Vancomycin: Teaching an Old Dog New Tricks

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Disclosure

Ryan Mynatt
Theravance: Advisory Board

All other planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.
Learning Objectives

• Identify the optimal pharmacokinetic/pharmacodynamic parameter used to guide vancomycin dosing calculations.
• Given two vancomycin levels, use pharmacokinetic parameters to calculate a dosing regimen to target area-under-the-curve.
• Compare and contrast the pros and cons of vancomycin delivered as a continuous vs. intermittent infusion.
AUC/MIC as the Most Rational Therapeutic Target

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I know what you’re thinking...
How do we currently dose vancomycin?

A. Trough-targeted nomogram
B. AUC-targeted nomogram
C. AUC-based, using 2 post-dose concentrations
D. AUC-based, using Bayesian kinetic software
• Originally first introduced in 1956, and ultimately approved in 1958 as a response to recent emergence of resistance in *Staphylococcus aureus*\(^1\)
  
  — Approved at total daily dose of 2gm; divided every 6-12 hours

• Subsequent reports demonstrated efficacy in treating larger numbers of patients\(^2,3\)

1. Levine DP. *Clin Inf Dis* 2006
Vancomycin Pharmacokinetics

- Intense study into PK of vancomycin began in early 1980s\(^1,2\)
  - Peak and trough targets first proposed by Geraci\(^3\)
  - Further characterized by Rotschafer and colleagues\(^4\)
- Pharmacodynamic target remained largely undefined

Vancomycin Pharmacokinetics

• However, over time, monitoring of peak concentrations began to be questioned¹
  • “The so-called therapeutic range of 30–40 mg/L and 5–10 mg/L, respectively”

• Clinicians began to look at trough-based monitoring, noting little differences in patient outcomes and reduced expenditures²
  • Driven by reduction in lab costs for monitoring versus nomogram-based dosing

1. Rybak MJ Clin Inf Dis 2006
Vancomycin Pharmacodynamics

• Pharmacodynamic researchers began to demonstrate and endorse the area-under-the-curve to minimum inhibitory concentration (AUC/MIC) ratio as the preferred parameter for therapeutic efficacy\(^1\-^5\)
  • Derived mostly from in-vitro and animal models

• However, evidence of relating AUC/MIC to outcomes in human disease largely remained unstudied until 2004

1. Ebert S. 27th Interscience Conference on Antimicrobial Agents and Chemotherapy ICAAC 1987
Moise-Broder and colleagues...

- Evaluated 24-hour AUC/MIC ratio and it’s relation to therapeutic efficacy in patients with *Staphylococcus aureus* lower respiratory tract infections
- Demonstrated improved clinical and bacteriological response rates in patients achieving higher AUC/MIC ratios
  - Included 108 patients; mean age 74 years (range 32 – 93 years)
  - AUC/MIC of $\geq 345$ mg*hr/L correlated with clinical efficacy at test of cure
  - No relationship between time above MIC (t>MIC) was demonstrated

Summary and recommendation:

“An AUC/MIC ratio of ≥400 has been advocated as a target to achieve clinical effectiveness with vancomycin. Animal studies and limited human data appear to demonstrate that vancomycin is not concentration dependent and that the AUC/MIC is a predictive pharmacokinetic parameter for vancomycin.”

“However, because it can be difficult in the clinical setting to obtain multiple serum vancomycin concentrations to determine the AUC and subsequently calculate the AUC/MIC, trough serum concentration monitoring, which can be used as a **surrogate** marker for AUC, is recommended as the most accurate and practical method to monitor vancomycin.”

Therapeutic Drug Monitoring Guidance

• Summary and recommendation:
  – Trough serum vancomycin concentrations are the most accurate and practical method for monitoring vancomycin effectiveness. Trough concentrations should be obtained just before the next dose at steady state conditions.

• (Level of evidence = II, grade of recommendation = B)

3. Am J Respir Crit Care Med 2005
Therapeutic Drug Monitoring Guidance

Summary and recommendation:
- Trough serum vancomycin concentrations are the most accurate and practical method for monitoring vancomycin effectiveness. Trough concentrations should be obtained just before the next dose at steady state conditions.

(Level of evidence = II, grade of recommendation = B)

Vancomycin serum trough concentrations of 15–20 mg/L are recommended to improve penetration, increase the probability of obtaining optimal target serum concentrations, and improve clinical outcomes.

(Level of evidence – III, Grade of recommendation B)

3. Am J Respir Crit Care Med 2005
Trough-based Dosing & Outcomes

- Trough concentrations represent a single exposure point at the end of the dosing interval
  - Fails to accurately describe exposure over time (i.e., course of therapy)
- Does this parameter correlate with desired outcomes?
  - Clinical and microbiological outcomes (cure, eradication, etc.)
- Does this parameter correlate with undesired outcomes?
  - Nephrotoxicity, ototoxicity
<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence of Nephrotoxicity</th>
<th>Vancomycin Trough Definition</th>
<th>Nephrotoxicity relative to Trough</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosso, et al. Antimicrob Agents Chemother 2011</td>
<td>19% (55/288)</td>
<td>Initial (within 2-5 days) or weighted average</td>
<td>&lt; 15 mg/L: 9% (13/146) ≥ 15 mg/L: 30% (42/142)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Cano, et al. Clin Therapeutics 2012</td>
<td>15% (29/188)</td>
<td>Initial (highest level within 96 hours)</td>
<td>&lt; 15 mg/L: 7% (7/99) ≥ 15 mg/L: 25% (22/89)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Chung, et al. Anaesth Intensive Care 2011</td>
<td>38% (28/73)</td>
<td>Initial, after 3-5 doses</td>
<td>&lt; 15 mg/L: 33% (16/48) ≥ 15 mg/L: 48% (12/25)</td>
<td>0.21</td>
</tr>
<tr>
<td>Hermsen, et al. Ex Opin Drug Safety 2010</td>
<td>16% (9/55)</td>
<td>Initial, after 3-5 doses</td>
<td>&lt; 15 mg/L: 10% (4/48) ≥ 15 mg/L: 31% (5/16)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hidayat, et al. Arch Int Med 2006</td>
<td>12% (11/95)</td>
<td>Mean</td>
<td>&lt; 15 mg/L: 0% (0/32) ≥ 15 mg/L: 17% (11/63)</td>
<td>0.01</td>
</tr>
<tr>
<td>Jeffres, et al. Clin Therapeutics 2007</td>
<td>43% (40/94)</td>
<td>Initial, after third dose</td>
<td>&lt; 15 mg/L: 29% (13/45) ≥ 15 mg/L: 55% (27/49)</td>
<td>0.01</td>
</tr>
<tr>
<td>Kralovicova, et al. Journal of Chemotherapy 1997</td>
<td>25% (50/198)</td>
<td>Not described</td>
<td>&lt; 15 mg/L: 21% (29/138) ≥ 15 mg/L: 35% (21/60)</td>
<td>NS</td>
</tr>
<tr>
<td>Kullar, et al. Clinical Inf Diseases 2011</td>
<td>18% (50/280)</td>
<td>Initial, prior to fourth dose</td>
<td>&lt; 15 mg/L: 16% (23/141) ≥ 15 mg/L: 19% (27/139)</td>
<td>NS</td>
</tr>
<tr>
<td>Kullar, et al. Pharmacotherapy 2011</td>
<td>5% (9/200)</td>
<td>Initial, prior to 4th or 5th dose</td>
<td>&lt; 15 mg/L: 1% (1/84) ≥ 15 mg/L: 7% (8/116)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Lodise, et al. Clinical Inf Diseases 2009</td>
<td>13% (21/166)</td>
<td>Initial, highest VT within first 4 days</td>
<td>&lt; 15 mg/L: 10% (14/139) ≥ 15 mg/L: 26% (7/27)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Minejima, et al. Antimicrob Agents Chemother 2011</td>
<td>19% (43/227)</td>
<td>Mean</td>
<td>&lt; 15 mg/L: 16% (25/155) ≥ 15 mg/L: 24% (17/72)</td>
<td>0.27</td>
</tr>
<tr>
<td>Prabaker, et al. J Hosp Medicine 2011</td>
<td>9% (31/348)</td>
<td>Mean</td>
<td>&lt; 15 mg/L: 8% (24/294) ≥ 15 mg/L: 13% (7/54)</td>
<td>0.11</td>
</tr>
<tr>
<td>Wunderlink, et al. Clinical Inf Diseases 2012</td>
<td>15% (50/333)</td>
<td>Median</td>
<td>&lt; 15 mg/L: 11% (24/215) ≥ 15 mg/L: 22% (26/118)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Zimmerman, et al. Pharmacotherapy 1995</td>
<td>18% (8/45)</td>
<td>Initial, after 4th dose</td>
<td>&lt; 15 mg/L: 0% (0/33) ≥ 15 mg/L: 67% (8/12)</td>
<td>Not stated</td>
</tr>
</tbody>
</table>
Vancomycin Trough & Efficacy

- Patel and colleagues, demonstrated that despite trough concentrations correlating with nephrotoxicity, they did not necessarily correlate with achieving effective AUC/MIC ratios\(^1\)
  - Especially when MIC > 1 mg/L in *Staphylococcus aureus*
- The ZEPHyR study, correlated increased troughs with nephrotoxicity, but demonstrated similar outcomes regardless of day 3 vancomycin trough\(^2\)
- Jeffres and colleagues demonstrated similar outcomes (mortality) in MRSA pneumonia irrespective of vancomycin trough concentration and AUC\(^3\)
  - Did not evaluate AUC/MIC ratio specifically

Vancomycin Trough & Efficacy

• Kullar and colleagues demonstrated improved outcomes with increasing vancomycin troughs (> 15mg/L) in 2 reports\textsuperscript{1,2}

• First, a single-center analysis of trough and exposure on outcomes in patients with MRSA bacteremia.
  – Predictor of failure included vancomycin trough < 15mg/L
  – Classification and Regression Tree (CART) analysis demonstrated patients with AUC/MIC < 421 experienced higher rates of failure

• Second, retrospective evaluation of nomogram-based dosing method
  – Increased treatment success noted in post-implementation group (60% vs. 45%; \( p=0.034 \))
  – However, failure seen again, with higher troughs (>20mg/L)

Is 15 – 20 mg/L Necessary?

• Neely and colleagues incorporated richly sampled studies in 47 patients with varying levels of renal function.
  – Trough-only data set “underestimated” AUC by 23% (CI, 11 to 33%; p=0.0001)
  – Using Bayesian modeling, a 5000 patient simulation was created, predicting that in adults with normal renal function 60% would achieve AUC/MIC (≥400) with troughs < 15 mg/L

Where is the Ceiling with AUC?

- **Suzuki** evaluated utility of peak monitoring in TDM of vancomycin in MRSA pneumonia\(^1\)
  - Significant differences in response vs. non-response in patients achieving higher AUC/MIC values
  - Nephrotoxicity was noted with higher AUC values (> 600)

- **Lodise** noted increasing AUC (≥1300) was associated with increased risk of nephrotoxicity
  - However, trough was only predictor of nephrotoxicity in the multivariate analysis

- **Chavada** evaluated the AUC\(_{24}\) nephrotoxicity threshold, demonstrating an AUC >563mg*hr/L was associated with increased toxicity
  - (40% [8/20] versus 11.2% [12/107]; \(P\) 0.002)

Key Takeaways: Part 1

• Therapeutic drug targets for vancomycin have continued to evolve over time
  – Increasing body of PK/PD evidence vs. historical recommendations

• A vancomycin trough-based monitoring approach may not accurately predict efficacy, but has been associated with toxicity
  – We can achieve these target AUC values with trough < 15 mg/L

• AUC-targeted therapy may more accurately predict both therapeutic efficacy and toxicity
  – Presents logistical challenges (to be discussed)
Keys to Early Target Attainment

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Do we currently employ a loading dose?

A. Yes, weight-based, single dose
B. No, do not use loading dose strategy
C. Yes, weight-based, fractionated dosing strategy
Loading Doses: To Load or Not?

- Post-2009 vancomycin guidelines, surveys report inconsistency with use of loading doses\(^1,2\)
  - Never, 22 (14%); Sometimes, 70 (43%); Always, 68 (42%)
  - Some reasons included, assessment of disease severity (43%), lack of supporting evidence (22.8%), and concerns for nephrotoxicity (20.1%)

- Loading doses (25 – 30mg/kg TBW) have been recommended to expedite achieving target trough concentrations\(^3\)
  - Recent meta-analysis concluded high-quality evidence to support this practice is lacking, though, loading doses may help attain target troughs (15 – 20mg/L) more rapidly\(^4\)
  - Only one study in pediatric patients looked at AUC\(_{24}\) specifically in context of loading dose, noting no difference in AUC between groups\(^5\)

Vancomycin Target Attainment

• Current evidence suggests trough-only monitoring does not accurately predict AUC
  – AUC-based methods may be more desirable, and potentially more clinically accurate/relevant

• How can clinicians begin to go about targeting the AUC?
  – Bayesian approach
  – Equation-based approach
Bayesian Approach

Based upon Bayes’ Theorem
- Basically a statistical theorem or “rule” that stipulates that one can describe the probability of an event, based upon prior knowledge or conditions that might be related to the event.

Bayesian Prior
Probability Distribution of:
Vd
Clearance
In 100 patients

Patient-specific
Measured drug concentrations

Bayesian Posterior
Probability Distribution (revised):
Allows AUC-estimation

Bayesian Approach

Structured Mathematical Model
- Should be built to best describe the pharmacokinetics of a given agent (vancomycin)

Density File
- Contains parameter estimates and their associated dispersion for the PK Model
- Aka “Bayesian prior”

Patient File
- Drug dosing information (i.e., Dose, frequency, infusion time)
- Measured drug concentrations

Patient Target File
- Contains target exposure profile and initial estimates of future dosing regimens

1. Pai M et al. *Advances in Drug Delivery Reviews* 2014
Beauty of Bayesian Software

- Advantages of Bayesian-based methods vs. traditional first-order pharmacokinetic monitoring are noted
  - Can be modified to include select pharmacokinetic models (i.e. 2-compartment model)
  - Not limited to trough-only
  - Samples do not necessarily need to be taken at steady state
  - Adaptive program???
Applications for Bayesian

- Bayesian software is now available to assist clinicians in implementing AUC-based intervention
  - In-depth review of each product is beyond the scope of our discussion here today
  - Likely will be associated with capital expenditures (i.e., software packages)

Equation-based Methodology

• Current evidence demonstrates that 2 post-dose peak and trough concentrations can be used to estimate daily AUC\textsuperscript{1,2}
  – Associated with reasonable precision and low bias
  – Allows characterization as monoexponential curve
  – Simple arithmetic can be used to generate AUC measurements
  – Can also be easily programmed to allow automatic computing

• May be useful, as it is a “real-world” snapshot of patient-specific pharmacokinetic parameters

Equation-based Methodology

• Current methodology to calculate AUC from 2-concentrations proposed by Begg, Barclay, and Duffull for aminoglycosides\(^1\) and later modified by Pai and Rodvold\(^2\)
  – Uses post-dose concentrations to characterize PK as mono-exponential decline function
  – Used to calculate AUC based on linear trapezoidal rules
• Limitation includes inability to accurately describe alpha-phase (i.e., distribution window)
  – Limits accuracy of overall AUC estimation

Equation-based Methodology

1. Detroit Medical Center, Guidelines for Vancomycin Dosing in Adults, Jan 2015
A Tale of Two Methods...

- Clinicians evaluating methodologies can come to question how the two compare in terms of AUC estimation.
- Pai, et al. compared Bayesian trough-only vs. 2 equation-based methods:
  - All methods accurately (low bias and high precision) reflected the referenced AUC values (Bayesian, full data set).
  - Equation based methods tended to “underestimate” the AUC value, but the median error (<2%) by these methods should be considered clinically insignificant.

Real World Experience with AUC

• In 2015 the Detroit Medical Center implemented AUC-based dosing as response to increasing reports of severe nephrotoxicity cases
  – Decided upon equation-based dosing scheme, targeting AUC of 400 – 600 mg*hr/L (based upon available upper limit toxicity thresholds)
  – Proposed 2-concentration (peak/trough) PK monitoring in selected groups of patients

1. Detroit Medical Center, Guidelines for Vancomycin Dosing in Adults, Jan 2015
Vancomycin Empiric Dosing Calculator

Patient Specific Data Input

PK/PD Specific Data Input
PK Estimate Output

**Vancomycin Empiric Dosing Calculator**

**CrCl Estimation by Cockcroft-Gault**

<table>
<thead>
<tr>
<th>Age</th>
<th>35 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
</tr>
<tr>
<td>SGR</td>
<td>0.7 mg/dL</td>
</tr>
<tr>
<td>Height</td>
<td>176 cm</td>
</tr>
<tr>
<td>Actual Weight (TBW)</td>
<td>80.0 kg</td>
</tr>
<tr>
<td>IBW</td>
<td>71.4 kg</td>
</tr>
<tr>
<td>Adj BW</td>
<td>kg</td>
</tr>
<tr>
<td>CrCl TBW</td>
<td>mL/min</td>
</tr>
<tr>
<td>CrCl AdjBW</td>
<td>mL/min</td>
</tr>
<tr>
<td>CrCl IBW</td>
<td>mL/min</td>
</tr>
</tbody>
</table>

**Dosing variables**

| Desired AUC | 500 mcg*h/mL |
| Desired Cmax | 35 mcg/mL |
| Desired Cmin | 12.5 mcg/mL |
| Weight to calculate CrCl & C2 | 143 mL/min |
| Weight to calculate VdL | 180 L |
| Vd coefficient | 0.65 L/kg |
| Kd equation | CrCl*0.0015 |
| Alternative CCl | mL/min |
| Alternative Dosing Weight | kg |
| Alternative Dosing Intake | 1 hour |

**Graph of 2000 mg IV over 2 hour(s) every 8 hours**

Alternative Regimen Recommendation
### Dose & Concentrations Input

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Input</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>1250 mg</td>
</tr>
<tr>
<td>Dosing interval</td>
<td>12 hrs</td>
</tr>
<tr>
<td>Date/time of Dose</td>
<td>11:00/9/24/17 11:00</td>
</tr>
<tr>
<td>Duration of Infusion</td>
<td>1.5 hr</td>
</tr>
<tr>
<td>Level 1</td>
<td>23.0 mcg/mL</td>
</tr>
<tr>
<td>Date/time of Level 1</td>
<td>12:45/9/24/17 12:45</td>
</tr>
<tr>
<td>Level 2</td>
<td>8.6 mcg/mL</td>
</tr>
<tr>
<td>Date/time of Level 2</td>
<td>22:42/9/24/17 22:42</td>
</tr>
</tbody>
</table>

### Step 1. Enter Current Dosing and Levels

- **First dose or steady state**: Steady state

### Calculated PK parameters

- $V_e$: 0.0989 L
- $t_{1/2}$: 7.0 hr
- $C_{max}$ for this interval: 23.6 mcg/mL
- $C_{min}$ for this interval: 8.3 mcg/mL
- $V_d$: 70.9 L
- Vancocycin CL: 116.9 ml/hr
- Steady state AUC at current dose/interval: 356.5 mg/hr/L

### Step 2. Calculate New Dosing Requirements

| Desired AUC | 500 mcg/hr/mL |
| Desired $C_{max}$ | 35 mcg/mL |
| Desired $C_{min}$ | 12.5 mcg/mL |
| Desired Infusion time | 1 hr |
| Calculated dose | 1667.7 mg |
| Calculated interval | 11.4 hr |

### Step 3. Calculate Predicted $C_{max}/C_{min}$ Based on New Dosing

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Input</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>1750 mg</td>
</tr>
<tr>
<td>Interval</td>
<td>12 hr</td>
</tr>
<tr>
<td>Infusion time</td>
<td>2.0 hr</td>
</tr>
<tr>
<td>Most recent dose given</td>
<td>9/24/17 11:00</td>
</tr>
<tr>
<td>Next dose due (Time when $C_{max}$ is achieved)</td>
<td>9/24/17 18:55</td>
</tr>
<tr>
<td>Calculated AUC</td>
<td>497.7 mcg/mL</td>
</tr>
<tr>
<td>Calculated $C_{max}$</td>
<td>32.2 mcg/mL</td>
</tr>
<tr>
<td>Calculated $C_{min}$</td>
<td>12.0 mcg/mL</td>
</tr>
</tbody>
</table>

### Modifiable Fields

- For Dose-Adjustment
- For PK Requirements

### Calculated Parameter Output
Real World Experience with AUC

- Single center, retrospective study from 2014 through 2015 receiving vancomycin pre & post-implementation of AUC-based dosing
  - Post implementation group targeted AUC of 400 – 600 mg*hr/L, secondary trough target of 10 – 20mg/L
  - Pre-implementation group included patients receiving trough-based dosing, with general target range of 10-20mg/L, with 15-20mg/L for severe infections

Real World Experience with AUC

• Overall, 1280 patients were included in the analysis
  – AUC guided dosing was independently associated with lower nephrotoxicity in both logistic regression (OR, 0.52; 95% CI, 0.34-0.80; \( P=0.003 \)) and Cox-proportional hazards regression (HR, 0.53; 95% CI, 0.35-0.78; \( P=0.002 \))
  – AUC-guided dosing was associated with lower total daily vancomycin doses, AUC values, and trough concentrations.

# Real World Experience with AUC

## Subgroup Analysis: Patients with bacteremia or pneumonia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Trough-Guided (n = 150)</th>
<th>AUC-Guided (n= 150)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmin(_{24}) (mg/L)</td>
<td>12.7 (8.9 – 16.6)</td>
<td>10.0 (5.7 – 13.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cmin(_{48}) (mg/L)</td>
<td>14.2 (10.3 – 19.5)</td>
<td>12.5 (8.3 – 16.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>AUC(_{0-24}) (mg*hr/L)</td>
<td>705 (540 – 883)</td>
<td>474 (360 – 611)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AUC(_{0-48}) (mg*hr/L)</td>
<td>663 (538 – 857)</td>
<td>532 (406 – 667)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data expressed as median (IQR)

Detroit Medical Center
Acute Care Adult Hospitals

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DRH</td>
<td>5.4%</td>
<td>6.3%</td>
<td>5.6%</td>
<td>7.0%</td>
<td>2.0%</td>
<td>3.8%</td>
<td>4.2%</td>
<td>4.4%</td>
<td>3.9%</td>
<td>4.2%</td>
<td>4.6%</td>
<td>2.7%</td>
</tr>
<tr>
<td>HUH</td>
<td>5.2%</td>
<td>7.2%</td>
<td>7.5%</td>
<td>8.1%</td>
<td>4.5%</td>
<td>3.2%</td>
<td>5.0%</td>
<td>2.9%</td>
<td>4.0%</td>
<td>4.4%</td>
<td>3.0%</td>
<td>3.3%</td>
</tr>
<tr>
<td>HVSH</td>
<td>5.7%</td>
<td>5.0%</td>
<td>4.4%</td>
<td>6.3%</td>
<td>4.9%</td>
<td>2.4%</td>
<td>0.7%</td>
<td>2.4%</td>
<td>2.5%</td>
<td>1.8%</td>
<td>3.7%</td>
<td>1.5%</td>
</tr>
<tr>
<td>SGH</td>
<td>5.7%</td>
<td>4.0%</td>
<td>3.6%</td>
<td>4.9%</td>
<td>2.3%</td>
<td>2.1%</td>
<td>2.5%</td>
<td>2.6%</td>
<td>2.5%</td>
<td>3.2%</td>
<td>2.8%</td>
<td>2.0%</td>
</tr>
<tr>
<td>All Sites</td>
<td>5.5%</td>
<td>5.7%</td>
<td>5.3%</td>
<td>6.5%</td>
<td>3.1%</td>
<td>3.0%</td>
<td>3.5%</td>
<td>3.4%</td>
<td>3.3%</td>
<td>3.6%</td>
<td>3.5%</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

Notes:
- Denominator includes all patients with vancomycin pharmacy dosing order, regardless of duration of treatment.
- ESRD patients are not included in this evaluation.
- Acute kidney injury (AKI) is defined as an increase SCr 0.5 mg/dL or 50% from baseline on 2 consecutive draws while receiving vancomycin.
- Includes all AKI cases that occurred during vancomycin treatment, regardless of etiology and concurrent nephrotoxins.
- DMC guidelines were revised to calculate vancomycin dosing according to area under the curve (AUC) in January 2015.
Key Takeaways:  Part 2

• Loading doses can potentially be employed to improve early target attainment
  – Little data demonstrating loading doses improve clinical outcomes

• Two main strategies exist to allow for implementation of AUC-targeted vancomycin dosing
  – Institutions should determine most appropriate method

• AUC-targeted vancomycin therapy can be employed to improve patient outcomes (nephrotoxicity)
  – However, future evaluations with respect to efficacy are needed
Intermittent and Continuous Infusion Calculations Targeting AUC

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What are pharmacists doing?

• 13.5% reporting at least some use of AUC
• >94% routinely using intermittent vs. continuous infusion
• More comfortable with AUC calculations for intermittent than continuous (48.1% vs. 22%)
Semi-Log Plot
Intermittent Infusion
Patient Case #1

Patient is a 42 y/o male with IVDA admitted to your hospital with concern for sepsis and endocarditis.

Patient weight = 64 kg
SCr 0.35 mg/dL

How might you use 2 level kinetics to calculate patient-specific parameters to target an AUC?
What loading dose would you recommend for this patient?

A. No loading dose
B. 1,000 mg
C. 1,250 mg
D. 1,500 mg
Loading Dose

- Vancomycin 1,750 mg x1 over 2 hours given at 0800
- Random level 1 = 42 mg/L @ 1200
- Random level 2 = 19 mg/L @ 2000
What do you calculate for the elimination rate constant (k)?

A. 0.075 hr⁻¹
B. 0.099 hr⁻¹
C. 0.150 hr⁻¹
D. 0.211 hr⁻¹
Calculate Elimination Rate Constant

\[ k = \frac{\ln\left(\frac{C_1}{C_2}\right)}{T} \]

\[ k = \frac{\ln\left(\frac{42}{19}\right)}{8} = 0.099 \text{ hr}^{-1} \]

\[ t_{1/2} = \frac{\ln(2)}{k} \]

\[ t_{1/2} = \frac{\ln(2)}{0.099 \text{ hr}^{-1}} = 7 \text{ hrs} \]
Calculate $C_{\text{max}}$

\[
C_{\text{max}} = \frac{c_1}{e^{-k(\Delta T)}}
\]

\[
C_{\text{max}} = \frac{42}{e^{-0.099(2)}}
\]

\[
C_{\text{max}} = 51.2 \frac{mg}{L}
\]
**Volume of Distribution**

**Simple:**

\[ V_d = \frac{\text{Loading Dose}}{C_{\text{max}}} \]

\[ V_d = \frac{1750 \, mg}{51.2 \, mg/L} \]

\[ V_d = 34.2 \, L \, (0.53 \, L \, \text{per kg}) \]
Clearance & TDD Required

\[ Cl = k \times V_d \]

\[ Cl = 0.099 \ (31.0) \]

\[ Cl = 3.07 \text{ L per hr} \]

\[ TDD = Cl \times AUC_{goal} \]

\[ TDD = 3.07 \ (500) \]

\[ TDD = 1535 \text{ mg per day} \]
Maintenance Dosing

\[ \tau = \ln \left( \frac{C_{\text{max,desired}}}{C_{\text{tr,desired}}} \right) \cdot \frac{k}{k} + t \]

\[ \tau = \ln \left( \frac{40}{10} \right) \cdot \frac{10}{0.099} + 1 \]

\[ \tau = \sim 15 \text{ hrs} \]

\[ MD = \frac{TDD}{24 \frac{t}{\tau}} \]

\[ MD = \frac{1500}{24 \frac{12}{12}} = 750 \text{ mg q12h} \]
Calculate Estimated PK Parameters With This Regimen

\[
\text{Predicted } C_{\text{max}} = \frac{MD}{V_d} \frac{1-e^{-k \tau}}{1-e^{-k(\tau-t)}}
\]

\[
\text{Predicted } C_{\text{max}} = \frac{750}{31.0} \frac{1-e^{-0.099(12)}}{1-e^{-0.099(12-1)}}
\]

\[
\text{Predicted } C_{\text{max}} = 34.8 \text{ mg/L}
\]

\[
\text{Predicted } C_{\text{min}} = 34.8 x e^{-0.099(12-1)}
\]

\[
\text{Predicted } C_{\text{min}} = 11.7 \text{ mg/L}
\]
Anatomy of AUC: Oversimplified
Estimate AUC of Proposed Regimen: Infusion

\[ AUC_{infusion} = \frac{(Predicted\ C_{\text{max}} + Predicted\ C_{\text{min}})}{2} \times t \]

\[ AUC_{infusion} = \frac{(34.8 + 11.7)}{2} \times 1 \]

\[ AUC_{infusion} = 23.3 \]
Estimate AUC of Proposed Regimen: Elimination

\[
AUC_{\text{elimination}} = \frac{\text{Predicted } C_{\text{max}} - \text{Predicted } C_{\text{min}}}{k}
\]

\[
AUC_{\text{elimination}} = \frac{34.8 - 11.7}{0.099} = 233.3
\]

\[
AUC_{0-24} = (AUC_{\text{infusion}} + AUC_{\text{elimination}}) \times \left(\frac{24}{\tau}\right)
\]

\[
AUC_{0-24} = (23.3 + 233.3) \times \left(\frac{24}{12}\right)
\]

\[
AUC_{0-24} = 513.2 \text{ mg·hr/L}
\]
Alternative Estimation of AUC

\[
AUC_{0-\infty} = \frac{Dose}{Cl} \\
AUC_{0-24} = \frac{Total \ Daily \ Dose}{Cl} \\
AUC_{0-24} = \frac{1500 \ mg}{3.07 \ L/hr} = 488.6 \ mg\cdot hr/L
\]
Assessing AUC at Steady State
Patient Case #2

63 y/o (weight=75kg) in MICU admitted for VAP (MRSA; MIC 1)
Renal function stable at 1.1 mg/dL
On vancomycin 1000 mg q24h infused over 1 hour @ 0800
Trough @ 0730 = 18 mg/L
Peak @ 1100 = 42 mg/L
Calculate Elimination Rate Constant \( (k) \)

\[
k = \frac{ln \frac{c_{peak}}{c_{trough}}}{T'}
\]

\( T' = \) Determined by subtracting the time difference \( b/t \) \( C_{pk} \) and \( C_{tr} \) from \( \tau \)

\[
k = \frac{ln^{42}}{18} \div \frac{24-(0.5+1+2)}{24-(0.5+1+2)}
\]

\[
k = 0.041 \text{ hr}^{-1}
\]

\[
t_{1/2} = \frac{ln(2)}{k}
\]

\[
t_{1/2} = \frac{ln(2)}{0.041} = 16.8 \text{ hrs}
\]
Back Extrapolate for $C_{\text{max}}$ and $C_{\text{min}}$

\[ C_{\text{max}} = \frac{C_{pk,\text{as drawn}}}{e^{-kt'}} \]

\[ C_{\text{max}} = \frac{42}{e^{-0.041(2)}} \]

$C_{\text{max}} = 45.6 \text{ mg/L}$

\[ C_{\text{min}} = C_{tr,\text{as drawn}} \times e^{-kt'} \]

\[ C_{\text{min}} = 18 \times e^{-0.041(0.5)} \]

$C_{\text{min}} = 17.6 \text{ mg/L}$
Assess AUC

\[ AUC_{\text{infusion}} = \frac{(C_{\text{max}} + C_{\text{min}})}{2} \times t = 31.6 \]

\[ AUC_{\text{elimination}} = \frac{C_{\text{max}} - C_{\text{min}}}{k} = 683 \]

\[ AUC_{0-24} = (AUC_{\text{infusion}} + AUC_{\text{elimination}}) \times \left(\frac{24}{t}\right) = 714.6 \text{ mg} \cdot \text{hr/L} \]
Based on the AUC, I would:

A. Continue current dosing
B. Change dosing to q12h to minimize peak concentration
C. Decrease dosing
D. Increase dosing
Dose Changes Using AUC

• Assume linear pharmacokinetics:

\[
TDD_{\text{new}} = \frac{TDD_{\text{current}}}{AUC_{\text{current}}} \times AUC_{\text{goal}}
\]

\[
TDD_{\text{new}} = \frac{1000\text{mg}}{714.6} \times 500 = 700\text{ mg}
\]
Benefits of $V_d$ Calculation

$$V_d = \frac{MD}{t} \times \frac{(1-e^{-kt})}{k(C_{max} - [C_{min} x e^{-kt}])} = 34.1 \text{ L} (0.46 \text{ L/kg})$$

$$Cl = k \times V_d = 0.041 \times (34.1) = 1.40 \text{ L/hr}$$

$$AUC_{0-24} = \frac{Total \ Daily \ Dose}{Cl} = 714 \text{ mg/hr/mL}$$

May use to model new regimen if desired
Continuous Infusion
Using Continuous Infusion

• Initial dosing:

\[ Dose = \frac{TDD}{24 \text{ hours}} \]
AUC Calculations at Steady State

\[ AUC_{0-24} = \text{Vancomycin level at steady state } \times 24 \]

\[ R_{in} = C_{ss} \times Cl \]
A patient on continuous infusion vancomycin has a steady state level of 24 mcg/mL. What is the $\text{AUC}_{0-24h}$?

A. 420 mg·hr/L  
B. 500 mg·hr/L  
C. 576 mg·hr/L  
D. 626 mg·hr/L
Nephrotoxicity Risk of Continuous Infusion Vancomycin

- Meta-analysis: Continuous associated with ↓ nephrotoxicity
  - RR = 0.61, 95% CI 0.47-0.80
- No significant differences in treatment failure or mortality
Focus on Those at Highest Risk?
Critically Ill Patients

Flannery AH. Presented at ACCP Annual Meeting, 2017
Pros and Cons of Continuous Infusions

**Pro:**
- AUC calculations easier and fewer assumptions
- Associations with less nephrotoxicity
- Reduced lab cost

**Con:**
- IV access issues & compatability
- Logistical level issues
- Phlebitis concerns
Practical Experience: 2 Centers

- Calculators pivotal to success
- Working with 2 levels after first dose
- Education
- Don’t forget: you already (sort of) know how to dose vancomycin
Key Takeaways

• Key Takeaway #1
  – Vancomycin AUC can be estimated with 2 levels using varying approaches in clinical practice

• Key Takeaway #2
  – Continuous infusion vancomycin may be associated with reduced nephrotoxicity, but a number of confounders present in the literature significantly limit any conclusions

• Key Takeaway #3
  – AUC monitoring is capable of being implemented—but be prepared to learn to adapt approach
Questions or Discussion?
Vancomycin: Teaching an Old Dog New Tricks

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