The ABCs of AUC-guided Vancomycin Dosing

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Disclosures

• I have nothing to disclose
Objectives

• Review vancomycin pharmacokinetics (PK) and pharmacodynamics (PD)

• Explain the rationale for AUC-guided vancomycin dosing

• Discuss key considerations for implementing AUC-guided vancomycin dosing

AUC = area under the curve
Let’s Take a Poll...

What is the primary vancomycin target at your institution?

A. Trough concentrations
B. Peak concentrations
C. $\text{AUC}_{24}$
D. 100% T$>$MIC
Let’s Take a Poll...

If you are not using AUC-guided vancomycin dosing at your institution, why not?

A. Trough-guided dosing is working fine
B. Other priorities
C. Lack of buy-in
D. Not sure where to start
What does #IDTwitter have to say?

Q1. What is the 🔥 hottest topic for dose optimization in 2019? Why do you think so? #ASPchat

<table>
<thead>
<tr>
<th>Topic</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanco AUC dosing</td>
<td>56%</td>
</tr>
<tr>
<td>BL prolonged infusions</td>
<td>27%</td>
</tr>
<tr>
<td>Daptomycin dosing</td>
<td>11%</td>
</tr>
<tr>
<td>Other</td>
<td>6%</td>
</tr>
</tbody>
</table>

348 votes · Final results
The ABCs of AUC-guided Vancomycin Dosing

A – Antimicrobial stewardship is key
ACTUAL FOOTAGE OF VANCOMYCIN

BEING STARTED IN THE HOSPITAL
What is antimicrobial stewardship?

“Anything and everything intended to improve patient outcomes and minimize the negative effects of antimicrobial use”
– Matt’s Definition
Antimicrobial Stewardship and Vancomycin

• Antibiotics are being considered:
  • Does this patient have an infection that requires vancomycin?

• Have appropriate cultures and diagnostics been obtained?
  • Consider MRSA nasal screening when appropriate (e.g., pneumonia)

• New clinical and microbiological data is available:
  • Is vancomycin still necessary?
  • Can an oral antibiotic be used instead?

• What duration of therapy is appropriate?
  • New mantra “shorter is better”

Adapted from: Tamma PD, et al. JAMA 2018
Antimicrobial Stewardship and Vancomycin

When vancomycin is appropriate, dose optimization provides the balance between efficacy and safety.
The ABCs of AUC-guided Vancomycin Dosing

B – Build buy-in using data
Dose Optimization Relies on Pharmacokinetics (PK) and Pharmacodynamics (PD)

KEY:
- MIC = minimum inhibitory concentration
- Cmax/MIC = maximum concentration to MIC ratio
- AUC/MIC = area under the curve to MIC ratio
- T>MIC = time above the MIC

Vancomycin PK-PD Target

Ebert S. [abstract 439]. American Society for Microbiology 1987; Washington, DC
2009 Vancomycin Consensus Guidelines

• AUC/MIC ≥400 has been advocated as the target for clinical effectiveness
• Trough-only monitoring can be used as a surrogate for AUC
• Target troughs of 15-20 mg/L in serious infections
• Maintain troughs above 10 mg/L to avoid resistance development

Relationship Between Trough and AUC_{24}

Trough “Snapshot” Doesn’t Tell the Whole Story

![Graph showing vancomycin concentration over time.

Treatment Failure in Patients with *Staphylococcus aureus* Bacteremia

- **Trough ≥15 mg/L**: OR 0.87; 95% CI [0.6, 1.25]
- **Trough <15 mg/L**: OR 0.41; 95% CI [0.31, 0.53]

Vancomycin $\text{AUC}_{24}$ and Mortality

Which PK/PD descriptor best describes the antibacterial activity of vancomycin?

A. Trough/MIC
B. Peak/MIC
C. AUC/MIC
D. 100% T>MIC
# Vancomycin Troughs and Nephrotoxicity

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>High troughs ≥15mg/L</th>
<th>Low trough &lt;15mg/L</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Bosso et al. (21)</td>
<td>42</td>
<td>142</td>
<td>13</td>
</tr>
<tr>
<td>Cano et al. (22)</td>
<td>22</td>
<td>89</td>
<td>7</td>
</tr>
<tr>
<td>Chung et al. (23)</td>
<td>12</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Hermsen et al. (30)</td>
<td>5</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Hidayat et al. (13)</td>
<td>11</td>
<td>63</td>
<td>0</td>
</tr>
<tr>
<td>Jeffres et al. (15)</td>
<td>27</td>
<td>49</td>
<td>13</td>
</tr>
<tr>
<td>Kralovicova et al. (31)</td>
<td>21</td>
<td>60</td>
<td>29</td>
</tr>
<tr>
<td>Kullar et al. (32)</td>
<td>8</td>
<td>116</td>
<td>1</td>
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<tr>
<td>Kullar et al. (8)</td>
<td>27</td>
<td>139</td>
<td>23</td>
</tr>
<tr>
<td>Lodise et al. (36)</td>
<td>7</td>
<td>27</td>
<td>14</td>
</tr>
<tr>
<td>McKamy et al. (38)</td>
<td>16</td>
<td>57</td>
<td>8</td>
</tr>
<tr>
<td>Minejima et al. (39)</td>
<td>17</td>
<td>72</td>
<td>25</td>
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<tr>
<td>Prabaker et al. (43)</td>
<td>7</td>
<td>54</td>
<td>24</td>
</tr>
<tr>
<td>Wunderink et al. (50)</td>
<td>26</td>
<td>118</td>
<td>24</td>
</tr>
<tr>
<td>Zimmermann et al. (51)</td>
<td>8</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

**Total events**: 256

**Total (95% CI)**: 1039

**1718 100.0% 2.67 [1.95, 3.65]**

**Heterogeneity**: Tau² = 0.14; Chi² = 23.89, df = 14 (P = 0.05); I² = 41%

**Test for overall effect**: Z = 6.13 (P < 0.000001)

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Vancomycin $\text{AUC}_{24}$ and Nephrotoxicity

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Low AUC</th>
<th>High AUC</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 AUC 0–24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allen 2017</td>
<td>23</td>
<td>176</td>
<td>0.46 [0.25, 0.87]</td>
<td></td>
</tr>
<tr>
<td>Chavada 2017</td>
<td>12</td>
<td>107</td>
<td>0.19 [0.06, 0.56]</td>
<td></td>
</tr>
<tr>
<td>Jumah 2018</td>
<td>3</td>
<td>35</td>
<td>1.97 [0.19, 20.22]</td>
<td></td>
</tr>
<tr>
<td>Suzuki 2012</td>
<td>3</td>
<td>24</td>
<td>0.11 [0.02, 0.73]</td>
<td></td>
</tr>
<tr>
<td>Zasowski 2017</td>
<td>7</td>
<td>209</td>
<td>0.28 [0.11, 0.72]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>551</td>
<td>268</td>
<td>0.36 [0.23, 0.56]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>48</td>
<td>51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 5.83$, df = 4 ($P = 0.21$); $I^2 = 31%$</td>
<td>Test for overall effect: $Z = 4.55$ ($P &lt; 0.000001$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.2 AUC 24–48</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Lodise 2017</td>
<td>26</td>
<td>124</td>
<td>0.54 [0.29, 1.00]</td>
<td></td>
</tr>
<tr>
<td>Zasowski 2017</td>
<td>8</td>
<td>219</td>
<td>0.29 [0.11, 0.73]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>343</td>
<td>192</td>
<td>0.45 [0.27, 0.75]</td>
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</tr>
<tr>
<td>Total events</td>
<td>34</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 1.18$, df = 1 ($P = 0.28$); $I^2 = 15%$</td>
<td>Test for overall effect: $Z = 3.06$ ($P = 0.002$)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for subgroup differences: $\chi^2 = 0.42$, df = 1 ($P = 0.52$), $I^2 = 0\%$


<650  >650
Vancomycin AUC\textsubscript{24} and Nephrotoxicity

Nephrotoxicity After Switching from Trough to AUC-guided Dosing

What about the MIC?

• No definite association between vancomycin MIC and outcomes

• More than 90% MRSA isolates have vancomycin MIC ≤1 mg/L

• MIC results are often not known until ~72 hours into therapy
  • AUC/MIC should be optimized early in the course of therapy (24-48 hours)

• There are major limitations to accuracy of MIC measurement
  • Methodology (BMD, Etest, automated systems)
  • Acceptable variability is ±1 dilution (cannot distinguish MIC of 1 mg/L from 0.5 mg/L or 2 mg/L)
  • Inoculum, incubation time, temperature, media, human error, etc.

What about the MIC?

- If MIC truly is 2, must achieve AUC of $\geq 800$ for $\text{AUC/MIC} \geq 400$
  - AUC greater than $\sim 600$ are known to increase the risk of toxicity

- Solution:
  - Treat as if MIC = 1
    - Simplifies the process – can simply target AUC 400-600
  - If patient not improving with AUC 400-600*, alternative agent $\gg$ unnecessary risk of toxicity
Which of the following is most correct regarding AUC-guided dosing versus trough-guided dosing?

A. AUC-guided dosing is more effective
B. AUC-guided dosing is easier
C. AUC-guided dosing is safer
D. AUC-guided dosing offers no advantage
Let’s summarize...

• Vancomycin AUC/MIC approximately ≥400 is considered optimal efficacy target
  • Largely based on retrospective studies of patients with MRSA bacteremia

• Trough is a poor surrogate for AUC, and AUC ≥400 can often be achieved with troughs <15

• AUC-guided dosing reduces risk of nephrotoxicity relative to trough-guided dosing

• Under most circumstances, consider MIC = 1 mg/L and assess clinical response
Still sweating over what to do?
The ABCs of AUC-guided Vancomycin Dosing

C – Consider your unique challenges
How is AUC determined?

Equation-based approach

Bayesian approach
Equation-based Approach

• First-order pharmacokinetic equations
  • Relies on two post-distributional levels (e.g., peak and trough)

• Implementation:
  • Manual calculations
  • Spreadsheet-based calculator
  • Online calculator
  • EMR-based calculator
Bayesian Approach

• Utilizes Baye’s Theorem
  • Describes probability of an event based on prior knowledge or conditions related to the event

Bayesian Prior (Model)
Probability of an individual’s PK based on information from prior patients

Patient-Specific
Dosing regimen and measured drug concentrations

Bayesian Posterior
Revised probability of an individual’s PK (estimates AUC and assists with dose optimization)

<table>
<thead>
<tr>
<th>Pros</th>
<th>Manual Calculations</th>
<th>Spreadsheet/Calculator-based Methods</th>
<th>EMR-based Calculator</th>
<th>Bayesian Software</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Free</td>
<td>• Free/relatively inexpensive</td>
<td>• “Free”</td>
<td>• A single level is often adequate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Pharmacist time spent (++)</td>
<td>Steady-state and specific timing (peak/ trough) not required</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adaptable to changes in clinical status</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EMR-integration offered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pharmacist time spent (+)</td>
</tr>
<tr>
<td>Cons</td>
<td>• Requires 2 steady-state levels</td>
<td>• Requires 2 steady-state levels</td>
<td>• Requires 2 steady-state levels</td>
<td>• Cost may be prohibitive</td>
</tr>
<tr>
<td></td>
<td>• Not adaptive</td>
<td>• Not adaptive</td>
<td>• Requires significant IT support to implement</td>
<td>Few commercially available products</td>
</tr>
<tr>
<td></td>
<td>• Most complex/prone to human error</td>
<td>• Pharmacist time spent (+++)</td>
<td>• Not adaptive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pharmacist time spent (++++)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Which Patients will be Excluded?

• None
  • Most possible with use of Bayesian software (models exist for challenging populations)

• Patients with meningitis or other central nervous infections
  • Troughs 15-20 mg/L recommended, but evidence supporting improved efficacy is lacking
  • Balance with risk of toxicity with troughs >15 mg/L

• Patients with acute kidney injury or receiving renal replacement therapy
  • Uncertainties, less predictable with traditional PK calculations (i.e., “snapshot”)
  • Fewer limitations with Bayesian software (i.e., more dynamic and better predictability)

• Those in which routine monitoring is unlikely to affect outcomes
  • Surgical prophylaxis
  • Uncomplicated skin and soft tissue infections
Effects on other stakeholders

• Likely increase in time spent collecting blood samples
• Consider increase in cost due to increase in number of samples needed for monitoring

• Education
  • Rationale for process change (patient safety as a priority)
  • Interpretation of new dosing targets
  • Do not be alarmed when peak values are reported
  • Communication is key
    • Report any delays in dosing so timing of blood sampling can be adjusted accordingly
    • Accurately report timing of blood sampling

Post-implementation Follow-up

• Goal is to improve patient safety/outcomes
• Continual quality improvement
• Track/report rate of vancomycin-associated acute kidney injury
  • Can help demonstrate success
    • Key stakeholders
    • Hospital committees
    • Joint Commission
  • Serves as positive feedback to staff (effort is making an impact)

Which of the following is/are necessary to successfully implement AUC-guided vancomycin dosing?

A. Ability to calculate AUC in your head
B. Understanding the rationale for AUC-guided dosing
C. Track progress and provide feedback to staff
D. B and C
The ABCs of AUC-guided Vancomycin Dosing

A – Antimicrobial stewardship is key
  • Ensure vancomycin use is appropriate

B – Build buy-in using data
  • More precise monitoring method
  • Significant safety advantage

C – Consider your unique challenges
  • Choose best strategy for your institution
  • Follow-up to ensure goals are being achieved
Questions?

BRACE YOURSELVES

NEW VANCOMYCIN GUIDELINES ARE COMING