Get Your Levels Out of the Trough: Moving from Trough-based to Area Under the Curve Vancomycin Monitoring

Mary R Shreffler, PharmD, BCPS
Family Medicine Clinical Pharmacist
OU Medical Center

OSHP 2019 Fall Meeting

Financial Disclosure and Resolution

- Under guidelines established by the Accreditation Council for Pharmacy Education (ACPE), disclosure must be made regarding financial relationships with commercial interests within the last 12 months.
- I have no relevant financial relationships or affiliations with commercial interests to disclose.
Learning Objectives

At the completion of this activity, pharmacists will be able to:

1. State the latest clinical practice recommendations for monitoring vancomycin
2. Describe the different methods for calculating area under the curve
3. Outline potential steps to transition to area under the curve vancomycin monitoring

Pre-Assessment Question 1

What is the best pharmacokinetic/pharmacodynamic parameter for monitoring vancomycin?

A. Time above MIC
B. Trough monitoring
C. AUC/MIC
D. Cmax:MIC
Pre-Assessment Question 2
What is one disadvantage to trapezoidal AUC dosing strategy?

A. Vancomycin drug level can be drawn at anytime
B. Does not allow for physiological changes in the patient
C. Can be used in patients on continuous renal replacement therapy
D. Equations may be integrated into a spreadsheet for use

Pre-Assessment Question 3
Which of the following have not been identified as a barrier to implementing an AUC dosing strategy?

A. Questionable benefit of AUC dosing
B. Provider unfamiliarity
C. Time for training
D. Lack of ID trained pharmacists
Discussion Outline

- Vancomycin
- Guideline Updates
- How to Calculate AUC
- Implementing AUC Monitoring

Vancomycin

- Glycopeptide
- Empiric and definitive treatment for gram-positive pathogens
- Notably for drug-resistant pathogens, MRSA
- Common indications:
  - Pneumonia, bacteremia, osteomyelitis, CNS infections
Guideline Updates

2009 Guidelines

- Summary and recommendations
- "An AUC/MIC ratio of $\geq 400$ 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 AUC/MIC is a predictive pharmacokinetic parameter for vancomycin."

Rybak MJ et al. AM J Health-Syst Pharm. 2009
2009 Vancomycin Guideline Continued

“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.”

- Trough goal of 15 to 20 mg/L for serious infections.
- Ensures achievement for AUC/MIC ratio of ≥ 400, as long as the vancomycin MIC is ≤ 1 mg/L


Trough Nephrotoxicity

- A meta analysis of 15 studies (n = 1718) compared troughs of 10-15 to 15-20.
- Acute kidney injury (AKI) was defined as an increase in serum creatinine of ≥ 0.5 mg/dL or ≥ 50% from baseline, confirmed on two consecutive measurement in all but 3 studies.
- Incidence of nephrotoxicity: 5 – 43%
- Time to nephrotoxicity: 4.3 to 17 days after start of therapy
- Increased nephrotoxicity with goals 15 – 20 (OR 267; 95% CI 1.81-5.37)

Trough vs AUC Nephrotoxicity

- A meta analysis of 2 observational, single center studies (n=1443) comparing trough to AUC dosing.
- AKI was defined as increase in serum creatinine of ≥ 0.5 mg/dL or ≥ 50% from baseline, confirmed on two consecutive measurements.
- AUC based dosing was associated with less AKI (OR 0.68, 95% CI 0.46 – 0.99)


2019 Vancomycin Guideline Updates

- Draft guidelines of therapeutic monitoring of vancomycin by IDSA, ASHP, PIDS, and SIDP were published online in February 2019
- Recommended major change includes:
  - Utilization of area under the curve (AUC) dosing over trough based dosing.
- Recommended minor changes include:
  - Capping loading doses at 3 grams
  - Every 12 hours dosing for continuous renal replacement therapy (CRRT) patients
  - Weekly levels in stable patients on vancomycin

Area Under the Curve Dosing

- “Trough only monitoring, with target between 15-20 mg/L, is no longer recommended for patients with serious infections due to MRSA”

- An AUC/MIC (minimum inhibitory concentration) target for 400-600 is recommended to improve efficacy and safety


Comparison of AUC vs Trough

Patients Excluded from AUC Dosing

- Central Nervous System Infections
  - AUC targets are not available
- Patients with unstable renal function
  - Acute kidney injury
  - Hemodialysis
  - CRRT
- Patients currently treated with trough of 10-15
  - Urinary tract infections
  - Skin and soft tissue infections

Heil EL, Claeys KC, Mynatt RP, et al Am J Health Syst Pharm. 2018

How to Calculate AUC
Bayesian Approach to AUC

- Based on Bayes Theorem
  - Bayesian Prior
    - Estimation on how the drug will behave based on previous population pharmacokinetics
    - A measured drug concentration after medication administration
    - Bayesian conditional posterior
    - Revised estimation based on new information

Bayesian AUC Calculations

**Advantages**
- Only one level needed, not necessarily at steady state
- May be faster to therapeutic dose
- Available software

**Disadvantages**
- Only electronic calculator
- Training
- Cost of software may be limiting
Review and Validation of Bayesian Dose-Optimizing Software

- Data set from a prospective observational study was utilized to compare commercially available Bayesian dose-optimizing software.
- Comparison were made based on accuracy and bias.
- Review of software for cost, clinical utility, functionality and ease of use.


Comparison of Software

<table>
<thead>
<tr>
<th>Software</th>
<th>Availability</th>
<th>Electronic Health Record Integration</th>
<th>Price</th>
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<tbody>
<tr>
<td>APK</td>
<td>Program to download and install</td>
<td>No</td>
<td>Single user, site, and personal use available</td>
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<tr>
<td>Precise PK</td>
<td>Program to download and install</td>
<td>No</td>
<td>Annual cost per institutions depending on quantity of devices</td>
</tr>
</tbody>
</table>
Trapezoidal Pharmacokinetics

- Utilized at Detroit Medical Center and Stanford Health Care
- Obtain peak and trough within the same dosing interval at steady state
- Sawchuk-Zaske kinetic equations
  - Calculate $K_e$, $t_{1/2}$, $C_{max}$, $C_{min}$, CL, and AUC


Trapezoidal Pharmacokinetics

**Advantages**
- Fewer assumptions
- Single look with patient specific information

**Disadvantages**
- Not adaptive
- Does not take into account physiological changes
- Best at steady state

Trapezoidal Example

- 2-level calculator for Detroit Medical Center

Implementing AUC Monitoring

Check List for Implementing an AUC Dosing Strategy

- Identify inclusions and exclusions
- Calculation support
- Monitoring and Lab considerations
- Education
- Post-implementation follow-up


Pharmacist Perceptions of Implementing an AUC Pharmacy to Dose Program

- A pre- and post-implementation survey sent to pharmacist and residents completing training for an AUC dosing protocol.
- Pharmacists were trained on AUC dosing by completing an online module, live training session, and competency exam.

Survey results
- Post training found an increase in pharmacist stating AUC/MIC ideal PK/PD parameter
- Pharmacist felt completing AUC is working at top of degree
- Increase in time evaluating vancomycin consults (8 min vs. 15 min)

What is everyone else doing?

- Survey distributed to health-systems assessing readiness of changing to AUC monitoring.
  - ¼ already AUC dosing
  - 2 point pharmacokinetics
  - Bayesian model
  - Population-based questions
  - Of those using trough based, majority didn’t have plans to change to AUC

Barriers and Implementation Issues

- Pharmacist/provider unfamiliarity
- Time allocation
- Training requirements
- Unclear benefit of AUC dosing
- Logistical issues

Conclusions

- AUC/MIC is preferred per updated guidelines for vancomycin monitoring
- Associated with less nephrotoxicity
- Various methods for AUC dosing, allows for health-system specific approaches to vancomycin AUC dosing

Post-Assessment Question 1

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Questions?

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