Optimizing Pharmacy to Dose Services in Special Populations

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Objectives

• Describe the basic pharmacokinetic and pharmacodynamics principles of vancomycin
• Predict how pharmacokinetic changes in specific patient populations may alter vancomycin concentrations
• Strategize dosing methods to expand antimicrobial stewardship efforts
History

- **1956**
  - Soil from Broneo Jungle
  - *Streptomyces orientalis*

- **1958**
  - 05865 approved by FDA
  - Vancomycin “to vanquish”
  - Mississippi Mud

- **1961**
  - First case of MRSA

- **1970s**
  - MRSA increases

- **1980s**
  - VRE

- **1990s/2000s**
  - C. Difficile, VISA, VRSA
  - CA-MRSA

Mechanism of Action

• Tricyclic glycopeptide antibiotic
• Inhibits the bacterial cell wall synthesis by binding to D-alanyl-D-alanine portion of the peptidoglycan wall
  • Alter cell wall permeability
  • Selectively inhibits RNA synthesis
Spectrum

• Gram positive
  • *Staphylococcus* spp.
  • *Streptococcus* spp.
  • *Enterococcus* spp.
  • *Clostridium difficile*
  • *Peptostreptococcus* spp.

• Bactericidal vs bacteriostatic

• Killing effect increases over time
Clinical Indications

- Skin and soft tissue infections
- Surgical prophylaxis
- Endocarditis
- Osteomyelitis
- Pneumonia
- Prosthetic joint infections
- Sepsis
- Clostridium difficile
- Febrile neutropenia
- Diabetic wound infections
Resistance

- **Vancomycin Resistant *Enterococcus spp.* (VRE)-1986**
  - Acquired or intrinsic van-type genes (A-G)
    - *vanA*
      - Inducible high-level resistance transmitted via conjugation on a transposon
      - Alteration in the terminal binding site from D-ala to D-lac
    - *vanB*
      - Variable inducible resistance transmitted chromosomally or via conjugation
      - Alteration in the terminal binding site from D-ala to D-lac
    - *vanC*
      - Low-level chromosomally mediated vancomycin resistance

Resistance

• **Hetero-resistant S. aureus (hVISA)- 1996**
  • Reduced susceptibility to vancomycin
  • MIC > 1.5 mcg/mL

• **Vancomycin Intermediate S. aureus (VISA)- 1996**
  • Cell wall thickening reduces access to active binding site for *S. aureus*
  • Associated with treatment failure and poor patient outcomes
  • MIC 4-8mg/L

• **Vancomycin resistant S. aureus (VRSA)- 2002**
  • Resistance material VanA gene is transferred through conjugation on plasmids from *E. faecalis*
  • Alters terminal binding site from D-ala to D-ala D-lac
  • MIC’s > 16 mg/L

Pharmacokinetic Concepts
Infusion

• Diluted in 100-500 mL
  • 5% dextrose or 0.9% normal saline

• Infusion generally run between 1-2 hours
  • Maximum infusion rate: 15 mg/min
  • >15 mg/min = higher risk of Red-Man Syndrome

• Intrathecal: 20 mg in preservative free NaCl

Rybak MJ. Am J Health Syst Pharm. 2009; 66:82-98
Absorption

- Intravenous: 100%

- Intraperitoneal: 40%

- Oral: <5%, Poor absorption, used in C. difficile only

- Intramuscular: erratic, not recommended due to tissue necrosis

Distribution

• Volume of distribution: 0.4-1 L/kg
  • \( V(L) = 0.17(\text{age}_{\text{years}}) + 0.22(\text{TBW}_{\text{kg}}) + 15 \)
  • Alterations in extracellular fluid spaces do not result in clinically significant changes in \( V_d \)

• \( V_d \) depends on weight

• Hydrophillic

• Protein binding: 55%
  • Bound to AAG

## Mean Population Volumes of Distribution

<table>
<thead>
<tr>
<th>Age</th>
<th>Volume L/kg (Mean +/- Std Dev)</th>
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<tbody>
<tr>
<td>Adults &gt; 16 - &lt; 65 years</td>
<td>0.62 +/- 0.15</td>
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<tr>
<td>Obese Adults</td>
<td>0.56 +/- 0.18</td>
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<tr>
<td>Adults with Chronic/Severe Renal Impairment</td>
<td>0.9 +/- 0.21</td>
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<tr>
<td>Geriatrics (&gt; 65 years)</td>
<td>0.76 +/- 0.06</td>
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<tr>
<td>Critically Ill</td>
<td>1.69 +/- 2.19</td>
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</table>

Distribution

• Multi-phasic: three distinct phases

• In patients with normal creatinine clearance
  1. Early distributive phase ($\pi$)- ~ 7 minutes
  2. ($\alpha$) - half-life of 30 minutes-1 hour
  3. ($\beta$) - half-life of 3-12 hours
    • Directly influenced by CrCl

Penetration

• Variable
• Affected by inflammation and disease state
  • Brain: 0-48%
  • Bone: 20%
  • Lung tissue: 5-41% (0-12.2 mg/L)
  • Bile: 50%
  • CSF:
    • Inflamed 15% (6.4-11.1 mg/L)
    • Noninflamed <1% (0-0.18 mg/L)
• Skin tissue penetration is lower patients with diabetes
Elimination

• Clearance depends on weight and organ function
  • Alterations in renal function affect vancomycin elimination

• 90% excreted as unchanged drug in the urine when given IV
  • Some renal tubular secretion is evident

• Oral doses are excreted primarily in the feces

• Non-renal elimination has negligible clinical effect

• $T_{1/2} \sim 6$ hours

Controversies in Vancomycin Therapy & Dosing
Pharmacodynamic Killing

- $C_{p_{\text{max}}}$
- AUC = Area under curve
- $T > \text{MIC}$
- MIC = Minimal inhibitory concentration
Pharmacodynamic Killing

- $T > MIC$ - Time Dependent Killing
- Peak/MIC – Concentration Dependent Killing
- $AUC_{0-24h}:MIC$ – Area Under Curve Dependent Killing

Ebert S. 1987 ICAAC
Pharmacodynamic Killing

• Historically time dependent killing

• Area under the curve may be a better parameter for determining outcome
  • $\text{AUC}_{0-24h} : \text{MIC} > 400$ correlates to serum peak of 40 mcg/mL and trough of 15 mcg/mL assuming an MIC < 1 mcg/mL

• Little consensus on which should be maximized in dosing
  • Limited human data

• Consider species, susceptibility, patient
Audience Response

Vancomycin Troughs are drawn for
A. Safety
B. Efficacy
Monitoring

Peak
- Justification?
  - Consider distribution
- Necessary to calculate $\text{AUC}_{0-24h}:\text{MIC}$

Trough
- Most accurate and practical for monitoring efficacy
- Troughs should be maintained $>10$ mg/L
  - 15-20mg/L improve penetration, increase obtaining target concentrations and improve clinical outcomes
- Concentrations $<10$ mg/L avoided
- Issues and problems
Dose

• Doses exceeding 2 grams are still controversial
  • Maximum per day

• Loading doses (LD)
  • (25-30mg/kg/dose) advocated for invasive infections and those with increased Vd

• Maintenance doses (MD)
  • (15-20mg/kg/dose) recommended for treatment

Lodise TP. Antimicrob Agents Chemother. 2008; 52:1330-6
Audience Response

At your facility, what weight do you dose vancomycin from?

A. Actual body weight
B. Ideal body weight
C. Adjusted body weight
D. It depends
Dosing Weight

ABW, IBW, or AdBW?

Actual Body Weight (ABW)

• Obesity >> correlation is not linear, thus a Dosing Body Weight (DBW) is used in obese patient greater than 140% IBW

• DBW = 0.4 (ABW-IBW) + IBW
  • Water in ~30% of adipose tissue
  • Hydrophilic drugs can penetrate and distribute (increases Vd)

Kubiak D. Open Forum Infect Dis. 2015; 2(4)
MIC $> 1$

- For isolates with an (MIC) $\leq 2 \, \mu g/mL$ the patient's clinical response should determine the continued use of vancomycin, independent of the MIC (A-III)
- Other MRSA options
- Consider source of infection and microbiology

Adverse Events

Concentration Independent
- Red Mans Syndrome
- Fever, phlebitis
- Neutropenia

Concentration Dependent
- Nephrotoxicity
  - Monotherapy 5-7%
  - Concomitant nephrotoxic drug 43%
- Ototoxicity
  - Reversible
  - Rare

Cantu TG. Clin Infect Dis. 1994; 18: 533-43
Vancomycin Dosing in Special Populations
Otherwise Healthy

**Standard dose:**
- 15 mg/kg/dose Q12
  - < 50 kg = 750 mg
  - 50 – 75 kg = 1000 mg
  - 75 – 90 kg = 1250 mg
  - 90 kg = 1500 mg
- CrCl >60 ml/min
- Age 21-75 years

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<tr>
<th>Parameter</th>
<th>Change</th>
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<td>Weight</td>
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<td>V_d</td>
<td>0.7 L/kg</td>
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<td>T_{1/2}</td>
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<tr>
<td>Elimination</td>
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<td>Dose</td>
<td>15 mg/kg</td>
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<td>Q12</td>
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MJ is a 55 y/o/m who presents with a LLE cellulitis skin infection. Which weight would you choose to dose the vancomycin on this patient? How would you dose vancomycin in this patient?

- Ht: 5’5”
- Wt: 150kg
- AdBW: 96.9kg
- IBW: 61.5kg
- CrCl 80ml/min
Obesity

- Increased body mass
- Altered free serum vancomycin concentration
- Increased blood flow secondary to cardiac output and blood volume
  - Increased clearance
  - More likely to have renal dysfunction from DM
- Dosing body weight
- Increased $V_d$ not proportional to weight

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<td>$T_{1/2}$</td>
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<td>Dose</td>
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<tr>
<td>Dosing Interval</td>
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Erstad B. and Grant K. Am J Health-Syst Pharm. 2002; 59:2105-10
Kubiak D. Open Forum Infect Dis. 2015; 2(4)
Elderly

- Body composition
  - Decrease total body water
  - Decrease lean body mass
  - Increase body fat
  - Decrease serum albumin
- CrCl often appears falsely elevated
- Pharmacist to dose
  - Opportunity for age protocol instead of standard CrCl protocol
- Barriers

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<td>SCr</td>
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<tr>
<td>CrCl</td>
<td>↑ Falsely, but ↓ overtime</td>
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<tr>
<td>V&lt;sub&gt;d&lt;/sub&gt;</td>
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<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;</td>
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<tr>
<td>Protein Binding</td>
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<td>Elimination</td>
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<td>Dose</td>
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<tr>
<td>Dosing Interval</td>
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Congestive Heart Failure

- Altered drug kinetics
  - Decreased CO
  - Decreased renal blood flow
- Vancomycin clearance decreases with decreasing cardiac function and decreasing CrCl
  - Also predicted by LVEF
- Increase LD
- Decrease MD

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<td>CrCl</td>
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<tr>
<td>$V_d$</td>
<td>↑</td>
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<tr>
<td>$T_{1/2}$</td>
<td>↑</td>
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<tr>
<td>Protein Binding</td>
<td>↓</td>
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<tr>
<td>Elimination</td>
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<tr>
<td>Dose</td>
<td>↑ LD  ↓ MD</td>
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<tr>
<td>Dosing Interval</td>
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BC is a 49 y/o/f with a history of COPD and T1DM. She was recently discharged from the hospital 8 days ago with an Rx for Levaquin and is seen today due to SOB. How would you dose vancomycin in this patient?

- Ht: 5’8”
- Wt: 50kg
- IBW: 63.9kg
- Cr: 0.6
- CrCl: 89.5ml/min
Underweight

- Decreased body mass
- Decreased production of creatinine falsely elevates the CrCl
- Vd
  - Hydrophilic drug may distribute more widely
  - Poor tissue binding and decreased perfusion
- Reduced hepatic metabolism or renal elimination
  - Increased T½

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<td>Weight</td>
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<td>SCr</td>
<td>↓</td>
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<tr>
<td>CrCl</td>
<td>↑ Falsely, but ↓</td>
</tr>
<tr>
<td>Vd</td>
<td>↓ ↑</td>
</tr>
<tr>
<td>T₁/₂</td>
<td>↑</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>↓</td>
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<td>Elimination</td>
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<td>Dose</td>
<td>↓</td>
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<tr>
<td>Dosing Interval</td>
<td>↑</td>
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Oshikoya: *Eur J Clin Pharmacol* 2010; 66; 1025-1035
Pediatric

- Vancomycin dosage of 60-70 mg/kg/day to achieve AUC/MIC > 400 in 75% of patients

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<td>CrCl</td>
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<td>V_d</td>
<td>↓</td>
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<tr>
<td>T_1/2</td>
<td>↓</td>
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<tr>
<td>Protein Binding</td>
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<td>Elimination</td>
<td>↑</td>
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<td>Dose</td>
<td>↑</td>
</tr>
<tr>
<td>Dosing Interval</td>
<td>↓</td>
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</table>

**excluding neonates

Le J. Pediatr Infect Dis J 2013. 32(4)e155-63
JR is a 65 y/o/m with a PCN allergy (swelling, age 28) who presents to the ED via squad with RR 25 bpm, HR 90 bpm, Temp 38.7 C, and complaints of painful urination. Upon checking his medical records, you see he has a history of *E. faecalis*. The physician in the ED asks for empiric antibiotics for JR’s suspected UTI.

- *How would you dose JR’s vancomycin?*
Sepsis

• Considerations
  • Dehydration
  • Loss of vascular tone
  • Shunting
  • Occlusion
  • Decreased CO
  • Increase in AAG

• Excretion
  • Renal excretion
  • Often related to AKI

• Third spacing, fluids, capillary leaking

• Higher dose because critically ill – monitor closely

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<tr>
<td>SCr</td>
<td>↑</td>
</tr>
<tr>
<td>CrCl</td>
<td>↑ early, ↓ late</td>
</tr>
<tr>
<td>$V_d$</td>
<td>↑</td>
</tr>
<tr>
<td>$T_{1/2}$</td>
<td>↑</td>
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<tr>
<td>Protein Binding</td>
<td>↑</td>
</tr>
<tr>
<td>Elimination</td>
<td>↓</td>
</tr>
<tr>
<td>Dose</td>
<td>↑</td>
</tr>
<tr>
<td>Dosing Interval</td>
<td>Will likely change throughout patient’s course</td>
</tr>
</tbody>
</table>

Crit Care Clin 2011;27:1-18
Smith BS. Chest 2012;141:1327-36
Acute Kidney Injury

- Unnecessary to modify loading doses
- Check for concomitant nephrotoxic agents
- An acute state
  - Adjust antibiotics accordingly
- Third spacing, fluids, capillary leaking

<table>
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<td>Protein Binding</td>
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Bauer, Larry A. "Vancomycin." *Applied Clinical Pharmacokinetics*,
UL is a 74 y/o/m with a history of MRSA. Linezolid IV was started empirically for cellulitis of the arm because of patient’s baseline SCr of 2.5. Today, UL’s SCr is 2.6. The antimicrobial stewardship team has been tasked with reducing linezolid DOT this quarter.

- **Continue linezolid?**
- **Recommend vancomycin?**
- **Other thoughts?**
Chronic Kidney Dysfunction

- $V_d$
  - 0.72-0.9 L/kg
- $T_{1/2}$ hours
  - CrCl 10-60 ml/min: 32.3
  - CrCl <10 ml/min: 146.7
- Protein binding
  - 20%
  - Increased free drug
- Drug will accumulate over time
- Consider indication

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<tr>
<td>Protein Binding</td>
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<td>Dose</td>
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<tr>
<td>Dosing Interval</td>
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Bauer, Larry A. "Vancomycin." *Applied Clinical Pharmacokinetics,*
Pregnancy

- GBS prophylaxis
  - Standard dosing
- Larger doses may be needed for therapeutic concentrations
- “Category C”

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<tr>
<td>CrCl</td>
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<td>V_&lt;sub&gt;d&lt;/sub&gt;</td>
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<td>T&lt;sub&gt;1/2&lt;/sub&gt;</td>
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<tr>
<td>Protein Binding</td>
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<td>Dose</td>
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<td>Dosing Interval</td>
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AM is a 63 y/o/f who gets dialysis every MWF. She is to be started on vancomycin for her diabetic foot ulcer. How would you dose vancomycin in this patient?

- Ht: 5’7”
- Wt: 68.2kg
- IBW: 61.6kg
- Cr: 2.5
- CrCl: 14.9 ml/min
Dialysis

• High-flux
  • 30-40% of drug is removed by standard HD session

• Consider redistribution following HD
  • VancT should be drawn prior to dialysis

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<td>$T_{1/2}$</td>
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<tr>
<td>Elimination</td>
<td>30-40% of dose</td>
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<tr>
<td>Dose</td>
<td>By VancT prior to dialysis</td>
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<tr>
<td>Dosing Interval</td>
<td>After dialysis</td>
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Amputation

- Decreased muscle mass
  - Decreased SCr
- Overestimate CrCl
  - Overall renal function will not change
- Consider site of amputation
- Consider presence of infection

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The recommendations in this presentation are meant to serve as a general framework for developing and strengthening a Pharmacist to Dose Vancomycin Policy. They are not intended to replace existing literature.
Optimizing Pharmacy to Dose Services in Special Populations

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References


References


