Curve Your Enthusiasm: Using AUC:MIC pharmacokinetics to optimize vancomycin dosing

AKPhA 2019

Ryan W. Stevens, PharmD, BCIDP
Infectious Diseases Clinical Pharmacy Specialist
Providence Alaska Medical Center
Phone: 907-212-2252
Email: ryan.stevens@providence.org
Objectives:

• Pharmacist:
  1. Describe the pharmacokinetics/pharmacodynamics of vancomycin and factors which may impact efficacy or dosing of this drug.
  2. Describe two methods of AUC:MIC vancomycin optimization and the pros/cons associated with each method.
  3. Apply a linear/logarithmic trapezoidal AUC calculation model to vancomycin dosing in a patient case.

• Technician:
  1. Describe the mechanism of action of vancomycin.
  2. Describe the basic pharmacokinetics/pharmacodynamics of vancomycin.
  3. Describe 3 complexities in vancomycin dosing and why they represent a challenge.
Pre-assessment:

- T/F: Vancomycin is a cell wall agent active at PBP2a
- Vancomycin follows which pharmacodynamic models?
  - T>MIC
  - AUC:MIC
  - Cmax:MIC
- The AUC which represents the pharmacodynamic target for efficacy is _____?
- The AUC which represents the threshold for toxicity is _____?
- Which of the following are benefits of Bayesian AUC calculators over trapezoidal models? (choose all that apply)
  - Less expensive
  - Ability to adjust for changes to patient physiology
  - Only requires one level
  - Provides more accurate estimate of AUC
History:

- Discovered by Eli Lilly Co.
  - 1950 – Program launch to discover antibiotics for penicillin resistant *S. aureus*.
  - 1952 – Antistaphylococcal activity seen in soil sample from Borneo. · *Streptomyces orientalis*
  - 1958 – First approval by FDA
- Initially dubbed “Mississippi Mud due to characteristic brown color.
  - Difficult to process/remove impurities
  - High degree of toxicities

https://en.wikipedia.org/wiki/Borneo
Papers published with “vancomycin” in the title:

Vancomycin utilization (US, France, Italy, Germany, UK, Netherlands):

Why?
MRSA’s Rise to Power:

- 1959: Methicillin developed (remember...vanco 1958)
- 1961: First methicillin resistant *S. aureus* (MRSA) identified
- 1960-1967: Infrequent hospital outbreaks in Europe and Australia
- 1968: First US hospital outbreak of MRSA in US (Boston, MA)
- 1968-mid 1990s: MRSA gradually increases in incidence as hospital acquired pathogen (primarily urban hospitals)
  - 1981: Large outbreak of MRSA in IVDU in Detroit
  - 1986: Discovery of MecA gene and PBP2a hyper-expression
  - Late 80s-Early 90s: Outbreak of MRSA among Australian Aboriginal populations without healthcare exposure
- 1999-2008: Decade of community-acquired MRSA epidemic
Vancomycin:

- **Class:** Glycopeptide
- **MOA:**
  - Inhibition of D-ALA-D-ALA cross linking of peptidoglycan
  - Bactericidal *(slowly)*
- **Spectrum:** Aerobic and anaerobic gram-positives
- **Adverse effects:**
  - “Red Man Syndrome” - >10%
    - Slow down the infusion
  - Nephrotoxicity (to be addressed later) – 5-40%
  - Neutropenia/leukopenia – 1-10%
  - Ototoxicity – 1-9% (most associated with levels >40 mcg/mL)
- **Pharmacodynamics:** AUC:MIC (>400 mg*h/L)
Nephrotoxicity:

- Acute glomerular nephritis (AGN)
- Rate:
  - Initially thought to be “high” secondary to impurities in early product (i.e. Mississippi mud)
  - IDSA Guidelines say < 5% incidence
    - Targeting old troughs: 5-10 mcg/mL
  - Now studies with new troughs: 5-43%
- Typical onset: 2-5 days into therapy
- Typical peak: 5-10 days into therapy
- Typical resolution time: >90% within 19 days
  - ~3% will require hemodialysis

Nephrotoxicity:

• Know Risk Factors in Adults:
  ▫ Concurrent nephrotoxins
    • Amphotericin, aminoglycosides, IV contrast, loop diuretics,
      ACEi/ARBs (?), and piperacillin/tazobactam
  ▫ ACC admission
  ▫ Vasopressor administration
    ▫ **Weight */= 101 Kg**
    ▫ **History of acute or chronic kidney injury**
    ▫ **Empiric vancomycin doses */= 4 gm/day**
    ▫ **Prolonged courses (*/=5 days)**
    ▫ **Unstable renal function at baseline**
    ▫ **Initial trough (within 96 hours) level */= 20 mcg/mL**
    ▫ **Elevated AUC levels 600-800 within 48 hrs of initiation**

Antimicrob Agent and Chemother 2008;52(4):1330-1336
Antimicrob Agents Chemother 2013;57(2): 734-744
AAC 2018;62(1):e01684-17
Toxicity:

- **Ototoxicity:**
  - Rate = 1-9% (older studies)
    - Currently relatively rare (esp. with monotherapy)
  - Irreversible
  - Additive when concurrent aminoglycoside use
  - Correlations with levels:
    - Older studies = vanco concentrations >40 mcg/mL
    - New studies = no correlation with levels
  - Usually high frequency hearing loss +/- tinnitus
    - Slow progression to total deafness

Other ADRs: $^{1,13}$

- Redman Syndrome: $>$10% (Infusion related)
- Eosinophilia/neutropenia: 1-10%
- Drug fever: 1-10%

CID 2013;57(12):1760-5.
Vancomycin Pharmacokinetics:

- **Absorption:**
  - Little to no oral absorption

- **Distribution:**
  - Volume of distribution: 0.4-1 L/Kg (bad CSF unless inflamed meninges)
  - Distribution phase (time): 0.5-1 hrs
  - Protein binding (50-55%)

- **Metabolism:**
  - Little to no hepatic metabolism

- **Excretion:**
  - Excreted primarily as unchanged drug in the urine
  - Half-life: 6-12 hrs (longer with renal impairment)
Pharmacodynamics:

Note: AUC:MIC is expressed as a ratio!!!!

AUC = Area under the curve (i.e. area under the

Lowest possible concentration that inhibits visible bacterial growth after 18-24 hours of incubation

https://www.ncbi.nlm.nih.gov/books/NBK266259/figure/introduction.f1/
**S. aureus** Vancomycin Susceptibility Breakpoints:

- **Per CLSI:**
  - $\leq 2 \text{ mcg/mL} = \text{Susceptible}$
  - $4 - 8 \text{ mcg/mL} = \text{Intermediate}$
  - $\geq 16 \text{ mcg/mL} = \text{Resistant}$

- **Current Evidence:**
  - Infections with MIC $>1 \text{ mcg/mL}$:
    - Slower clearance of organism
    - Longer durations of vancomycin therapy
    - Higher vancomycin failure rate
    - Increased rate of mortality (bacteremia studies)


VISA and hVISA:

- **VISA = Vancomycin intermediate* *S. aureus**
  - First noted in Japan in 1997
  - Vancomycin MIC of 4-8 mcg/mL
  - **Mechanisms:**
    - Increased cell wall thickness
    - Decreased D-ala-D-ala crosslinking
    - Decreased peptidoglycan turnover (remodeling)
    - Altered surface protein profile

- **hVISA = heterogeneously vancomycin intermediate* *S. aureus**
  - Mixed population:
    - Some organisms with MIC of ≤2 mcg/mL
    - Some organisms with MIC of 4-8 mcg/mL
  - Usually precedes full blown VISA

“VRSA...the bacteria which must not be named...”

- **VRSA = Vancomycin Resistant S. aureus**
  - Resistance mediated by VanA or VanB genes
    - Native to *Enterococcus faecium* (VRE)
    - Resistance mediated by binding site alteration
      - D-ALA-D-ALA $\rightarrow$ D-ALA-D-LAC

Oritavancin
Ceftaroline
Delafloxacin
Linezolid
Tedizolid


https://www.inverse.com/article/22110-harry-potter-spell-ranking

Current Guideline Recommendations:

• Per IDSA Guideline
  ▫ “Based on evidence suggesting that S. aureus exposure to trough serum vancomycin concentrations of <10 mg/L can produce strains with VISA like characteristics, it is recommended that trough serum vancomycin concentrations always be maintained above 10 mg/L to avoid development of resistance. (Level of evidence = III, grade of recommendation = B.)”

Current Guideline Recommendations:

- Per IDSA Guidelines:
  - “Based on the potential to improve penetration, increase the probability of optimal target serum vancomycin concentrations, and improve clinical outcomes for complicated infections such as bacteremia, endocarditis, osteomyelitis, meningitis, and hospital acquired pneumonia caused by S. aureus, total trough serum vancomycin concentrations of 15–20 mg/L are recommended. **Trough serum vancomycin concentrations in that range should achieve an AUC/MIC of ≥400 in most patients if the MIC is ≤1 mg/L.** (Level of evidence = III, grade of recommendation = B.)”
Current Guideline Recommendations:

• Goal trough 15-20 mcg/mL:
  ▫ Endocarditis, MRSA bacteremia, osteomyelitis, meningitis, and MRSA pneumonia
  ▫ Septic arthritis and necrotizing fasciitis

• Goal trough 10-15 mcg/mL
  ▫ All other indications and organisms

• But all-in-all... AUC:MIC ratio >400 mg*hr/L
### MIC Variation by Testing Method:

**TABLE 1 Comparison of BMD with the automated systems and Etest MIC results**

<table>
<thead>
<tr>
<th>Consensus log₂ MICs per BMD method</th>
<th>Susceptibility testing system (no. tested)</th>
<th>No. (%) of isolates with a log₂ dilution variationa (compared to the reference BMD) of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>−2</td>
</tr>
<tr>
<td>0.25 &lt; MIC &lt; 8</td>
<td>MicroScan prompt (210)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>MicroScan turbidity (207)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Phoenix (210)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Vitek 2 (210)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td></td>
<td>Etest (210)</td>
<td>77 (36.7)</td>
</tr>
<tr>
<td>MIC = 0.5</td>
<td>MicroScan prompt (52)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>MicroScan turbidity (51)</td>
<td>—</td>
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<tr>
<td></td>
<td>Phoenix (52)</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>Etest (210)</td>
<td>—</td>
</tr>
<tr>
<td>MIC = 1</td>
<td>MicroScan prompt (120)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>MicroScan turbidity (118)</td>
<td>—</td>
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<td></td>
<td>Phoenix (120)</td>
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</tr>
<tr>
<td>MIC = 2</td>
<td>MicroScan prompt (25)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>MicroScan turbidity (25)</td>
<td>—</td>
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<tr>
<td></td>
<td>Phoenix (25)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Vitek 2 (25)</td>
<td>2 (8.0)</td>
</tr>
<tr>
<td></td>
<td>Etest (25)</td>
<td>—</td>
</tr>
</tbody>
</table>

*—, no value found at this dilution.

Pharmacodynamics/Targets:

• **Goal: AUC:MIC ratio > 400 mg*h/L**
  - *AAC 2013;57(4):1654-1663*
    - MRSA Bacteremia (unspecified BMD)
    - “...obtaining a higher vancomycin AUC/MIC (in this case, >373) within 96 hours was associated with reduced mortality” (Survival rate 84.3% vs. 71.6%, p = 0.043)
  - *CID 2011;52(8):975-981*
    - MRSA Bacteremia (presumably E-test but both BMD and E-test done)
    - “Patients with vancomycin area under the curve at 24 hours to MIC ratios <421 were found to have significantly higher rates of failure as compared to those with AUC24hr to MIC ratios of >421 (61.2% vs. 48.6%, p = 0.038).”
  - *Am J Health Syst Pharm 2000;57(suppl 2):S4-S9*
    - MRSA Pneumonia (presumably BMD)
    - Suggested AUC:MIC ratio of 345 for “successful clinical outcome”
Pharmacodynamics/Targets:

  - Meta-analysis of 9 cohort studies
  - High AUC:MIC = ≥400 / Low AUC:MIC = <400
  - High AUC:MIC ≥400 associated with:
    - 53% lower mortality rates (RR = 0.47 / CI 0.31-0.7)
    - 61% lower rate of treatment failure (RR = 0.39 / CI .28-0.55)
  - “Subgroup analysis showed that results were consistent whether MIC values were determined by BMD or E-test”
Pharmacodynamics/Targets Summary:

- AUC:MIC Ratio of 400 does appear to be appropriate pharmacodynamic target for *S. aureus*.

- But do current trough goal recommendations correlate with this AUC target?
Trough Correlation with AUC:MIC:

- **Methods:**
  - 100 patients w/ various confirmed MRSA infections
  - Trough (4 groups) vs. estimated AUC ≥400
  - 94% of MRSA isolates had MIC of 1 mcg/mL (VITEK 2)

- **Results:**
  - Troughs 15-20 mcg/mL did not increase likelihood of AUC target attainment vs. troughs 10-15 mcg/mL (45.7% vs. 51.6%, p=0.82)
  - Troughs >10 mcg/mL increased odds of AUC target attainment vs. troughs ≤10 mcg/mL (50% vs. 21.4%, p = 0.045).

- **Toxicity:**
  - Mean trough in patients developing VIN was 19.5 mcg/mL vs. 14.5 mcg/mL in the group not developing VIN (p <0.01)

- **Conclusion:**
  - Higher trough goal = No increase in AUC target attainment and increased in VIN incidence.

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**J Pharm Prac 2017;30(3):329-335.**

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Trough Correlation with AUC:MIC:

- **AAC 2014;58(1):309-316.**
  - PK Data from 47 patients across 3 studies (Total of 569 vancomycin levels)
  - Methods:
    - AUC with trough (AUC\textsubscript{T}) and AUC with peak-trough (AUC\textsubscript{PT}) vs. AUC with full data set (AUC\textsubscript{F}).
  - Results:
    - AUC\textsubscript{T} and AUC\textsubscript{PT} underestimated vs. AUC\textsubscript{F}.
      - AUC\textsubscript{T} = 11-33% (p < 0.0001) / AUC\textsubscript{PT} = 14% (p <0.0001)
      - Assuming normal renal function and MIC of 1 mcg/mL an AUC \geq 400 was achieved with:
        - Trough <15 mcg/mL = ~60% patients
        - Trough <10 mcg/mL = ~32% patients
        - Median trough to produce AUC \geq 400 = 11.9-13.3 mcg/mL
        - Upper limit of exposure safety without nephrotoxicity risk = AUC 700
    - Conclusion:
      - Current trough goals do not correlate well with AUC targets.
      - AUC margin of toxicity = 700
Trough Correlation with AUC:MIC:

- **CID 2011;52(8):969-974.**
  - 9,999 Monte Carlo simulations on 4 different regimens using a series of fixed creatinine clearance values.

- **Trough of 15-20 mcg/mL produce:**
  - 100% target attainment if MIC ≤ 1 mcg/mL
  - ~30% target attainment if MIC = 2 mcg/mL

- **Trough of 10-15 mcg/mL produce:**
  - 100% target attainment if MIC = 0.5 mcg/mL
  - ~70% target attainment if MIC = 1 mcg/mL
  - ~30% target attainment if MIC = 2 mcg/mL
Trough Correlation with AUC:MIC Summary:

- IDSA vancomycin dosing guidelines concerning troughs of 15-20 mcg/mL:
  - “Trough serum vancomycin concentrations in that range should achieve an AUC/MIC of ≥400 in most patients if the MIC is ≤1 mg/L.”

- Trough goals of 15-20 mcg/mL **ARE** likely to hit AUC targets in MRSA with MIC 1 mcg/mL.
  - **Problem:**
    - High trough goal not often necessary to produce AUC target of ≥400.
    - Increased risk of nephrotoxicity

When to throw in the towel...

- *Staphylococcus aureus* MIC > 1 mcg/mL
  - MIC 1.5 = AUC 600
    - Difficult to achieve/maintain...but not impossible
    - ? Increased nephrotoxicity
  - MIC 2 = AUC 800
    - EXTREMELY difficult to reliably achieve/maintain.
    - Increased nephrotoxicity

**Which MIC?**

- E-test (over estimates)
- Automated broth dilution (under-estimates)

http://positivelyaging.org/2016/06/27/the-power-of-i-dont-know/
All-in-all:

- **Vancomycin** = AUC:MIC pharmacodynamics
- **Goal AUC = 400 / Toxic AUC = 600-800 (700)**
- **Troughs = not the best predictor of true AUC**

Bye Bye, Troughs
Hello, AUC:MIC 500-650

Troughs are going away
AUC:MIC goal 500-650
I DON'T KNOW HOW TO DO AUC-MIC KINETICS...

IT'S OK...I'LL SHOW YOU...

...BUT I JUST GOT USED TO TROUGHS...
AUC Methods: Bayesian Approach

• Based on Bayes’ Theorem
  ▫ Establishes sequential relationship between:
    1. Estimation of a patient’s PK parameters PRIOR TO administration of the drug based on PK distribution in prior patients. (Bayesian prior)
    2. Measured drug concentrations AFTER admin of drug
    3. Revised estimation of that patient’s PK parameter values after dosing, patient drug levels, and prior patients are taken into consideration. (Bayesian conditional posterior)
AUC Methods: Bayesian Approach

Example:

• You lose your cell phone...
  ▫ You know it is somewhere in your house...
    • When you have lost it prior it is usually in your room... You go there. (Bayesian prior)
    • You have someone call you.
    • It isn’t in your room → Based on the fact it isn’t in your room but is in your house you proceed to the next room a little closer to finding it. (Bayesian conditional posterior)

• You get a vanco consult...
  ▫ You assess the patient’s demographic information
    • Based on demographics and population history in other patients you start an empiric regimen (Bayesian prior)
    • You get a vancomycin level
    • AUC is subtherapeutic → Based on the empiric dose, initial level, and population data you adjust the dose. (Bayesian conditional posterior)
AUC Methods: Bayesian Approach

• The basics:
  1. A single patient’s dosing is estimated based on a large bank of PK data with the drug in a population (Bayesian prior)
  2. A level is collected
  3. Level helps further adjust PK estimates within the known population (Bayesian conditional posterior)
# AUC Methods: Bayesian Approach

<table>
<thead>
<tr>
<th><strong>Pros:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>“Free” available software</td>
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<tr>
<td>Only one level required</td>
</tr>
<tr>
<td>No requirement for steady state prior to level</td>
</tr>
<tr>
<td>Adaptive to physiologic changes</td>
</tr>
<tr>
<td>Quicker predictions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Cons:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Electronic calculator only</td>
</tr>
<tr>
<td>Training, time, and workflow integration</td>
</tr>
<tr>
<td>Concerns for patient data security</td>
</tr>
<tr>
<td>Cost of software</td>
</tr>
</tbody>
</table>
AUC Methods: Bayesian Approach

- **BestDose™**
  - New version is currently under development ($1000)
  - Old version = “free”
  - USC – Laboratory of Applied Pharmacokinetic and Bioinformatic (Michael Neely)

- **DoseMeRx™**
  - Not free...
    - $490/mo ($4,900/year) basic
    - $990/mo for “team”
    - $3,990/mo for hospital
  - Integrates into eHR (Cerner and EPIC)

- **PrecisePK™**
  - Not free...
    - $99/mo individual
    - $595/mo for “institution” (20 devices)
    - $995/mo for “enterprise” (unlimited)

- **InsightRx™**
  - ? Cost
  - Multiple drug models
  - EHR integration (Cerner and EPIC)
AUC Methods: Bayesian Approach

  - Prospective trial of trough dosing vs. Bayesian AUC dosing (BestDose™ → www.lapk.org)
    - Hypothesis:
      - Primary: “AUC-guided treatment of a patient is more likely to be therapeutic than trough concentration-guided treatment.”
      - Secondary: “Vancomycin dosing, concentrations, and nephrotoxicity would be lower with Bayesian estimation-assisted, AUC-guided TDM than with standard trough concentration guided TDM.
    - Methods:
      - Year 1 (n = 75): Trough (10-20 mcg/mL) depending on infection
      - Year 2 (n = 88): Bayesian AUC dosing with trough sample
      - Year 3 (n = 89): Bayesian AUC dosing with “optimally timed sample”
        - Mmopt → optimal sampling time algorithm based on critical point of separation.
AUC Methods: Bayesian Approach

• AAC 2018;62(2):1-12. (continued)
  ▫ Results:
    • Baseline demographics similar
      ▪ Most common indication SSTI (46% across all 3 years)
        ▫ More pneumonia and bacteremia in year 3
      ▪ MIC = ≤1 mcg/mL in 88% of isolates (all ≤2 mcg/mL)
    • Primary:
      ▪ 19% troughs (28% in year 1) vs. 70% of associated AUCs were therapeutic
        ▫ Of the 215 therapeutic AUCs:
          ▪ 31% associated with trough <10 mcg/mL
          ▪ 68% associated with trough <15 mcg/mL
    • Secondary:
      ▪ 8% nephrotox (year 1) vs. 0% (yr 2) and 2% (yr 3) – p = 0.01
        ▫ Median trough with nephrotox = 15.7 vs. 8.7 without – p = 0.02
        ▫ Median AUC with nephrotox = 625 vs. 423 without – p = 0.06
AUC Methods: Bayesian Approach

* AAC 2018;62(2):1-12. (continued)

  ▫ **Summary:**
  - Bayesian AUC monitoring is...
    - More accurate
    - Follows the actual pharmacodynamic target (AUC) of the drug
    - Is associated with less nephrotoxicity
    - Requires less levels than trough based monitoring
      ▫ **Mean # samples per patient:**
        ▫ Year 1 = 3.6
        ▫ Year 2 = 2.1
        ▫ Year 3 = 2.4

*Note additional study reviewing outcomes of AUC: AAC 2017;61:e01293-17.*
# AUC Methods: Trapezoidal Model

## Pros:
- Manual (?) if truly a pro) or programed (Excel) calculation
- Aids with prediction of next dose given two patient specific levels
- Free

## Cons:
- Complex formulas/procedures
- Requires (at least) 2 levels
- Cannot adapt model for physiologic changes
- Increased time requirement for staff
- Initial dosing based on population assumptions
- May underestimate true AUCs
AUC Methods: Trapezoidal Model

- **Estimate Initial Regimen:**
  - Vanco Clearance: \(((\text{CrCL} \times 0.75) \times 0.06) = \text{CL Vanco}\)
    - Vanco clearance = 70-80% creatinine clearance
  - Volume distribution:
    - 0.83 L/kg if CrCl <60 ml/min
    - 0.57 L/kg if CrCl ≥60 ml/min
  - Elimination rate constant: \(\text{Ke} = \frac{\text{CL Vanco}}{\text{Vd}}\)
  - Recommended interval: \(\ln(\text{peak}) - \ln(\text{trough})/k\)
  - Recommended dose: \(\text{dCmax} \times k \times (1-e^{-k \times \text{dTint}})\)
    - \(\text{dCmax}\) = desired peak (usual 30 mcg/ml)
    - \(\text{dTint}\) = desired dosing interval (as calculated above)
AUC Methods: Trapezoidal Model

- **Estimate Initial Regimen (continued):**
  - **Estimated AUC:**
    - AUC: total 24 hour vancomycin dose/CL Vanco
  - **Estimated AUC - Option 2:**
    - Cmax = \((D/Tinf)\times(1-e^{-k\times Tinf})/(Vd\times k\times(1-e^{-k\times Tint}))\)
    - Cmin = Cmax\times(e^{-k\times(Tint-Tinf)})
    - Followed by Lin/Log Trapezoidal rule (more to come)

*Note: Tinf = infusion time / Tint = Dosing interval*
AUC Methods: Trapezoidal Model

**Trapezoidal Procedure:**

1. **2 Level Kinetics (while at steady state):**
   - Post-infusion level: 1 hour after end of the infusion
   - Trough level: 0.5 hour prior to the next infusion
   - Work with what you have:
     - Ideally two levels are on same curve...not always reality.
     - Above level timing is idea, but can work with other times as long as you account for timing in calculations.

Hosp Pharm 2009;44:751-765
AUC Methods: Trapezoidal Model

2. Calculate your:
   ▫ Elimination rate constant (k)
   ▫ Volume of distribution
   ▫ Vanco clearance
   ▫ Lin trapezoidal rule
   ▫ Logarithmic trapezoidal rule

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

\[ V_d = \frac{(\text{Dose}/t') \cdot (1 - e^{-kt'})}{k \left( C_{\text{max}} - [C_{\text{min}} \cdot e^{-kt'}] \right)} \]

\[ Cl_{\text{VANCO}} = V_d \cdot k \]

\[ \text{Lin trap} = \frac{(C_1 + C_2)}{2} \cdot (t_2 - t_1) \]

\[ \text{Log trap} = \frac{(C_2 - C_3) \cdot (t_3 - t_2)}{\ln \left( \frac{C_2}{C_3} \right)} \]

Don’t forget to multiple AUC by dosing interval

Hosp Pharm 2009;44:751-765
AUC Methods: Trapezoidal Model

Notes:
\[ C_1 = \text{trough} \]
\[ C_2 = \text{peak} \]
\[ C_3 = \text{trough} \]

These are not your levels, but rather extrapolated using your levels and patient specific PK parameters.

In most circumstances \( C_1 \) and \( C_3 \) should be the same.

Don’t forget to multiple AUC by dosing interval.
AUC Methods: Trapezoidal Model

3. Adjust dosing:
   - AUC:MIC ≥400 but <700? (Perhaps 500-650)
     - Yes: Continue current dose
     - No: Use patient specific PK (from levels) to calculate new regimen (paying close attention to predicted AUC).

- **Note:** If adjusting dosing regimen requires adjustment of frequency then best to reconfirm new AUC with 2 level kinetics.
AUC Methods: Trapezoidal Model

• Remember: Trapezoidal AUC methods may underestimate AUC as compared to Bayesian methods

VN Patient Case:

• VN is a 27 y/o female admitted for fever, malaise, chills, and night sweats over the last 5 days.
• Height: 63” / Weight: 71 Kg
• PMH: IVDU, asthma, thigh stab wound
• WBC 21 (16% bands), SCr 0.45 mg/dL, Tmax 101.2F, CRP 130 mg/L, ESR >90
• New murmur noted (TTE Pending)
• Blood Cultures: GPC clusters in 2/2 sets (positive after 10 hrs) → MRSA by blood PCR

• What regimen would you start this patient on?
VN Patient Case:

• She is started on vancomycin 1500 mg (~25 mg/kg) IV x 1 dose followed by 1 g (~15 mg/kg) IV q8hrs.
  ▫ Estimated AUC: 587
  ▫ Estimated Peak/Trough: 36.5/15.1

• On HD3 (at steady state) levels drawn:
  ▫ 2 hours after dose finished infusing = 37.1 mcg/mL
  ▫ 0.5 hrs prior to next dose = 17.6 mcg/mL
Conclusions:

- Anticipate shift of IDSA guideline recommended dosing to AUC:MIC driven methods.
  - Anticipated new IDSA targets: AUC 500-650
  - Vancomycin pharmacodynamic target = AUC 400
    - *S. aureus* ONLY
    - Primarily studied in bacteremia and pneumonia
  - Risk of toxicity with AUC >700
- Methods:
  - Bayesian dosing software
  - Trapezoidal dosing model
Objectives:

**Pharmacist:**
1. Describe the pharmacokinetics/pharmacodynamics of vancomycin and factors which may impact efficacy or dosing of this drug.
2. Describe two methods of AUC:MIC vancomycin optimization and the pros/cons associated with each method.
3. Apply a linear/logarithmic trapezoidal AUC calculation model to vancomycin dosing in a patient case.

**Technician:**
1. Describe the mechanism of action of vancomycin.
2. Describe the basic pharmacokinetics/pharmacodynamics of vancomycin.
3. Describe 3 complexities in vancomycin dosing and why they represent a challenge.
Post-assessment:

• T/F: Vancomycin is a cell wall agent active at PBP2a
• Vancomycin follows which pharmacodynamic models?
  ▫ T>MIC
  ▫ AUC:MIC
  ▫ Cmax:MIC
• The AUC which represents the pharmacodynamic target for efficacy is _400_?
• The AUC which represents the threshold for toxicity is _700_?
• Which of the following are benefits of Bayesian AUC calculators over trapezoidal models? (choose all that apply)
  ▫ Less expensive
  ▫ Ability to adjust for changes to patient physiology
  ▫ Only requires one level
  ▫ Provides more accurate estimate of AUC
Questions?