IS IT TIME TO REPLACE VANCOMYCIN?
A discussion stemming from patient cases

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Disclosure

Daniel J. G. Thirion, Pharm.D., FCSHP

None to declare
Learning Objectives

1. Describe the current evidence supporting the use of vancomycin for treatment of complicated MRSA infections
2. Describe the limits of using vancomycin
Properties of the Ideal Antibiotic to Treat MRSA Infections

- Rapid bactericidal killing
- Excellent tissue penetration
- Consistent pharmacokinetics and pharmacodynamics that allow for predictable dosing
- Low potential for development of resistance on treatment
- Low side effect profile
- Demonstrated clinical and microbiological efficacy
Vancomycin Under the Microscope

- Do we understand the vanco? (*in vitro*)
- Resistance (visa, hvisa, mic creep)
- Vanco levels? (Pk)
- Pharmacodynamics
- Clinical failures?
- Dosing (loading dose)
# Vancomycin MICs

<table>
<thead>
<tr>
<th></th>
<th>NCCLS (previous)</th>
<th>CLSI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S</strong></td>
<td>$\leq 4 \mu g/mL$</td>
<td>$\leq 2 \mu g/mL$</td>
</tr>
<tr>
<td><strong>I</strong></td>
<td>8-16 $\mu g/mL$</td>
<td>4-8 $\mu g/mL$</td>
</tr>
<tr>
<td><strong>R</strong></td>
<td>&gt;32 $\mu g/mL$</td>
<td>$\geq 16 \mu g/mL$</td>
</tr>
</tbody>
</table>
IMPACT OF MODERATE VS HIGH-INOCULUM MRSA ON ACTIVITIES OF ANTIMICROBIALS

Laplante K, et al. AAC 2004;48:4665
Vancomycin Resistance in *S. aureus* is rare in Canada

- **VISA**
  - Intermediate susceptible, 8-16 ug/mL
  - Thickened cell wall

- **VRSA**
  - Vancomycin resistant, 1st reported 2002
  - *vanA* gene

- **hVISA**
  - Subpopulation of susceptible *S. aureus* (MRSA) that may express intermediate resistance
hVISA may not be Clinically Relevant

- Outcomes of hVISA-MRSA compared to vanco susceptible MRSA: prospective evaluation

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

Michael I. Retnakar, Ben Longo, John C. Rotschafer, Robert Moeller, Jr., William Craig, Marianne Billeter, Joseph R. Dalotuio, and Donald R. Livine

Vancomycin is a glycopeptide antibiotic that has been in clinical use for nearly 50 years as a penicillin alternative to treat penicillin-producing strains of Staphylococcus aureus. It is one of the most widely used antibiotics in the United States for the treatment of serious gram-positive infections involving methicillin-resistant S. aureus (MRSA). Early use of vancomycin was associated with a number of adverse effects, including infusion-related toxicities, nephrotoxicity, and possible osteotoxicity. Upon further investigation, it appears that the impurities in early formulations of vancomycin caused many of these adverse events. Its overall use was curtailed significantly with the development of semi-synthetic penicillins (e.g., methicillin, oxacillin, nafcillin) that were considered less toxic. However, the steady rise in the number of MRSA infections since the early 1990s has once again brought vancomycin into the forefront as the primary treatment for infections caused by this organism.

Over the years, vancomycin has been one of the most studied antibiotics. Extensive pharmacokinetic studies in a variety of patient populations and the availability of commercial drug assays have allowed clinicians to target serum vancomycin concentrations precisely in a relatively narrow...
TDM of Vancomycin

- 15-20 mg/kg/dose ABW IV q8-12h in normal renal function (BII)
- Loading dose of 25-30 mg/kg (ABW) in seriously ill patients (CIII)
- 1 g IV q12h acceptable for SSTI and normal renal function, non obese (BII)
- Monitor trough levels (not peaks) (BII)
- Aim for 15-20 mg/L (BII)

Target Pharmacodynamics is Known

- Associated with $\text{AUC24/MIC} \geq 400$
- Clinical and bacteriologic response superior when threshold is reached ($p=0.0046$)
  - More rapid bacterial eradication ($p=0.0402$)
  - Relationship between time to bacterial eradication and time to improvement in pneumonia score ($p<0.0001$)

# Newer Alternative Agents

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Class</th>
<th>NOC Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinupristin-Dalfopristin</td>
<td>Streptogramin</td>
<td>1999</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Oxazolidinone</td>
<td>2001</td>
</tr>
<tr>
<td>Tigecycline (black box by FDA)</td>
<td>Glycylcycline</td>
<td>2006</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Lipopeptide</td>
<td>2007</td>
</tr>
<tr>
<td>Ceftobiprole (rejected by FDA)</td>
<td>Cephalosporin</td>
<td>2008</td>
</tr>
</tbody>
</table>
Vancomycin on Trial

- Approved for use in 1958
- Increasing and now extensive use since 1960s
- Is there an alternative that has appropriately demonstrated superiority?
- Does resistance preclude the use of vancomycin in Canada?
- Is there an alternative that has a demonstrated better safety profile?
- Is there a more reasonable economic way of doing things?
Daptomycin vs Vancomycin/Gent for MRSA Bacteremia or Right-Sided Endocarditis

Figure 1. The Kaplan–Meier plot of overall survival. Wilcoxon $P = 0.25$, log-rank $P = 0.42$. 

“Cross-resistance” with Vancomycin and Daptomycin

Membrane permeability is compromised

Table 1. Effect of increasing vancomycin MICs on daptomycin susceptibility for Staphylococcus aureus isolates.

<table>
<thead>
<tr>
<th>Vancomycin MIC, μg/mL</th>
<th>Daptomycin MIC ≤1 μg/mL</th>
<th>Daptomycin MIC ≥2 μg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2</td>
<td>812 (97)</td>
<td>30 (3)</td>
</tr>
<tr>
<td>4</td>
<td>11 (20)</td>
<td>43 (80)</td>
</tr>
<tr>
<td>8–16</td>
<td>1 (7)</td>
<td>15 (93)</td>
</tr>
<tr>
<td>≥32</td>
<td>5* (100)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Note: * Five S. aureus isolates with vanA-mediated resistance.

However, vanA-mediated resistance does not seem to impact daptomycin susceptibility

Tenover FC et al. Int J Antimicrob Ag 2009;33:564
Bennett JW et al. Diagn Microbiol Infect Dis 2008;60:437
Facts about nosocomial pneumonia (NP)

- Mortality rates in NP vary depending on the patient population, with HAP mortality as high as 30% to 60%, lower in clinical drug trials 18-25%, higher in epidemiological trials.

- Mortality in VAP varies from 24% to 60%, with the higher mortality rates occurring when VAP is accompanied by acute lung injury (ALI) or adult respiratory distress syndrome (ARDS).

- The majority of deaths that occur during or after an episode of NP are commonly related to the underlying medical conditions rather than being directly attributable to NP.

Linezolid vs Vanco in MRSA pneumonia
Mortality: Kaplan-Meier Plot – 60 Days: ITT

94 subject deaths (15.7%) in linezolid arm
100 subject deaths (17.0%) in vancomycin arm

Wunderink RG, et al. CID 2012;54:621
Vancomycin Trough Levels - HA-MRSA Pneumonia

Trial not designed to evaluate vancomycin troughs

Wunderink RG, et al. CID 2012;54:621
Emergence of resistance with linezolid

Garcia MS, et al. JAMA 2010;303:2260
Vancomycin 1g q12 h or linezolid 600 mg q12h IV/po (if MRSA present or suspected)

"Additional studies are warranted to advise clinicians of the optimal agents and dosages for treating P aeruginosa and MRSA HAP and VAP."
Safety: Choose your Poison

- RCT-open label trial: MRSA infections (pneumonia, SSTIs, sepsis) in Japan

<table>
<thead>
<tr>
<th>AE</th>
<th>Linezolid, n = 100</th>
<th>Vancomycin, n = 51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients reported (%)</td>
<td>55 (55.0)</td>
<td>22 (43.1)</td>
</tr>
<tr>
<td>Total (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lab test abnormal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diarrhoea</td>
<td>6 (6.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>liver function abnormal</td>
<td>10 (10.0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>renal function abnormal</td>
<td>6 (6.0)</td>
<td>4 (7.8)</td>
</tr>
<tr>
<td>anaemia*</td>
<td>13 (13.0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>leucopenia</td>
<td>7 (7.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>thrombocytopenia*</td>
<td>19 (19.0)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>hyponatraemia</td>
<td>7 (7.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>rash</td>
<td>2 (2.0)</td>
<td>3 (5.9)</td>
</tr>
</tbody>
</table>

- V: Reversible nephrotoxicity
- L: Reversible hematological abnormalities
- L: longer exposure neurotoxicity

Safety Monitoring

- Vancomycin
  - Nephrotoxicity
  - DI: nephrotoxic meds
- Daptomycin
  - LFTs, CK
  - DI: statins, rhabdomyolysis
- Linezolid
  - Plts
  - DI: MOAI, SSRIs
Closing Position

- Require appropriate demonstration (studies) to satisfy criteria of superior efficacy and equivalent or superior safety
- Require epidemiology of severe infections caused by MRSA (local)
- Require outcomes data on severe infections according to vancomycin dosing and MIC (international)