VANCOMYCIN IN 2008: 52 Years Later… Have We Figured It Out Yet?

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Learning Objectives
1. Describe the pharmacokinetic and pharmacodynamic properties of vancomycin.
2. Describe the toxicities associated with vancomycin.
3. Describe the evidence behind therapeutic drug monitoring (TDM) and the “evolving” target concentrations for vancomycin.
4. Discuss the clinical implications between vancomycin and MRSA, VISA, and VRSA.
5. Explain how TDM can be applied in clinical decision-making to optimize vancomycin therapy in the following scenarios:
   a) Short-term treatment
   b) Long-term treatment
   c) Treatment of severe infections.
6. Determine if vancomycin TDM is relevant in your clinical practice.

Question

ANSWER:

Outline

1. What is vancomycin used for?
2. Is vancomycin a bacteriocidal or bacteriostatic drug?
3. What are the pharmacokinetic/pharmacodynamic properties of vancomycin?
4. How have we been dosing vancomycin?
5. What are the toxicities of vancomycin?
6. What was the evidence for vancomycin levels (i.e. the “old” target range)?
7. How should we be dosing vancomycin now (i.e. based on “new” evidence)?
8. Is vancomycin a good drug for MRSA?
9. What are the optimal dosing and monitoring strategies for vancomycin?
   • Cases
10. Are vancomycin levels relevant in my clinical practice?

1. What is vancomycin used for?
1. What is vancomycin used for?

**Historical Overview**

(Moellering Jr. CID 2006;42(Suppl 1):S3-4)

– 1956
  • Soil from Borneo
  • *Streptomyces (Amycolaptosis) orientalis*
  • Vancomycin derived from “vanquish”

– 1958
  • Approved by FDA
  • “Mississippi mud”
  • Ototoxic and nephrotoxic

– 1961
  • MRSA first reported

– 1970’s
  • New preparations
  • MRSA increases

– 1980’s
  • Nomogram
    – Moellering
    – Matzke
  • VRE reported

– 1990’s
  • Vancomycin TDM questioned
  • VRE increases; vancomycin restrictions

– 2000’s
  • VISA
  • VRSA
  • CA-MRSA
  • *Clostridium difficile*

1. What is vancomycin used for?

**Microbiological Activity**

– *Staphylococcus (S. aureus, S. epidermidis, MRSA)*
– *Streptococcus (viridans S., S. bovis)*
– *Enterococcus*
– Diphtheroids
– *Clostridium difficile*

1. What is vancomycin used for?

**Clinical Indications**

– Endocarditis (native/prosthetic valve)
– Endocarditis prophylaxis
– Osteomyelitis
– Pneumonia
– Pseudomembranous colitis
– Septicemia
– Severe/life-threatening infections
– Soft-tissue infections
– Other
  • CNS infections, febrile neutropenia, line infections, prosthetic joint infection, surgical prophylaxis

**ANSWER:**

• Vancomycin is effective for the treatment of infections caused by Gram-positive organisms (including *S. aureus*, *Strep.*, and *Enterococcus*).
FACT OR FICTION?

2. Is vancomycin a bacteriocidal or bacteriostatic drug?

A. Bacteriocidal
B. Bacteriostatic
C. Other

Pharmacodynamic Properties

– Bacteriocidal vs. bacteriostatic
  • In vitro activity based on
    – Minimal inhibitory concentration (MIC)
    – Minimal bacteriocidal concentration (MBC)
  • Bacteriocidal
    – MIC/MBC similar
  • Bacteriostatic
    – MIC is lower than the MBC

Mechanism of Action

– Glycopeptide
  • Binds to peptidoglycan precursor
    – D-alanyl-D-alanine terminating pentapeptide
  • Inhibits incorporation of monomers into peptidoglycan chain
  – Disrupts cell wall synthesis

2. Is vancomycin a bacteriocidal or bacteriostatic drug?

Bacteriostatic antimicrobial

Concentration of antibiotic

<table>
<thead>
<tr>
<th>Time</th>
<th>Concentration of antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC</td>
<td>Bacteriostatic antimicrobial</td>
</tr>
<tr>
<td>MBC</td>
<td>Bacteriocidal antimicrobial</td>
</tr>
</tbody>
</table>

Vancomycin

– But why do clinicians feel that vancomycin is bacteriostatic?
2. Is vancomycin a bacteriocidal or bacteriostatic drug?

- Vancomycin activity affected by other factors
  • Bacteriocidal (MIC/MBC)
    – 4-5 times MIC
  • Bacterial burden
    – Size
    – Growth phase
      » Stationary
      » Exponential
  • Clinical activity
  • Penetration into tissues
    – Inflammation

ANSWER:

- Vancomycin is a bacteriocidal drug.
- Numerous factors affect its activity.
- Concentrations <4-5 times MIC are considered bacteriostatic.

3. What are the pharmacokinetic/pharmacodynamic properties of vancomycin?

Pharmacokinetic Properties

- Multi-compartmental (2-3 compartments)
- Protein binding ~50%
- Volume of distribution ~0.6L/kg (0.5-0.9 L/kg)
- ~90% renally eliminated unchanged via glomerular filtration
- $T_{1/2}$ ~6h (normal renal function)

(Birt J & Chandler MHH. Ther Drug Monit 1990)
(Welch L, Leader WG, Chandler MHH. Clin Pharm 1993)
(Leader WG, Chandler MHH. Curr Pharmaceut 1995)

In Clinical Practice

• Assume 1-Compartment Model

<10% overall AUC

Vd = $\frac{K_o(1-e^{-Kt})}{C_{spk}K(1-e^{-K\tau})}$
3. What are the pharmacokinetic/pharmacodynamic properties of vancomycin?

Pharmacodynamic Properties
- Concentration-independent kill
  • Initial killing effect of daptomycin and vancomycin against *S. aureus*

Pharmacokinetic/Pharmacodynamic Properties
- Pharmacokinetics
  • Time course of antimicrobial concentrations in body; effect of body on drug
    - ADME, AUC, Cmax
- Pharmacodynamics
  • Antimicrobial effect on the target; effect of drug on body or microorganisms
    - MIC, MBC
- Pharmacokinetics/Pharmacodynamics
  • Surrogate parameters determine doses that optimize efficacy and reduce resistance selection
    - AUC/MIC, Cmax/MIC, T>MIC

**ANSWER:**
- AUC/MIC, Cmax/MIC, T>MIC
- Difficult to calculate AUC/MIC clinically
  - Trough surrogate marker
- ATS guidelines for HAP/VAP
  (Am J Respir Crit Care Med 2005;171:388-416)
  - Troughs of 15-20 mg/L for MRSA pneumonia
- Maintain concentrations 4-5 times MIC
- Higher concentrations required for sequestered infections
  - CNS infection and pneumonia

**ANSWER:**
- AUC/MIC is the best pharmacokinetic-pharmacodynamic predictor of activity.
- Vancomycin is a concentration-independent (time-dependent) antibiotic.
  - Its activity peaks at 4-5 times MIC.
4. How have we been dosing vancomycin?

- Vancocin® Package Insert (Vancomycin HCl Injection, USP)
  - Adult patients with normal renal function
    - Usual daily intravenous dose is 2 g divided either as 500 mg every 6 hours or 1 g every 12 hours
    - Other patient factors, such as age or obesity, may call for modification of usual intravenous daily dose


<table>
<thead>
<tr>
<th>METHOD</th>
<th>PK MODEL</th>
<th>TARGET CONCENTRATION(S) (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Package Insert</td>
<td>-</td>
<td>Peak (2h after end of infusion): 25</td>
</tr>
<tr>
<td>Moellering Nomogram (1981)</td>
<td>3-compartment</td>
<td>Average: 15</td>
</tr>
<tr>
<td>Matzke Nomogram (1984)</td>
<td>1-compartment</td>
<td>Peak (5h after end of infusion): 30</td>
</tr>
<tr>
<td>Nielsen Method (1975)</td>
<td>-</td>
<td>Trough: 7.5</td>
</tr>
<tr>
<td>Rotschafer Method (1982)</td>
<td>2-compartment</td>
<td>Peak: 30-45</td>
</tr>
<tr>
<td>Lake Method (1985)</td>
<td>-</td>
<td>Trough: 5-10</td>
</tr>
<tr>
<td>Karam Nomogram (1999)</td>
<td>-</td>
<td>Trough: 5-20</td>
</tr>
</tbody>
</table>


- Nielsen Method
- Rotschafer Method
- Lake Method
- Karam Nomogram

……and many, many more……
4. How have we been dosing vancomycin?

• “Clinically relevant” PEAK concentration?

   LOCAL GUIDELINES
   • VGH: 3h after end of 1h infusion: 15 to 25 mg/L
   • SPH: 3h after end of 1h infusion: 15 to 20 mg/L (back-extrapolate to end of infusion: 20 to 30 mg/L)
   • C&W: 1h after end of 1h infusion: 20 to 40 mg/L

ANSWER:
• Even more flavours than Baskin Robbins has ice cream!

5. What are the toxicities of vancomycin?

Toxicities of Vancomycin
– Impurities contributed to adverse reactions
– Purity increased from 1960’s to 1980’s
   • Adverse events decreased

– Unrelated to serum concentrations
   • Fever, chills, phlebitis
   • Red man syndrome
   • Neutropenia
   • Associated with serum concentrations
     • Ototoxicity
     • Nephrotoxicity

Neutropenia
   • Absolute neutrophil count <1000 cells/mm³
   – Incidence
     • 2-8% incidence
     • Associated with prolonged therapy (>14 d)
   – Proposed mechanism
     • Immune-mediated destruction of neutrophils
     • Direct suppression of bone marrow
   – VGH experience

Ototoxicity
• Damage to cochlea or auditory nerve

   Incidence

   Proposed mechanism
   • Affects high frequency sensory hairs in cochlea, then middle and low frequency hairs
   • High-tone deafness occurs before low-tone deafness; permanent hearing loss
5. What are the toxicities of vancomycin?

Nephrotoxicity

- >0.5 mg/dL (44 µmol/L) or >50% increase in creatinine; or 50% drop in CrCl from baseline

- Incidence
  - 0-17% vancomycin monotherapy
    - Uncommon with typical regimens
  - 7-35% with concomitant aminoglycoside
    - 3-4-fold increase

- Proposed mechanism
  - Stimulates oxygen consumption and ATP in proximal tubule
  - Oxidative stress damages glomeruli and proximal tubules

ANSWER:

- Impurities contributed to initial adverse reactions.

- Toxicities unrelated to serum concentrations:
  - Fever, chills, phlebitis
  - Red man syndrome
  - ? Neutropenia.

- Toxicities associated with serum concentrations (low incidence with monotherapy):
  - Ototoxicity
  - Nephrotoxicity.

6. What was the evidence for vancomycin levels (i.e. the “old” target range)?

Ototoxicity

(Cantu et al. CID 1994;18:533-43)
- In 1958, Geraci described 6 patients with bacterial endocarditis on vancomycin
  - 2 cases of ototoxicity
    - Serum vancomycin concentration 80 to 100 µg/mL
    - “…serum vancomycin concentrations in all patients should be monitored to reduce the risk of ototoxicity…”

6. What was the evidence for vancomycin levels?

Ototoxicity

(Cantu et al. CID 1994;18:533-43)
- 53 published cases in ~35 years of clinical use
  - 36 patients received prior or concomitant aminoglycoside (n=31) or erythromycin (n=5)
  - 3 patients not receiving other ototoxic agents had pneumococcal meningitis

(Cantu et al. CID 1994;18:533-43)
6. What was the evidence for vancomycin levels?

**Nephrotoxicity**

Reported Cases of Nephrotoxicity with Vancomycin

<table>
<thead>
<tr>
<th>Case reports</th>
<th>Questionable causality</th>
<th>Evaluable</th>
<th>AMG</th>
<th>No AMG</th>
<th>Other causes</th>
<th>Evaluable</th>
<th>Other nephrotoxic agents not reported</th>
<th>3 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>167</td>
<td>85</td>
<td>82</td>
<td>41</td>
<td>41</td>
<td>20</td>
<td>21</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

6. What was the evidence for vancomycin levels?

**Nephrotoxicity**

- Associated with troughs >10 µg/mL
  - Yes
  - No
    (Downs NJ et al. Arch Intern Med 1989; 149:1777-81)

6. What was the evidence for vancomycin levels?

**Efficacy**

- In studies of patients with normal renal function
- Doses of vancomycin
  - (1 g every 12 hours or 7.5 mg/kg every 6 hours)
    - Effective for staphylococcal or streptococcal infections in empirical treatment of febrile neutropenic patients with cancer
  - Peak and trough serum concentrations of vancomycin ranged from 18 to 47 µg/mL and from 2 to 13 µg/mL, respectively.
6. What was the evidence for vancomycin levels?

Efficacy

– “Long experience has indicated that a daily dose of 2 g for adults with normal renal function is effective and reasonably safe. Therefore, the concentrations of vancomycin in serum which are achieved when 2 g is administered to healthy adults can be regarded as the therapeutic levels…”

(Healy et al. Antimicrob Agents Chemother 1987;31:393-7)

6. What was the evidence for vancomycin levels?

Impact of Vancomycin TDM on Patient Outcomes

<table>
<thead>
<tr>
<th>REFERENCES</th>
<th>POP</th>
<th>DESIGN</th>
<th>N</th>
<th>OUTCOMES (P &lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Welty and Copa 1994</td>
<td>Impact of TDM vs. non-TDM on patient care</td>
<td>Prospective Cohort</td>
<td>61 TDM 55 non-TDM</td>
<td>Length of hospital stay: 36.8 vs. 44.5 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Toxicity: 7% vs. 24%</td>
</tr>
<tr>
<td>Del Mar Fernandez de Gatta et al. 1996</td>
<td>Cost-effectiveness analysis of TDM in heme/onc</td>
<td>Prospective Randomized</td>
<td>37 TDM 33 non-TDM</td>
<td>Nephrotoxicity: 13.5% vs. 42.4%</td>
</tr>
</tbody>
</table>

(Healy et al. Antimicrob Agents Chemother 1987;31:393-7)
6. What was the evidence for vancomycin levels?

To Monitor or Not to Monitor or How to Monitor: The Never-Ending Debate (1958→2008)


Vancomycin Levels

- Top 10 Drug Levels in the Lower Mainland (VCH, PHC, FHA, C&W)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug</th>
<th>Number of Serum Concentration Measurements / Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tacrolimus</td>
<td>17,708</td>
</tr>
<tr>
<td>2</td>
<td>Vancomycin</td>
<td>11,591</td>
</tr>
<tr>
<td>3</td>
<td>Cyclosporine</td>
<td>11,228</td>
</tr>
<tr>
<td>4</td>
<td>Aminoglycosides</td>
<td>9,576</td>
</tr>
<tr>
<td>5</td>
<td>Phenytoin</td>
<td>8,865</td>
</tr>
<tr>
<td>6</td>
<td>Digoxin</td>
<td>8,474</td>
</tr>
<tr>
<td>7</td>
<td>Valproic Acid</td>
<td>6,364</td>
</tr>
<tr>
<td>8</td>
<td>Carbamazepine</td>
<td>3,533</td>
</tr>
<tr>
<td>9</td>
<td>Sirolimus</td>
<td>2,206</td>
</tr>
<tr>
<td>10</td>
<td>Lithium</td>
<td>2,177</td>
</tr>
</tbody>
</table>

Answer:

- Evidence for TDM was controversial with most of the literature published before the concepts of “EBM” and optimal dosing based on AUC/MIC.

- Initial toxicities prompted “TDM for all.”

- Dosage of 1 g q12h was considered “effective” (and the concentrations achieved in healthy adults were regarded as “therapeutic”).
7. How should we be dosing vancomycin now (i.e. based on “new” evidence)?

Four Landmark Studies

1. Moise-Broder et al. (Clin Pharmacokinet 2004;43:925–42)
   - Pharmacodynamics of Vancomycin with other Antimicrobials in Patients with *Staphylococcus aureus* Lower Respiratory Tract Infections

2. Jeffres et al. (Chest 2006;130:947–55)

3. Hidayat et al. (Arch Intern Med 2006;166:2138–44)


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7. How should we be dosing vancomycin now?

**Results**

- N=108; median age 74 yrs (32-93 yrs); 67.6% ICU
- AUC24/MIC optimal clinical/bacteriological response if \( \geq 400 \)
- No relationship between % Time\( > \)MIC and infection response

![Graph showing Time (days of therapy) vs. bacterial eradication vs vancomycin.](image)

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7. How should we be dosing vancomycin now?

**Conclusion**

- Clinical/bacteriological response superior with higher AUC24/MIC
- No relationship between % Time\( > \)MIC
- Bacterial eradication of *S. aureus* (both MSSA and MRSA) more rapid with target threshold AUC24/MIC
- *S. aureus* killing rates slower with vancomycin than other antistaphylococcal antibacterials

7. How should we be dosing vancomycin now?

- **Limitations**
  - Retrospective
  - Half of patients received >1 antibiotic
  - AUC data based on simulations using CrCl (not serial measured vancomycin concentrations)
  - Mixed MSSA and MRSA infections

- **Bottom line**
  - $AUC_{24}/MIC$ ratio of ≥400 appears to be a good predictor of outcome.


7. How should we be dosing vancomycin now?

- **Limitations**
  - Retrospective
  - Small sample size; ICU
  - Extrapolated AUC from CrCl
  - AUC alone reported
  - Not assess clinical outcome relative to MIC
  - Not evaluate time to achieve trough of >15 µg/mL as predictor of outcome

- **Bottom line**
  - Hypothesis generating; unclear whether troughs or AUC better

(Jeffres et al. CHEST 2006;130:947–955)

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7. How should we be dosing vancomycin now?

- **Design**
  - R, Obs cohort, SC (JAN99 to JUN05-6.5 yrs)

- **Objectives**
  - Determine if vancomycin troughs or AUC associated with mortality in HCAP MRSA

- **Intervention**
  - Retrospective data collection

- **Inclusion**
  - HCAP MRSA in BAL semi-quantitative cultures

- **Exclusion**
  - Polymicrobial BAL, vancomycin <72 h, CA-MRSA, DNR

- **Endpoints**
  - Mortality

(Jeffres et al. CHEST 2006;130:947–955)

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7. How should we be dosing vancomycin now?

- **Results**
  - N=102; age 59.4 ± 15.3 yrs
  - Mortality
    - 32 patients (31.4%)

<table>
<thead>
<tr>
<th></th>
<th>SURVIVOR</th>
<th>NON-SURVIVOR</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>VANCOMYCIN TROUGH CONCENTRATIONS (mean ± SD):</td>
<td>13.6 ± 5.9 µg/mL</td>
<td>13.9 ± 6.7 µg/mL</td>
<td>p = 0.866</td>
</tr>
<tr>
<td>AUC VALUES</td>
<td>351 ± 143 µg/h/mL</td>
<td>354 ± 109 µg/h/mL</td>
<td>p = 0.941</td>
</tr>
</tbody>
</table>

- Stratification of trough concentrations and AUC no relationship with hospital mortality

(Jeffres et al. CHEST 2006;130:947–955)

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7. How should we be dosing vancomycin now?

- **Limitations**
  - Retrospective
  - Small sample size; ICU
  - Extrapolated AUC from CrCl
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- **Bottom line**
  - Hypothesis generating; unclear whether troughs or AUC better

(Jeffres et al. CHEST 2006;130:947–955)
7. How should we be dosing vancomycin now?

- **Design**
  - R cohort (AUG04 to JUN05)

- **Objectives**
  - Evaluate efficacy and risk of nephrotoxicity when targeting vancomycin unbound troughs of ≥4 times MIC

- **Intervention**
  - Vancomycin dosed at ≥4 times MIC of MRSA
    - Comparison of low-MIC (<1 µg/mL) vs. high-MIC (≥1.5 µg/mL)

- **Inclusion**
  - Nosocomial MRSA infection

- **Endpoints**
  - Clinical response, nephrotoxicity, and mortality

**Results**

- N=95; mean age 72.5 ± 15.6 yrs
  - Pneumonia (77%) and/or bacteremia
  - 51(54%) infected with high-MIC 2 µg/mL

- Response rate 73% if target trough attained

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>LOW-MIC &lt;1 µg/mL</th>
<th>HIGH-MIC 2 µg/mL</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Response</strong></td>
<td>34/40 (85%)</td>
<td>24/39 (62%)</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>4/44 (10%)</td>
<td>11/51 (24%)</td>
<td>P&lt;0.01</td>
</tr>
</tbody>
</table>

- Nephrotoxicity in high-trough group 11/63 (12%)

**Conclusions**

- MRSA strains with vancomycin MIC (2 µg/mL) require aggressive dosing to achieve trough greater than 15 µg/mL.

- Consider combination or alternative therapy for invasive infections if MIC at 2 µg/mL

**Limitations**

- Retrospective cohort design
- Small sample size
  - Power
  - Target levels not achieved in all high-MIC pts
- Not test heterogeneous resistance to vancomycin
  - Overlap in susceptibility range

**Bottom line**

- MRSA with MIC of 2 µg/mL may be more difficult to treat

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Probability of achieving AUC/MIC of >400 for high-dose vancomycin treatment (trough concentration >15 µg/mL) and low-dose vancomycin treatment (trough concentration ≤15 µg/mL). Adapted from Jeffres et al. (Mohr. CID 2007;44:1536-42)
7. How should we be dosing vancomycin now?

4. Soriano et al. (CID 2008;46:193-200)
   - Influence of Vancomycin Minimum Inhibitory Concentration on the Treatment of Methicillin-resistant Staphylococcus aureus Bacteremia

| P | In pts with MRSA bacteremia on vancomycin, |
| I | Do patients with MRSA isolates with higher MIC’s |
| C | Have worse outcomes than those with lower MIC’s |
| O | In terms of mortality? |

7. How should we be dosing vancomycin now?

• Results
  - N=414
  - Vancomycin MIC
    - 1 µg/mL (N=109)
    - 1.5 µg/mL (N=213)
    - 2 µg/mL (N=92)
  - 28% (116/414) mortality

<table>
<thead>
<tr>
<th>Vancomycin MIC</th>
<th>N</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 µg/mL</td>
<td>109</td>
<td>28%</td>
</tr>
<tr>
<td>1.5 µg/mL</td>
<td>213</td>
<td>28%</td>
</tr>
<tr>
<td>2 µg/mL</td>
<td>92</td>
<td>28%</td>
</tr>
</tbody>
</table>

7. How should we be dosing vancomycin now?

• Limitations
  - Retrospective
  - Vancomycin levels target of >10 µg/mL
  - Lack of AUC/MIC data

• Bottom line
  - MRSA with MIC of 2 µg/mL may be more difficult to treat

7. How should we be dosing vancomycin now?

• Design:
  - R (1991 to 2005-15 yrs)

• Objectives:
  - Evaluate if higher vancomycin MIC associated with mortality in MRSA bacteremia

• Intervention:
  - Empirical vancomycin for MRSA
    - MIC of 1 µg/mL, MIC of 1.5 µg/mL, MIC of 2 µg/mL
    - Inappropriate empirical treatment

• Inclusion:
  - MRSA bacteremia

• Endpoints:
  - Mortality

7. How should we be dosing vancomycin now?

• Continuous infusion
  - In ICU patients
    - Randomized, cross-over study
    - No significant in vitro killing activity
    - Better serum bactericidal titres >1:8 in continuous infusion
  - In healthy subjects
    - No difference in bactericidal titres between groups
  - In severe staphylococcal infections
    - No difference in patient outcome

• Summary
  - Continuous infusion unlikely to improve outcome

7. How should we be dosing vancomycin now?

Continuous infusion

- In ICU patients
  - Randomized, cross-over study
  - No significant in vitro killing activity
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- In healthy subjects
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- In severe staphylococcal infections
  - No difference in patient outcome

• Summary
  - Continuous infusion unlikely to improve outcome


7. How should we be dosing vancomycin now?

ANSWER:
- AUC/MIC is best PK/PD parameter.
  - AUC/MIC >400
- MIC of 2 µg/mL may be more difficult to treat.
- Paradigm shift
  - Dosing and monitoring for efficacy rather than toxicity

ANSWER: (continued)
- Dose
  - Troughs of 15-20 mg/L will achieve AUC/MIC >400 if MIC is ≤1 mg/L.
  - For severe infections, aim for troughs of 15-20 mg/L.
  - Loading dose may be considered in seriously ill.
  - For MIC ≥2 mg/L
    - AUC/MIC >400 is not achievable with conventional dosing methods if renal function is normal.

8. Is vancomycin a good drug for MRSA?

Clinical and Laboratory Standards Institute (CLSI)
(Mohr et al. CID 2007:44)
- Changed vancomycin breakpoint for S. aureus
- Higher clinical failures with MIC of 4 µg/mL

<table>
<thead>
<tr>
<th>PERIOD</th>
<th>SUSCEPTIBLE (µg/mL)</th>
<th>INTERMEDIATE (µg/mL)</th>
<th>RESISTANCE (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE 2006</td>
<td>≤4</td>
<td>8-16</td>
<td>≥32</td>
</tr>
<tr>
<td>PRESENT</td>
<td>≤2</td>
<td>4-8</td>
<td>≥16</td>
</tr>
</tbody>
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VISA
(Vancomycin-intermediate S. aureus or Glycopeptide-intermediate S. aureus)
- In 1996, first case in Japan
- Mechanism
  - Overproduction of D-Ala-D-Ala
  - Thickened cell wall
  - Binds vancomycin
  - Reduce availability to intracellular targets
- Epidemiology
  - Dialysis, MRSA bacteremia with CVC/graft, prolonged vancomycin
  - MIC ≥4 µg/mL rare

hVISA
(Heteroresistant VISA)
- VISA subpopulation within a susceptible S. aureus population
- Clinical significance unclear
  - In retrospective study, prolonged bacteremia 3 wks longer
  - Unclear if heteroresistance caused prolonged bacteremia or vancomycin caused hVISA emergence
- Laboratory
  - Difficult to identify; no validated test
  - CLSI lowered MIC breakpoint to 4 µg/mL to identify
  - Loading doses not studied; may benefit in preventing hVISA
8. Is vancomycin a good drug for MRSA?

VRSA
(Vancomycin-resistant S. aureus)
- First reported in 2002 in Michigan
- Mechanism
  - Plasmid-mediated transfer of VanA gene from VRE
  - Synthesis of alternative cell wall terminal peptide (D-ala-D-lac) rather than D-ala-D-ala

8. Is vancomycin a good drug for MRSA?

MRSA
- Identified in 1959
- Mechanism
  - mecA gene on staphylococcal cassette chromosome (SCCmec)
  - Encodes for PBP 2a; low affinity for beta-lactams
- 5 types of SCCmec
  - HA-MRSA (multidrug resistant)
    - I, II, and III
  - CA-MRSA (not multidrug resistant)
    - IV and V

8. Is vancomycin a good drug for MRSA?

MRSA
Number of Patients Colonized/Infected with MRSA, Ontario, 1992-2005

8. Is vancomycin a good drug for MRSA?

ANSWER:
- IN CANADA, vancomycin is an effective agent for the treatment of MRSA.
- Alternative drugs
  - Ceftibiprole
  - Daptomycin
  - Linezolid
  - Tigecycline
  - Dalbavancin, Oritavancin, Telavancin…

9. What are the optimal dosing and monitoring strategies for vancomycin?

Cases
9. What are the optimal dosing and monitoring strategies for vancomycin?

Case 1
– 25 years-old, 70 kg male develops a surgical site wound infection post right humerus fracture repair. The infection appears to be superficial. Wound cultures from purulent drainage shows 3+polys, 3+ Gram+ cocci and grows MRSA susceptible to vancomycin. You recommend initiating vancomycin and would like to treat for 7 days.

1. What dosage would you recommend?
2. What levels would you target?
3. Would you recommend drawing levels?
4. How would you monitor this patient?
5. What if this patient were morbidly obese?

1. What dosage would you recommend?
   a) Vancomycin 1 g (15 mg/kg) IV q12h
   b) Vancomycin 1 g (15 mg/kg) IV q8h
   c) Other

2. What levels are you targeting?
   a) 5-10 mg/L
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     e) Other

– How would you monitor this patient?
   a) For clinical resolution without levels.
   b) For clinical resolution with a peak and trough level immediately following first dose
   c) For clinical resolution with a peak and trough level at steady state
   d) For clinical resolution with a trough level at steady state
   e) Other
9. What are the optimal dosing and monitoring strategies for vancomycin?

Case 2
- 70 years-old, 70 kg patient is admitted with a MRSA bacteremia. ECHO is suggestive of a mitral valve endocarditis. Your team wishes to initiate vancomycin for a total of 6 weeks.

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Case 3
- 68 years-old, 70 kg female admitted with decreased LOC and symptoms of meningismus. She has a history of anaphylaxis with penicillin. The CSF Gram stain reveals 2+ polys and 2+ Gram-positive cocci. The ED physician wishes to initiate vancomycin.

1. What dosage would you recommend?
2. What levels would you target?
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4. How would you monitor this patient?
5. What if her renal function deteriorates?

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5. What if her renal function deteriorates?
   a) Empirically adjust dose based on estimated renal function.
   b) Draw a peak and trough.
   c) Draw a random level.
   d) It depends.

10. Are vancomycin levels relevant in my clinical practice?

Guidelines
1. University of Kentucky
2. American Society of Health-System Pharmacy, Infectious Diseases Society of America, & Society of Infectious Diseases Pharmacists (ASHP, IDSA, and SIDP)
3. Tim and Mary

University of Kentucky
(http://www.hosp.uky.edu/pharmacy/gsp/default.html)
• When to do levels
   - NO levels
     • Adult patients <60 yrs with normal body weight, stable renal function with CrCl >40 mL/min and short course of therapy (<7 days)

University of Kentucky
(http://www.hosp.uky.edu/pharmacy/gsp/default.html)
• When to do levels
  - 2 steady-state levels
    (Peak and trough or 2 post-peak; modified Sawchuk-Zaske)
      • Higher doses of vancomycin required to penetrate site of infection or treat life-threatening infection
        – Meningitis, endocarditis, pneumonia, and sepsis
      – For above situations
        • 1 peak/random (modified Sawchuk-Zaske; if level drawn after 1st dose)
        • 3 levels (trough, peak, and post-peak; Sawchuk-Zaske; if levels not drawn at steady state)
10. Are vancomycin levels relevant in my practice?

University of Kentucky

- What levels to target
  - Peak 20-40 µg/mL (at 1 hr after end of 1 hr infusion)
  - Trough 5-15 µg/mL
  - Trough 15-20 µg/mL for life-threatening infections

ASHP, IDSA, SIDP guidelines

- When to do levels
  - Monitor troughs (only)
    - Patients receiving aggressive dosing or at high risk of toxicity (IIIB)
    - Unstable renal function (IIB)
    - Prolonged courses of therapy >3-5 days (IIB)
    - At least one steady-state trough (IIB)
    - Once weekly trough concentrations for targets of 15-20 mg/L (IIIB)
    - More frequent in hemodynamically unstable patients (IIIB)

Tim and Mary’s Guidelines

- What levels to target
  - For complicated infections
    - Minimum trough should be >10 mg/L to avoid development of resistance (IIIB)
    - 15-20 mg/L recommended to improve penetration
  - What dose to give
    - 15-20 mg/kg TBW q8-12h in normal renal function
      - When MIC ≤1 mg/L (IIIB)
    - In complicated infections
      - Loading dose of 25-30 mg/kg TBW (IIIB)

- What levels to target
  - 5-15 mg/L in uncomplicated infections
    - Examples
      - If MIC=1, then target trough for "free vanco" would be 4 to 5 mg/L; total vanco target would be 8-10 mg/L;
      - If MIC=1.5, then total vanco target would be 12-15 mg/L.
  - 15-20 mg/L in severe infections

- When to do levels
  - Troughs for treatment >7 days
  - Peak* and trough in severe infections, concomitant nephrotoxic and/or ototoxic agents, unstable renal function, obesity, pregnancy, and pediatrics

*Main reason for drawing peaks would be to calculate pharmacokinetic parameters to optimize dosages, rather than for targeting a specific peak.

- Identify early on if dose requires escalation
- Prevent perpetuation of dosing error
- Initial calculation of pharmacokinetic parameters to avoid further chasing of levels
- Estimate renal function (e.g. pediatrics)
10. Are vancomycin levels relevant in my practice?

- Will the results of the drug assay make a significant difference in the clinical decision-making process (i.e. provide more information than sound clinical judgment alone)?

**VANCOMYCIN IN 2008:**
Have We Figured It Out Yet?

**ANSWER:**
We've figured out some, but not all!
After 52 years, we still have more questions than answers!!

1) How do we best achieve AUC/MIC targets?
2) How do we optimize therapy by using AUC/MIC values?
3) Do trough concentrations <10 mg/L lead to resistance?
4) Do trough concentrations >20 mg/L lead to toxicity?
5) What is the relevance of free (unbound) vancomycin concentrations?
6) Etc., etc., etc…

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- Sheryl A. Zelenitsky, BScPhm, PharmD
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QUESTIONS?

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Absence of proof is not proof of absence.

-William Cowper