Vancomycin Dosing: Bayesian derived AUC/MIC vs. trough only monitoring

Meagan Ellinger PharmD
Vancomycin Dosing: Bayesian Derived AUC/MIC vs. Trough Only Monitoring

Meagan Ellinger, PharmD
PGY-1 Pharmacy Resident
Parkview Health

The speaker has no actual or potential conflicts of interest in relation to this presentation.
Background

- Area under the curve ($\text{AUC}_{24}$)
  - Total concentration of drug in the body for a 24 hour duration
- Minimum inhibitory concentration (MIC)
  - Minimum concentration needed in the body to inhibit bacterial growth
- AUC/MIC ratio
  - Concentration of drug in the body for a 24 hour duration divided by the organisms MIC
- Trough
  - Lowest concentration of drug in the body
  - Surrogate marker for AUC

Vancomycin concentration

- 15 mcg/mL
- 24 hours

Time
## Previous Studies

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>Meta-analysis (15 studies)</td>
<td>Retrospective cohort (n=1,280)</td>
<td>Retrospective cohort (n=21,285)</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Incidence of nephrotoxicity</td>
<td>Incidence of nephrotoxicity</td>
<td>Frequency and risk factors for elevated vancomycin concentrations</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>Troughs ≥ 15 mcg/mL were associated with increased nephrotoxicity compared to troughs &lt; 15 mcg/mL (OR 2.67 [95% CI: 1.95-3.65])</td>
<td>AUC-guided dosing was associated with less nephrotoxicity compared to trough-guided dosing (OR 0.52 [95% CI: 0.34-0.80])</td>
<td>Patients with elevated concentrations had longer durations of vancomycin therapy (p&lt;0.001) and longer lengths of stay (p=0.03)</td>
</tr>
</tbody>
</table>
A Bayesian-derived AUC/MIC ratio of 400 to 600 should be advocated as the target to achieve clinical efficacy while improving patient safety.
The most accurate and optimal way to manage vancomycin dosing is through **AUC-guided dosing and monitoring**.

1. Utilize 1st order pharmacokinetic calculations to estimate AUC based on collection of two concentrations

2. Collect one or two concentrations to estimate AUC with the use of Bayesian software programs

Rybak et al. 2019
Benefits of Bayesian Kinetics

- Compared to 2 point pharmacokinetics:
  - Reduced lab sticks to the patient
  - Less frequent monitoring
  - Fewer timing issues with lab draws

- Compared to the trough-based method:
  - Non-inferior efficacy with potentially improved safety
  - Equivalent or less lab costs
  - Shorter hospital length of stay, if reduced complications
New guidelines recommend targeting which of the following when dosing and monitoring vancomycin therapy?

A. Trough 15-20 mcg/mL
B. AUC 400-600
C. AUC < 400
D. Trough 20-25 mcg/mL
New guidelines recommend targeting which of the following when dosing and monitoring vancomycin therapy?

A. Trough 15-20 mcg/mL
B. AUC 400-600
C. AUC < 400
D. Trough 20-25 mcg/mL
Studies have found that utilizing AUC/MIC-based dosing for vancomycin can:

A. Reduce the risk of developing acute kidney injury (AKI)
B. Increase the total daily dose of vancomycin
C. Increase overall hospital use of vancomycin
D. Lead to higher trough concentrations
Studies have found that utilizing AUC/MIC-based dosing for vancomycin can:

A. Reduce the risk of developing acute kidney injury (AKI)
B. Increase the total daily dose of vancomycin
C. Increase overall hospital use of vancomycin
D. Lead to higher trough concentrations
To investigate whether Bayesian derived AUC/MIC dosing results in reduced incidence of acute kidney injury (AKI) compared to trough-based dosing in patients being treated with vancomycin at our hospital.
Parkview Regional Medical Center (PRMC)

- Parkview Health
- Community hospital
- Level II trauma center
- 460 adult and pediatric inpatient beds
- 6 critical care units
Vancomycin Pharmacy Dosing Protocol

**Loading dose**
- 25 mg/kg (max 2500 mg)
- Indications: endocarditis, meningitis, osteomyelitis, pneumonia, sepsis

**Maintenance dose**
- 15 mg/kg (max 1500 mg)
- Adjust frequency for renal function (Creatinine clearance)

**Target trough:**
- 10-15 mcg/mL (mild/moderate skin & soft tissue infections and urinary tract infections)
- 15-20 mcg/mL (all other indications)
Study Design

• Single center
• October 2019 to March 2020
• Prospective enrollment with retrospective analysis
  • 8 study team members
  • Institutional Review Board approved
  • Informed consent not required (AUC dosing adopted per hospital policy)
• Grant was obtained to cover the cost of the temporary use of the pharmacokinetic software program
<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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</thead>
<tbody>
<tr>
<td>• Pharmacy-to-dose consult for ongoing vancomycin therapy</td>
<td>• Pregnancy/breastfeeding</td>
</tr>
<tr>
<td>• ≥ 18 years old</td>
<td>• Receiving vancomycin prior to admission</td>
</tr>
<tr>
<td>• Admitted to PRMC</td>
<td>• Peri-operative vancomycin</td>
</tr>
<tr>
<td>• At least one vancomycin concentration obtained</td>
<td>• Renal replacement therapy</td>
</tr>
</tbody>
</table>
Given limited data for using trough concentrations alone to estimate AUC in certain populations…

- Guidelines recommend obtaining **two concentrations** for patients meeting the following criteria:
  - Critically ill
  - Unstable renal function
  - BMI ≥ 40 kg/m²

- Patients not meeting the above criteria had an AUC estimated based off the collection of **one concentration**
**Study Design**

**Control group**
- Trough based
- Managed by non-study team pharmacists per PRMC trough-based dosing protocol

**AUC/MIC group**
- Bayesian, one level
  - Target AUC: 500
  - Non-critically ill
  - Stable renal function
  - BMI < 40 kg/m²
- Bayesian, two levels
  - Critically ill
  - Unstable renal function
  - BMI ≥ 40 kg/m²
Study Workflow

1. Study team identifies patients with a pharmacy to dose consult for vancomycin
2. Initiate AUC/MIC dosing utilizing Bayesian pharmacokinetic software
3. Obtain concentration(s) within 24-48 hours to calculate AUC/MIC
4. Continue or adjust dosing to target AUC/MIC of 400-600
Endpoints

- Primary endpoint:
  - Incidence of AKI as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria
    - Rise in serum creatinine by $\geq 0.3$ mg/dL within 48 hours or $\geq 1.5$ times baseline within 7 days

- Secondary endpoints:
  - Average total daily dose of vancomycin (mg/kg)
  - Intensive care unit (ICU) length of stay (LOS)
  - Total LOS
  - Receipt of at least one concomitant nephrotoxin
  - Total days receiving vancomycin
AUC/MIC patients with a calculated AUC were matched to control patients in a 1:2 manner based on:

<table>
<thead>
<tr>
<th>Matching</th>
<th>Age</th>
<th>Renal function (Cockcroft-Gault)</th>
<th>ICU vs non-ICU</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 40 years</td>
<td>&lt; 44 mL/min</td>
<td>Any ICU stay &lt; 24 hours during admission</td>
<td>&lt; 30 kg/m²</td>
</tr>
<tr>
<td></td>
<td>≥ 40 years</td>
<td>45 – 64 mL/min</td>
<td></td>
<td>30 – 40 kg/m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65 – 100 mL/min</td>
<td>Any ICU stay ≥ 24 hours during admission</td>
<td>&gt; 40 kg/m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 100 mL/min</td>
<td></td>
<td></td>
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</tbody>
</table>
Statistical Analysis

- Primary endpoint
  - Categorical data was assessed with the Chi square test

- Secondary endpoints
  - Continuous data were assessed with the T-test

- Secondary analysis
  - Intention-to-treat

- Subgroup analysis in the AUC/MIC group comparing one vs two concentrations
# Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>AUC/MIC dosing (n = 101)</th>
<th>Trough dosing (n = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>63.0 (54.0 – 72.0)</td>
<td>62.5 (54.0 – 72.8)</td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>41.6%</td>
<td>36.6%</td>
</tr>
<tr>
<td>Race, white (%)</td>
<td>94.1%</td>
<td>91.6%</td>
</tr>
<tr>
<td>Weight (kg), median (IQR)</td>
<td>87.5 (69.7 – 104.3)</td>
<td>88.5 (69.3 – 104.3)</td>
</tr>
<tr>
<td>BMI (kg/m²), median (IQR)</td>
<td>29.4 (24.4 – 35.3)</td>
<td>29.7 (24.4 – 34.7)</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min), median (IQR)</td>
<td>83.8 (54.3 – 109.4)</td>
<td>82.9 (54.2 – 112.9)</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>AUC/MIC, one level (n = 64)</th>
<th>AUC/MIC, two levels (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>64.5 (51.8 – 73.3)</td>
<td>62.0 (55.0 – 71.0)</td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>45.3%</td>
<td>35.1%</td>
</tr>
<tr>
<td>Race, white (%)</td>
<td>93.8%</td>
<td>94.6%</td>
</tr>
<tr>
<td>Weight (kg), median (IQR)</td>
<td>84.2 (67.4 – 94.5)</td>
<td>105.2 (85.0 – 136.5)</td>
</tr>
<tr>
<td>BMI (kg/m²), median (IQR)</td>
<td>28.0 (24.3 – 31.2)</td>
<td>35.3 (27.0 – 45.1)</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min), median (IQR)</td>
<td>83.7 (56.4 – 105.4)</td>
<td>84.2 (48.4 – 123.4)</td>
</tr>
<tr>
<td>ICU admission &gt;24 hours (%)</td>
<td>12.5%</td>
<td>35.1%</td>
</tr>
</tbody>
</table>
Primary Outcome (Per Protocol)

AUC/MIC Dosing (n = 101)
- 13% AKI
- 87% No AKI

Trough Dosing (n = 202)
- 16% AKI
- 84% No AKI

p = 0.49
Primary Outcome (Intention-to-Treat)

AUC/MIC Dosing (n = 231)
- 15% AKI
- 85% No AKI

Trough Dosing (n = 1378)
- 15% AKI
- 85% No AKI

p = 0.97
Average Daily Vancomycin Dose (Per Protocol)

<table>
<thead>
<tr>
<th></th>
<th>Dose (mg), median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC/MIC dosing</td>
<td>2525 (2020 – 3162)</td>
</tr>
<tr>
<td>Trough dosing</td>
<td>3180 (2461 – 3991)</td>
</tr>
</tbody>
</table>

\[ p < 0.05 \]
## Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>AUC/MIC dosing (n = 101)</th>
<th>Trough dosing (n = 202)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU LOS (days), median (IQR)</td>
<td>4.8 (2.8 – 7.4)</td>
<td>5.6 (3.4 – 9.6)</td>
<td>0.24</td>
</tr>
<tr>
<td>Total LOS (days), median (IQR)</td>
<td>5.9 (3.3 – 8.9)</td>
<td>5.3 (3.3 – 8.6)</td>
<td>0.76</td>
</tr>
<tr>
<td>Total days on vancomycin,</td>
<td>2.1 (1.5 – 3.2)</td>
<td>1.8 (1.1 – 2.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receipt of 1+ concomitant</td>
<td>86.1%</td>
<td>84.2%</td>
<td>0.65</td>
</tr>
<tr>
<td>nephrotoxin(s)</td>
<td></td>
<td></td>
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</table>
### Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>AUC/MIC, one level (n=64)</th>
<th>AUC/MIC, two levels (n=37)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average daily dose of vancomycin (mg/kg), median (IQR)</td>
<td>2527 (1916 – 3158)</td>
<td>3396 (2324 – 4351)</td>
<td>0.35</td>
</tr>
<tr>
<td>ICU LOS, median (IQR)</td>
<td>3.3 (3.0 – 6.8)</td>
<td>3.8 (2.3 – 6.6)</td>
<td>0.25</td>
</tr>
<tr>
<td>Total LOS, median (IQR)</td>
<td>5.7 (3.0 – 8.5)</td>
<td>5.0 (3.3 – 8.0)</td>
<td>0.45</td>
</tr>
<tr>
<td>Total days on vancomycin, median (IQR)</td>
<td>2.4 (1.5 – 3.4)</td>
<td>1.6 (1.0 – 2.6)</td>
<td>0.78</td>
</tr>
<tr>
<td>AUC, median (IQR)</td>
<td>421 (364 – 502)</td>
<td>423 (307 – 475)</td>
<td></td>
</tr>
</tbody>
</table>
Concomitant Nephrotoxins

**AUC/MIC Dosing**

- 14% None
- 18% One
- 30% Two
- 38% Three or more

**Trough Dosing**

- 16% None
- 13% One
- 34% Two
- 37% Three or more

<table>
<thead>
<tr>
<th>Medication</th>
<th>AUC/MIC (n = 101)</th>
<th>Trough (n = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin/tazobactam</td>
<td>70 (69.3%)</td>
<td>127 (62.9%)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>34 (33.7%)</td>
<td>66 (32.7%)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>12 (11.9%)</td>
<td>35 (17.3%)</td>
</tr>
</tbody>
</table>
Conclusions

- There was no difference in AKI between the AUC-guided and trough-based dosing groups
  - All of the patients with AKI received at least one concomitant nephrotoxin
  - Combination of vancomycin and piperacillin/tazobactam can increase risk of AKI compared with other broad-spectrum regimens
- Clinically and statistically significant difference in average total daily dose of vancomycin
  - AUC/MIC patients received on average 650 mg less than trough patients
  - Potential cost savings
- No significant difference in LOS or ICU LOS
  - Overall low enrollment of ICU patients
Limitations

- Single center, small sample size
- Limited enrollment with only project pharmacist(s) able to enroll patients in the AUC/MIC dosing group
- Retrospective data review (for the trough dosing patients)
- High rate of vancomycin discontinuation before concentrations could be obtained
- Low enrollment of ICU patients and patients with poor renal function
Future Directions

• Expanded enrollment
  • ICU patients
  • Patients with poor renal function
• Explore other AUC dosing calculators
Acknowledgements

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- Jenna C. Deininger, PharmD


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Meagan Ellinger, PharmD
PGY-1 Pharmacy Resident
Parkview Health
meagan.ellinger@parkview.com
Concomitant Nephrotoxins

- Acyclovir, ganciclovir, valacyclovir, valganciclovir
- Amphotericin B (liposomal and conventional)
- Amikacin, gentamicin, tobramycin
- Captopril, enalapril, enalaprilat, lisinopril
- Carboplatin, cisplatin
- Cefotaxime, ceftazidime, cefuroxime
- Cidofovir, foscarnet
- Colistimethate
- Cyclosporine, methotrexate, sulfasalazine
- Dapsone
- Furosemide, torsemide, bumetanide
- Gadopentetate dimeglumine, gadoextate disodium, iodixanol, iopamidol, ioversol, iohexol, gadobutrol
- Ibuprofen, ketorolac
- Ifosfamide
- Lithium
- Mesalamine
- Nafcillin, piperacillin/tazobactam
- Sirolimus, tacrolimus
- Topiramate
- Zonisamide