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

Paul M. Tulkens, MD, PhD *

Cellular and Molecular Pharmacology & Centre for Clinical Pharmacy
Louvain Drug Research Institute
Université catholique de Louvain, Brussels, Belgium

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

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  – 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

• first isolated in 1953 by Edmund Kornfeld at Eli Lilly & Co.\textsuperscript{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)

\textsuperscript{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: 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)
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How to measure vancomycin MIC: 2 main problems

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

• vancomycin MICs are not homogenous in a given high inoc

MW:1449.253 g/mol

FIG 1 Vancomycin population analysis profile of S. aureus GRP-0169 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

Hetero-resistance: how to see it ...
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).

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 warnings 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

![Diagram showing Vancomycin and Pharmacodynamics]
Vancomycin – AUC$_{24h}$ and efficacy

1. In vitro model mimicking the human PK

Vancomycin – $\text{AUC}_{24\text{h}}$ and efficacy

1. In vitro model mimicking the human PK

![Graph showing the relationship between drug exposure and efficacy](image)

You need at least 400!

Pharmacodynamics of Vancomycin and Other Antimicrobials in Patients with \textit{Staphylococcus aureus} Lower Respiratory Tract Infections

Pamela A. Moise-Broder,\textsuperscript{1} Alan Forrest,\textsuperscript{1,2} Mary C. Birmingham\textsuperscript{1} and Jerome J. Schentag\textsuperscript{1,2}

\textsuperscript{1} CPL Associates, LLC, Amherst, New York, USA
\textsuperscript{2} University at Buffalo School of Pharmacy and Pharmaceutical Sciences, Buffalo, New York, USA
Vancomycin – $AUC_{24h}$ and efficacy

2. In vivo (clinical study) – clinical success

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin $AUC_{24/MIC}$ value (\geq350)</td>
<td>7.19</td>
<td>1.91, 27.3</td>
<td>0.0036</td>
</tr>
<tr>
<td>MSSA as pathogen</td>
<td>3.88</td>
<td>1.10, 14.8</td>
<td>0.0359</td>
</tr>
<tr>
<td>Single lobe involvement</td>
<td>6.32</td>
<td>1.56, 25.6</td>
<td>0.0099</td>
</tr>
<tr>
<td>Baseline serum albumin (per 1 g/dL)</td>
<td>3.73</td>
<td>1.09, 12.8</td>
<td>0.0364</td>
</tr>
<tr>
<td>Baseline CLCR (per 1 mL/min)</td>
<td>1.04</td>
<td>1.01, 1.07</td>
<td>0.0154</td>
</tr>
</tbody>
</table>

$AUC_{24/MIC}$ = 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.

Vancomycin – $\text{AUC}_{24h}$ and efficacy

![Graph showing the relationship between $\text{AUC}_{24}$ and culture-positive patients over time.](image)

**Fig. 4.** Time (days of therapy) to bacterial eradication vs vancomycin $\text{AUC}_{24}$/MIC $<$400 and $\text{AUC}_{24}$/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 $\text{AUC}_{24}$/MIC groups differed significantly ($p = 0.0402$). $\text{AUC}_{24}$/MIC = steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration.

Why is a so large AUC$_{24h}$/MIC needed?

Vancomycin Tissular Penetration is poor


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. $\text{Cl}_{\text{cr}}$

$$\text{AUC}_{24} = \frac{D}{[(\text{CL}_{\text{CR}} \times 0.79) + 15.4] \times 0.06}$$

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.

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

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

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

Vancomycin and MIC (EUCAST distributions)

S. aureus
(no diff. between MSSA and MRSA)

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

Vancomycin / Staphylococcus aureus
EUCAST MIC Distribution - Reference Database 2011-10-08

Limit of the wild type population and EUCAST breakpoint ( \( > \) is resistant)

Epidemiological cut-off: WT \( \leq 2 \) mg/L

Clinical breakpoints: S \( \leq 2 \) mg/L, R > 2 mg/L

87754 observations (33 data sources)
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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 …

What if you target a "high" trough level?

**Studied 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

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,2,3,4 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,6,7 and Henry F. Chambers1,2


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 ...

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\(^1\), Kathleen A Hazlewood\(^1\), Sara D Brouse\(^1\), Christopher A Giuliano\(^3\), Krystal K Haase\(^3\), Christopher R Frei\(^4\), Nicolas A Forcade\(^4\), 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

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

**infusion:** 30 mg/kg/day

---

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 m²
Dosing adjustment...

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

Fig. 2. Linear correlation between 24-h creatinine clearance (CL\textsubscript{Cr}) and serum vancomycin concentration on Day 1. The serum vancomycin concentration displayed a significant direct correlation with CL\textsubscript{Cr} in 93 septic critically ill patients (r\textsubscript{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 MIC > 2 mg/L

5. do not forget to detect heteroresistance… (use E-test)
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    - why
    - how we do it…
    - do the others do the same
Vancomycin: continuous infusion

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

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

\textsuperscript{a} Pharmacologie cellulaire et moléculaire et Centre de pharmacie clinique, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium

\textsuperscript{b} Laboratoire de microbiologie, Service d'infectiologie et Département de pharmacie, CHU Mont-Godinne, Yvoir, Belgium
Vancomycin: continuous infusion

• Why $\rightarrow$ 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

40% incorrect sample timing
Observational study – results

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

vancomycin peak (n=49)

vancomycin trough (n=83)

*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

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

\(^a\) 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

<table>
<thead>
<tr>
<th>Quantitative methods (clinical trials)</th>
<th>Qualitative methods (interviews, observations, notes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘how many’?</td>
<td>‘why?’ and ‘how?’ (hypothesis generating)</td>
</tr>
<tr>
<td>what is the % of inappropriate TDM?</td>
<td>why/how does inappropriate TDM occur?</td>
</tr>
<tr>
<td>what is the impact of x on this %?</td>
<td></td>
</tr>
<tr>
<td>large, random samples</td>
<td>small, purposive samples</td>
</tr>
</tbody>
</table>

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# 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).

<table>
<thead>
<tr>
<th>Socio-cultural and structural elements</th>
<th>- inertia of practice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- lack of motivation and personal involvement</td>
</tr>
<tr>
<td></td>
<td>- insufficient interdisciplinary collaboration</td>
</tr>
<tr>
<td></td>
<td>- unclear definition of responsibilities</td>
</tr>
<tr>
<td></td>
<td>- ill-adapted techniques</td>
</tr>
<tr>
<td>Training and information</td>
<td>- insufficient (post-) graduate education</td>
</tr>
<tr>
<td></td>
<td>- ‘teacher-centred’ learning approach</td>
</tr>
<tr>
<td></td>
<td>- incomplete and/or difficult to apply local guidelines</td>
</tr>
<tr>
<td></td>
<td>- conflict between local guidelines and external guidelines</td>
</tr>
<tr>
<td>harm-benefit ratio of TDM</td>
<td>- patient too frail</td>
</tr>
<tr>
<td></td>
<td>- unnecessary samplings for the information gained</td>
</tr>
</tbody>
</table>
Qualitative study – results

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

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…”

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”
TDM of vancomycin by continuous infusion

AUC24h /MIC independent of the mode of administration

Continuous infusion

Twice daily dosing
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)

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>minimal AUC (mg*L$^{-1}$*h)</th>
<th>target Css (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>400</td>
<td>16.6</td>
</tr>
<tr>
<td>2</td>
<td>800</td>
<td>33.3</td>
</tr>
<tr>
<td>4</td>
<td>1600</td>
<td>66.6</td>
</tr>
</tbody>
</table>
vancomycin CI: which serum concentration should we target?

vancomycin CI: which serum concentration should we target?

**efficacy**

- **MIC = 1.5 mg/L**
- **25-30 mg/L**
- **VAN serum conc. (mg/L)**
- **400**

**toxicity**

- **CSS vancomycin > 28 mg/L**
- **increased nephrotoxicity risk**
- **[OR 21.236; P = 0.004]**


How to reach the serum target concentration target with CI?

1. loading dose: the correct scheme *

\[ C_t = \frac{D_l}{V_d} \]

loading dose

**Target serum concentration**

**Volume of distribution**

\[ \text{loading dose (in mg/kg)} = C_t \text{ (mg/L)} \times V_d \text{ (L/kg)} \]

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

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

\[ C_{ss} = \frac{K_o}{Cl} \]

Target serum concentration

Clearance *

infusion rate

daily dose (in mg) = 24 \times \text{clearance (L/h)} \times C_{ss}

* assuming linear pharmacokinetics
How to reach the serum target concentration target with CI?

2: infusion *

\[
\text{In} = \text{infusion} = \text{clearance} \cdot \text{Out}
\]

once a bath is at 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: \(\text{in} = \text{out}\)…)

* during the infusion, the necessary dose (in 24h or per min) is only dependent upon the clearance
2. Clinical evaluation: study outline

- Discontinuous infusion (n=18)
- CrCl <30 mL/min (n=13)
- Moribund patients (n=5)

Eligible patients (n=130)

Clinical evaluation

- Neutropenic fever (n=12)
- Concomitant infection at another site (n=10)
- Unconfirmed diagnosis (n=12)

Toxicity (n=94)

Efficacy (n=59)
2. Pharmacokinetic evaluation: study outline

- **MIC determination (n=52)**
  - **enrolled for PK analysis (n=56) a**
  - **insufficient PK data (n=11)**
  - **PK evaluable patients (n=48)**
    - **detailed PK analysis**
    - **no MIC available (n=16)**
  - **PK/PD evaluable patients (n=32)**

- **enrolled patients (n=94)**

**a** signed informed consent for additional blood sampling
**b** standard of care only
2. Relationship between $AUC_{24h}/MIC$ and clinical efficacy: outline

- enrolled for PK analysis ($n=56$)\(^a\)
  - PK evaluable patients ($n=48$)
    - no MIC available
    - PK/PD evaluable patients ($n=32$)
      - multiple bacteria or multiple antibiotics ($n=12$)
      - correlation PK/PD – clinical outcome of vancomycin ($n=20$)

\(^a\) 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

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

Total vancomycin concentrations over time in all patients with >3 measures at any time (n=91)

Target concentration reached at time 0 h
7. Total vancomycin serum concentrations

![Graph showing total vancomycin concentrations over time.](image)

- **Graph Description**: The graph illustrates the total vancomycin concentrations over time in all patients with > 3 measures at any time (n=91).
- **Key Observation**: The concentrations decline to 20 mg/L within 6h, indicating an initial infusion rate that is low.

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7. Total vancomycin serum concentrations

A total vancomycin concentrations over time in all patients with > 3 measures at any time (n=91)

After increasing the rate of infusion (in 57% of patients) targeted value reached and maintained from 96h
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

<table>
<thead>
<tr>
<th>Actual concentration (measured)</th>
<th>Dose adaptation</th>
</tr>
</thead>
</table>
| 0-5 mg/L                        | • Add a loading dose (20 mg/kg)  
• Increase of the rate of infusion (+ 8 mL/h) \(^a\) |
| 6-10 mg/L                       | • Add a loading dose (15 mg/kg)  
• Increase of the rate of infusion (+ 6 mL/h) \(^a\) |
| 11-15 mg/L                      | • Add a loading dose (10 mg/kg)  
• 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  
• 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...
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

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

* 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

<table>
<thead>
<tr>
<th></th>
<th>mean (%)</th>
<th>min-max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of CI</td>
<td>99</td>
<td>95-100</td>
</tr>
<tr>
<td>Follow-up TDM recommendations</td>
<td>96</td>
<td>95-100</td>
</tr>
</tbody>
</table>
qualitative study – results one year after the end of the study

**global satisfaction of HCP with CI**

<table>
<thead>
<tr>
<th></th>
<th>global satisfaction score* ( /5)</th>
<th>min-max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicians** (n=7)</td>
<td>4.5</td>
<td>4-5</td>
</tr>
<tr>
<td>nurses (n=10)</td>
<td>4.3</td>
<td>3.5-5</td>
</tr>
<tr>
<td>laboratory personnel (n=8)</td>
<td>4.4</td>
<td>4-5</td>
</tr>
</tbody>
</table>
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...

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

van Maarseveen EM, 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.

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


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

Saugel B¹, Gramm C², Wagner J³, 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.saugel@gmx.de.

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

³Ill. 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