Vancomycin

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Objectives

- Identify the mechanism/s of action and resistance (VRE) of vancomycin. Be able to define resistance using MIC values.
- Identify whether vancomycin exhibits concentration dependent or independent bacterial killing and an appropriate monitoring parameter/s.
- Be able to identify CDC (MMWR) approved and non-approved uses of vancomycin.
- Be able to identify an appropriate pharmacokinetic method to characterize vancomycin as well as appropriate values for peak & trough concentrations.
- Be able to identify merits and drawbacks to monitoring patients with serum concentrations.
- Be able to identify the impact of CDP-1 on the therapeutic monitoring of vancomycin and what can be done to prevent the problem.
- Identify 3 relatively common adverse drug reactions associated with vancomycin.
Thanks to PENICILLIN
...He Will Come Home!
Vancomycin Background

- By the 1950’s, it was apparent that penicillin was not going to remain effective for Staphylococci
- Prompted search for biologic source for new drug
- Came from a soil sample containing *S. orientalis* received from a medical missionary in Africa
- Because of impurities in initial extracts, originally called “Mississippi Mud”
- Named vancomycin because it was going to vanquish penicillinase producing *S. aureus*
- Impurities associated with infusion reactions
Vancomycin General Use Data

Kirst, HA AAC 42:1305,1998

- Approximately 800,000 patients receive vancomycin each year
- Use approximates $125-150 million in the USA and $250 million worldwide
- 74% of use is in the ICU and 24% non-ICU
- 42% is empiric, 35% for documented infections, & 23% for prophylaxis
Vancomycin

- Introduced in the mid to late 1950’s
- Over the years has undergone several different formulation changes
- Bactericidal drug with a limited antimicrobial spectrum
- Primarily used for Gram positive infections
S. aureus #29213 vs Vancomycin Under Aerobic Conditions

Log CFU/mL

Growth control with alpha phase
Growth control
40 µg/mL with alpha phase
40 µg/mL
20 µg/mL
10 µg/mL
5 µg/mL

Time (Hours)

Vancomycin Pharmacodynamic Profile

- Concentration independent killer
  - Goal is to maintain unbound $C_{p-min} > MIC$
- Long terminal half-life
  - Avoid need for continuous infusion
- Large distribution volume
  - Avoid need to drive drug to infected site
    - Possible exceptions meningitis & endocarditis
- Low protein binding
  - High free fraction of active drug
Vancomycin

- Clinically effective and well tolerated
- Favorable pharmacokinetic profile
- PAE of several hours for gram positive bacteria
- Bacterial resistance increasing
  - Enterococci and S. haemolyticus
- Becoming more dependent on vancomycin for resistant organisms
Multiple Mechanisms of Action for Vancomycin

- Prevents the polymerization of the phosphodisaccharide-pentapeptide-lipid complex – primary effect
- Alters permeability of the cell membrane
- Selectively inhibits RNA synthesis
- Bacterial resistance to all 3 modes of action unlikely

Antimicrobial Resistance Patterns

- 80 to 90% of *S. aureus* and *S. epidermidis* are beta-lactamase producers
- 2 to 50% of *S. aureus* are MRSA
- 10-80% of *S. epidermidis* are MRSE
- Trend of *S. haemolyticus* and enterococci toward vancomycin resistant
- Concern that enterococcal plasmid will be transferred to *S. aureus* (VRSA)
# Enterococcal Vancomycin Resistance

<table>
<thead>
<tr>
<th></th>
<th>Van A</th>
<th>Van B</th>
<th>Van C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>Resistant</td>
<td>Sensitive</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Plasmid</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Inducible</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Species</td>
<td><em>E. faecium</em></td>
<td><em>E. faecium</em></td>
<td><em>E. caselilavus</em></td>
</tr>
<tr>
<td></td>
<td><em>E. faecalis</em></td>
<td><em>E. faecalis</em></td>
<td><em>E. gallinarum</em></td>
</tr>
</tbody>
</table>

*Jones R: Chall Infect Dis 1(3)1-6, 1993*
Vancomycin as an Antibiotic
Vancomycin: The Gold Standard

- Until the introduction of quinupristin/dalfopristin & linezolid, vancomycin was the last line of defense for MRSA.
- Because vancomycin served as a product of last resort, the drug has not rigorously evaluated in regards to efficacy or toxicity.
- For these reasons, we may have an altered perception of the drug.
Is Vancomycin Bigger, Better, & More Powerful?

- Karchmer Editorial

- Data suggests
  - Vancomycin kills bacteria at a slower rate than beta-lactam
  - Higher mortality with vancomycin treated patients vs beta-lactam
    - Gonzalez: CID 29:1171, 1999
  - Cloxacillin/gentamcin significantly better than Vancomycin or Teicoplanin/gentamicin in short course therapy of R-Endo
    - Fortun: CID 33:120-125, 2001
  - Vancomycin is an independent risk factor for the development of gram negative bacteremia
  - Independent risk factor for VRE
Antimicrobial Activity

Vancomycin vs. Nafcillin

- Poorer clinical outcome for vancomycin in bacteremia and endocarditis
- Longer duration of bacteremia
- Should vancomycin be used for MSSA infections?

Median Duration of Bacteremia & Fever in MRSA Endocarditis


<table>
<thead>
<tr>
<th></th>
<th>Median Duration</th>
<th>Median Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bacteremia Days</td>
<td>Fever Days</td>
</tr>
<tr>
<td>All</td>
<td>9 (6-11)</td>
<td>7 (4-9)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>7 (5-11)</td>
<td>7 (3-8)</td>
</tr>
<tr>
<td>Vanc/Rifampin</td>
<td>9 (6-13)</td>
<td>7 (3-10)</td>
</tr>
<tr>
<td>Left Sided</td>
<td>9 (3-10)</td>
<td>7 (N/A)</td>
</tr>
<tr>
<td>Right Sided</td>
<td>7 (5-11)</td>
<td>8 (3-10)</td>
</tr>
</tbody>
</table>

(95% CI)
# Vancomycin vs. Nafcillin for S. aureus

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Antibiotic</th>
<th>Duration +BC</th>
<th>Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korzeniowski</td>
<td>N</td>
<td>Mean 3.4d</td>
<td>22/35 (63%)</td>
</tr>
<tr>
<td>(1982)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chambers</td>
<td>N+T</td>
<td>19/20 sterile 48hrs</td>
<td>47/50 (94%)</td>
</tr>
<tr>
<td>(1988)</td>
<td>V+T</td>
<td>1 pt (+BC 12&amp;14d)</td>
<td>1/3 (33%)</td>
</tr>
<tr>
<td>Small (1990)</td>
<td>V</td>
<td>2Pt(+BC 7-16d)</td>
<td>8/13 (62%)</td>
</tr>
<tr>
<td>Levine (1991)</td>
<td>V</td>
<td>Median 7d</td>
<td>18/22 (82%)</td>
</tr>
<tr>
<td></td>
<td>V+R</td>
<td>Median 9d</td>
<td>18/20 (90%)</td>
</tr>
</tbody>
</table>

Karchmer Editorial (1991)
32 MRSA & 54 MSSA bacteremic pneumonia cases were compared

MRSA patients were older & had predisposing conditions

Mortality was significantly higher in MSSA patients treated with vancomycin vs cloxacillin, 47% vs 0%, respectively.

Multivariate analysis mortality odds ratio were as follows for these clinical variables septic shock (OR=61), vancomycin treatment (OR=14), & respiratory distress (OR=8)
Empiric Use of Vancomycin Associated with Increased Risk of Gram Negative Bacteremia
Van Houten MA Pediatr Infect Dis J 20:171-177, 2001

- Retrospective case-controlled trial evaluated empiric vancomycin use for suspected bacteremia
- 105 pediatric patients with GNB & 225 control patients
- Risk factors for GNB
  - Prior antibiotics, antacids, steroids, prior surgery, ventilation, TPN, invasive procedures, & intensity score
  - Vancomycin only antibiotic that remained positively associated with GNB in multivariant analysis
  - Vancomycin OR 3.88
  - Restricting analysis to specific subgroups did not change the relationship of vancomycin with GNB
Appropriate Utilization of Vancomycin
& Preventing the Emergence of Resistance
Appropriate Use of Vancomycin

MMWR (Volume September 22, 1995)

- CDC: Federal Register (May 17, 1994). Preventing the Spread of Vancomycin Resistance Report from the Hospital Infection Control Practices Advisory Committee
  - Vancomycin < Beta-lactams for staphylococci
  - Vancomycin when serious beta-lactam allergy
  - AAC fails to respond to metronidazole
  - SBE prophylaxis per AHA
  - Antibiotic prophylaxis for implantation of prosthetic device
Inappropriate Use of Vancomycin

MMWR (Volume 44  September 22, 1995)

- Routine surgical prophylaxis
- Empiric therapy for neutropenic patients
- 1 + BC for coagulase negative staphylococci
- Continued empiric usage
- Prophylaxis for central or local catheter
- Selective gut decontamination
- MRSA colonization
- Primary treatment of AAC
- Routine therapy or prophylaxis for CAPD or HD
- Topical application or irrigation
Vancomycin Prescribing Patterns

- Retrospective study May 1993-April 1994, N = 135 patients
- Appropriate or inappropriate usage defined using CDC criteria
- 83/135 (61%) of vancomycin usage was inappropriate
- Question whether U.S. hospitals doing an adequate job controlling usage

Johnson SV et al. Pharmacotherapy 1995
Wide Overuse of Antibiotic Cited in Study
WSJ (September 4, 1997)

- 7,147 medicare patients in 131 hospitals studied in 1995
- 63% of vancomycin orders did not follow CDC guidelines
- No difference in comparing large urban teaching centers to small rural hospitals
- Beth Israel-Deaconess - fliers & lectures did not alter prescribing behavior
Vancomycin Resistant Staphylococci
Vancomycin Susceptibility

- **Sensitive (VSSA)**
  - Vancomycin MIC < 4 mg/L

- **Intermediate (VISA or GISA)**
  - Vancomycin MIC = 8-16 mg/L

- **Resistant (VRSA)**
  - Vancomycin MIC > 32 mg/L
Vancomycin Resistant S. aureus

Hiramatsu K et. al.. JAC 40:135-146, 1997
MMWR July 11, 1997: p. 624-629

- Reported strain called Mu-50
- Homoresistant
- Negative for vanA, vanB, vanC1, vanC2, & van C3
- Mechanism of resistance unknown
Vancomycin Intermediate S. aureus (VISA) or GISA

- Strains reported in Michigan and New Jersey
  - NEJM 340:493, 1999
- Strain reported in New York
  - NEJM 340:517, 1999
- VISA’s all different organisms with different antibiotic susceptibility
- All patients would have met CDC usage criteria
  - MRSA infection + VRE colonization or infection
  - Long term therapy
  - Renal impairment in many patients
Vancomycin Tolerance in S. pneumoniae

- Absence or malfunction of $vnc\ S$ gene which renders S. pneumoniae sensitive to vancomycin
- Problem in triggering autolysis
- Mutant strains appear better DNA scavengers
  - Promote more antibiotic resistance
  - Significant problem to have a community pathogen with this capability
Pharmacokinetic Properties of Vancomycin
EXIT 80
COUNTY 29
Alpha
Infusion Distribution ($\alpha$) and Elimination

Distribution ($\alpha$) and Elimination

Elimination ($\beta$)

Log Serum Concentration

$C_P(t) = Ae^{-\alpha t} + Be^{-\beta t}$

Central Compartment $V_C$

Peripheral Compartment $V_P$

$K_0$

$K_{12}$

$K_{21}$

$K_{EL}$

Time
One Compartmental Modeling of Vancomycin

- Infusion
- True Peak
- Distribution or Alpha Phase
- Elimination or Beta Phase
One Compartmental Modeling

- Regression line is a hybrid of the alpha & beta phase
- Pharmacokinetic parameters are a mythical value
  - No literature based reference point for “Cpmax”
    - Peak is not the true peak value
  - True Vd not measured
  - Half-life is underestimated
Vancomycin Peak Concentration

- Geraci suggested range 30-40 mg/L
- Sparse data to document range
- Probably plays little or no role regarding efficacy or toxicity
- Clinicians obtain “peak” vancomycin concentrations 0 to 3 hours post infusion
Vancomycin Trough Concentration

- Geraci suggested range 5 to 10 mg/L
- Also, little if any data to support this recommendation
- Probably a useful monitoring parameter
  - Concentration independent killer
  - Level of bacterial sensitivity
Therapeutic Drug Monitoring of Vancomycin
Vancomycin Dosing Methods

- Empiric (500mg Q6H or 1gm Q12H)
- Body weight (20-40 mg/kg/day)
- Nomogram (Based on no, 1, or 3 compartment PK’s)
  - Nielsen
  - Matzke
  - Moellering
  - Lake
- Bayesian
# Vancomycin Dosing Methods

**Zokufa, H.Z. et. al. Pharmacother 9:10-16,1989**

<table>
<thead>
<tr>
<th>Cpmax (mg/L)</th>
<th>Matzke</th>
<th>Neilsen</th>
<th>Moellering</th>
<th>Lake-Peterson</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40</td>
<td>30(100%)</td>
<td>2(7%)</td>
<td>3(10%)</td>
<td>6(20%)</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>0(0%)</td>
<td>24(80%)</td>
<td>24(80%)</td>
<td>11(36%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cpmin(mg/L)</th>
<th>Matzke</th>
<th>Neilsen</th>
<th>Moellering</th>
<th>Lake-Peterson</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 10</td>
<td>6(20%)</td>
<td>4(13%)</td>
<td>2(6%)</td>
<td>7(23%)</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>19(64%)</td>
<td>19(64%)</td>
<td>15(50%)</td>
<td>11(36%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cpmax and Cpmin (mg/L)</th>
<th>Matzke</th>
<th>Neilsen</th>
<th>Moellering</th>
<th>Lake-Peterson</th>
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</thead>
<tbody>
<tr>
<td>30-40 &amp; 5-10</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>1(3%)</td>
<td>7(23%)</td>
</tr>
</tbody>
</table>
Vancomycin Monitoring

- Use CDC clinical indication criteria
- May need to monitor to prevent VISA
- Cpn = 5 to 10 mg/L probably appropriate
  - Protein binding approximately 40%
  - Gram positive MIC’s 1.5 mg/L
  - Nomograms produce Cpmin < 5 mg/L in 50-60% of patients
  - If Cpmin 5-10 mg/L, 10-15 mg/kg dose will not produce “toxic” Cpmax
Vancomycin Dosing:

Dose
(mg/kg/24 hours) = 0.227 CrCl + 5.67

<table>
<thead>
<tr>
<th>CrCl (ml/min per 70kg)</th>
<th>Dosage Interval (hours)</th>
</tr>
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<tbody>
<tr>
<td>&gt; 65</td>
<td>8</td>
</tr>
<tr>
<td>40-65</td>
<td>12</td>
</tr>
<tr>
<td>20-39</td>
<td>24</td>
</tr>
<tr>
<td>10-19</td>
<td>48</td>
</tr>
</tbody>
</table>

Rodvold et al. AAC 32:848, 1988
Vancomycin Analysis

- In-vitro & in-vivo vancomycin breaks down over time to form CDP-1
- Both vancomycin (factor B) and CDP-1 measured as vancomycin by TDx™ assay
  - Vancomycin concentration overstated by 20-50%
- In-vivo problem function of time and patient’s renal function

Saunders NJ 34th ICAAC (Abstract A31)
Vancomycin FPI Assays
Roberts, W.L. Pharmacother 1999

FPI Methods

- **Abbott AxSYM, Abbott TDx/ TDxFLx, Oxis/ Innofluor-FPIA, & Roche Cobas Integra**
  - 1232/ 2400 labs using Abbott AxSYM
  - Will cross react with CDP
- **Abbott AxSYM Vancomycin II**
  - Monoclonal antibody not affected by CDP comparable to HPLC & EMIT
Toxicity of Vancomycin
How often does vancomycin therapy fail or has to be discontinued?

inezolid compassionate use protocol:

9 sites enrolled 671 patients treating 700 infections

physician reason for enrollment

- 110 patients vancomycin allergy (15.7%)

• Prior to alternative antibiotics, if patients were allergic to vancomycin we would desensitize patients

M. Birmingham 2001
Ototoxicity and Nephrotoxicity of Vancomycin

- Nephrotoxicity maybe associated with Cpmin > 20 mg/L (limited data)
- Geraci suggested ototoxicity associated with peaks of 80 to 100 mg/L
  - 1958 report, vancomycin serum concentrations obtained 3 to 6 hours after administration
  - Other reports have suggested ototoxicity with Cpmax < 80 mg/L
    - Levels drawn 1 hr or more after infusion
Red Neck or Red Man Syndrome

- Flushing/maculopapular rash of upper body with hypotension
  - Difference between patients & volunteers
- Usually associated with rapid (>12 mg/Kg/Hr) IV infusions
  - Also reported with slower infusions
- Conflicting reports that reaction the result of histamine release
  - Other chemical mediator may be responsible
Conclusions

- Vancomycin is probably not the antibiotic most clinicians believe it to be:
  - Kills gram positive organisms slowly
  - May contribute to the risk of mortality or therapeutic failure
  - May contribute to gram negative super-infection
  - Independent risk factor for VRE
  - Complicated pharmacokinetic profile
  - Real risks of toxicity or intolerance
  - Compliance with MMWR usage guidelines are at best mixed and the guidelines themselves need to be updated