Vancomycin Dosing
Implementing the 2020 Guidelines

Webinar
June 3, 2020
Presenters

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Albany College of Pharmacy & Health Sciences

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Cedars-Sinai Medical Center
Implementing the 2020 Vancomycin Guidelines
What You Need To Know

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Clinical Pharmacist, Stratton VA Medical Center
Albany, New York
Recommendations for Vancomycin Dosing and Therapeutic Drug Monitoring (Simplified)

- In patients with suspected or definitive serious MRSA infections, an individualized target AUC/MIC<sub>BMD</sub> ratio of 400 to 600 (assuming a vancomycin MIC<sub>BMD</sub> of 1 mg/L) should be advocated to achieve clinical efficacy while improving patient safety (A-II).

- Given the importance of early, appropriate therapy, vancomycin targeted exposure should be achieved early during the course of therapy, preferably within the first 24 to 48 hours (A-II).

- When the MIC<sub>BMD</sub> >1 mg/L, the probability of achieving an AUC/MIC target of ≥400 is low with conventional dosing; higher doses may risk unnecessary toxicity, and the decision to change therapy should be based on clinical judgment.

- When the MIC<sub>BMD</sub> <1 mg/L, we do not recommend decreasing the dose to achieve the AUC/MIC target.
Recommendations for Vancomycin Dosing and Therapeutic Drug Monitoring (Simplified 2)

- Trough-only monitoring, with a target of 15 to 20 mg/L, is no longer recommended, based on efficacy and nephrotoxicity data in patients with serious infections due to MRSA (A-II).

- There is insufficient evidence to provide recommendations on whether trough-only or AUC-guided vancomycin monitoring should be used among patients with noninvasive MRSA or other infections.

The clinical benefits of maintaining vancomycin trough values in 15-20 mg/L have not been well described.\textsuperscript{1-7} 

Link between clinical success and vancomycin trough values only observed in one study among MRSA bacteremic patients.\textsuperscript{3}

- Failure among patients with troughs < 15 mg/L: 61%
- Failure among patients with troughs between 15-20 mg/L: 40%
- Failure rate among patients with trough > 20 mg/L: 50%

Vancomycin-Induced Nephrotoxicity in “15-20 mg/L” Trough Era: A Systematic Review and Meta-Analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Troughs &gt; 15 mg/L</th>
<th>Troughs &lt; 15 mg/L</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Bosso et al (3)</td>
<td>42</td>
<td>142</td>
<td>13</td>
<td>146</td>
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<tr>
<td>Cano et al (4)</td>
<td>22</td>
<td>89</td>
<td>7</td>
<td>99</td>
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<td>Chung et al (7)</td>
<td>12</td>
<td>25</td>
<td>16</td>
<td>48</td>
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<tr>
<td>Herzemsen et al (19)</td>
<td>5</td>
<td>16</td>
<td>4</td>
<td>39</td>
</tr>
<tr>
<td>Hidayat et al (20)</td>
<td>11</td>
<td>63</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Jeffres et al (24)</td>
<td>27</td>
<td>49</td>
<td>13</td>
<td>45</td>
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<tr>
<td>Kralovicova et al (26)</td>
<td>21</td>
<td>60</td>
<td>29</td>
<td>138</td>
</tr>
<tr>
<td>Kullar et al (27)</td>
<td>27</td>
<td>139</td>
<td>23</td>
<td>141</td>
</tr>
<tr>
<td>Kullar et al (28)</td>
<td>8</td>
<td>116</td>
<td>1</td>
<td>84</td>
</tr>
<tr>
<td>Lodise et al (36)</td>
<td>7</td>
<td>27</td>
<td>14</td>
<td>139</td>
</tr>
<tr>
<td>McKamy et al (38)</td>
<td>16</td>
<td>57</td>
<td>8</td>
<td>110</td>
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<tr>
<td>Minejima et al (40)</td>
<td>17</td>
<td>72</td>
<td>25</td>
<td>155</td>
</tr>
<tr>
<td>Prabaker et al (49)</td>
<td>7</td>
<td>54</td>
<td>24</td>
<td>294</td>
</tr>
<tr>
<td>Zimmerman et al (63)</td>
<td>8</td>
<td>12</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>921</td>
<td>1,503</td>
<td>100.0%</td>
<td>2.76 [1.94, 3.93]</td>
</tr>
<tr>
<td>Total events</td>
<td>230</td>
<td>177</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.18; Chi^2 = 23.80, df = 13 (P = 0.03); I^2 = 45%
Test for overall effect: Z = 5.66 (P < 0.00001)

Larger Vancomycin Doses Are Associated With An increased Incidence of Nephrotoxicity


This information was presented at the “Implementing The New Vancomycin Guidelines: What You Need To Know” webinar held on June 3, 2020
Trough Value Alone is a Poor Surrogate of AUC
# The VAN AUC Threshold for Toxicity

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Breakpoints for Nephrotoxic Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lodise 2009</td>
<td>Retrospective – all infection types</td>
<td>Nephrotoxicity risk ↑ 2.5-fold if ( AUC \geq 1,300 ) Nephrotoxicity risk ↑ 1.13-fold every 1 mg/L trough ↑</td>
</tr>
<tr>
<td>Suzuki 2012</td>
<td>Retrospective – MRSA LRTI</td>
<td>Nephrotoxicity: ( AUCs\ 600-800 ) (most patients) Non-Nephrotoxicity: AUCs 400-600 (most patients)</td>
</tr>
<tr>
<td>Le 2015</td>
<td>Retrospective – all infection types</td>
<td>Nephrotoxicity risk ↑ 3.7-fold if ( AUC \geq 800 ) Nephrotoxicity risk ↑ 2.5-fold if trough ≥ 15</td>
</tr>
<tr>
<td>Finch 2017</td>
<td>Retrospective – all infection types</td>
<td>Nephrotoxicity risk ↓ ~2-fold using AUC-guided dosing AUC-guided cohort: median AUC 474 (360–611) Trough-guided cohort: median ( AUC 705 ) (540–883)</td>
</tr>
<tr>
<td>Lodise 2019</td>
<td>Multi-center, prospective, observational – MRSA BSI</td>
<td>Risk of nephrotoxicity highest when ( AUC \geq 793 )</td>
</tr>
<tr>
<td>Neely 2018</td>
<td>Prospective – all infection types</td>
<td>Nephrotoxicity: median ( AUC 625 )</td>
</tr>
<tr>
<td>Zasowski 2018</td>
<td>Retrospective – BSI, LRTI</td>
<td>Nephrotoxicity ↑ 3-4-fold if: ( AUC \geq 677 ) or trough ≥ 18.8</td>
</tr>
</tbody>
</table>

Impact of Area Under the Curve-Targeted Dosing on Vancomycin-Associated Nephrotoxicity

Treatment Group

- Trough Monitoring
- AUC Monitoring

P < 0.001
Bayesian Estimated Vancomycin Exposure Profile

<table>
<thead>
<tr>
<th></th>
<th>Trough-guided dosing group (n = 150)</th>
<th>AUC-guided dosing group (n = 150)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_{\text{min24}})  (\text{mg/liter})</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>(C_{\text{min48}})  (\text{mg/liter})</td>
<td>14.2 (10.3–19.5)</td>
<td>12.5 (8.3–16.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>(\text{AUC}_{0–24}) (\text{mg \cdot h/liter})</td>
<td>705 (540–883)</td>
<td>474 (360–611)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(\text{AUC}_{24–48}) (\text{mg \cdot h/liter})</td>
<td>663 (538–857)</td>
<td>532 (406–667)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^{a}\) Data represent the median (IQR)

This information was presented at the “Implementing The New Vancomycin Guidelines: What You Need To Know” webinar held on June 3, 2020.
Consequences of Vancomycin-Associated Acute Kidney Injury

- For most patients, vancomycin-associated AKI (VA-AKI) is mild and resolves within one week after discontinuation of therapy.
- However, even mild cases of VA-AKI have been linked to a variety of adverse outcomes including increased in-hospital mortality, length of stay (LOS) and healthcare resource utilization.
- Data suggest that AKI is often accompanied by remote organ dysfunction, which increases a patient’s susceptibility to a number of conditions (e.g., cardiovascular events, infections due to immunosuppression, etc.) over time.
Vancomycin Exposure Profile and Outcomes Among Patients with Serious MRSA Infections

- Limited clinical data in support of the AUC/MIC ratio > 400 target among patients with infections due to MRSA.¹-³
- Most published vancomycin exposure-response clinical evaluations¹-³ used a simple formula based on total daily vancomycin dose and estimated renal function to estimate the AUC.
  - It is nearly impossible to generate valid estimates of exposure variables in a given individual based on glomerular filtration estimation formulas alone due to the presence of wide inter-patient exposure variability.

AUC = Area under the concentration–time curve
Cₘₐₓ = Maximum plasma concentration

Prospective Observational Evaluation of the Association between the Day 2 Vancomycin Exposure and Failure Rates among Adult, Hospitalized Patients with MRSA Bloodstream Infections (PROVIDE)

- **Study Design**
  - Prospective, multi-center, observational study of adult patients with confirmed MRSA bloodstream infections treated with vancomycin.
  - A validated Bayesian method will be used to estimate the vancomycin exposure profile with limited blood concentration data.

- **Primary Study Objectives**
  - To estimate the difference in failure rates among “evaluable” patients who have vancomycin AUC\(_{\text{DAY2/MICBMD}}\) ratios ≥ 650 relative to those with AUC\(_{\text{DAY2/MICBMD}}\) ratios < 650.
  - To estimate the difference in failure rates among “evaluable” patients who have AUC\(_{\text{DAY2/MICETEST}}\) ratios ≥ 320 relative to those with AUC\(_{\text{DAY2/MICETEST}}\) ratios < 320.

- **Sample size**: 250 evaluable subjects
  - Sufficient power (>80%) at a two-sided alpha of 0.05 to detect a ~15-20% difference in failure rates between dichotomous AUC\(_{\text{DAY2/MIC}}\) exposure variables.

Definition: Failure defined as death within 30 days of index MRSA blood culture OR persistent bacteremia ≥ 7 days after initiation of vancomycin therapy and before therapy completion. Abbreviations: AUC: area under the curve; MIC\(_{\text{BMD}}\): minimum inhibitory concentration values by broth microdilution method; MIC\(_{\text{ETEST}}\): minimum inhibitory concentration value by ETEST™ method.
Comparisons of Outcomes between AUCDAY2/MIC Exposure Groups

Failure*

- AUCDay2/MIC \( \geq 650 \)
  - RD=0.07, 95% CI: -0.03 - 0.17
  - aRD=0.03, 95% CI: -0.06 - 0.11
- AUCDay2/MIC \( \geq 320 \)
  - RD=0.10, 95% CI: 0.01 - 0.19
  - aRD=0.08, 95% CI: -0.07 - 0.23

Acute Kidney Injury**

- AUCDay2/MIC \( \geq 650 \)
  - RD=0.17, 95% CI: 0.05 - 0.28
  - aRD=0.15, 95% CI: 0.02 - 0.29
- AUCDay2/MIC \( \geq 320 \)
  - RD=0.12, 95% CI: -0.00 - 0.24
  - aRD=0.09, 95% CI: -0.04 - 0.22

*All variables associated with failure at \( P \leq 0.1 \) and considered at model entry included: prior receipt of vancomycin, type of MRSA infection (community vs. hospital/healthcare), “other” source of infection, pre-existing valvular heart disease, heart failure, APACHE, age, creatinine clearance at baseline, infective endocarditis, and presence of prosthetic material.

**Patients with Baseline Serum Creatinine (< 2.0 mg/dL). All variables associated with acute kidney injury at \( P \leq 0.1 \) and considered at model entry included: race, prior surgery, urinary source, prior hospital length of stay, creatinine clearance baseline, and prior vancomycin.
Study findings suggest that daily 2 AUCs should be maintained between 400-515 to maximize efficacy and minimize the likelihood of AKI.
AUC vs. AUC/MIC guided dosing

- The MIC value is of less importance for several reasons.
  - There is a narrow range of vancomycin MIC values by broth microdilution (the gold standard) among contemporary MRSA isolates (observed here and in other studies), with values of 0.5 or 1 mg/L in most institutions.
  - There is inherent imprecision of MIC measurement, with a range of accuracy of ± 1 log2 dilutions.
  - MIC values are typically not available within the first 72 hours of index culture collection.
  - There is a high degree of variability between MIC testing methods typically used in health care institutions relative to the broth microdilution MIC method.
Bayesian and Equation-Based Approaches to Estimating the AUC

This information was presented at the “Implementing The New Vancomycin Guidelines: What You Need To Know” webinar held on June 3, 2020.
Bayesian Approach to AUC Estimation

- Bayesian software only requires four specific components
  - Structural mathematical model that best describes the pharmacokinetics of a given agent
  - Density file, which contains the parameter estimates and their associated dispersion for the embedded structural PK model (Bayesian prior)
  - Patient file that contains their drug dosing and collected PK data
  - Patient “target” file which contains the target exposure profile and initial estimates of future dosing regimens

- With this information, the Bayesian dose optimization software calculates a Bayesian posterior parameter value file or that patient.
  - The dose optimization software then calculates the optimal dosing regimen based on the specified exposure profile in the target file
Advantages of Bayesian Approach to AUC Estimation

- Innovative treatment schemas such as front-loading doses with a transition to a lower maintenance dosing regimen can be designed to rapidly achieve target concentrations within the first 24 to 48 hours among critically ill patients.
- Concentration-time information does not need to be collected at “steady-state” (after the 3rd or 4th dose).
- Ability to include covariates, such as CL\textsubscript{CR}, in the structural PK models (Bayesian prior density file) that account for the pathophysiological changes that readily occur in critically ill patients.
- It is preferred to obtain 2 PK samples to estimate the AUC with the Bayesian approach (A-II).
  - A trough concentration alone may be sufficient to estimate the AUC with the Bayesian approach in some patients, but more data across different patient populations are needed to confirm the viability of using trough-only data (B-II).
Equation-Based Approach to AUC Estimation

- Use of a post-distributional peak (1-2 hours post infusion) and trough concentrations can be used to determine the daily AUC value with reasonable precision and low bias with simple first-order PK formulas.

- Simple to use and can be programmed into electronic medical system to automatically compute the AUC.

- Disadvantages
  - Highly preferably to have concentration time data over same dosing interval (peak and trough data).
  - Can only provide a snapshot of the AUC for the sampling period.
  - May provide unreliable estimates when drug is not near steady-state conditions.
Equation-Based Approach to AUC Estimation

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## Valid Estimation of the Vancomycin AUC with Trough only Data using Bayesian Estimation Software

<table>
<thead>
<tr>
<th>AUC Estimation Method</th>
<th>Number of Samples</th>
<th>AUC (mg*h/L)</th>
<th>Ratio of computed AUC to reference AUC</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayesian</td>
<td>All</td>
<td>250 [84.1, 688]</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Bayesian</td>
<td>Trough only</td>
<td>259 [82.9, 573]</td>
<td>1.0 [0.74, 1.28]</td>
<td>0.948</td>
</tr>
<tr>
<td>Equation-based method 1</td>
<td>Peak and Trough</td>
<td>239 [90.6, 662]</td>
<td>0.99 [0.83, 1.16]</td>
<td>0.971</td>
</tr>
<tr>
<td>Equation-based method 2</td>
<td>Peak and Trough</td>
<td>247 [100, 675]</td>
<td>1.02 [0.85, 1.22]</td>
<td>0.987</td>
</tr>
</tbody>
</table>

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Evaluation of a Bayesian Approach to Estimate Vancomycin Exposure in Obese Patients with Limited Pharmacokinetic Sampling: A Pilot Study

<table>
<thead>
<tr>
<th>Model</th>
<th>AUC&lt;sub&gt;FULL&lt;/sub&gt; (95% CI)</th>
<th>AUC&lt;sub&gt;PT&lt;/sub&gt; (95% CI)</th>
<th>Ratio to AUC&lt;sub&gt;FULL&lt;/sub&gt; (95% CI)</th>
<th>R²</th>
<th>AUC&lt;sub&gt;T&lt;/sub&gt; (95% CI)</th>
<th>Ratio to AUC&lt;sub&gt;FULL&lt;/sub&gt; (95% CI)</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>437 (296 – 617)</td>
<td>393 (275 – 576)</td>
<td>0.91 (0.87 – 0.95)</td>
<td>0.997</td>
<td>574 (379 – 725)</td>
<td>1.30 (1.19 – 1.40)</td>
<td>0.986</td>
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<tr>
<td>2</td>
<td>478 (305 – 683)</td>
<td>456 (300 – 659)</td>
<td>0.96 (0.93 – 0.99)</td>
<td>0.998</td>
<td>511 (336 – 682)</td>
<td>1.04 (0.97 – 1.13)</td>
<td>0.982</td>
</tr>
<tr>
<td>3</td>
<td>469 (314 – 628)</td>
<td>489 (274 – 620)</td>
<td>0.99 (0.94 – 1.04)</td>
<td>0.997</td>
<td>401 (275 – 482)</td>
<td>0.87 (0.77 – 0.97)</td>
<td>0.974</td>
</tr>
<tr>
<td>4</td>
<td>489 (309 – 604)</td>
<td>412 (308 – 613)</td>
<td>0.93 (0.84 – 1.01)</td>
<td>0.990</td>
<td>520 (278 – 735)</td>
<td>1.13 (0.81 – 1.44)</td>
<td>0.851</td>
</tr>
<tr>
<td>1</td>
<td>437 (296 – 617)</td>
<td>393 (275 – 576)</td>
<td>0.91 (0.87 – 0.95)</td>
<td>0.997</td>
<td>574 (379 – 725)</td>
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Conclusions

- Despite its subsequent widespread integration in clinical practice, the clinical benefits of maintaining higher vancomycin trough values have not been well described.

- Revise consensus guidelines recommend AUC-guided dosing.
  - Bayesian software and first-order PK calculator can be used to reliably estimate the AUC with limited PK samples.

- Stewardship teams play a critical role in implementation and assessment of vancomycin AUC-guided dosing programs.
Developing an AUC-Based Dosing Implementation Plan and Defining a New Vancomycin Dosing Protocol


Ethan A. Smith, PharmD, BCIDP
Program Coordinator – Antimicrobial Stewardship
Cedars-Sinai Medical Center
GP is a 32 year old, healthy male, no past medical history

Presents with 3-day history of left thigh pain/redness

Vitals in the emergency department
- HR: 120 beats/min | BP: 100/60 mmHg
- Temp: 102°F (38.9 °C) | WBC: 18,000/mm³ | SCr: 0.7 mg/dL

Blood cultures drawn, GP admitted

Vancomycin 1,000 mg Q8h + Ceftriaxone 2,000 mg Q24h
Some Food… Vanco For Thought

- Blood cultures @ 12 hours = MRSA by rapid diagnostics
- GP has clinically stabilized, VAN trough due before 5th dose
  - Trough goal per protocol = 15-20 mg/L
  - GP’s trough = 13.6 mg/L

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Poll Question #3

• What should be done?
  a) Continue 1,000 mg Q8h
  b) Increase to 1,250 mg Q8h
  c) Need more information
  d) 🦭…change to daptomycin (hint: no)
Blood cultures @ 12 hours = MRSA by rapid diagnostics

GP has clinically stabilized, VAN trough due before 5th dose
  ◦ Trough goal per protocol = 15-20 mg/L
  ◦ GP’s trough = 13.6 mg/L

What should be done?
  a) Continue 1,000 mg Q8h
  b) Increase to 1,250 mg Q8h
  c) Need more information
  d) 🤷‍♂️...change to daptomycin (hint: no)
Some Food... Vanco For Thought

- Additional information reveals...

- **Continue 1,000 mg Q8h (trough 13.6mg/L):**
  - Calculated $AUC_{0-24} = 582$ mg•hr/L
  - *Therapeutic* $AUC_{0-24} = 400-600$ mg•hr/L

- **Increase to 1,250 mg Q8h:**
  - Estimated trough $\frac{13.6 \text{ mg/L}}{1,000 \text{ mg}} = \frac{x \text{ mg/L}}{1,250 \text{ mg}} \implies x = 17$ mg/L
  - Corresponding $AUC_{0-24} = 748$ mg•hr/L
  - Nephrotoxicity ↑ if $AUC_{0-24} > 700-800$ mg•hr/L

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Troughs are poorly correlated with AUC.

Dosing Outdated

AUC

Troughs are a suboptimal dosing target

Insight Path

Data/Illustration

Action

Insights

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Step 1 – Identify The Scope of the “Problem”

- What are the current vancomycin (VAN) dosing processes?
  - Trough-based or AUC-based?
  - What calculators or nomograms are being used?
  - Who is dosing vancomycin (physicians, pharmacists, other)?

- What are the barriers to implementing a new process?
  - How do we break the 15-20 mg/L trough goal habit?
  - Staff familiarity, adaptability?
  - What financial resources are available?
  - What computer/technical resources are available?
  - Who is available to take the lead?
Step 2 – Determine How AUC is Calculated

• “Home-Grown” Excel® Calculator
  ◦ What equations are going to be used?
  ◦ Who has the expertise to program/validate the calculator?
  ◦ Where will this calculator be available?
  ◦ What processes need to be in place if calculator crashes?

• 3rd-Party Bayesian Software
  ◦ What models are needed and is a test-platform available?
  ◦ How many users are required?
  ◦ Which program is most cost-effective?
  ◦ Will EHR integration be desired?
To Bayesian, or not to Bayesian

- Must make a determination what is most practical & budget-friendly for each institution

<table>
<thead>
<tr>
<th>Parameters</th>
<th>First-Order Equations</th>
<th>Bayesian Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>Patient-Specific</td>
<td>Population + Patient-Specific</td>
</tr>
<tr>
<td>Formulas</td>
<td>Simple</td>
<td>Complex</td>
</tr>
<tr>
<td>Flexibility</td>
<td>Static</td>
<td>Predictive/Adaptive</td>
</tr>
<tr>
<td>Levels Needed</td>
<td>Peak/Trough <strong>Required</strong></td>
<td>Trough-Only <strong>OR</strong> Peak/Trough</td>
</tr>
<tr>
<td>Obtaining Levels</td>
<td>Steady-State</td>
<td>First 24-48 Hours</td>
</tr>
<tr>
<td>Level Timing</td>
<td>Precise Timing <strong>Required</strong></td>
<td>Timing “Agnostic”</td>
</tr>
</tbody>
</table>

Justifying the $$$ for Bayesian Software

• **Nephrotoxicity & AUC Dosing – Detroit Medical Center**
  ◦ Pre-implementation: nephrotoxicity rate = 6%
  ◦ Post-implementation: nephrotoxicity rate = 3%
  50% Relative Reduction

• **Hypothetical Medical Center** (1,500 courses of VAN/year)
  ◦ 1,500 x 0.06 = 90 cases of nephrotoxicity/year
  ◦ 90 x $15,639* = $1,407,510/year
  ◦ 50% reduction = 45 cases of nephrotoxicity prevented
  ◦ 45 x $15,639* = $703,755/year due to toxicity avoided
  ◦ Bayesian software: $5,000-$30,000/year
  ◦ **Cost avoidance: $675,000+**

*2003 study – cost adjusted for inflation

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Step 3 – Buy-in from Key Stakeholders

• Who are the key players?
  ◦ Pharmacist expert/champion?
  ◦ Physician expert/champion?
  ◦ What committees/divisions need to approve?
  ◦ Timeline for IT review of 3rd-party software?
  ◦ Timeline for legal to review 3rd-party software contracting?

• How to present the information?
  ◦ Improved safety/efficacy (patient outcomes)
  ◦ Potential for reduction in costs (reduction in AKI / level monitoring)
Step 4.1 – Revise VAN Dosing Policies

- Determine who is excluded from AUC-based dosing
  - VAN for surgical prophylaxis
  - Peritoneal dialysis patients
  - Hemodialysis patients (if not using Bayesian)
  - Continuous Renal Replacement Therapy (CRRT)
    - Depending on ability to do continuous infusion
    - Others?

- Provide guidance on organism and MIC
  - Assume MIC = 1 mg/L for *S. aureus*
  - Don’t lower AUC goal if MIC < 1 mg/L
  - For non-*S. aureus* – AUC goal 400-600 mg•hr/L or trough 15-20 mg/L?
Step 4.2 – Revise VAN Dosing Policies

• Provide guidance on choosing a Bayesian dosing model
  ◦ Will vary depending on models purchased
  ◦ Definitions for obesity
  ◦ When to use 1-compartment vs. 2-compartment model

• Provide guidance on trough-only or peak-trough TDM
  ◦ 2020 guidelines recommend 2-level TDM
  ◦ What is the likelihood that 2-level TDM can be broadly implemented?
  ◦ Is there any data supporting single-level TDM?
  ◦ What happens when patients go home on vancomycin?
Bayesian software was able to reliably estimate AUC with trough-only PK sampling

- Trough-only PK = calculated AUCs ≈ 80-100% of reference
- If aiming for AUC in middle of goal range (~500), the slight variation in calculated AUC is unlikely to substantially impact target attainment
- Single-level AUC estimation = improvement over trough goals 15-20
- Two-level AUC estimation further improved accuracy of calculated AUCs (≈ 90-100% of reference) consider 2 levels for:
  - Hemodynamic instability or dynamic renal function
  - Critical illness or severe infection
Step 5.1 – Implementation

• After necessary approvals have been secured
  ◦ Determine a practical “go-live date”
  ◦ Assign roles/responsibilities for aspects of implementation
  ◦ Develop staff training packet/reference
  ◦ Consider local CE presentation/inservice(s)
  ◦ If using Bayesian software, training may be included from vendor
  ◦ Develop case-based competency, users to pass competency prior to using new dosing processes

• Arrange provider-oriented education
  ◦ Residents, ID providers, high-volume hospitalists
Step 5.2 – Implementation

• Consider utilizing “superuser” process
  ◦ Identify interested pharmacists
  ◦ Choose pharmacists from different areas/shifts
  ◦ Superusers to serve as experts for their areas
  ◦ Develop a more comprehensive training process (essential reading materials, more in-depth/live training)
  ◦ Encourage superusers to answer questions/consults prior to staff reaching out to coordinators/managers
  ◦ Consider those who volunteered for superuser in yearly evaluations/career ladders
Step 5.3 – Implementation Checklist

• Tying steps 5.1 and 5.2 together
  ◦ The “playbook” or “roadmap” for ensuring the transition goes smoothly and to hold participants accountable
  ◦ Break down larger tasks into smaller goals
  ◦ Establish deadlines for each aspect to meet go-live date
  ◦ Schedule times for training(s)/inservice(s)
  ◦ Re-present at division/committee meetings closer to the go-live date as a reminder
  ◦ Ensure ample time for staff to review and pass competencies and ask questions

This information was presented at the “Implementing The New Vancomycin Guidelines: What You Need To Know” webinar held on June 3, 2020
Step 6.1 – Post-Implementation

• **Vancomycin rounds**
  ◦ Daily opportunity for front-line staff to “ask the expert”
  ◦ Encourage staff to submit interesting/challenging cases, disseminate to all staff
  ◦ Identify opportunities to revise dosing policies/workflows (if needed)

• **Staff resources**
  ◦ Develop a “living” FAQ document that is updated on a regular basis
  ◦ Post educational materials in a location that is easily accessible, so front-line staff can revisit as necessary
  ◦ Consider a “how-to” video series on a regular basis
Step 6.2 – Post-Implementation

**METRICS!!**

- How will you define your success?
- Rates of creatinine increase?
- First level(s) in therapeutic range?
- Time to therapeutic AUC?
- What baseline metrics do you have – can you directly compare?
- Are there any automated reports you can leverage?
- What groups of key-stakeholders need to see data?
- Track as a stewardship metric for accreditation (e.g. Joint Commission)
Conclusions

• No one-size-fits-all approach to calculate AUCs
  ◦ Depends on many factors, including hospital demographics
  ◦ Avoidance of toxicity is key in justifying costs

• An exercise in change management vs. clinical application
  ◦ The clinical why is easily justified, the how presents the biggest challenge
  ◦ Breaking old habits is hard
  ◦ Cannot extrapolate assumptions of traditional trough-based dosing to AUC-based dosing (particularly a Bayesian approach)
  ◦ Utilize high-performers as superusers
References


Resources
Start a Free Trial:
www.doseme-rx.com/start-trial

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