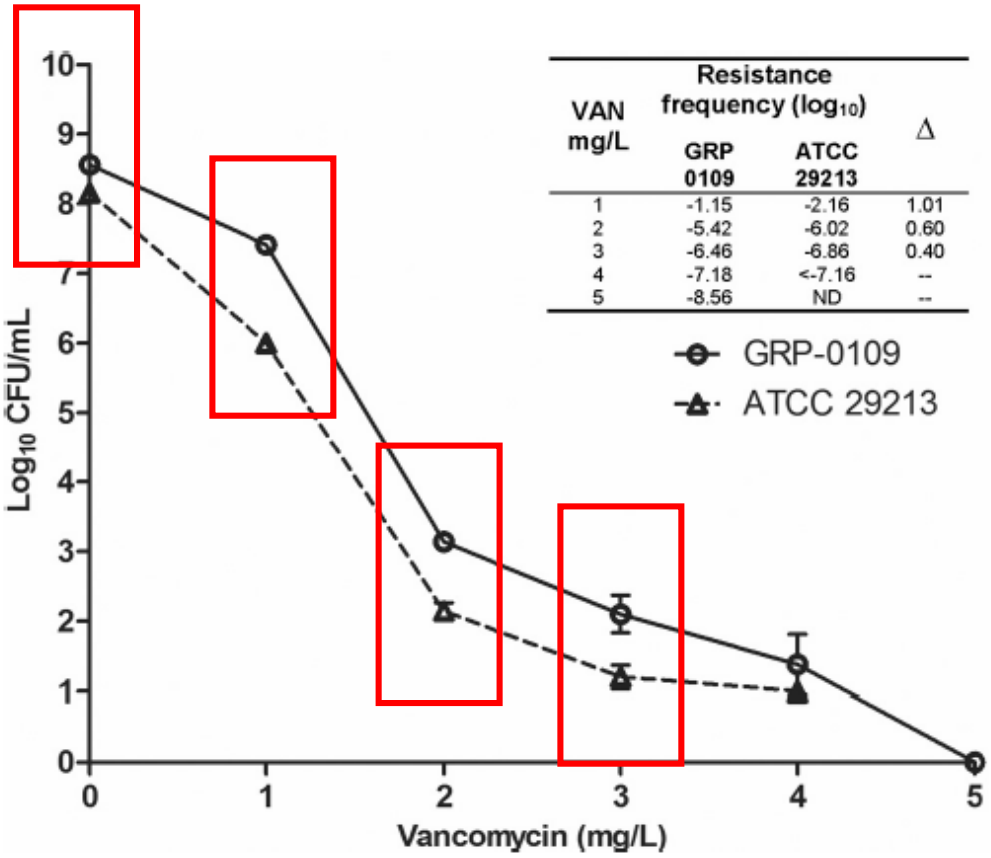
# Heteroresistance: development during treatment..

**high starting inoculum**




| VAN mg/L | Resistance frequency ($log_{10}$) GRP 0109 | ATCC 29213 | Δ |
|---|---|---|---|
| 1 | -1.15 | -2.16 | 1.01 |
| 2 | -5.42 | -6.02 | 0.60 |
| 3 | -6.46 | -6.86 | 0.40 |
| 4 | -7.18 | <-7.16 | -- |
| 5 | -8.56 | ND | -- |

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 warning for failures
- **gradient techniques (1-10 mg/L)**
  - shows the presence and quantifies to which level heteroresistance is observed.

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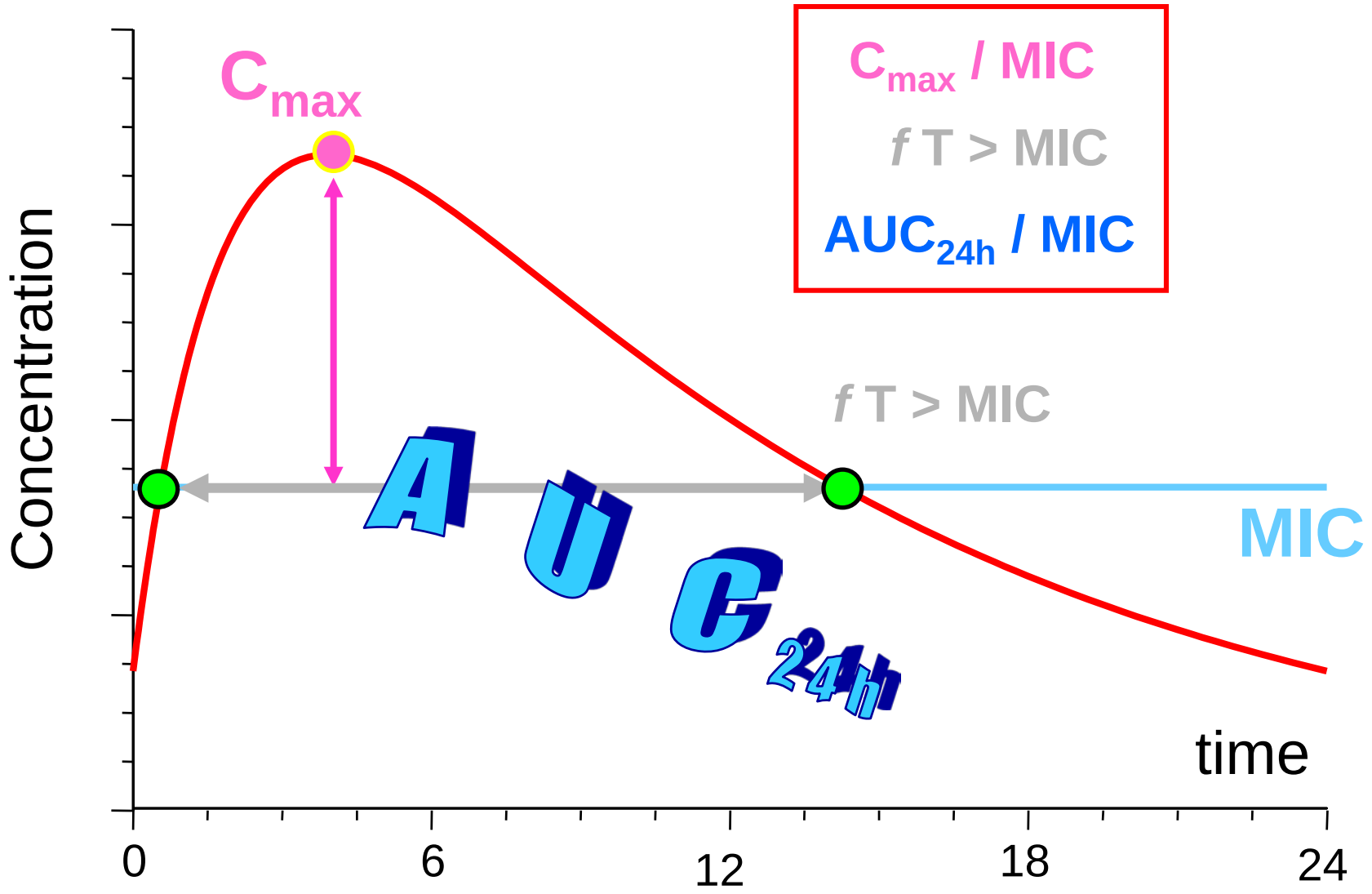
# Vancomycin and Pharmacodynamics

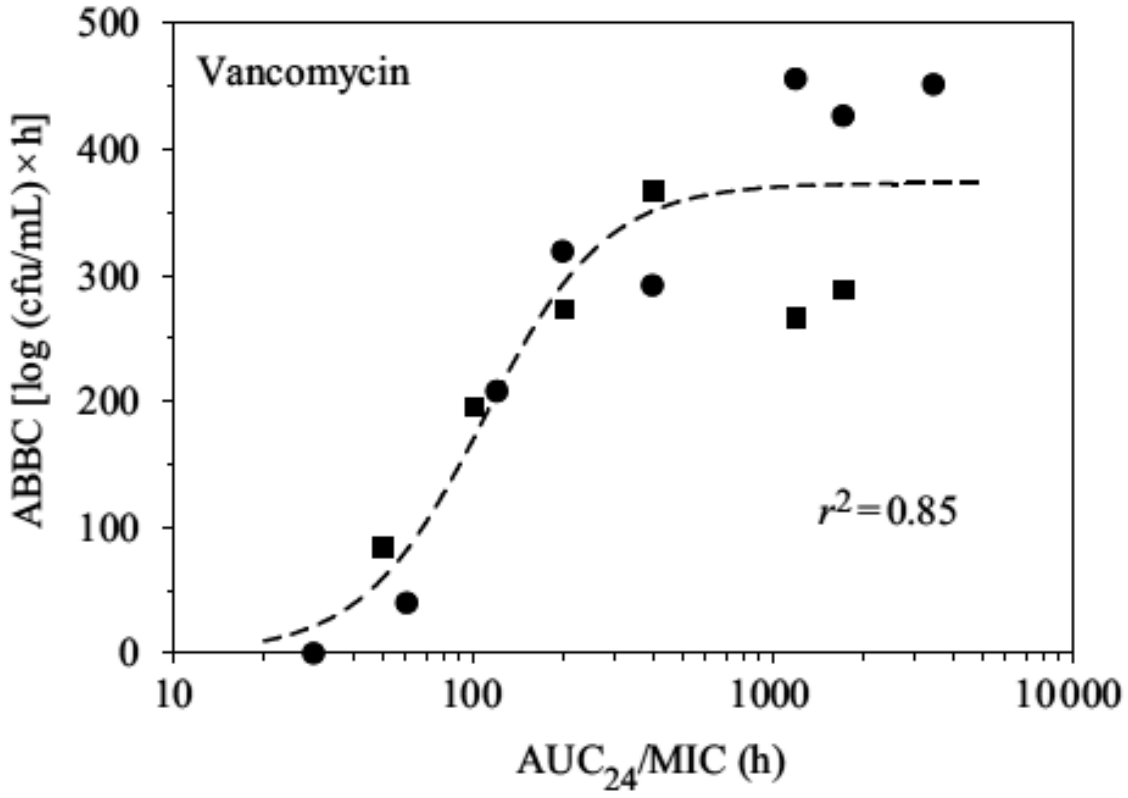
- Vancomycin is an $AUC_{24h}$-MIC dependent antibiotic



# Vancomycin – $AUC_{24h}$ and efficacy

## 1. In vitro model mimicking the human PK

**efficacy**




**drug exposure**

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

# Vancomycin – $AUC_{24h}$ and efficacy

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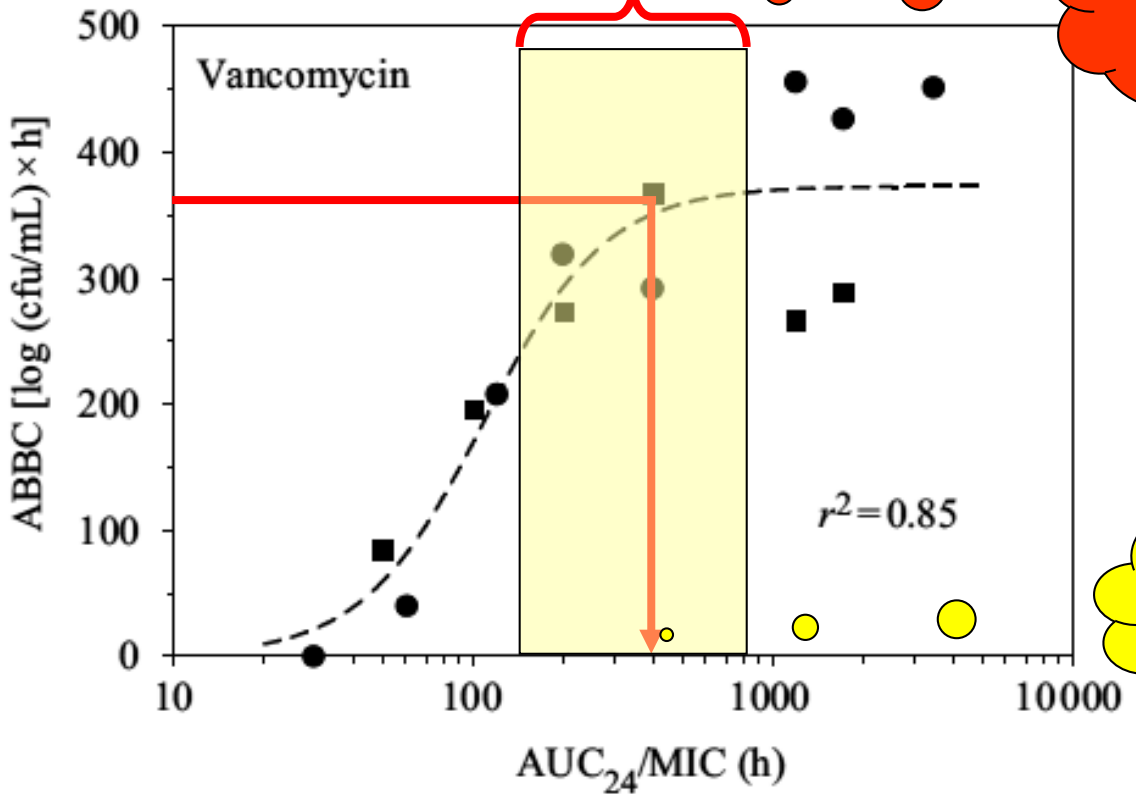


Typical range in patients

You need at least 400 !

drug exposure

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

# Vancomycin – $AUC_{24h}$ and efficacy

ORIGINAL RESEARCH ARTICLE

Clin Pharmacokinet 2004; 43 (13): 925-942
0312-5963/04/0013-0925/$31.00/0

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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. Birmingham*[1] 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 $CL_{CR}$ (per 1 mL/min) | 1.04 | 1.01, 1.07 | 0.0154 |

**$AUC_{24}$/MIC** = steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration; **$CL_{CR}$** = creatinine clearance; **MSSA** = methicillin-susceptible *Staphylococcus aureus*.

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

# Vancomycin – $AUC_{24h}$ and efficacy

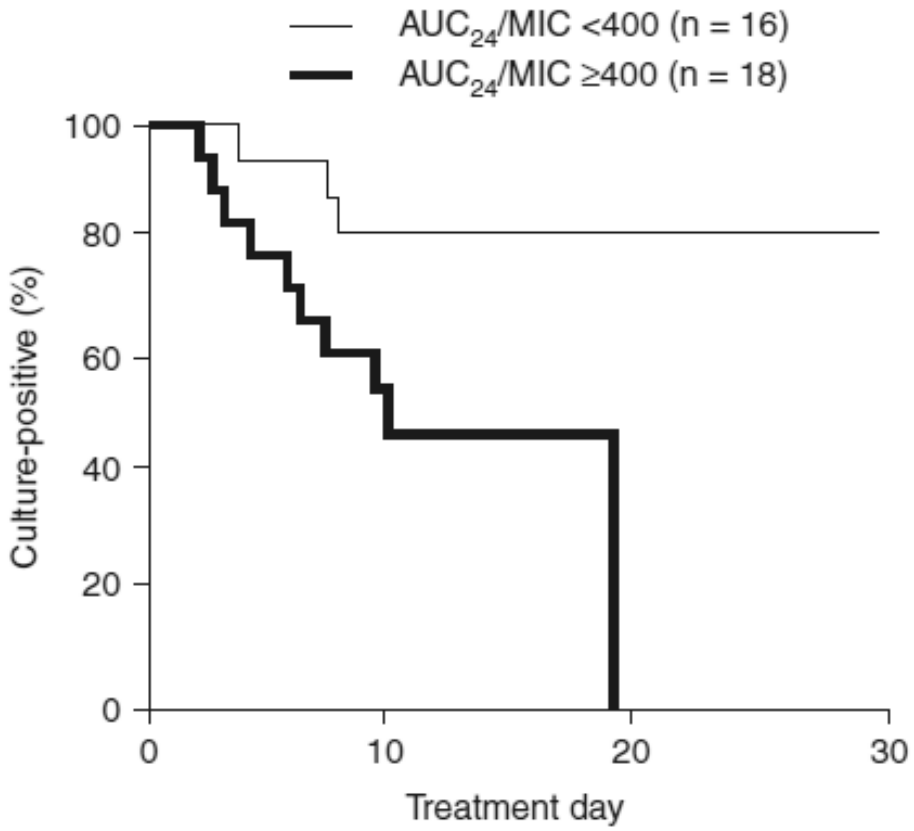


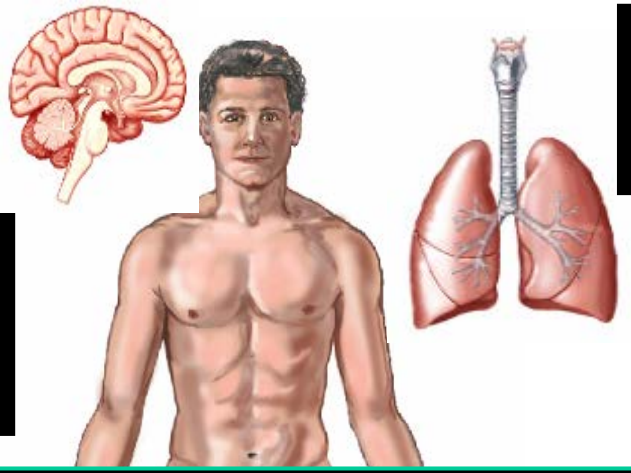

**Fig. 4.** Time (days of therapy) to bacterial eradication vs vancomycin $AUC_{24}$/MIC <400 and $AUC_{24}$/MIC ≥400 illustrated by a Kaplan-Meier survival plot of day of therapy vs the percentage of patients remaining culture-positive on that day. The two $AUC_{24}$/MIC groups differed significantly (p = 0.0402). **$AUC_{24}$/MIC** = 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 ?

CNS: <10%

Sternal bone[1]: 57%
Heart valve[4]: 12%



Epithelial lining fluid[3]: 18%

Lung tissue[2]: 17%–24%

## Vancomycin Tissular Penetration is poor

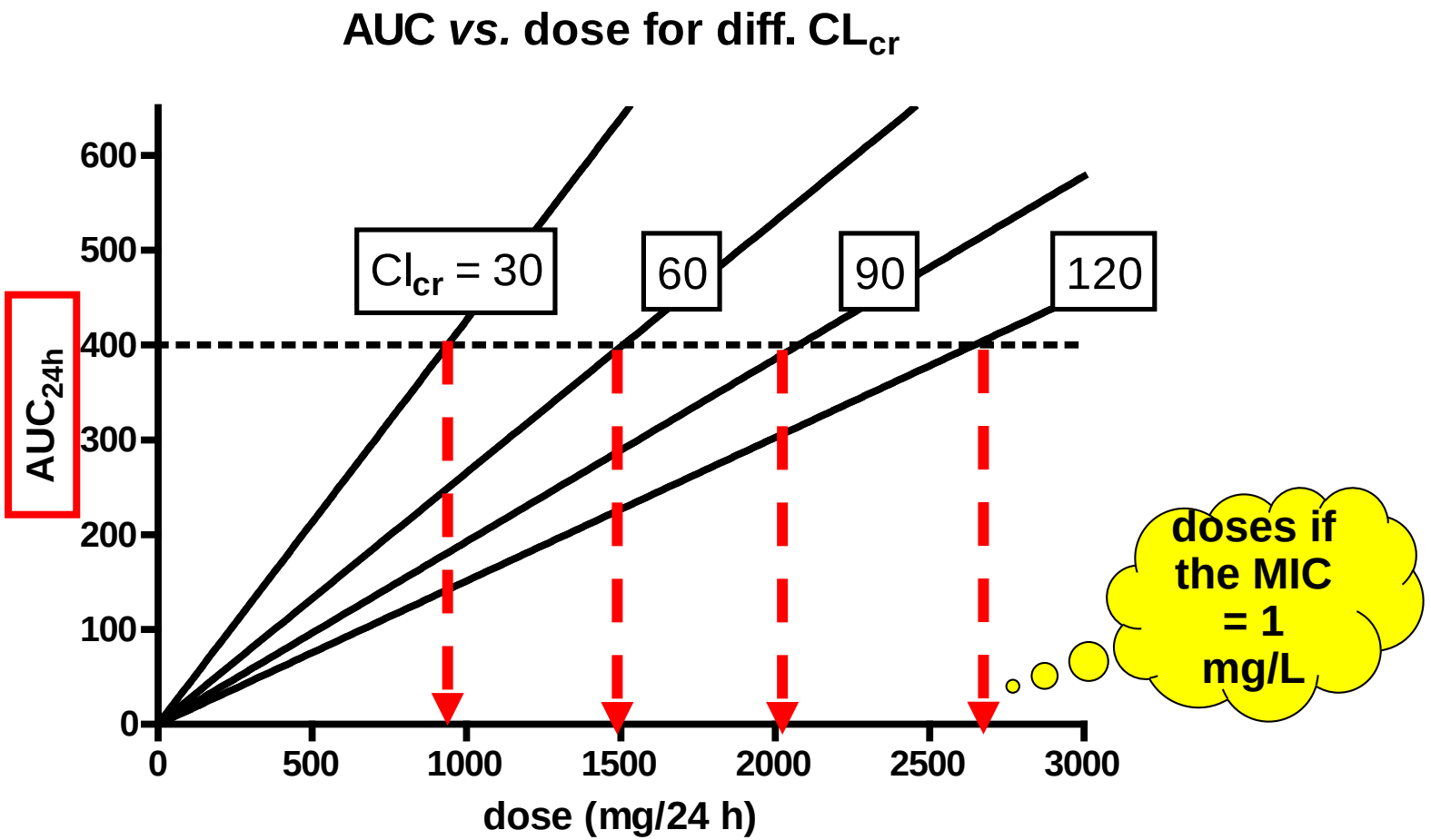
Bone[5]: 7%–13%

Fat[4]: 14%
Muscle[4]: 9%

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 ?

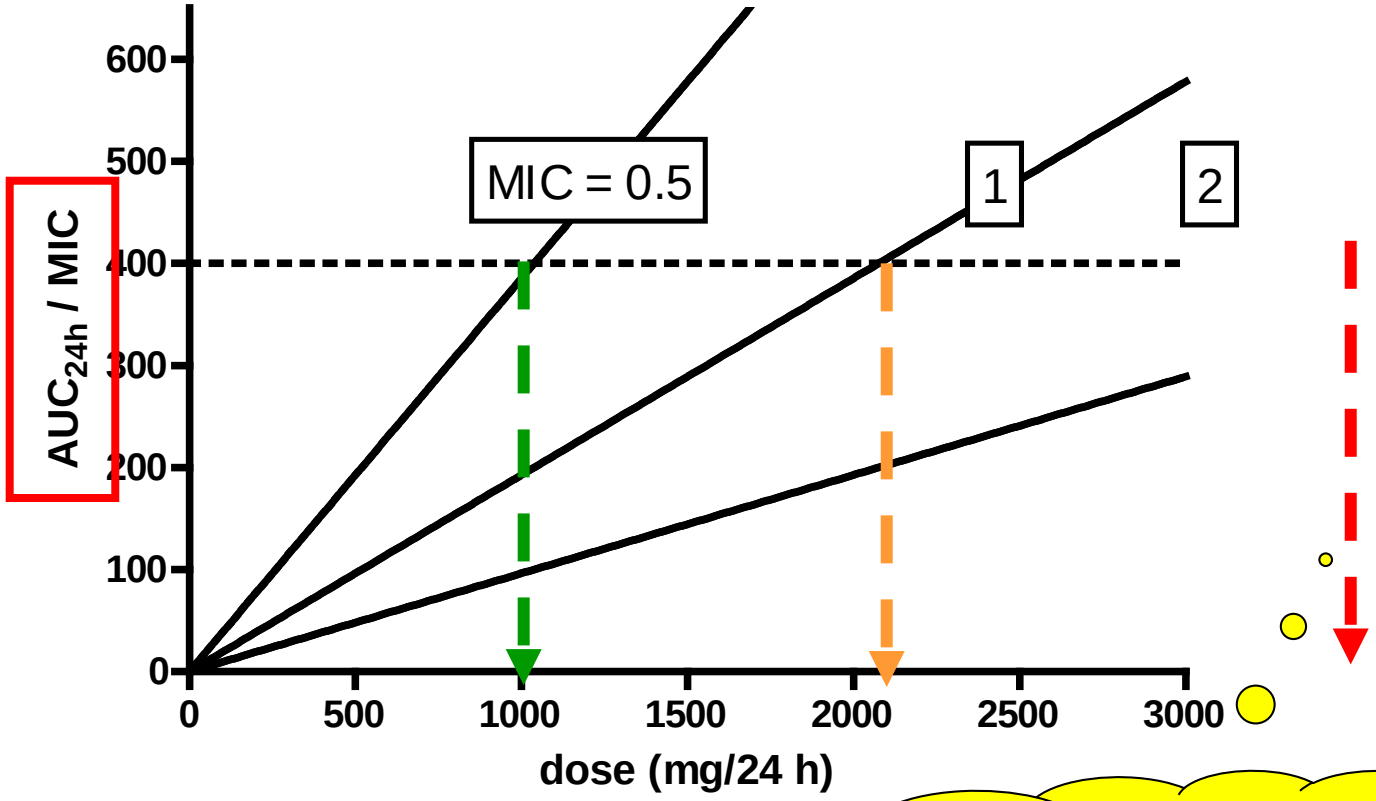



$$AUC_{24} = \frac{D}{[(CL_{CR} \times 0.79) + 15.4] \times 0.06}$$

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**

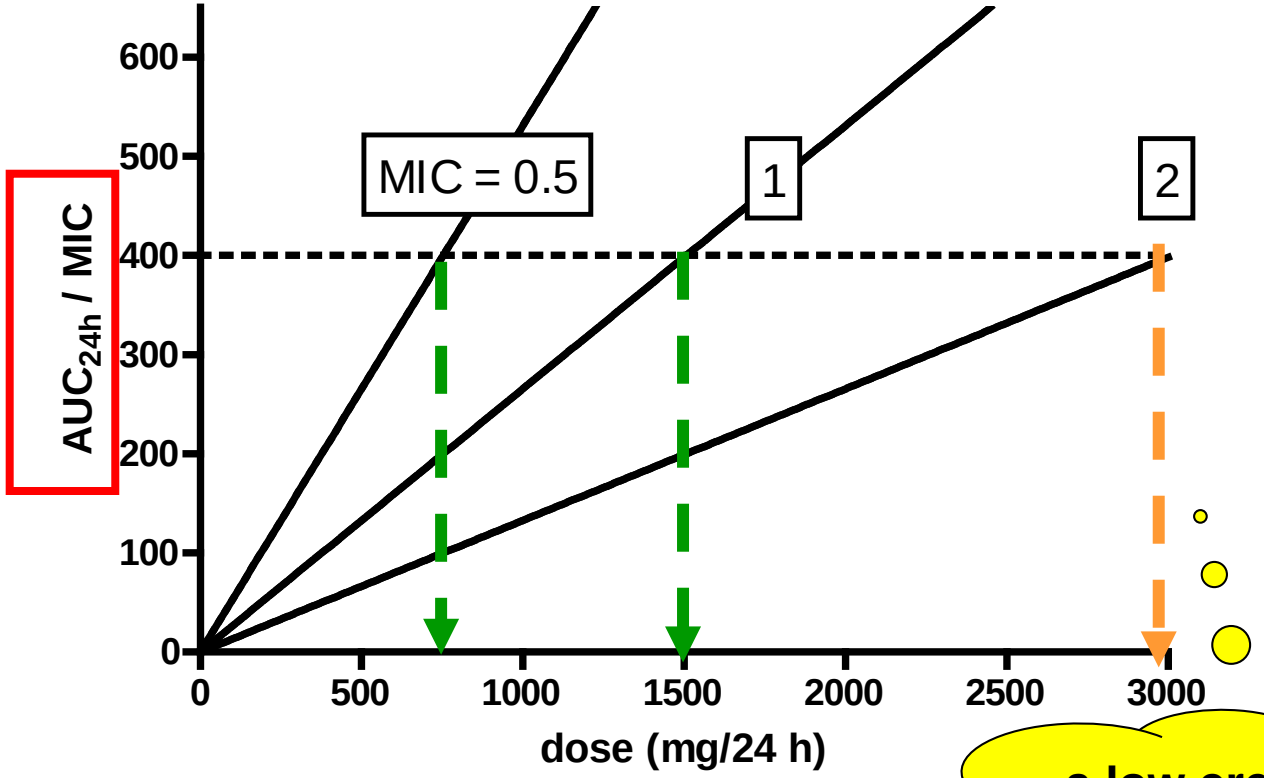



**if the MIC is 2, you may have problems**

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

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

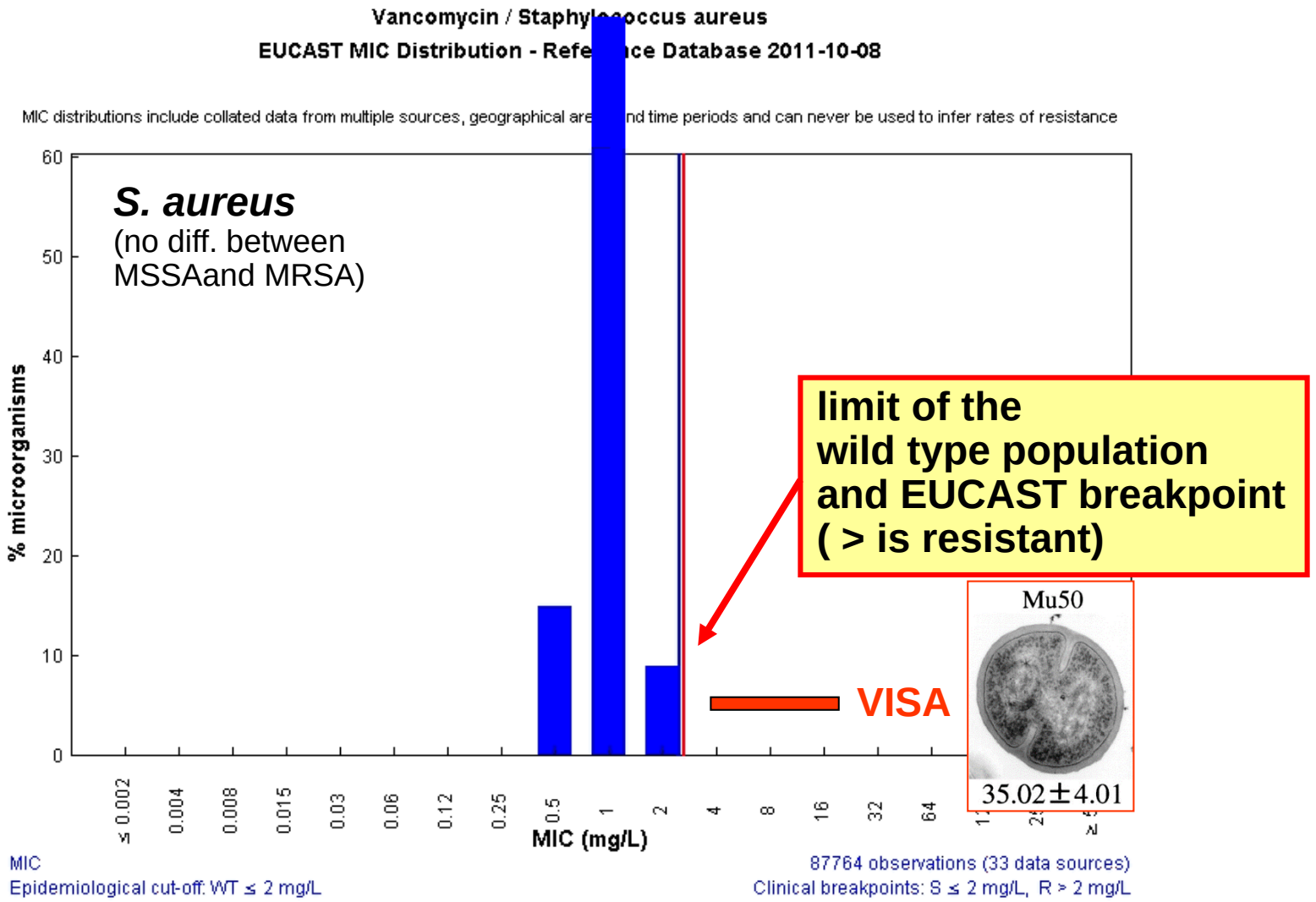
**$AUC_{24h}$ / MIC *vs.* dose for diff. MIC and $CL_{cr}$=60 mL/min**




**a low creatinine clearance helps !**

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

# 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 ≥ 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 ± 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

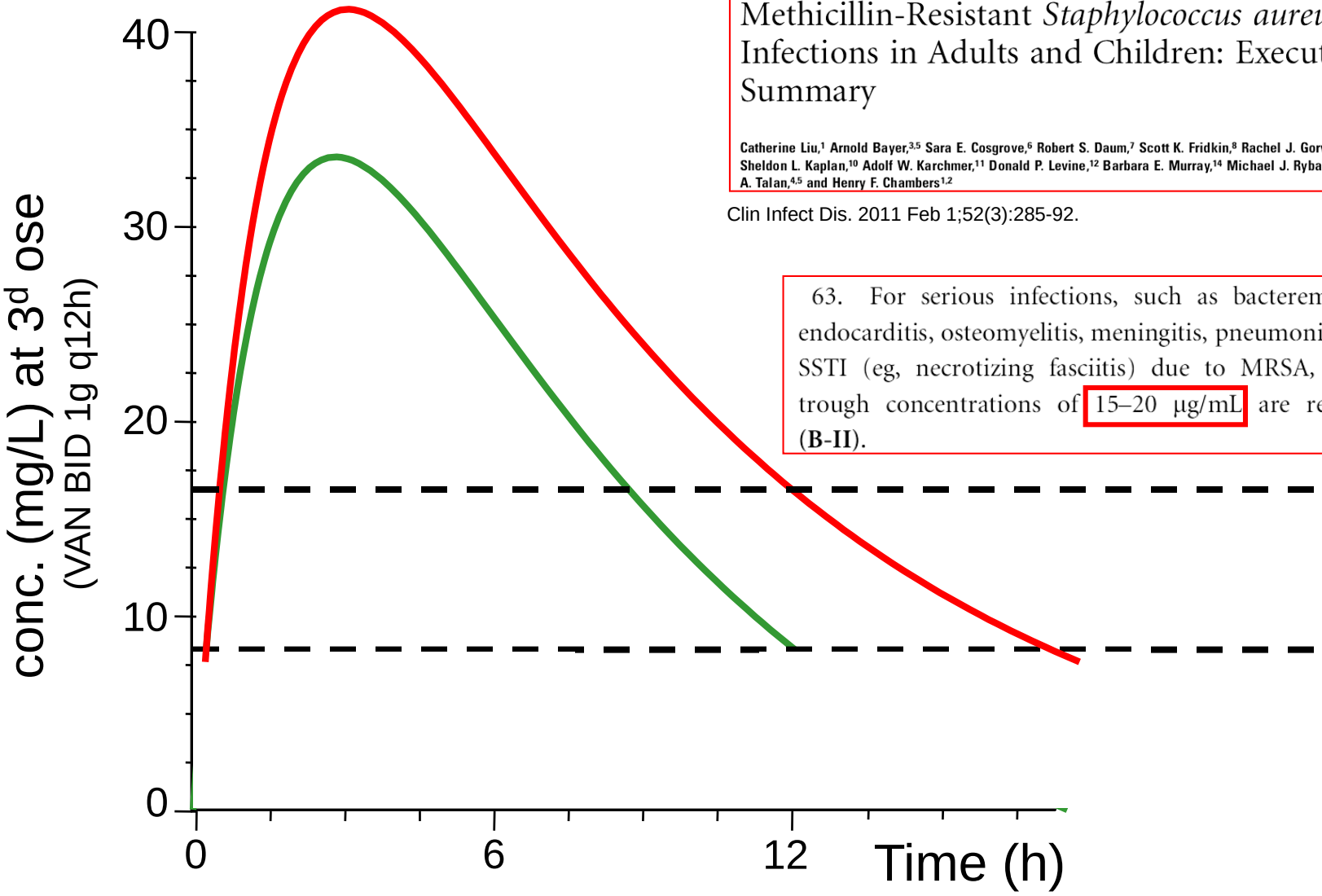
IDSA GUIDELINES

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

BMC Pharmacology & Toxicology

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 Haase[3], Chistopher R Frei[4], Nicolas A Forcade[4,10], Todd Bell[5], Roger J Bedimo[6] and Carlos A Alvarez[1,2]

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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 Haase[3], Chistopher R Frei[4], Nicolas A Forcade[4,10], Todd Bell[5], Roger J Bedimo[6] and Carlos A Alvarez[1,2]

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

ELSEVIER

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

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# 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 !**

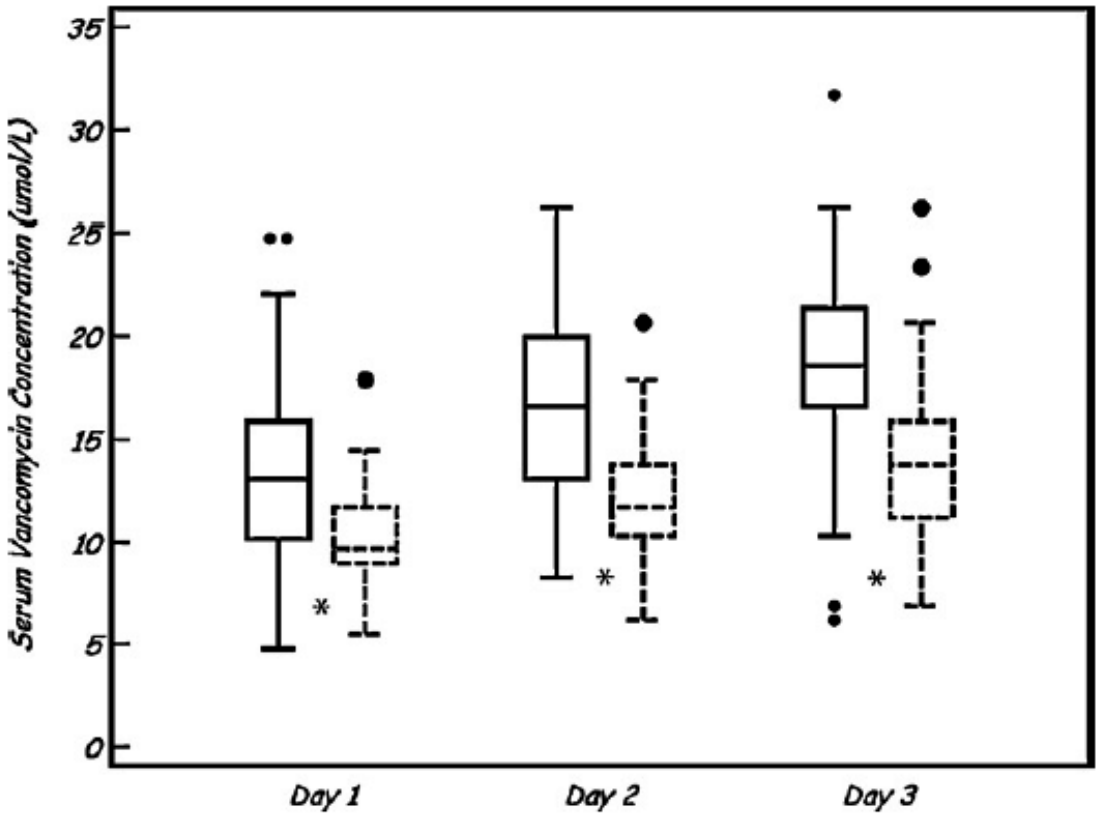


**Fig. 1.** Box and whisker plots showing the evolution of median (interquartile range) serum vancomycin concentrations on the studied days (Days 1–3) and comparison between Group A [control group without augmented renal clearance (ARC); continuous line] and Group B (study group with ARC; dashed line).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

ARC was defined as CLCr > 130 mL/min/1.73 $m^2$

# Dosing adjustment…

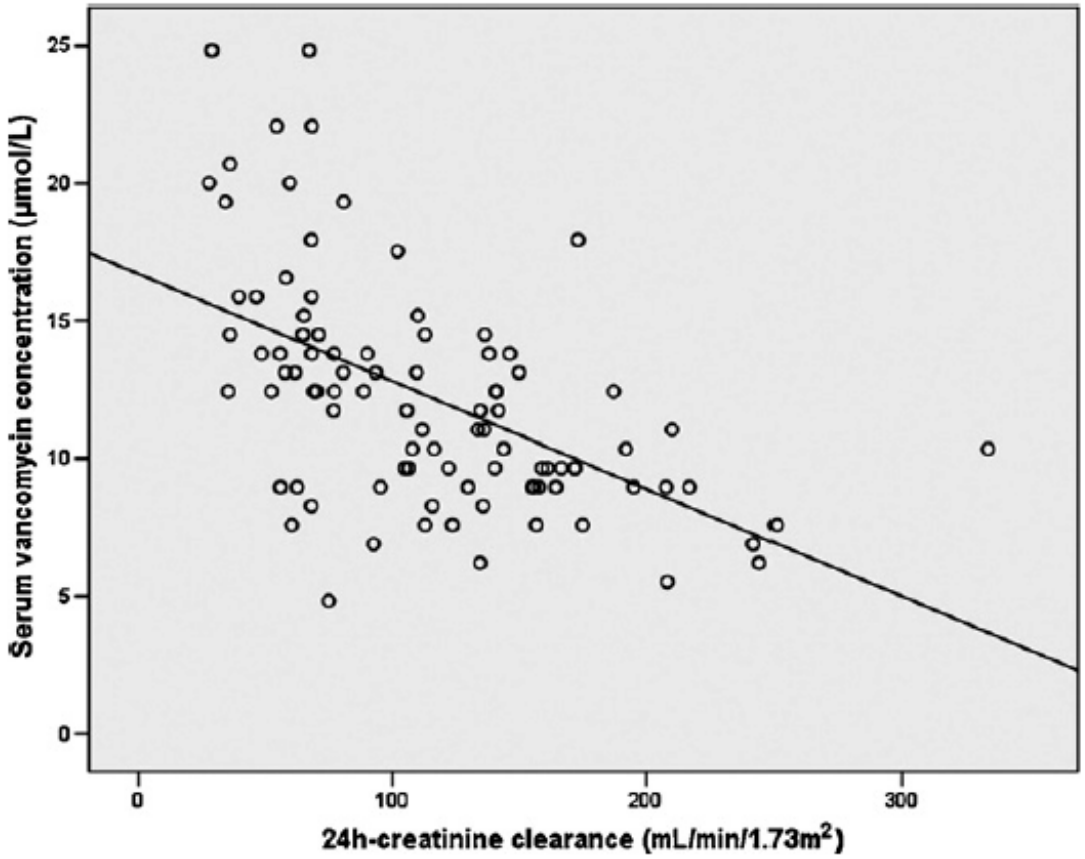


**Fig. 2.** Linear correlation between 24-h creatinine clearance ($CL_{Cr}$) and serum vancomycin concentration on Day 1. The serum vancomycin concentration displayed a significant direct correlation with $CL_{Cr}$ in 93 septic critically ill patients ($rS = -0.57$; $P < 0.01$).

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

# Vancomycin: provisional conlusions

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 MIC > 2 mg/L
5. do not forget to detect heteroresistance… (use E-test)

# 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 did it …
    - do the others do the same ?
  - unconventional uses of vancomycin (a few words)

# 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]

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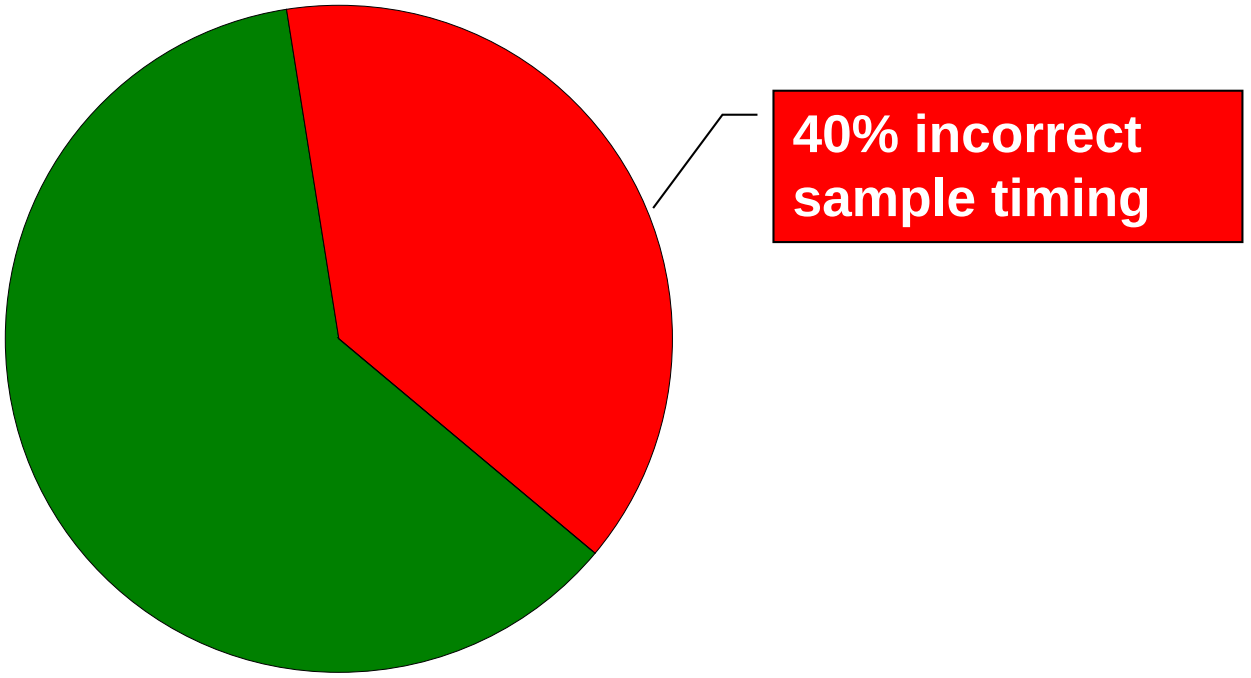
[b] *Laboratoire de microbiologie, Service d'infectiologie et Département de pharmacie, CHU Mont-Godinne, Yvoir, Belgium*

# Vancomycin: continuous infusion

- Why ? → **monitoring serum levels with the conventional mode is impossible…**
- How we did it…
- Do the others do the same ?

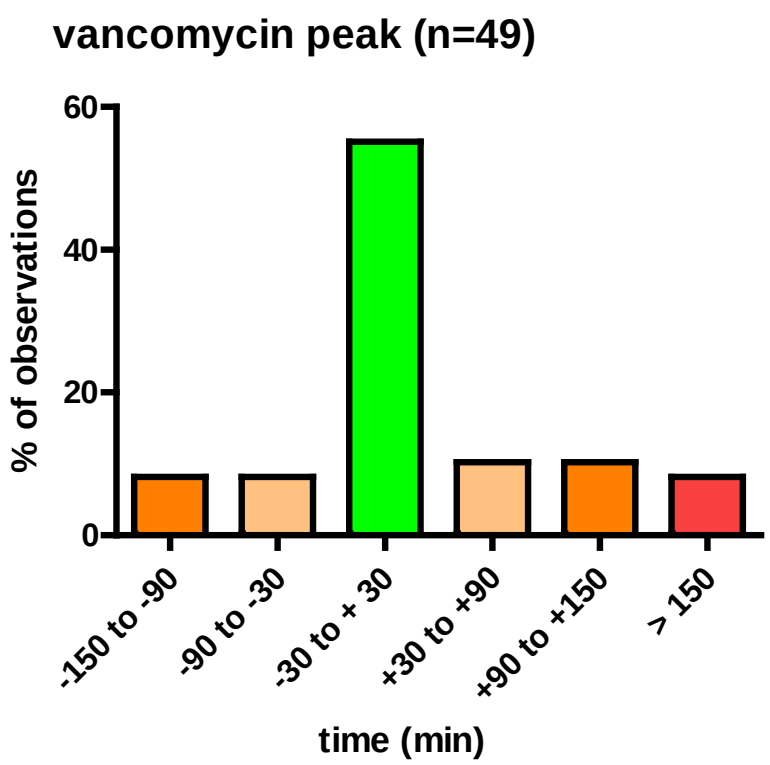
# Observational study – results

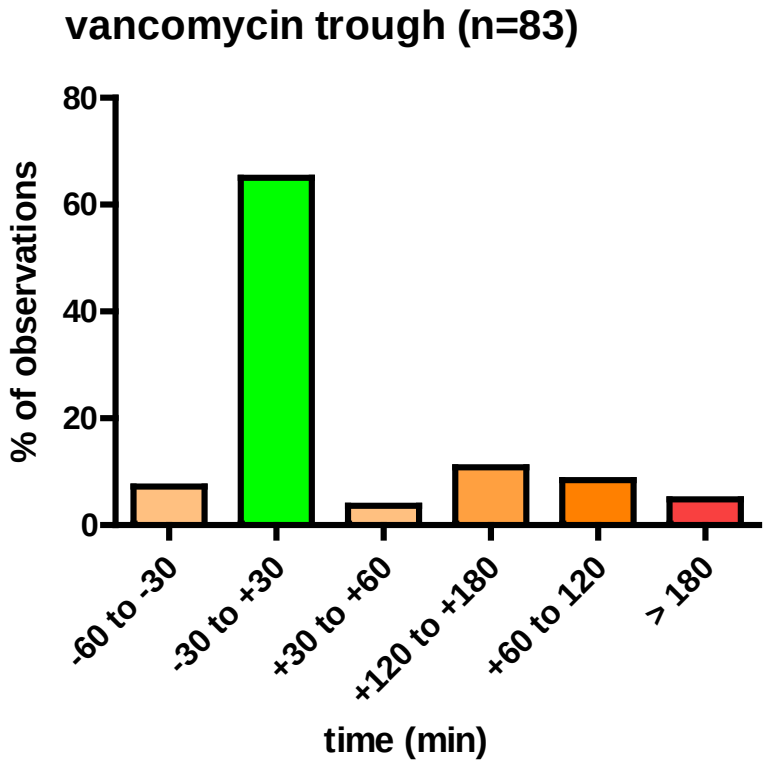



*within 30 min. of recommended sample timing: peak 2h after the end of infusion, trough: just before the next dose

# 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) |
| *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."*

# 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”**

Concentration

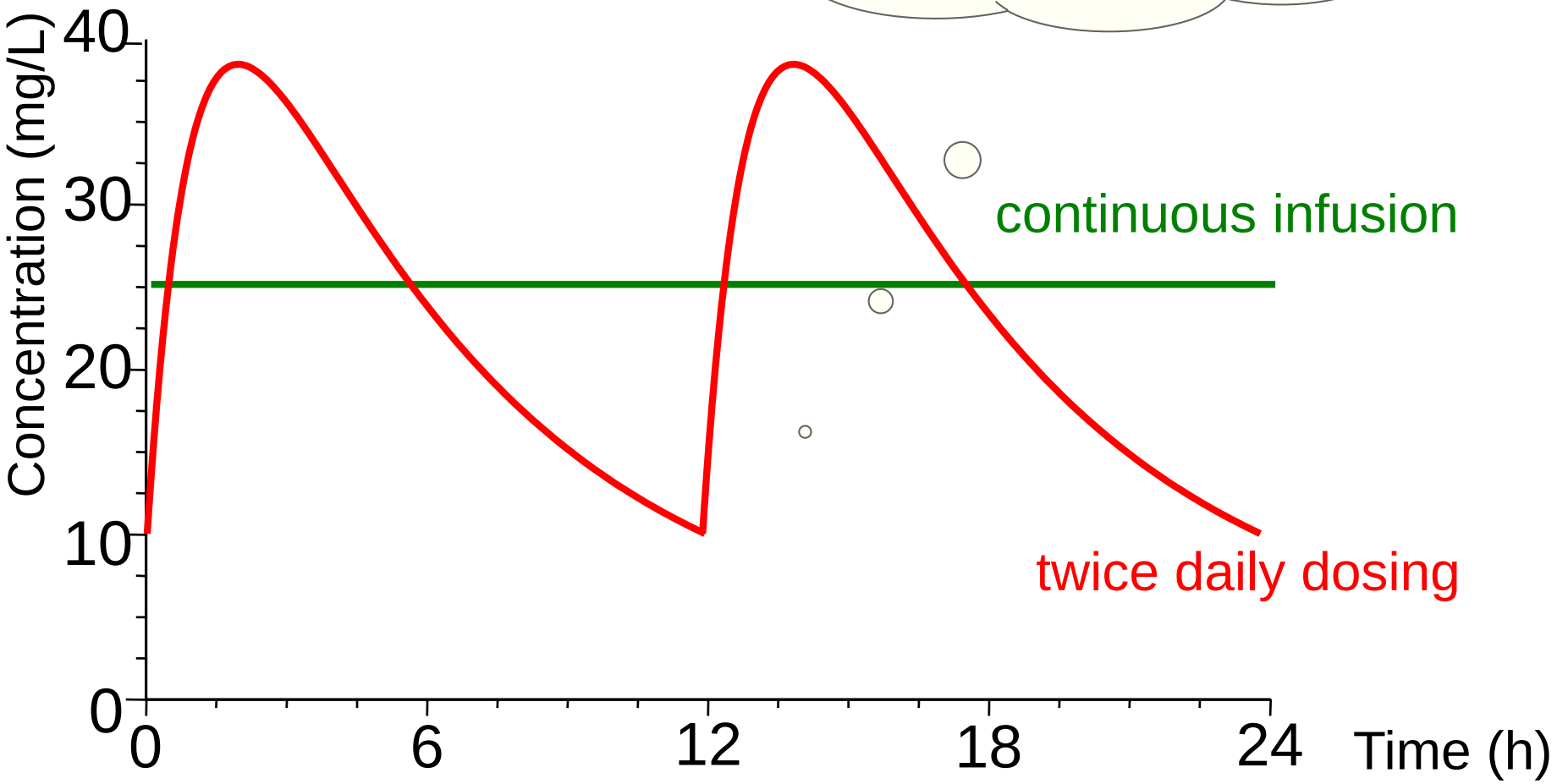
continuous infusion

Time (h)

0 6 12 18 24

## TDM of vancomycin by continuous infusion

**AUC24h /MIC independent of the mode of administration**



# Vancomycin: continuous infusion

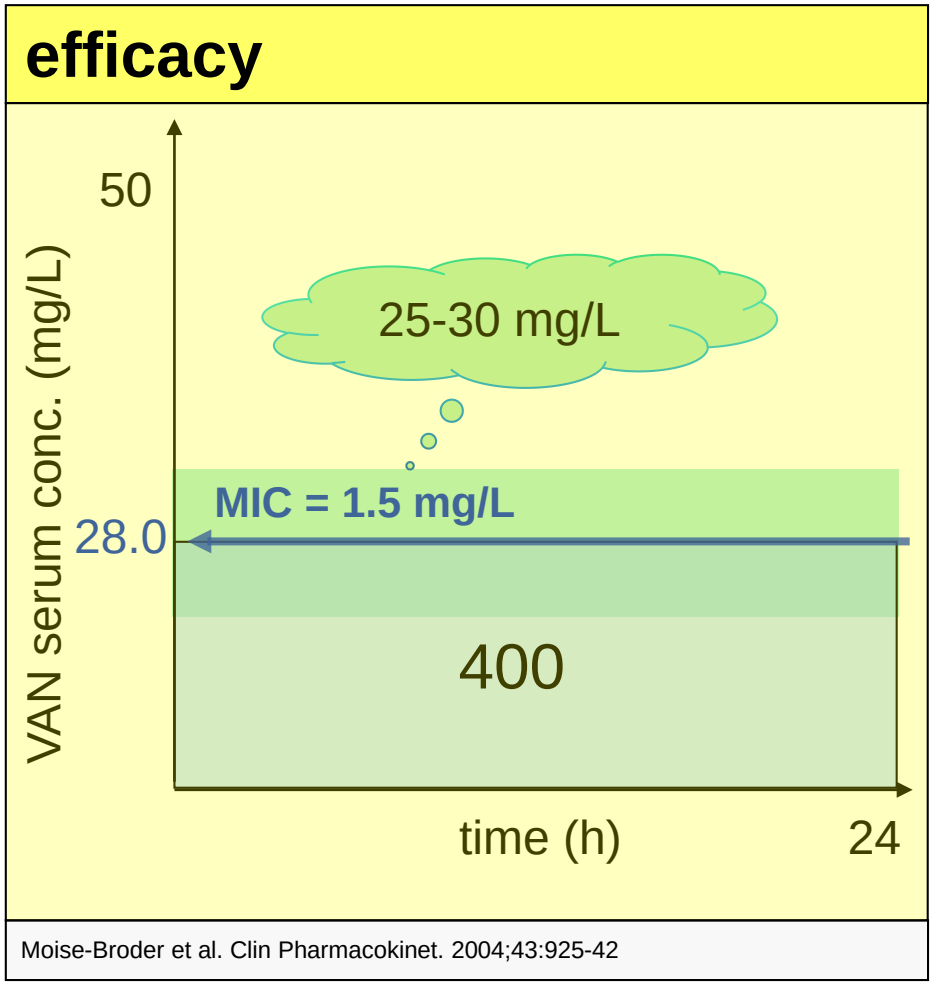
- Why ? → **monitoring serum levels with the conventional mode is impossible…**
- How: **the details of what we did**
- Do the others do the same ?

# 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 |

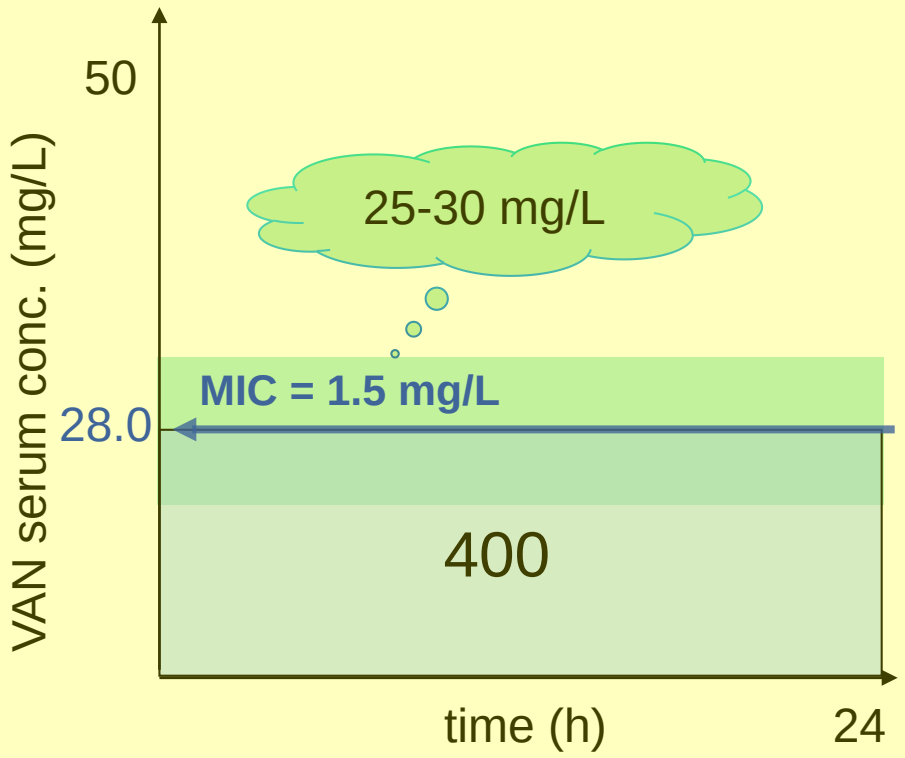
# vancomycin CI: which serum concentration should we target?




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

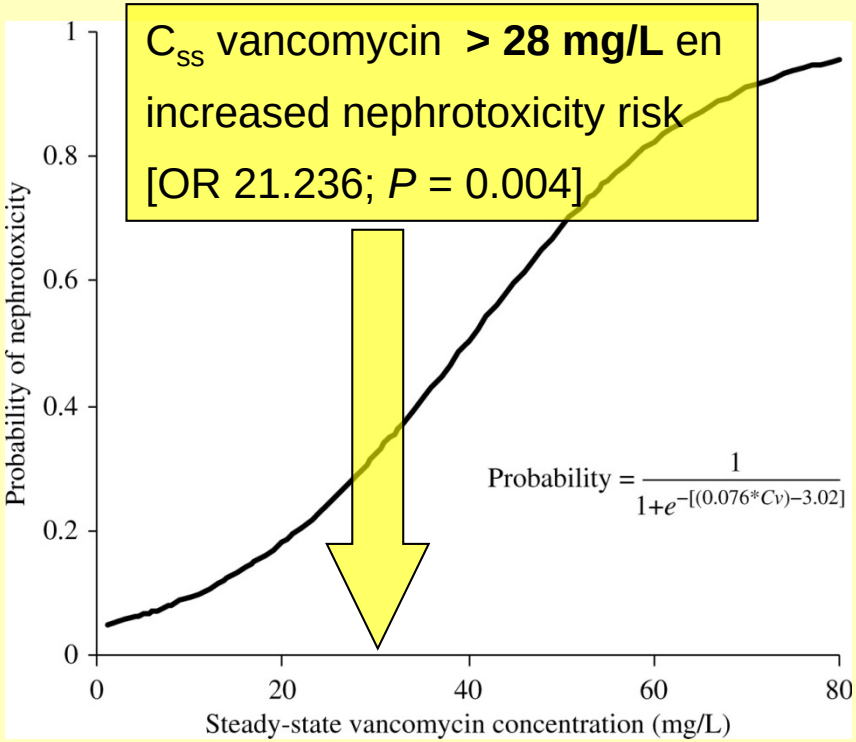
# vancomycin CI: which serum concentration should we target?

## efficacy



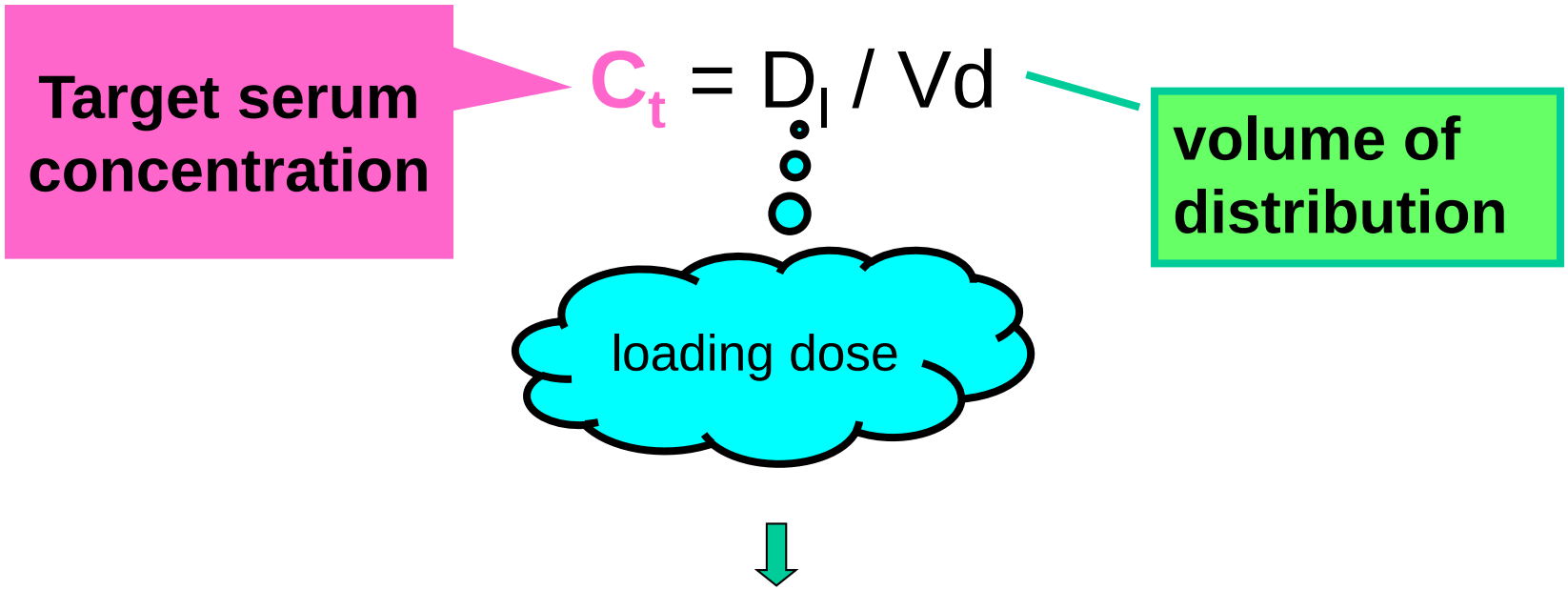

Moise-Broder et al. Clin Pharmacokinet. 2004;43:925-42

## toxicity




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 *

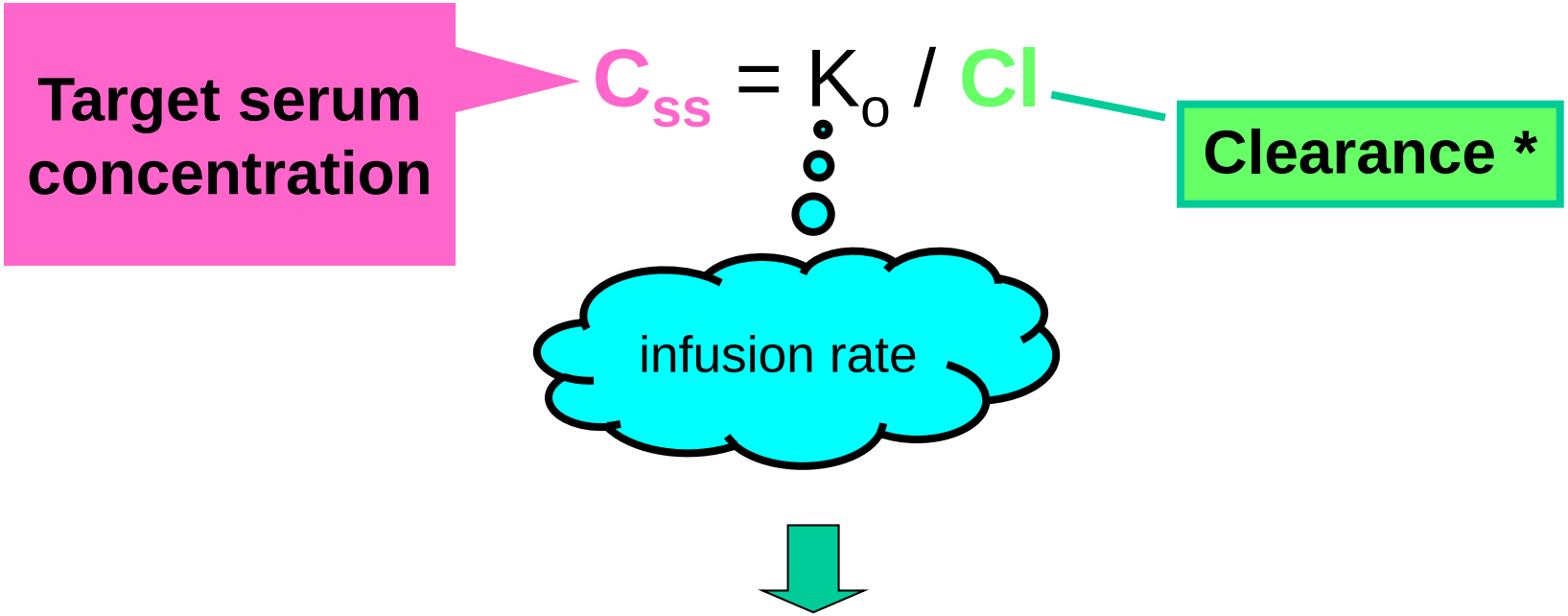



**loading dose** (in mg/kg) = $C_t$ (mg/L) x **Vd** (L/kg)

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

* assuming linear pharmacokinetics

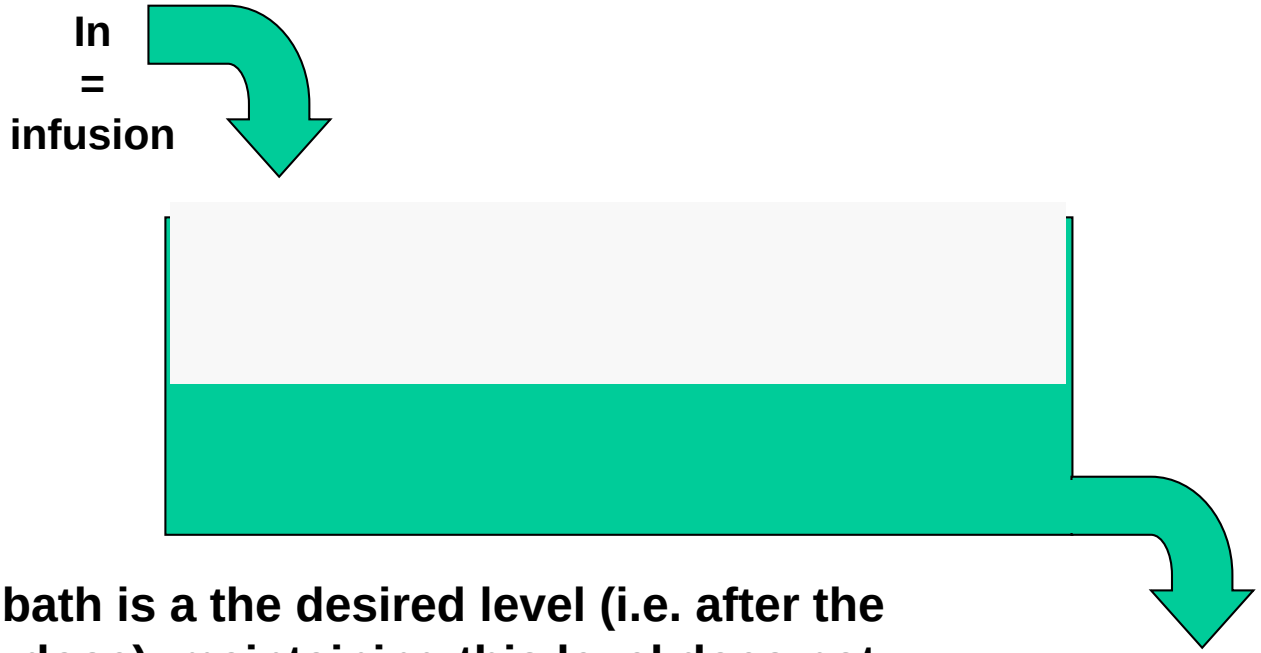
# How to reach the serum target concentration target with Cl? 2: infusion *




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

* assuming linear pharmacokinetics

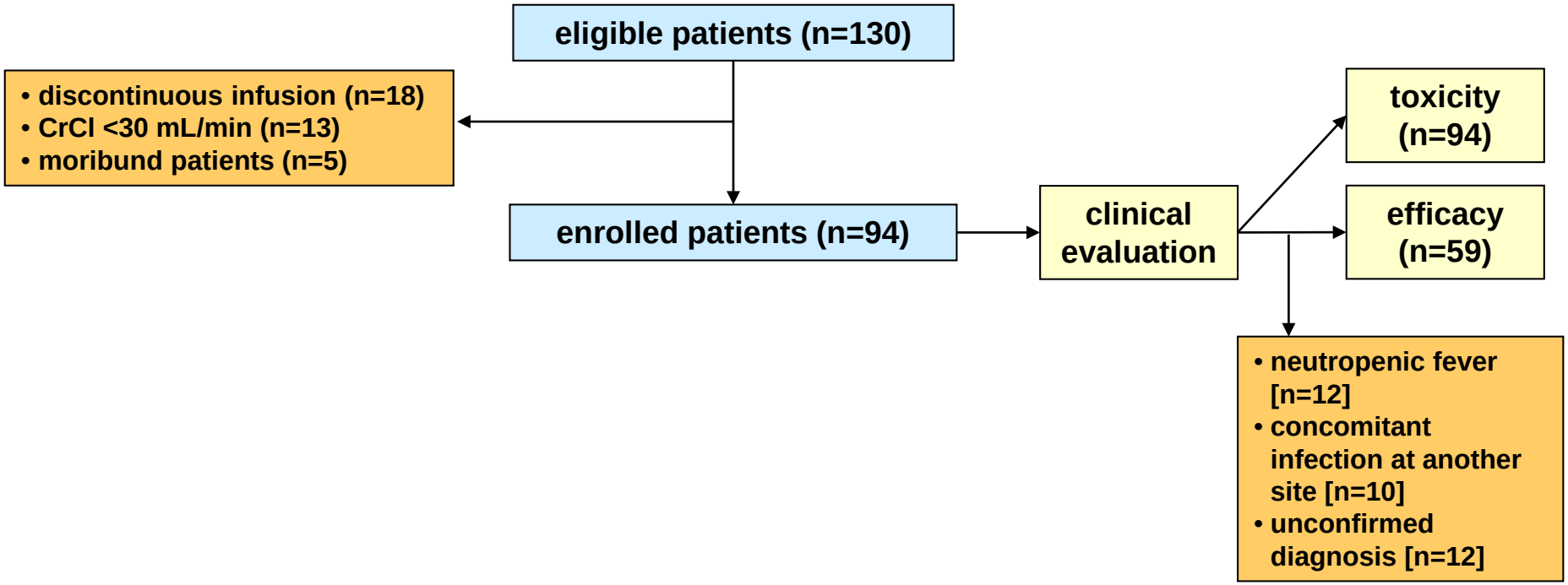
# How to reach the serum target concentration target with CI?
# 2: infusion *



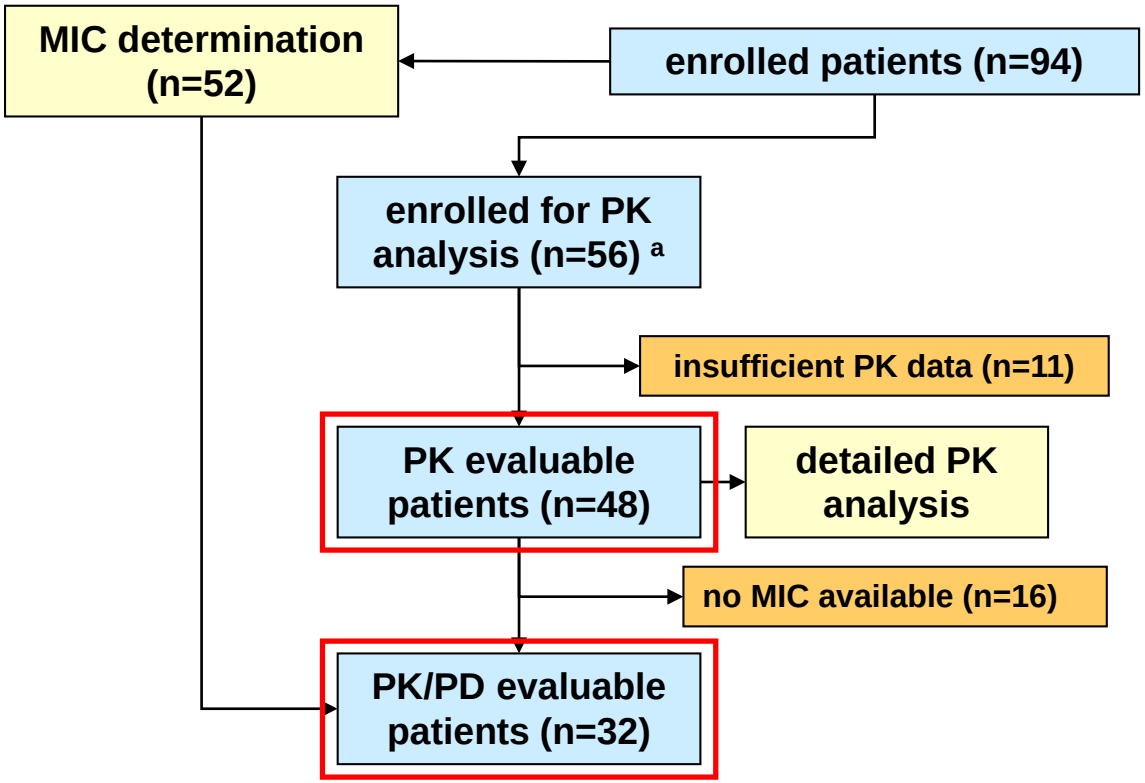

**once a bath is a the desired level (i.e. after the loading dose), maintaining this level does not depend upon its volume but of the ratio of tap and drain flows ( which musts be equal: in = out…)**

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

# 2. Clinical evaluation: study outline

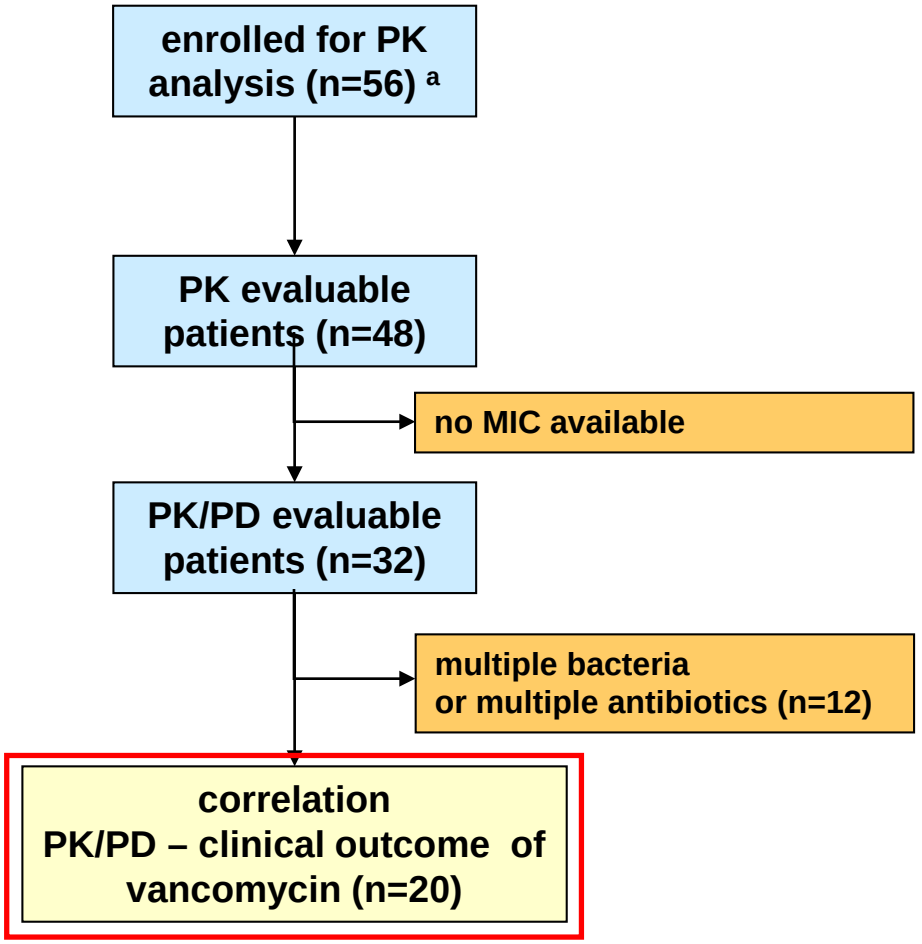


# 2. Pharmacokinetic evaluation: study outline




[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:

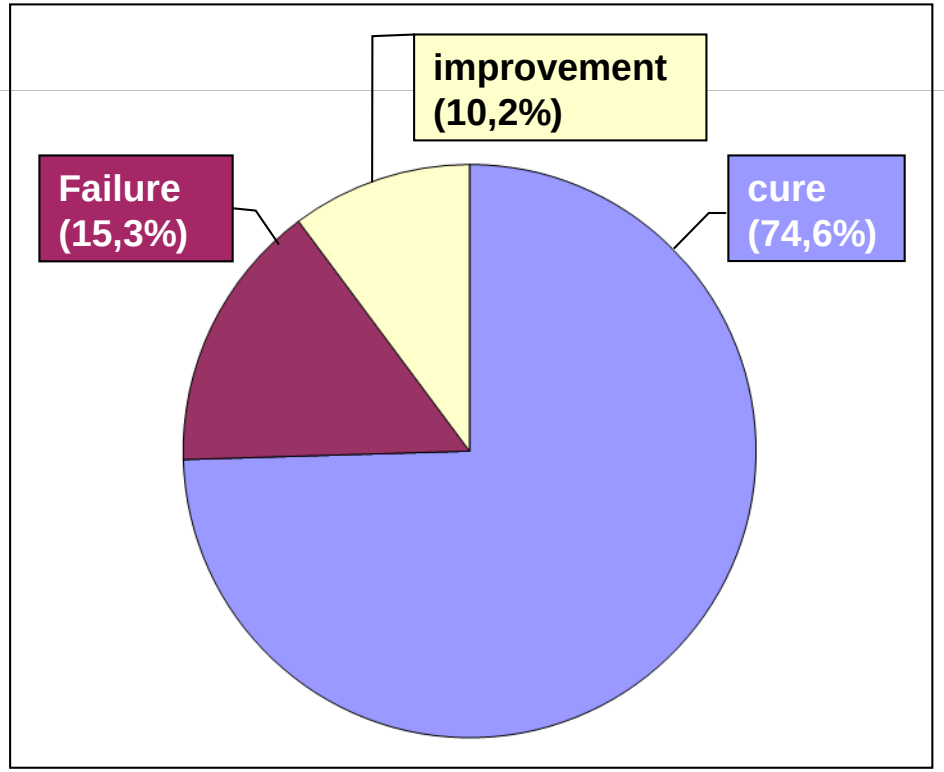
  (i) disappearance of all major signs of infection;

  (ii) normalization of body temperature;

  (iii) marked decrease of CRP.

- at EOT and at 6 months
- assessment retrospectively validated

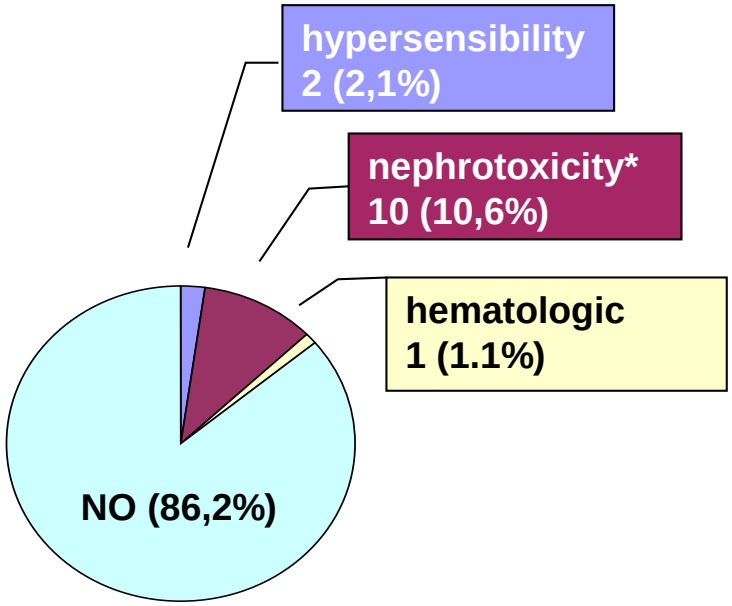
  by 2 ID physicians



## 3. Toxicity

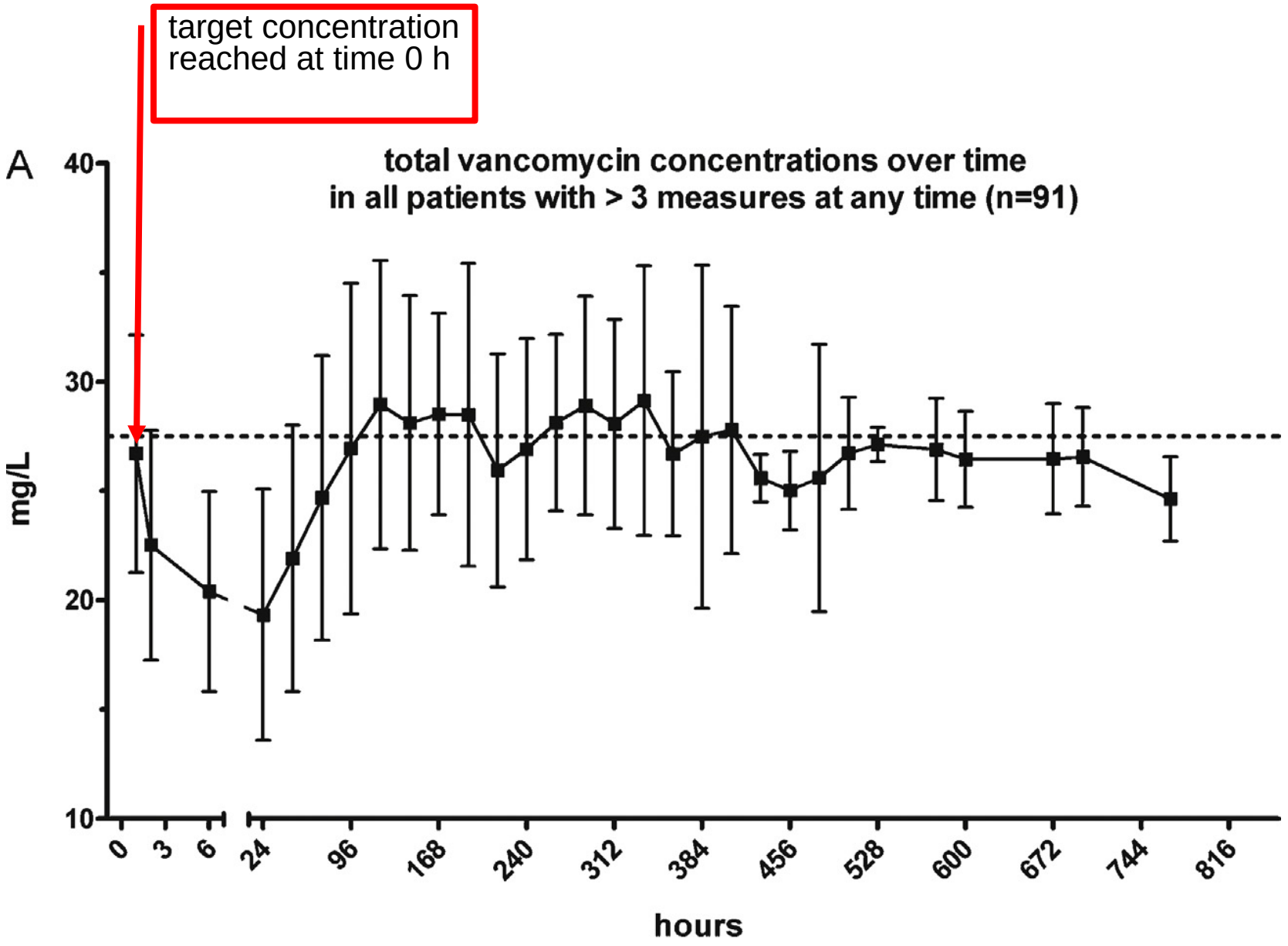
Adverse events observed in all enrolled patients (n = 94).

- 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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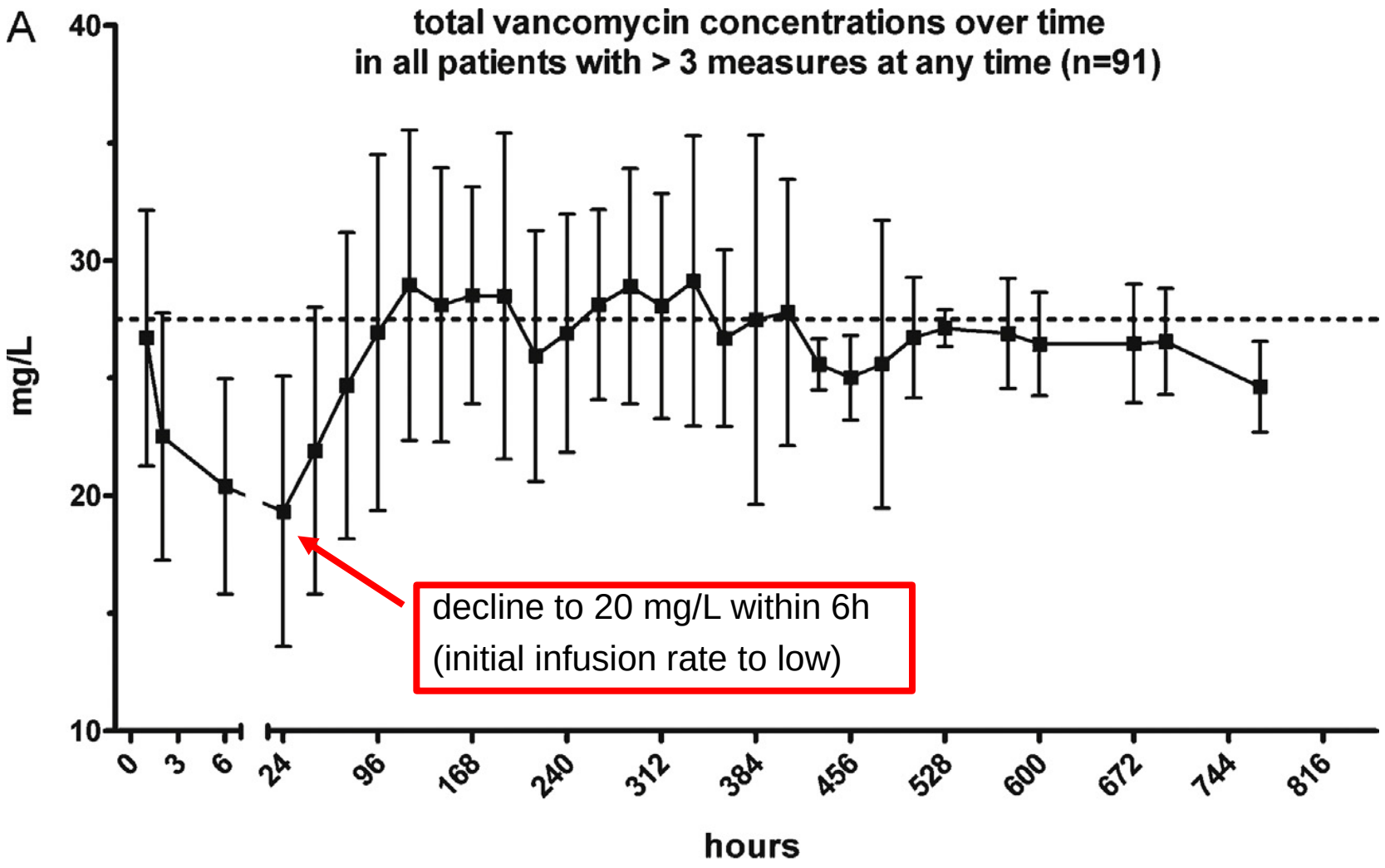

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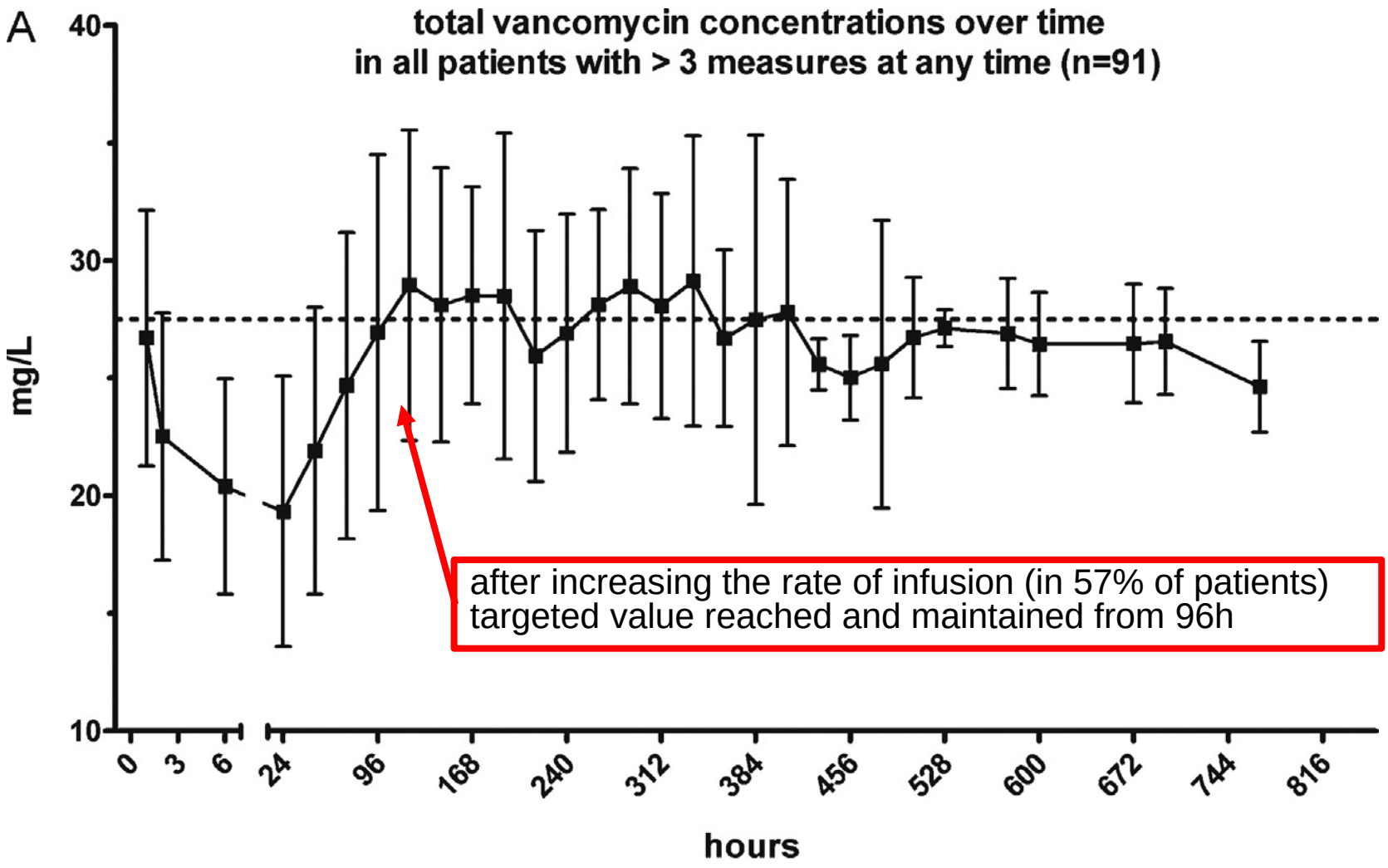
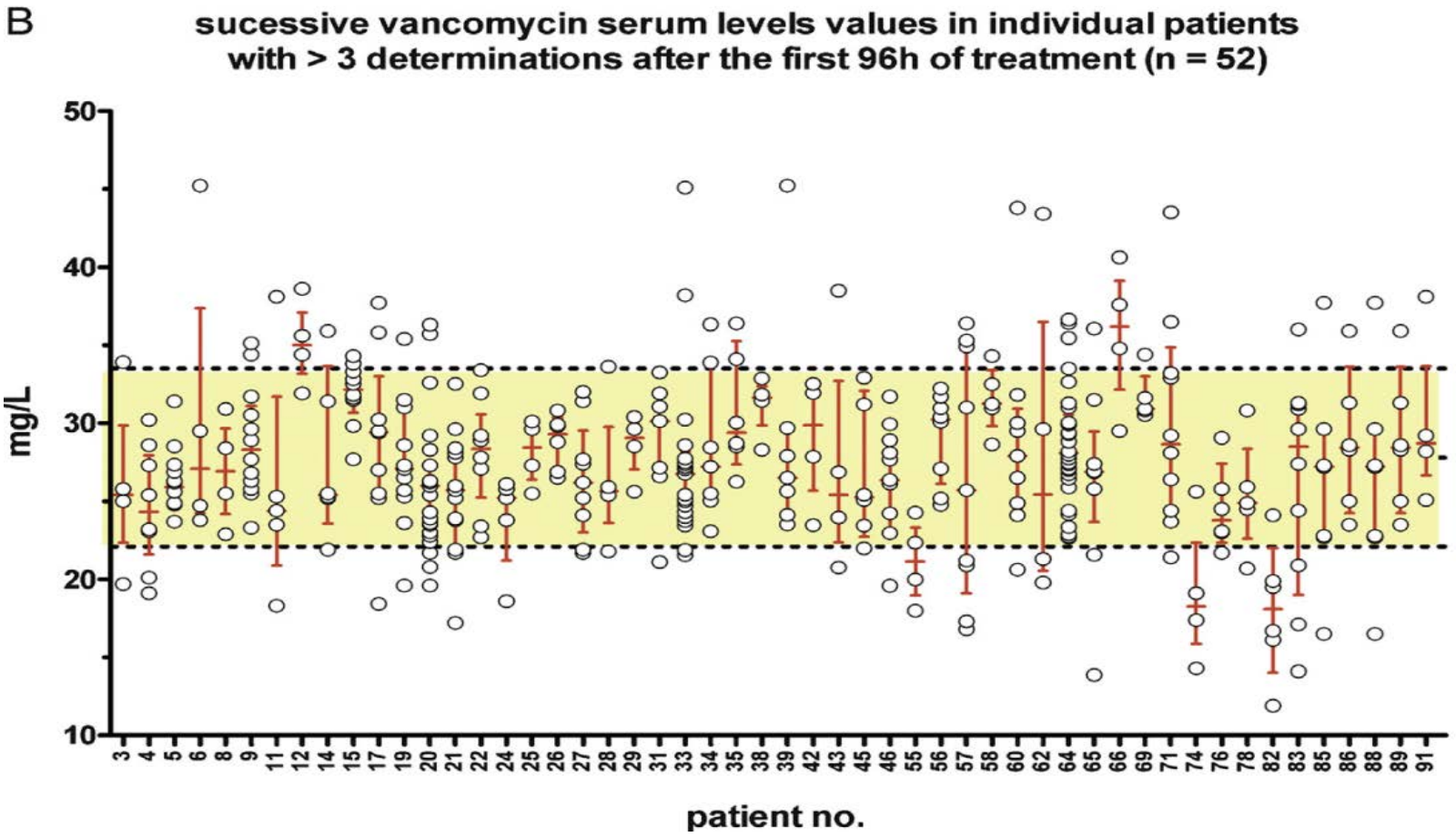
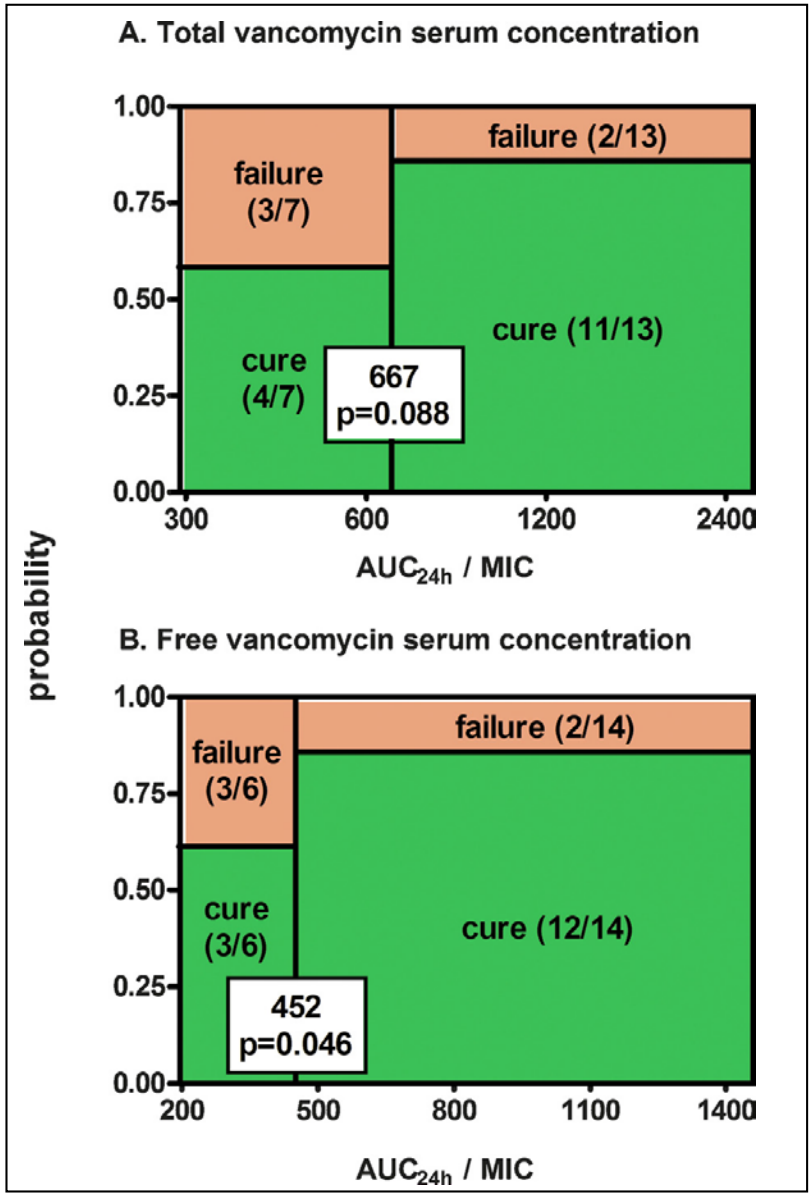


# 7. Total vancomycin serum concentrations




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

# 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 | • Add a loading dose (20 mg/kg)<br>Increase of the rate of infusion (+ 8 mL/h) [a] |
| 6-10 mg/L | • Add a loading dose (15 mg/kg)<br>• Increase of the rate of infusion (+ 6 mL/h) [a] |
| 11-15 mg/L | • Add a loading dose (10 mg/kg)<br>• Increase of the rate of infusion (+ 4 mL/h) [a] |
| 16-25 mg/L | • Increase of the rate of infusion (+ 2 mL/h) [a] |
| 26-30 mg/L | • No change |
| 31-35 mg/L | • Decrease of the rate of infusion (- 2 mL/h) [a] |
| > 35 mg/L | • STOP infusion for 6 h<br>• Decrease of the rate of infusion (- 4 mL/h) [a]<br>• 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 %)

## 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."*

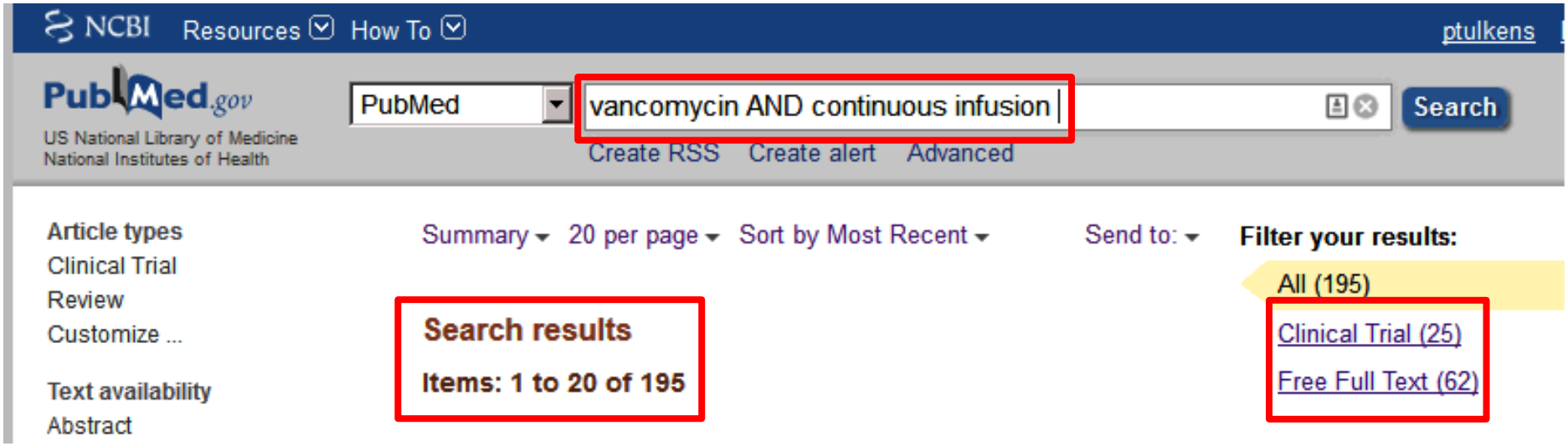
# Continuous infusion in Mont-Godinne

- 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 ?



# 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 EM[1], Bouma A, Touw DJ, Neef C, van Zanten AR.

**Author information**

[1]Department 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.**

Saugel B[1], Gramm C[2], Wagner JY[3], Messer M[2], Lahmer T[2], Meidert AS[2], Schmid RM[2], Huber W[2].

**Author information**

[1]II. Medizinische Klinik und Poliklinik, Klinikum rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, 81675 München, Germany. Electronic address: bernd.saugel@gmx.de.
[2]II. Medizinische Klinik und Poliklinik, Klinikum rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, 81675 München, Germany.
[3]III. 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 did it…
    - do the others do the same ?
  - **unconventional uses of vancomycin**

# Vancomycin and *Acinetobacter baumanii* ?

Infect Dis Ther (2014) 3:69–81
DOI 10.1007/s40121-014-0051-9

REVIEW

## A Review of Novel Combinations of Colistin and Lipopeptide or Glycopeptide Antibiotics for the Treatment of Multidrug-Resistant *Acinetobacter baumannii*

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The proposed mechanism of synergy relates to the cell membrane permeabilizing ability of colistin.

Colistin causes an electrostatic interaction with LPS (lipid A), disrupting the outer membrane of the Gram-negative bacteria.

This allows the otherwise large vancomycin molecules to pass through the outer LPS layer and reach the site of action at the cell wall [23, 24].

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**Table 1** Summary of in vitro studies of vancomycin (VAN), teicoplanin (TEC), telavancin (TLV), and daptomycin (DAP) in combination with colistin (COL)

| References | Isolates tested (*n*) | Antimicrobials tested | Synergy studies performed | Results |
|---|---|---|---|---|
| Gordon et al. [23] | ACB ATCC 19606<br>Epidemic MDRAB [5]<br>Clinical MDRAB [35] | VAN + COL | Checkerboard assay with FICI<br>2-well synergy<br>Synergy Etest (0.5 × MIC COL)<br>Synergy time-kill curves (1 mg/L COL, 20 mg/L VAN, 48 h) | Checkerboard and two-well demonstrated synergy in 4/6 isolates tested<br>Synergy kill curves resulted in sustained bactericidal activity for 48 h for 5/6 isolates tested<br>Synergy Etest on all 40 isolates resulted in VAN MIC decrease from >256 mg/L to range 48–0.016 mg/L |
| Wareham et al. [27] | ACB ATCC 19606<br>Epidemic MDRAB [5] | TEC + COL | Checkerboard assay with FICI<br>Synergy Etest (0.5 × MIC COL)<br>Synergy time-kill curves (1 mg/L COL, 20 mg/L TEC, 24 h) | Checkerboard demonstrated synergy in all 6 isolates tested<br>Synergy time-kill curves resulted in sustained bactericidal activity for 24 h for all 6 isolates tested<br>Synergy Etest on all 6 isolates resulted in TEC MIC decrease from >256 mg/L to 1–2 mg/L |
| Vidaillac et al. [29] | ACB ATCC 19606<br>Clinical ACB isolates [2]*<br>PSA ATCC 27853<br>Clinical PSA isolates [2]*<br>KP ATCC 7000603<br>Clinical KP isolates [2]* | VAN + COL | Checkerboard assay with FICI<br>Synergy time-kill curves (0.25 × MIC and 0.5 × MIC each agent, 24 h) | Checkerboard assay demonstrated synergy in all ACB isolates tested but not KP or PSA isolates (FICI >0.5)<br>Synergy time-kill curves achieved bactericidal activity in 2–4 h and sustained through 24 h in ACB, no synergy demonstrated in COL-resistant KP or PSA |

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**Table 1** continued

| References | Isolates tested (*n*) | Antimicrobials tested | Synergy studies performed | Results |
|---|---|---|---|---|
| Phee et al. [24] | ACB ATCC 19606<br>Clinical ACB isolates [5]<br>Epidemic ACB isolates [6]<br>Epidemic ACB isolates$^{R}$ [2]<br>Epidemic *E. coli* [7]<br>Epidemic *K. pneumoniae* [3]<br>Epidemic *E. cloacae* [2]<br>Epidemic PSA [4] | DAP + COL | Synergy Etest (0.125–0.75 mg/L COL), sensitization factor | DAP MIC decreased to 4–64 mg/L in COL-susceptible ACB, sensitization factor ≥2 for all COL-susceptible ACB not COL-resistant, no increase in sensitization factor for other isolates |
| Galani et al. [31] | Clinical ACB isolates [10]<br>Clinical ACB isolates$^{R}$ [4] | DAP + COL | Synergy Etest (0.5 × MIC COL, 5 mg/L COL)<br>Synergy time-kill curves 0.25×, 0.5×, and 1 × MIC COL, 5 mg/L COL, 10 mg/L DAP, 24 h) | Etest synergy demonstrated with subinhibitory concentrations of COL for only COL-susceptible isolates<br>Sustained killing seen in 9 of 10 COL-susceptible with 1 × MIC COL, killing was not achieved again COL-resistant isolates |

*ACB Acinetobacter baumannii*, *ATCC* American type culture collection, *DOR* doripenem, *FICI* fractional inhibitory concentration index, *KP Klebsiella pneumoniae*, *MIC* minimum inhibitory concentration, *NCTC* national collection of type cultures, *PSA Pseudomonas aeruginosa*, *R* COL-resistant isolate

*1/2 clinical isolates COL R

# Vancomycin and *Acinetobacter baumanii* ?

**But no published clinical data so far !**

# 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 did …
    - do the others do the same ?
  - unconventional uses of vancomycin

# This is the end (for the time being) !

## But ask questions