Vancomycin:
What is new (since 2011) ?

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

With the support of Wallonie-Bruxelles-International
Contents of the presentation

• Vancomycin
  – short summary
  – how to measure MICs
  – high doses in America ... and the risks
  – continuous infusion of vancomycin: why and how
Vancomycin History

- 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 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)
Vancomycin and Pharmacodynamics

- Vancomycin is an $\text{AUC}_{24\text{h}}$-MIC dependent antibiotic

\[
C_{\text{max}} / \text{MIC} \quad f \ T > \text{MIC}
\]

\[
\text{AUC}_{24\text{h}} / \text{MIC}
\]
Vancomycin – AUC$_{24h}$ and efficacy

1. In vitro model mimicking the human PK

Vancomycin – AUC$_{24h}$ and efficacy

1. In vitro model mimicking the human PK

You need at least 400!

Vancomycin and MIC (EUCAST distributions)

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

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

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

MIC (mg/L)

% microorganisms

0 10 20 30 40 50 60

0 0.002 0.004 0.006 0.008 0.01 0.015 0.02 0.025 0.05 0.1 0.2 0.5 1 2 4 8 16 32 64

(VISA)

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

MSSA and MRSA

35.02 ± 4.01

Mu50

Epidemiological cut-off: WT ≤ 2 mg/L

87764 observations (33 data sources)

Clinical breakpoints: S ≤ 2 mg/L, R > 2 mg/L
Vancomycin – AUC$_{24h}$ and efficacy

**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. Schentag¹,²*

1. CPL Associates, LLC, Amherst, New York, USA
2. University at Buffalo School of Pharmacy and Pharmaceutical Sciences, Buffalo, New York, USA
## Vancomycin – $\text{AUC}_{24h}$ 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 $\text{AUC}_{24h}/\text{MIC}$ value $\geq 350$</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 $\text{CL}_{\text{CR}}$ (per 1 mL/min)</td>
<td>1.04</td>
<td>1.01, 1.07</td>
<td>0.0154</td>
</tr>
</tbody>
</table>

$\text{AUC}_{24h}/\text{MIC} = \text{steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration; } \text{CL}_{\text{CR}} = \text{creatinine clearance; } \text{MSSA} = \text{methicillin-susceptible Staphylococcus aureus.}$

Vancomycin – $\text{AUC}_{24h}$ 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 ($p = 0.0402$). $\text{AUC}_{24}/\text{MIC} = \text{steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration.}$
How to calculate the $AUC_{24h}$ with the conventional BID schedule?

**AUC vs. dose for diff. CL\textsubscript{cr}**

![Graph showing AUC vs. dose for different CL\textsubscript{cr} values]

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

How to calculate the $\text{AUC}_{24h}$ with the conventional BID schedule?

$\text{AUC}_{24h} / \text{MIC}$ vs. dose for diff. MIC and $\text{CL}_{cr}=90$ mL/min

If the MIC reaches 2, you may have problems.

How to calculate the $\text{AUC}_{24h}$ with the conventional BID schedule?

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

A low creatinine clearance helps!

How to measure vancomycin MIC: 2 main problems

• vancomycin diffuses poorly in agar

MW: 1449.253 g/mol

• vancomycin MICs are not homogenous in a given high inoculum population

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

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 warning for failures

• gradient techniques (1-10 mg/L)
  – shows the presence and quantifies to which level heteroresistance is observed.
A comparison between broth microdilution and E-test

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 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 …

A recent paper...


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.
A recent paper...

• 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.
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,1,5 Sara E. Cosgrove,6 Robert S. Daum,7 Scott K. Fridkin,8 Rechel J. Gorwitz,9 Sheldon L. Kaplan,10 Adolfo W. Karchmer,11 Donald P. Levine,12 Barbara E. Murray,14 Michael J. Rybak,12,13 David A. Talan,15 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).
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 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 II¹²*, Kathleen A Hazlewood¹⁷, Sara D Broué¹⁸, Christopher A Giuliano³⁸, Krystal K Haase³, Christopher R Frei⁴, Nicolas A Forcade⁴¹⁰, Todd Bell⁵, Roger J Bedimo⁶ and Carlos A Alvarez¹²
Dosing adjustment…

- 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
over 1 h

**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$_{CR}$) 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 MIC > 2 mg/L
5. do not forget to detect heteroresistance… (use E-test)
Vancomycin: continuous infusion

• Why
• How

• Does it work in a whole hospital?
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.

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</th>
<th>Qualitative methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>(clinical trials)</td>
<td>(interviews, observations, notes)</td>
</tr>
<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>
# 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

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”
TDM of vancomycin by continuous infusion

AUC24h /MIC independent of the mode of administration

continuous infusion

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

Implementation of a Protocol for Administration of Vancomycin by Continuous Infusion: Pharmacokinetic, Pharmacodynamic and Toxicological aspects
E. Ampe, PharmD; B. Delaere, MD; J.D. Hecq, PharmD, PhD; P.M. Tulkens, MD, PhD; Y. Glupczynski, MD

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?

**Efficacy**

![Graph showing VAN serum concentration vs. time](image)

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

vancomycin CI: which serum concentration should we target?

**effficacy**

- **MIC = 1.5 mg/L**
- **25-30 mg/L**
- **400 vancomycin CI**: which serum concentration should we target?

**toxicity**

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


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 (in mg/kg) = \(C_t\) (mg/L) x \(V_d\) (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 CI? 2: infusion *

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

Target serum concentration

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 *

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

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 must 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

- enrolled patients (n=94)
  - discontinuous infusion (n=18)
  - CrCl <30 mL/min (n=13)
  - moribund patients (n=5)

- eligible patients (n=130)
  - toxicity (n=94)
  - efficacy (n=59)

- clinical evaluation
  - neutropenic fever [n=12]
  - concomitant infection at another site [n=10]
  - unconfirmed diagnosis [n=12]
2. Pharmacokinetic evaluation: study outline

- **MIC determination (n=52)**
  - **enrolled patients (n=94)**
    - **enrolled for PK analysis (n=56)**
      - **PK evaluable patients (n=48)**
        - **detailed PK analysis**
        - **no MIC available (n=16)**
      - **insufficient PK data (n=11)**
      - **PK/PD evaluable patients (n=32)**

*a signed informed consent for additional blood sampling

*b standard of care only
2. Relationship between $\text{AUC}_{24h}/\text{MIC}$ and clinical efficacy: outline

- enrolled for PK analysis (n=56)
  - 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)

- signed informed consent for additional blood sampling
- 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

- Target concentration reached at time 0 h

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

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

- Decline to 20 mg/L within 6h (initial infusion rate to low)
7. Total vancomycin serum concentrations

After increasing the rate of infusion (in 57% of patients), the targeted value was reached and maintained from 96 hours.
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

<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 $\text{AUC}_{24h}/\text{MIC}$-ratio of 667 necessary for optimal efficacy in our context … MIC of 1 mg/L is probably the limit for vancomycin…
### Observational study – results after implementation of CI

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

<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] (a)</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] (b)</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</td>
<td>96</td>
<td>95-100</td>
</tr>
<tr>
<td>recommendations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
qualitative study – results one year after the end of the study

<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.”
Conclusions for continuous infusion

• 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.
Disclosures and slides availability

Financial support from

• the Belgian *Fonds de la Recherche Scientifique* (and other federal and regional funding agencies) for basic research on pharmacology and toxicology of antibiotics and related topics and for support to a PhD fellow (D. Das)

• the Université catholique de Louvain for support to E. Ampe (vancomycin studies)

• the Belgian Public Federal Service "Public Health" for "Appropriate antibiotic use" studies in General Practice

• Research grant from Bophar Pharmaceuticals B.V., importer of colistimethate in Belgium (from Forest Pharmaceuticals UK)

• Wallonie-Bruxelles International for this presentation and my activities in Vietnam

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