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Vancomycin: Teaching an Old Dog New Tricks

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Disclosure

Ryan Mynatt

Theravance: Advisory Board

All other planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.

Learning Objectives

- Identify the optimal pharmacokinetic/pharmacodynamic parameter used to guide vancomycin dosing calculations.
- Given two vancomycin levels, use pharmacokinetic parameters to calculate a dosing regimen to target area-under-the-curve.
- Compare and contrast the pros and cons of vancomycin delivered as a continuous vs. intermittent infusion.

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AUC/MIC as the Most Rational Therapeutic Target

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I know what you're thinking…

Image obtained from Google
Accessed 9/23/2017

How do we currently dose vancomycin?

A. Trough-targeted nomogram
B. AUC-targeted nomogram
C. AUC-based, using 2 post-dose concentrations
D. AUC-based, using Bayesian kinetic software

Obligatory Vancomycin Talk Slide

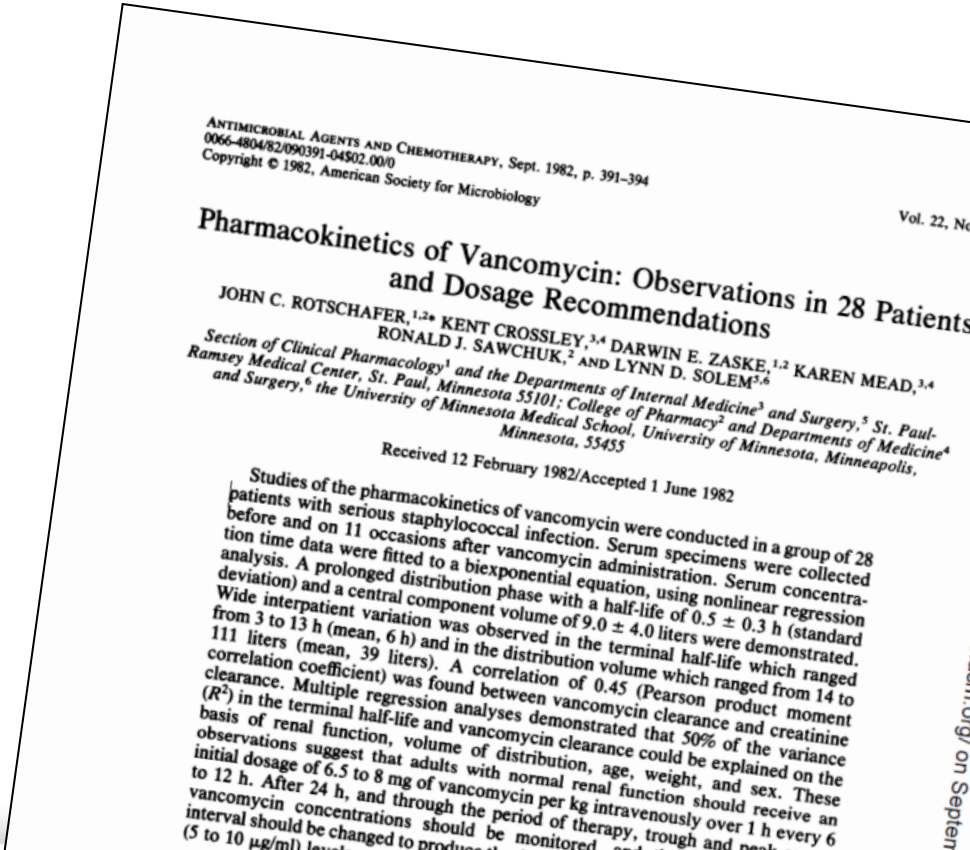
- **Originally first introduced in 1956, and ultimately approved in 1958 as a response to recent emergence of resistance in *Staphylococcus aureus*[1]**
  - Approved at total daily dose of 2gm; divided every 6-12 hours

- **Subsequent reports demonstrated efficacy in treating larger numbers of patients[2,3]**

1. Levine DP. ***Clin Inf Dis*** 2006
2. Geraci JE, Heilman FR. ***Proc Staff Meet Mayo Clin*** 1960
3. Kirby WM, et al. ***New Eng J Med*** 1960

Vancomycin Pharmacokinetics

- **Intense study into PK of vancomycin began in early 1980s[1,2]**
  - Peak and trough targets first proposed by Geraci[3]
  - Further characterized by Rotschafer and colleagues[4]
- **Pharmacodynamic target remained largely undefined**



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 1982, p. 391–394
0066-4804/82/090391-04$02.00/0
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Vol. 22, No

Pharmacokinetics of Vancomycin: Observations in 28 Patients and Dosage Recommendations

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Section of Clinical Pharmacology[1] and the Departments of Internal Medicine[3] and Surgery,[5] St. Paul-Ramsey Medical Center, St. Paul, Minnesota 55101; College of Pharmacy[2] and Departments of Medicine[4] and Surgery,[6] the University of Minnesota Medical School, University of Minnesota, Minneapolis, Minnesota, 55455

Received 12 February 1982/Accepted 1 June 1982

Studies of the pharmacokinetics of vancomycin were conducted in a group of 28 patients with serious staphylococcal infection. Serum specimens were collected before and on 11 occasions after vancomycin administration. Serum concentration time data were fitted to a biexponential equation, using nonlinear regression analysis. A prolonged distribution phase with a half-life of 0.5 ± 0.3 h (standard deviation) and a central component volume of 9.0 ± 4.0 liters were demonstrated. Wide interpatient variation was observed in the terminal half-life which ranged from 3 to 13 h (mean, 6 h) and in the distribution volume which ranged from 14 to 111 liters (mean, 39 liters). A correlation of 0.45 (Pearson product moment correlation coefficient) was found between vancomycin clearance and creatinine clearance. Multiple regression analyses demonstrated that 50% of the variance (R^2) in the terminal half-life and vancomycin clearance could be explained on the basis of renal function, volume of distribution, age, weight, and sex. These observations suggest that adults with normal renal function should receive an initial dosage of 6.5 to 8 mg of vancomycin per kg intravenously over 1 h every 6 to 12 h. After 24 h, and through the period of therapy, trough and peak vancomycin concentrations should be monitored, and the dosage interval should be changed to produce [illegible] (5 to 10 μg/ml) level

1. Krogstad DJ et al. ***J Clin Pharmacol*** 1980
2. Moellering RC, et al. ***Ann Int Med*** 1981
3. Geraci JE ***Mayo Clin Proceed*** 1977
4. Rotschafer JC, et al. ***Antimicrob Agents Chemother*** 1982

Vancomycin Pharmacokinetics

- **However, over time, monitoring of peak concentrations began to be questioned[1]**
  - *"The so-called therapeutic range of 30–40 mg/L and 5–10 mg/L, respectively"*

- **Clinicians began to look at trough-based monitoring, noting little differences in patient outcomes and reduced expenditures[2]**
  - Driven by reduction in lab costs for monitoring versus nomogram-based dosing

1. Rybak MJ ***Clin Inf Dis*** 2006
2. Karam CM, et al. ***Pharmacother*** 1999

Vancomycin Pharmacodynamics

- **Pharmacodynamic researchers began to demonstrate and endorse the area-under-the-curve to minimum inhibitory concentration (AUC/MIC) ratio as the preferred parameter for therapeutic efficacy[1-5]**
  - Derived mostly from in-vitro and animal models

- **However, evidence of relating AUC/MIC to outcomes in human disease largely remained unstudied until 2004**

1. Ebert S. ***27th Interscience Conference on Antimicrobial Agents and Chemotherapy ICAAC*** 1987
2. Knudsen JD, et al. ***Antimicrob Agents Chemother*** 2000
3. Craig WA ***Clin Inf Dis*** 1998
4. Rybak MJ ***Clin Inf Dis*** 2006
5. Craig WA, Andes DR. ***Paper presented at 46th Interscience Conference on Antimicrobial Agents and Chemotherapy ICAAC*** 2006

Moise-Broder and colleagues…

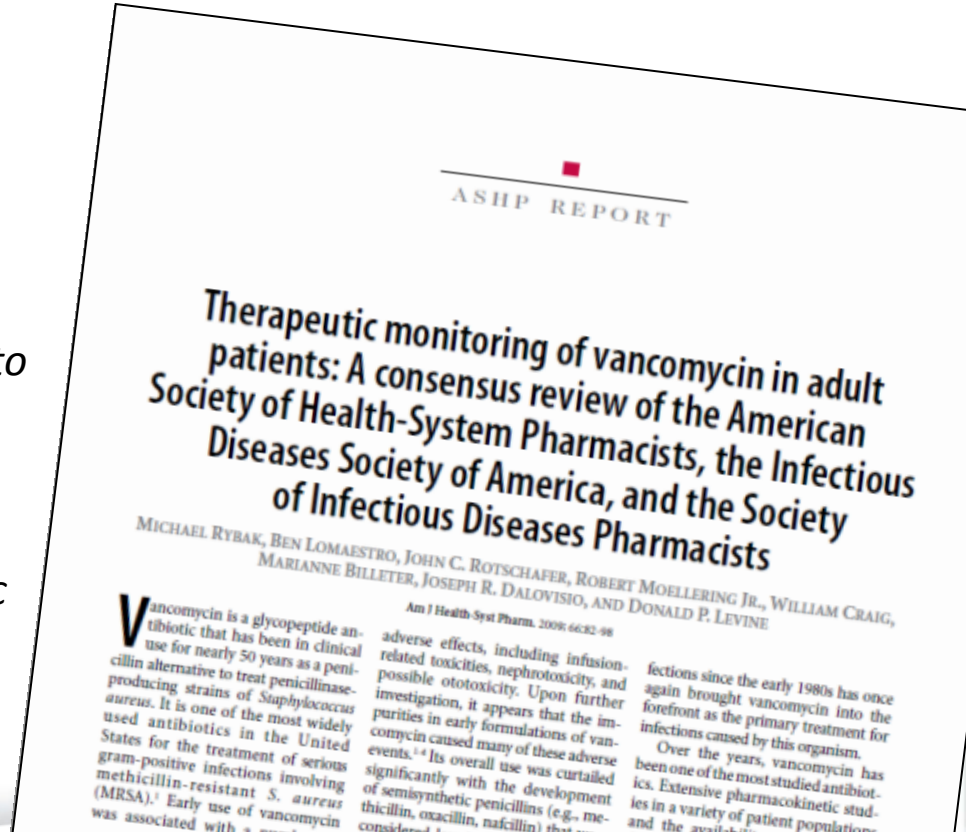
- **Evaluated 24-hour AUC/MIC ratio and it's relation to therapeutic efficacy in patients with *Staphylococcus aureus* lower respiratory tract infections**
- **Demonstrated improved clinical and bacteriological response rates in patients achieving higher AUC/MIC ratios**
  - Included 108 patients; mean age 74 years (range 32 – 93 years)
  - AUC/MIC of ≥ 345 mg*hr/L correlated with clinical efficacy at test of cure
  - No relationship between time above MIC (t>MIC) was demonstrated

1. Moise-Broder PA, et al. ***Clin Pharmacokin*** 2004

Therapeutic Drug Monitoring Guidance

- **Summary and recommendation:**

  "An AUC/MIC ratio of ≥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 the AUC/MIC is a predictive pharmacokinetic parameter for vancomycin."



ASHP REPORT

Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists

MICHAEL RYBAK, BEN LOMAESTRO, JOHN C. ROTSCHAFER, ROBERT MOELLERING JR., WILLIAM CRAIG, MARIANNE BILLETER, JOSEPH R. DALOVISIO, AND DONALD P. LEVINE

Am J Health-Syst Pharm. 2009; 66:82-98

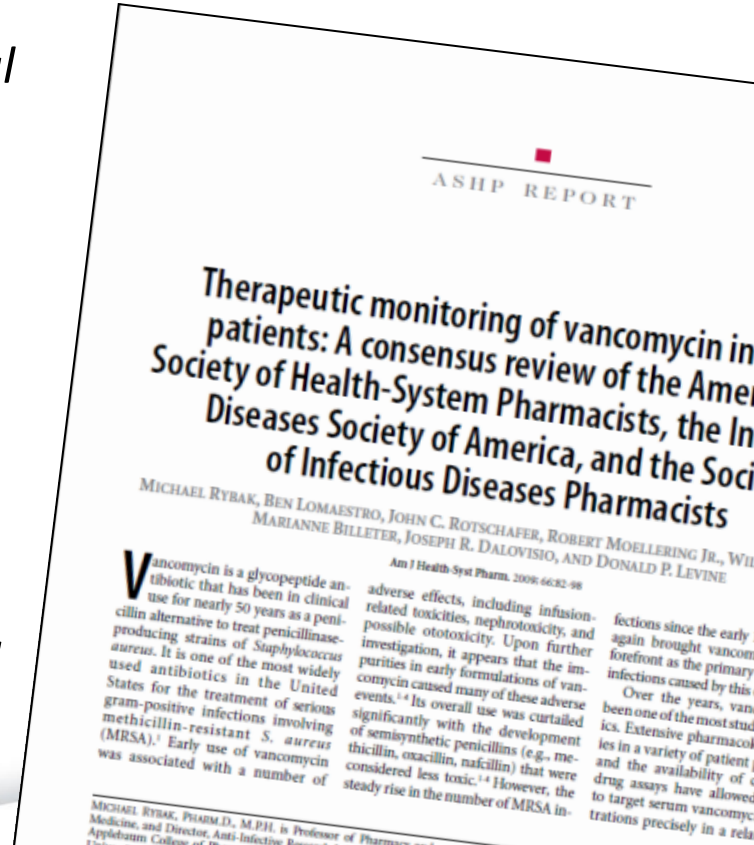
Vancomycin is a glycopeptide antibiotic that has been in clinical use for nearly 50 years as a penicillin alternative to treat penicillinase-producing strains of *Staphylococcus aureus*. It is one of the most widely used antibiotics in the United States for the treatment of serious gram-positive infections involving methicillin-resistant *S. aureus* (MRSA).[1] Early use of vancomycin was associated with a ... adverse effects, including infusion-related toxicities, nephrotoxicity, and possible ototoxicity. Upon further investigation, it appears that the impurities in early formulations of vancomycin caused many of these adverse events.[1-4] Its overall use was curtailed significantly with the development of semisynthetic penicillins (e.g., methicillin, oxacillin, nafcillin) that ... fections since the early 1980s has once again brought vancomycin into the forefront as the primary treatment for infections caused by this organism.

Over the years, vancomycin has been one of the most studied antibiotics. Extensive pharmacokinetic studies in a variety of patient populations and the ...

1. Rybak MJ, et al. ***Am J Health-Syst Pharm*** 2009

Therapeutic Drug Monitoring Guidance

"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."*



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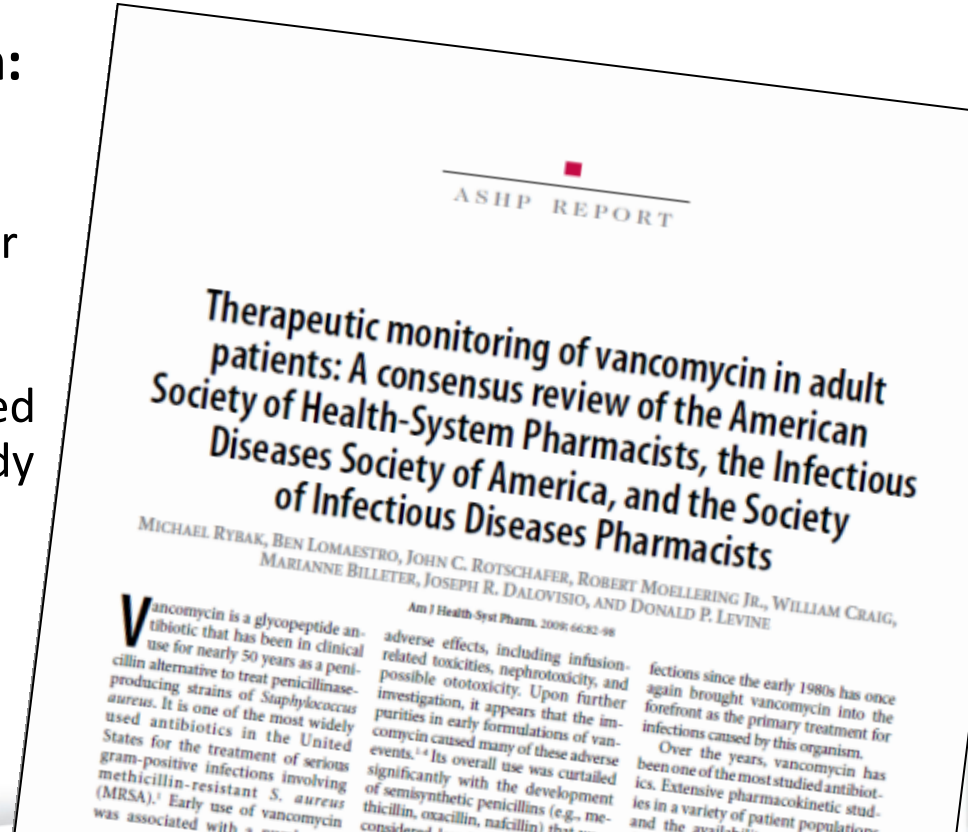
Over the years, van been one of the most stud ics. Extensive pharmacol ies in a variety of patient and the availability of drug assays have allowed to target serum vancomyc trations precisely in a rela

MICHAEL RYBAK, PHARM.D., M.P.H., is Professor of Pharm Medicine, and Director, Anti-Infective Applebaum College of

1. Rybak MJ, et al. ***Am J Health-Syst Pharm*** 2009

Therapeutic Drug Monitoring Guidance

- **Summary and recommendation:**
  - Trough serum vancomycin concentrations are the most accurate and practical method for monitoring vancomycin effectiveness. Trough concentrations should be obtained just before the next dose at steady state conditions.
- **(Level of evidence = II, grade of recommendation = B)**



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1. Rybak MJ, et al. ***Am J Health-Syst Pharm*** 2009
2. Tunkel A, et al. ***Clin Inf Dis*** 2004
3. ***Am J Respir Crit Care Med*** 2005

Therapeutic Drug Monitoring Guidance

- **Summ**
  - Tro
    cor
    acc
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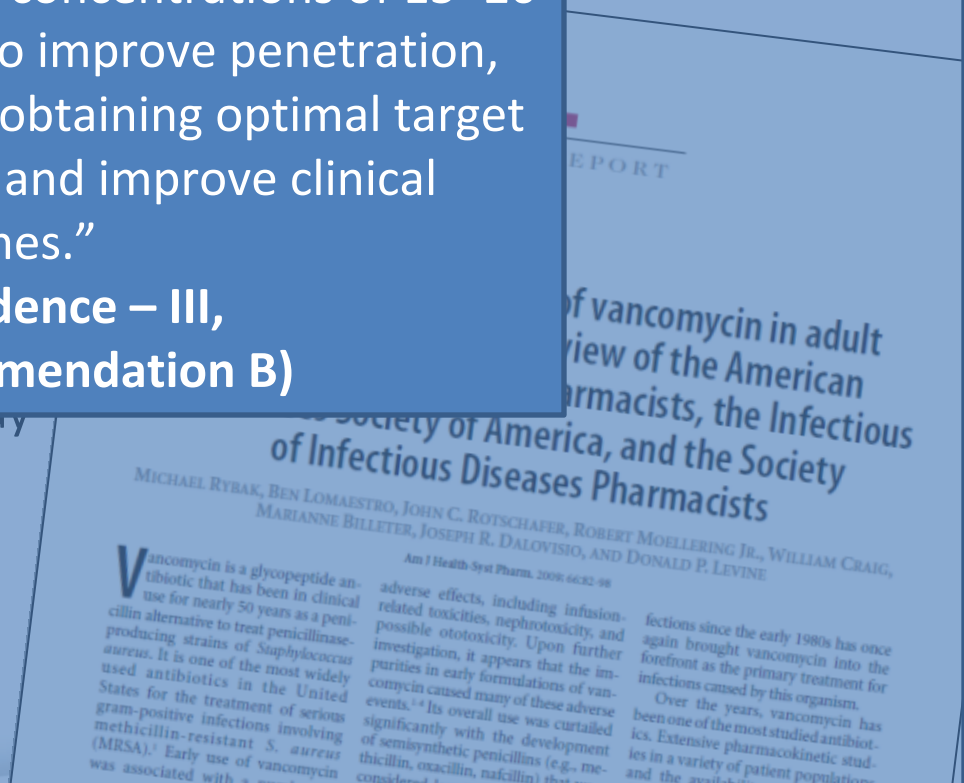
    just before the next dose at steady state conditions.
- **(Level of evidence = II, grade of recommendation = B)**

"Vancomycin serum trough concentrations of 15–20 mg/L are recommended to improve penetration, increase the probability of obtaining optimal target serum concentrations, and improve clinical outcomes."

(Level of evidence – III, Grade of recommendation B)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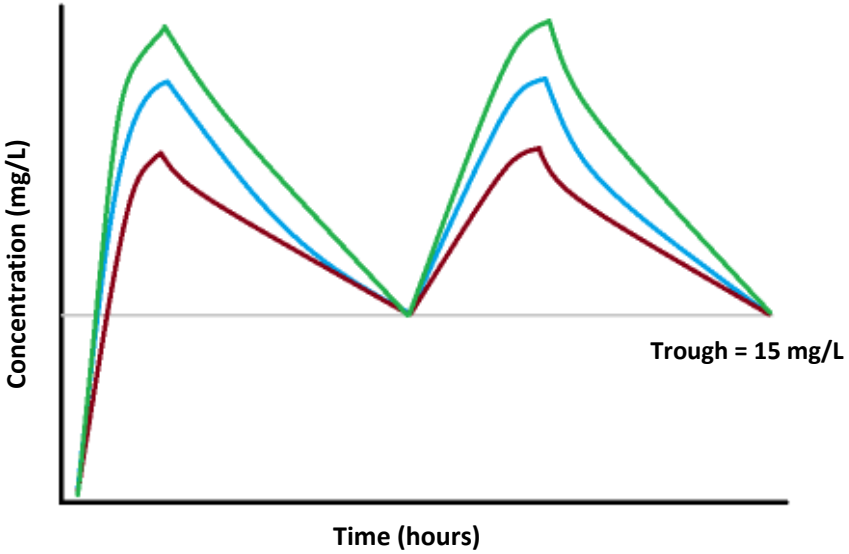
Trough-based Dosing & Outcomes

- **Trough concentrations represent a single exposure point at the end of the dosing interval**
  - Fails to accurately describe exposure over time (i.e., course of therapy)
- **Does this parameter correlate with desired outcomes?**
  - Clinical and microbiological outcomes (cure, eradication, etc.)
- **Does this parameter correlate with undesired outcomes?**
  - Nephrotoxicity, ototoxicity



Vancomycin Trough Relative to Vancomycin-Associated Nephrotoxicity in 2013 Meta-Analysis (Adults),

Study	Incidence of Nephrotoxicity	Vancomycin Trough Definition	Nephrotoxicity relative to Trough		*P*-value
			< 15 mg/L	≥ 15 mg/L	
Bosso, et al. *Antimicrob Agents Chemother* 2011	19% (55/288)	Initial (within 2-5 days) or weighted average	9% (13/146)	30% (42/142)	< 0.01
Cano, et al. *Clin Therapeutics* 2012	15% (29/188)	Initial (highest level within 96 hours)	7% (7/99)	25% (22/89)	< 0.01
Chung, et al. *Anaesth Intensive Care* 2011	38% (28/73)	Initial, after 3-5 doses	33% (16/48)	48% (12/25)	0.21
Hermsen, et al. *Ex Opin Drug Safety* 2010	16% (9/55)	Initial, after 3-5 doses	10% (4/39)	31% (5/16)	0.04
Hidayat, et al. *Arch Int Med* 2006	12% (11/95)	Mean	0% (0/32)	17% (11/63)	0.01
Jeffres, et al. *Clin Therapeutics* 2007	43% (40/94)	Initial, after third dose	29% (13/45)	55% (27/49)	0.01
Kralovicova, et al. *Journal of Chemotherapy* 1997	25% (50/198)	Not described	21% (29/138)	35% (21/60)	NS
Kullar, et al. *Clinical Inf Diseases* 2011	18% (50/280)	Initial, prior to fourth dose	16% (23/141)	19% (27/139)	NS
Kullar, et al. *Pharmacotherapy* 2011	5% (9/200)	Initial, prior to 4th or 5th dose	1% (1/84)	7% (8/116)	Not stated
Lodise, et al. *Clinical Inf Diseases* 2009	13% (21/166)	Initial, highest VT within first 4 days	10% (14/139)	26% (7/27)	<0.05
Minejima, et al. *Antimicrob Agents Chemother* 2011	19% (43/227)	Mean	16% (25/155)	24% (17/72)	0.27
Prabaker, et al. *J Hosp Medicine* 2011	9% (31/348)	Mean	8% (24/294)	13% (7/54)	0.11
Wunderlink, et al. *Clinical Inf Diseases* 2012	15% (50/333)	Median	11% (24/215)	22% (26/118)	Not stated
Zimmerman, et al. *Pharmacotherapy* 1995	18% (8/45)	Initial, after 4th dose	0% (0/33)	67% (8/12)	Not stated

Vancomycin Trough & Efficacy

- **Patel and colleagues, demonstrated that despite trough concentrations correlating with nephrotoxicity, they did not necessarily correlate with achieving effective AUC/MIC ratios[1]**
  - Especially when MIC > 1 mg/L in *Staphylococcus aureus*
- **The ZEPHyR study, correlated increased troughs with nephrotoxicity, but demonstrated similar outcomes regardless of day 3 vancomycin trough[2]**
- **Jeffres and colleagues demonstrated similar outcomes (mortality) in MRSA pneumonia irrespective of vancomycin trough concentration and AUC[3]**
  - Did not evaluate AUC/MIC ratio specifically

1. Patel N, et al. ***Clin Inf Dis*** 2011
2. Wunderlink, et al. ***Clin Inf Dis*** 2012
3. Jeffres MN, et al. ***Chest*** 2006

Vancomycin Trough & Efficacy

- **Kullar and colleagues demonstrated improved outcomes with increasing vancomycin troughs (> 15mg/L) in 2 reports[1,2]**
- **First, a single-center analysis of trough and exposure on outcomes in patients with MRSA bacteremia.**
  - Predictor of failure included vancomycin trough < 15mg/L
  - Classification and Regression Tree (CART) analysis demonstrated patients with AUC/MIC < 421 experienced higher rates of failure
- **Second, retrospective evaluation of nomogram-based dosing method**
  - Increased treatment success noted in post-implementation group (60% vs. 45%; p=0.034)
  - However, failure seen again, with higher troughs (>20mg/L)

1. Kullar R, et al. ***Pharmacother*** 2012
2. Kullar R, et al. ***Clin Inf Dis*** 2011

Is 15 – 20 mg/L Necessary?

- **Neely and colleagues incorporated richly sampled studies in 47 patients with varying levels of renal function.**
  - Trough-only data set “underestimated” AUC by 23% (CI, 11 to 33%; p=0.0001)
  - Using Bayesian modeling, a 5000 patient simulation was created, predicting that in adults with normal renal function 60% would achieve AUC/MIC (≥400) with troughs < 15 mg/L

1. Neely MN, et al. ***Antimicrob Agents Chemother*** 2014

Where is the Ceiling with AUC?

- **Suzuki evaluated utility of peak monitoring in TDM of vancomycin in MRSA pneumonia[1]**
  - Significant differences in response vs. non-response in patients achieving higher AUC/MIC values
  - Nephrotoxicity was noted with higher AUC values (> 600)
- **Lodise noted increasing AUC (≥1300) was associated with increased risk of nephrotoxicity**
  - However, trough was only predictor of nephrotoxicity in the multivariate analysis
- **Chavada evaluated the AUC_{24} nephrotoxicity threshold, demonstrating an AUC >563mg*hr/L was associated with increased toxicity**
  - (40% [8/20] versus 11.2% [12/107]; *P* 0.002)

1. Suzuki Y, et al. ***Chemother*** 2012
2. Lodise T, et al. ***Clin Inf Dis*** 2014
3. Chavada R, et al. ***Antimicrob Agents Chemother*** 2017

Key Takeaways: Part 1

- **Therapeutic drug targets for vancomycin have continued to evolve over time**
  - Increasing body of PK/PD evidence vs. historical recommendations
- **A vancomycin trough-based monitoring approach may not accurately predict efficacy, but has been associated with toxicity**
  - We can achieve these target AUC values with trough < 15 mg/L
- **AUC-targeted therapy may more accurately predict both therapeutic efficacy and toxicity**
  - Presents logistical challenges (to be discussed)

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Keys to Early Target Attainment

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Do we currently employ a loading dose?

A. Yes, weight-based, single dose
B. No, do not use loading dose strategy
C. Yes, weight-based, fractionated dosing strategy

Loading Doses: To Load or Not?

- **Post-2009 vancomycin guidelines, surveys report inconsistency with use of loading doses[1,2]**
  - Never, 22 (14%); Sometimes, 70 (43%); Always, 68 (42%)
  - Some reasons included, assessment of disease severity (43%), lack of supporting evidence (22.8%), and concerns for nephrotoxicity (20.1%)
- **Loading doses (25 – 30mg/kg TBW) have been recommended to expedite achieving target trough concentrations[3]**
  - Recent meta-analysis concluded high-quality evidence to support this practice is lacking, though, loading doses may help attain target troughs (15 – 20mg/L) more rapidly[4]
  - Only one study in pediatric patients looked at AUC_{24} specifically in context of loading dose, noting no difference in AUC between groups[5]

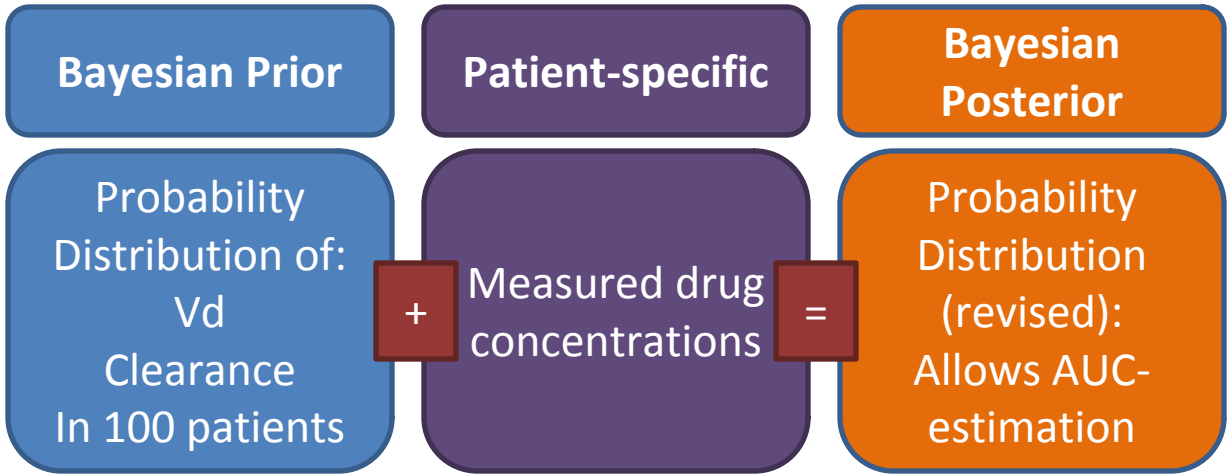
1. Davis SL, et al. ***Pharmacother*** 2013
2. Flannery A, et al. ***Abstract presented at Society of Critical Care Meeting (SCCM)*** 2018
3. Rybak MJ, et al. ***Am J Health-Syst Pharm*** 2009
4. Reardon J, et al. ***Ann Pharmacother*** 2015
5. Demirjian A, et al. ***Ped Inf Dis J*** 2013

Vancomycin Target Attainment

- **Current evidence suggests trough-only monitoring does not accurately predict AUC**
  - AUC-based methods may be more desirable, and potentially more clinically accurate/relevant
- **How can clinicians begin to go about targeting the AUC?**
  - Bayesian approach
  - Equation-based approach

Bayesian Approach

- **Based upon Bayes' Theorem**
  - Basically a statistical theorem or "rule" that stipulates that one can describe the probability of an event, based upon prior knowledge or conditions that might be related to the event



1. Pai M et al. ***Advan Drug Del Rev*** 2014

Bayesian Approach

Structured Mathematical Model	• Should be built to best describe the pharmacokinetics of a given agent (vancomycin)
Density File	• Contains parameter estimates and their associated dispersion for the PK Model • Aka “Bayesian prior”
Patient File	• Drug dosing information (i.e., Dose, frequency, infusion time) • Measured drug concentrations
Patient Target File	• Contains target exposure profile and initial estimates of future dosing regimens

1. Pai M et al. ***Advan Drug Del Rev*** 2014

Beauty of Bayesian Software

- **Advantages of Bayesian-based methods vs. traditional first-order pharmacokinetic monitoring are noted**
  - Can be modified to include select pharmacokinetic models (i.e. 2-compartment model)
  - Not limited to trough-only
  - Samples do not necessarily need to be taken at steady state
  - Adaptive program????

1. Pai M et al. ***Advan Drug Del Rev*** 2014

Applications for Bayesian

- **Bayesian software is now available to assist clinicians in implementing AUC-based intervention**
  - In-depth review of each product is beyond the scope of our discussion here today
  - Likely will be associated with capital expenditures (i.e., software packages)

1. Fuchs A, et al. ***Clin Pharmacokin*** 2013

Equation-based Methodology

- **Current evidence demonstrates that 2 post-dose peak and trough concentrations can be used to estimate daily AUC[1,2]**
  - Associated with reasonable precision and low bias
  - Allows characterization as monoexponential curve
  - Simple arithmetic can be used to generate AUC measurements
  - Can also be easily programmed to allow automatic computing
- **May be useful, as it is a "real-world" snapshot of patient-specific pharmacokinetic parameters**

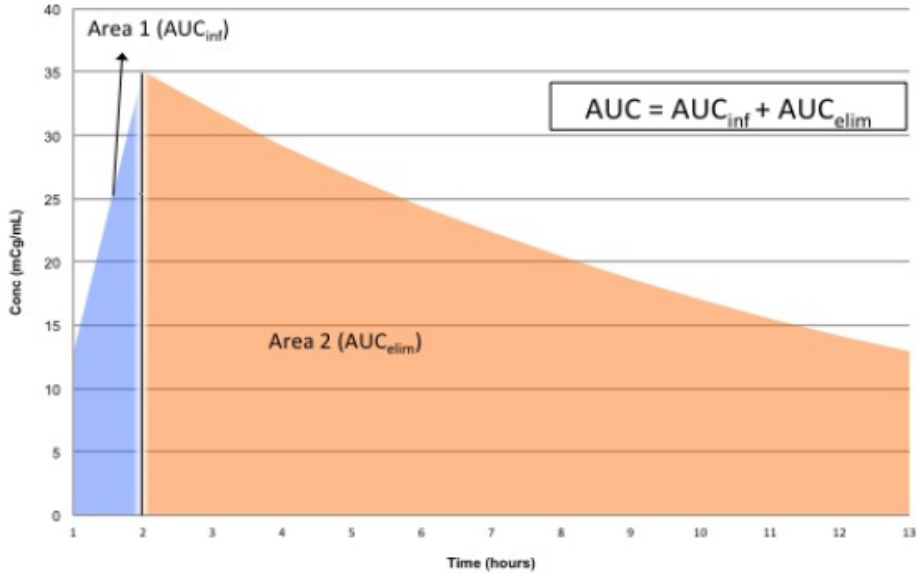
1. Pai M et al. ***Diag Microbiol Inf Dis*** 2014
2. Fuchs A, et al. ***Clin Pharmacokin*** 2013

Equation-based Methodology

- **Current methodology to calculate AUC from 2-concentrations proposed by Begg, Barclay, and Duffull for aminoglycosides[1] and later modified by Pai and Rodvold[2]**
  - Uses post-dose concentrations to characterize PK as mono-exponential decline function
  - Used to calculate AUC based on linear trapezoidal rules
- **Limitation includes inability to accurately describe alpha-phase (i.e., distribution window)**
  - Limits accuracy of overall AUC estimation

1. Begg EJ et al. ***Br J Clin Pharmacokin*** 1995
2. Pai M et al. ***Diag Microbiol Inf Dis*** 2014

Equation-based Methodology



The AUC for a given dosing interval can be estimated by adding the 2 trapezoidal areas, area 1 (AUC_{inf}) and area 2 (AUC_{elim}). Multiplying this value by the number of doses per 24 hour period yields the AUC_{24}.

7. Estimate Dose Required to Achieve Targets

When vancomycin AUC_{24} and trough are targeted:

Step 1: estimate vancomycin clearance (L/hr)

Step 2: estimate the total daily dose required (mg)

Step 3: determine appropriate MD. Round to nearest 250 mg.

Step 4: calculate predicted steady-state C_{max} for new dosing regimen

Step 5: calculate predicted steady-state C_{min} for new dosing regimen

Step 6: calculate predicted steady-state AUC_{24} based on new dosing regimen (see figure in Section 6)

a. Use linear trapezoidal rule to calculate AUC during infusion

b. Use logarithmic trapezoidal rule to calculate AUC during elimination

c. Sum areas from above and multiply by # doses per 24 hours

When only trough is targeted (i.e. not AUC_{24}):

Step 1: determine C_{max} required to maintain desired trough ($C_{min,des}$)

Step 2: determine dose needed to maintain desired C_{max}

$$Cl_{van} = k_e \times$$

$$TDD = Cl_{van} * Desire$$

$$MD = \frac{TDD}{\left(\frac{24}{Tau}\right)}$$

$$C_{max} = \frac{\left(\frac{Dose}{Vd}\right)}{(1 - e^{-k*Ta}}$$

$$C_{min} = C_{max} * (e^{-k_e*(Ta}$$

$$AUC_{inf} = \frac{(C_{max} + C_{min})}{2}$$

$$AUC_{elim} = \frac{(C_{max} - C_{min})}{k_e}$$

$$AUC_{24} = (AUC_{inf} + AUC_{elim}) *$$

$$C_{max} = \frac{C_{min}}{(e^{-k_e*(Tau-}}$$

1. Detroit Medical Center, Guidelines for Vancomycin Dosing in Adults, Jan 2015

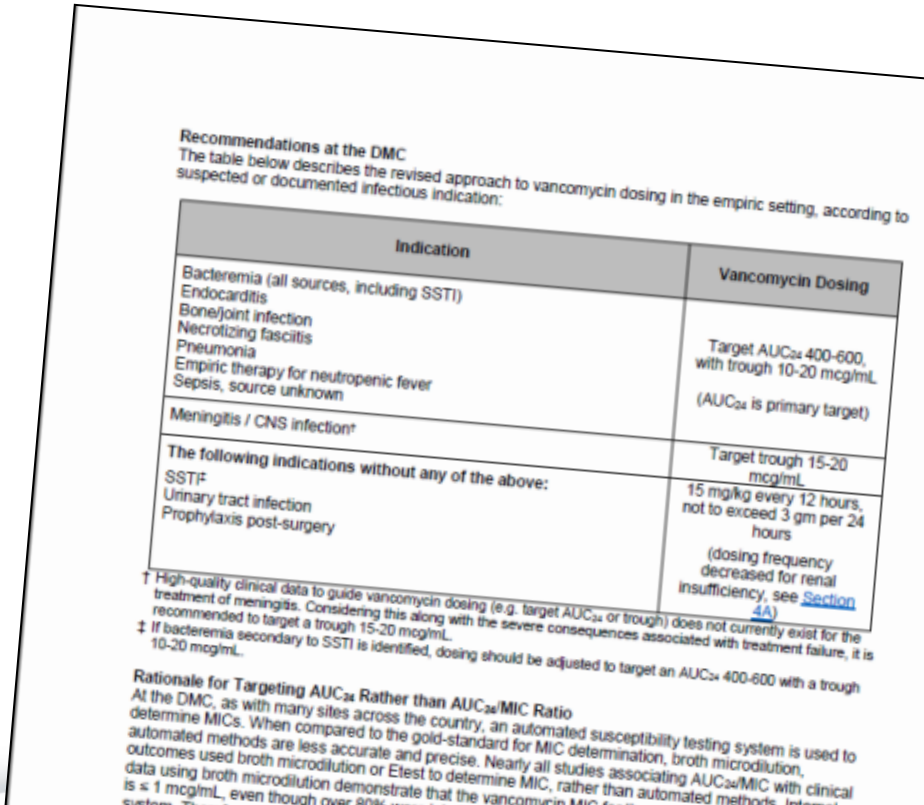
A Tale of Two Methods…

- **Clinicians evaluating methodologies can come to question how the two compare in terms of AUC estimation**
- **Pai, et al. compared Bayesian trough-only vs. 2 equation-based methods**
  - All methods accurately (low bias and high precision) reflected the referenced AUC values (Bayesian, full data set)
  - Equation based methods tended to “underestimate” the AUC value, but the median error (<2%) by these methods should be considered clinically insignificant

1. Pai M et al. ***Advan Drug Del Rev*** 2014

Real World Experience with AUC

- **In 2015 the Detroit Medical Center implemented AUC-based dosing as response to increasing reports of severe nephrotoxicity cases**
  - Decided upon equation-based dosing scheme, targeting AUC of 400 – 600 mg*hr/L (based upon available upper limit toxicity thresholds)
  - Proposed 2-concentration (peak/trough) PK monitoring in selected groups of patients



Recommendations at the DMC

The table below describes the revised approach to vancomycin dosing in the empiric setting, according to suspected or documented infectious indication:

Indication	Vancomycin Dosing
Bacteremia (all sources, including SSTI) Endocarditis Bone/joint infection Necrotizing fasciitis Pneumonia Empiric therapy for neutropenic fever Sepsis, source unknown	Target AUC_{24} 400-600, with trough 10-20 mcg/mL (AUC_{24} is primary target)
Meningitis / CNS infection†	Target trough 15-20 mcg/mL
The following indications without any of the above: SSTI‡ Urinary tract infection Prophylaxis post-surgery	15 mg/kg every 12 hours, not to exceed 3 gm per 24 hours (dosing frequency decreased for renal insufficiency, see Section 4A)

† High-quality clinical data to guide vancomycin dosing (e.g. target AUC_{24} or trough) does not currently exist for the treatment of meningitis. Considering this along with the severe consequences associated with treatment failure, it is recommended to target a trough 15-20 mcg/mL.

‡ If bacteremia secondary to SSTI is identified, dosing should be adjusted to target an AUC_{24} 400-600 with a trough 10-20 mcg/mL.

Rationale for Targeting AUC_{24} Rather than AUC_{24}/MIC Ratio

At the DMC, as with many sites across the country, an automated susceptibility testing system is used to determine MICs. When compared to the gold-standard for MIC determination, broth microdilution, automated methods are less accurate and precise. Nearly all studies associating AUC_{24}/MIC with clinical outcomes used broth microdilution or Etest to determine MIC, rather than automated methods. Interpretation is ≤ 1 mcg/mL, even though over 90% [illegible]

1. Detroit Medical Center, Guidelines for Vancomycin Dosing in Adults, Jan 2015

http://intrawebcns/upload/docs/Pharmacy%20Services/Infectious%20Diseases/PKdosingCALC14.xls

File Edit View Insert Format Tools Data Go to Favorites Help

Vancomycin Empiric Dosing Calculator

CrCl Estimation by Cockcroft-Gault		
Age	35	years
Gender	Male	
SCr	0.7	mg/dL
Height	176	cm
Actual Weight (TBW)	80.0	kg
IBW	71.4	kg
AdjBW		kg
CrCl TBW	167	mL/min
CrCl AdjBW		mL/min
CrCl IBW	149	mL/min

Switch to Touch Friendly View

Reset | Main | AMG

M: 2.3*(inches over 60)+50; F: 2.3*(inches over 60)+45.5
IBW+0.4*(TBW-IBW)
(140-age)*TBW/[72*SCr] (females *0.85)
(140-age)*AdjBW/[72*SCr] (females *0.85)
(140-age)*IBW/[72*SCr] (females *0.85)

Dosing variables		
Desired AUC	500	mcg*h/mL
Desired Cmax	35	mcg/mL
Desired Cmin	12.5	mcg/mL
Weight to calculate CrCl & K_e	IBW	149 mL/min
Weight to calculate Vd	TBW	80 kg
Vd coefficient	0.65	L/kg
K_e equation	CrCl*0.0016	238 hr-1
Alternative CrCl		mL/min
Alternative Dosing Weight		kg
Infusion time	1	hours

Usual range 400-600 mcg*h/
Usual range 30-40 mcg/L
Usual range 10-20 mcg/L
Usual range 0.6-1 L/kg
Results in most aggressive do
younger, mostly male patient

V_d	52.0	L
K_e	0.238	h^{-1}
$t_{1/2}$	2.9	hours
Calculated dose	1373.1	mg
Calculated Interval	5.3	hours
Dose	2000	mg
Interval	8	hours
Infusion time	2.0	hours
Calculated AUC	485.0	mcg*h/mL
Calculated Css max	45.2	mcg/mL
Calculated Css min	10.8	mcg/mL

80 kg * 0.65 L/kg
CrCl = 149 mL/min Ke = CrCl*0.0016
ln(2)/0.238
Total daily dose / (# / calculated interval)
(ln([desired trough]/[desired peak]) / [-K_e]) + infusion time

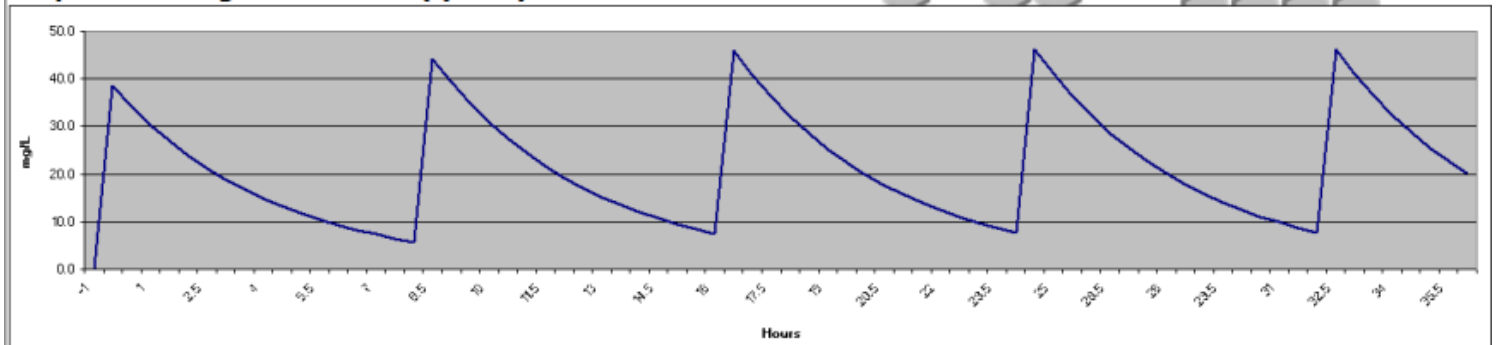
Next best match:
2250mg IV every 8h

Reset dosing

Patient Specific Data Input

PK/PD Specific Data Input

Graph of 2000 mg IV over 2 hour(s) every 8 hours



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Usual range 0.6-1 L/kg

Results in most aggressive do

younger, mostly male patient

PK Estimate Output

V_d	52.0	L
K_e	0.238	h^{-1}
$t_{1/2}$	2.9	hours
Calculated dose	1373.1	mg
Calculated Interval	5.3	hours

80 kg * 0.65 L/kg

CrCl = 149 mL/min Ke = CrCl*0.0016

ln(2)/0.238

Total daily dose / (# doses/interval)

(ln([desired trough]/[desired peak]) / [-K_e]) + infusion time

Dose	2000	mg
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Infusion time	2.0	hours
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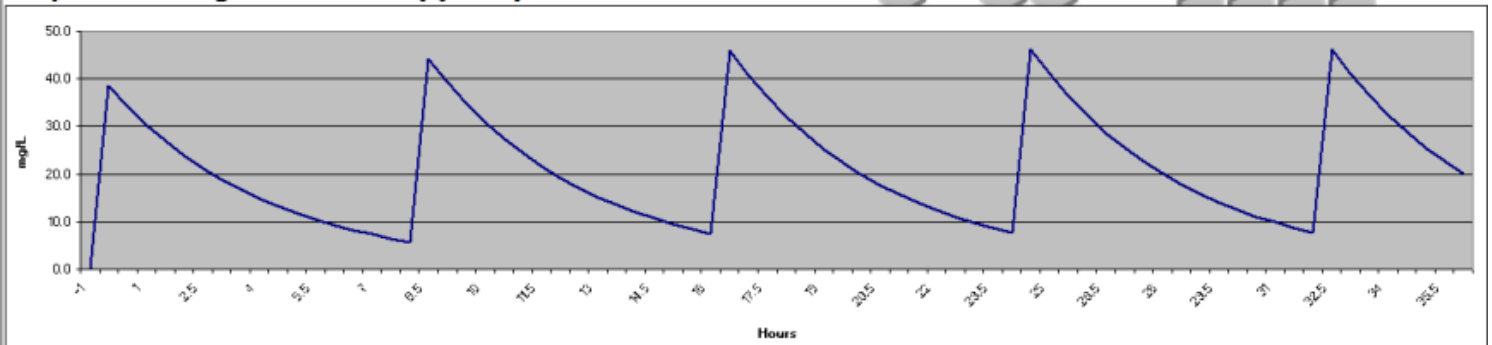
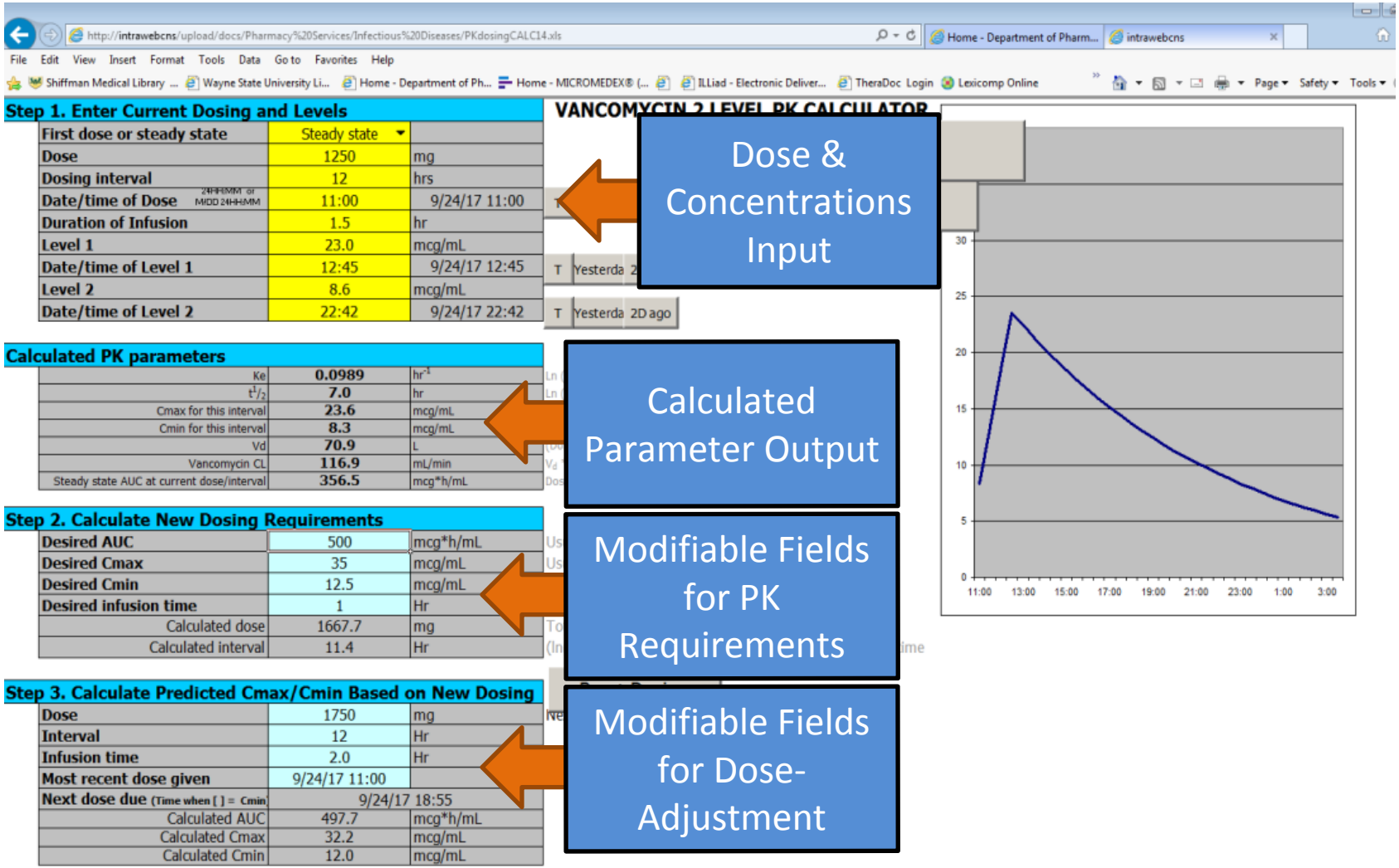
Reset dosing

Alternative Regimen Recommendation

Graph of 2000 mg IV over 2 hour(s) every 8 hours




Step 1. Enter Current Dosing and Levels
First dose or steady state
Steady state
Dose
1250
mg
Dosing interval
12
hrs
Date/time of Dose
11:00
9/24/17 11:00
Duration of Infusion
1.5
hr
Level 1
23.0
mcg/mL
Date/time of Level 1
12:45
9/24/17 12:45
Level 2
8.6
mcg/mL
Date/time of Level 2
22:42
9/24/17 22:42
Calculated PK parameters
Ke
0.0989
hr-1
t1/2
7.0
hr
Cmax for this interval
23.6
mcg/mL
Cmin for this interval
8.3
mcg/mL
Vd
70.9
L
Vancomycin CL
116.9
mL/min
Steady state AUC at current dose/interval
356.5
mcg*h/mL
Step 2. Calculate New Dosing Requirements
Desired AUC
500
mcg*h/mL
Desired Cmax
35
mcg/mL
Desired Cmin
12.5
mcg/mL
Desired infusion time
1
Hr
Calculated dose
1667.7
mg
Calculated interval
11.4
Hr
Step 3. Calculate Predicted Cmax/Cmin Based on New Dosing
Dose
1750
mg
Interval
12
Hr
Infusion time
2.0
Hr
Most recent dose given
9/24/17 11:00
Next dose due (Time when [ ] = Cmin
9/24/17 18:55
Calculated AUC
497.7
mcg*h/mL
Calculated Cmax
32.2
mcg/mL
Calculated Cmin
12.0
mcg/mL
Dose & Concentrations Input
Calculated Parameter Output
Modifiable Fields for PK Requirements
Modifiable Fields for Dose-Adjustment
30
25
20
15
10
5
0
11:00
13:00
15:00
17:00
19:00
21:00
23:00
1:00
3:00

Real World Experience with AUC

- **Single center, retrospective study from 2014 through 2015 receiving vancomycin pre & post-implementation of AUC-based dosing**
  - Post implementation group targeted AUC of 400 – 600 mg*hr/L, secondary trough target of 10 – 20mg/L
  - Pre-implementation group included patients receiving trough-based dosing, with general target range of 10-20mg/L, with 15-20mg/L for severe infections

1. Finch NA, et al. ***Antimicrob Agents Chemother*** 2017

Real World Experience with AUC

- **Overall, 1280 patients were included in the analysis**
  - AUC guided dosing was independently associated with lower nephrotoxicity in both logistic regression (OR, 0.52; 95% CI, 0.34-0.80; *P*=0.003) and Cox-proportional hazards regression (HR, 0.53; 95% CI, 0.35-0.78; *P*=0.002)
  - AUC-guided dosing was associated with lower total daily vancomycin doses, AUC values, and trough concentrations.

1. Finch NA, et al. ***Antimicrob Agents Chemother*** 2017

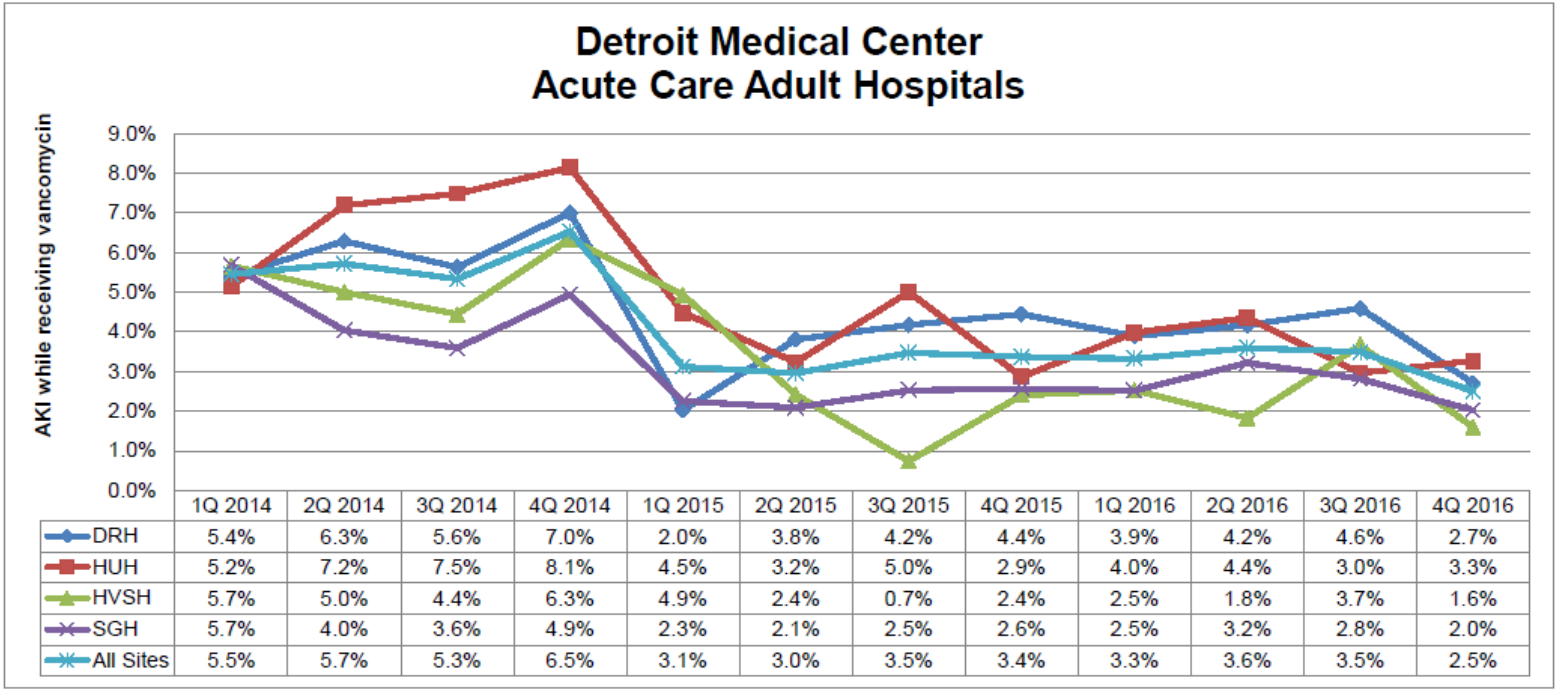
Real World Experience with AUC

Subgroup Analysis: Patients with bacteremia or pneumonia

Variable	Trough-Guided (n = 150)	AUC-Guided (n= 150)	*P* value
$Cmin_{24}$ (mg/L)	12.7 (8.9 – 16.6)	10.0 (5.7 – 13.4)	<0.001
$Cmin_{48}$ (mg/L)	14.2 (10.3 – 19.5)	12.5 (8.3 – 16.7)	0.003
$AUC_{0\text{-}24}$ (mg*hr/L)	705 (540 – 883)	474 (360 – 611)	<0.001
$AUC_{0\text{-}48}$ (mg*hr/L)	663 (538 – 857)	532 (406 – 667)	<0.001

Data expressed as median (IQR)

1. Finch NA, et al. ***Antimicrob Agents Chemother*** 2017



	1Q 2014	2Q 2014	3Q 2014	4Q 2014	1Q 2015	2Q 2015	3Q 2015	4Q 2015	1Q 2016	2Q 2016	3Q 2016	4Q 2016
DRH	5.4%	6.3%	5.6%	7.0%	2.0%	3.8%	4.2%	4.4%	3.9%	4.2%	4.6%	2.7%
HUH	5.2%	7.2%	7.5%	8.1%	4.5%	3.2%	5.0%	2.9%	4.0%	4.4%	3.0%	3.3%
HVSH	5.7%	5.0%	4.4%	6.3%	4.9%	2.4%	0.7%	2.4%	2.5%	1.8%	3.7%	1.6%
SGH	5.7%	4.0%	3.6%	4.9%	2.3%	2.1%	2.5%	2.6%	2.5%	3.2%	2.8%	2.0%
All Sites	5.5%	5.7%	5.3%	6.5%	3.1%	3.0%	3.5%	3.4%	3.3%	3.6%	3.5%	2.5%

Notes:

- Denominator includes all patients with vancomycin pharmacy dosing order, regardless of duration of treatment.
- ESRD patients are not included in this evaluation.
- Acute kidney injury (AKI) is defined as an increase SCr 0.5 mg/dL or 50% from baseline on 2 consecutive draws while receiving vancomycin.
- Includes all AKI cases that occurred during vancomycin treatment, regardless of etiology and concurrent nephrotoxins.
- DMC guidelines were revised to calculate vancomycin dosing according to area under the curve (AUC) in January 2015.

Key Takeaways: Part 2

- **Loading doses can potentially be employed to improve early target attainment**
  - Little data demonstrating loading doses improve clinical outcomes
- **Two main strategies exist to allow for implementation of AUC-targeted vancomycin dosing**
  - Institutions should determine most appropriate method
- **AUC-targeted vancomycin therapy can be employed to improve patient outcomes (nephrotoxicity)**
  - However, future evaluations with respect to efficacy are needed

ashp MIDYEAR 2017
Clinical Meeting & Exhibition

Intermittent and Continuous Infusion Calculations Targeting AUC

Alexander H. Flannery, Pharm.D., BCCCP, BCPS
Critical Care Pharmacist, Medical Intensive Care Unit
University of Kentucky HealthCare
Lexington, KY

@AFlanneryPharmD

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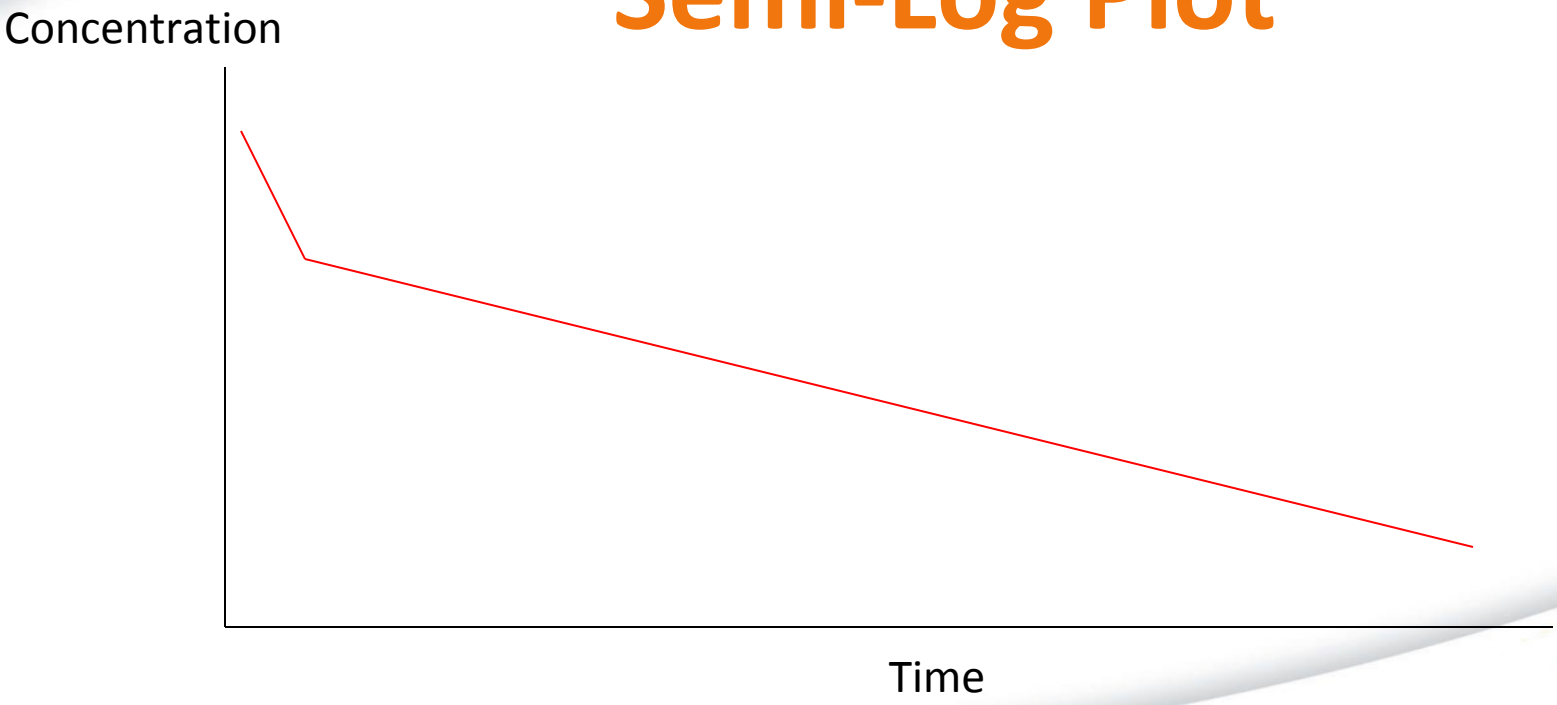
What are pharmacists doing?

- 13.5% reporting at least some use of AUC
- >94% routinely using intermittent vs. continuous infusion
- More comfortable with AUC calculations for intermittent than continuous (48.1% vs. 22%)

Flannery AH. To be presented at 2018 SCCM Congress

Semi-Log Plot



Intermittent Infusion

Patient Case #1

Patient is a 42 y/o male with IVDA admitted to your hospital with concern for sepsis and endocarditis.

Patient weight = 64 kg

SCr 0.35 mg/dL

How might you use 2 level kinetics to calculate patient-specific parameters to target an AUC?

What loading dose would you recommend for this patient?

A. No loading dose
B. 1,000 mg
C. 1,250 mg
D. 1,500 mg

Loading Dose

- Vancomycin 1,750 mg x1 over 2 hours given at 0800
- Random level 1 = 42 mg/L @ 1200
- Random level 2 = 19 mg/L @ 2000

What do you calculate for the elimination rate constant (k)?

A. 0.075 hr^{-1}

B. 0.099 hr^{-1}

C. 0.150 hr^{-1}

D. 0.211 hr^{-1}

Calculate Elimination Rate Constant

- $k = \frac{\ln(\frac{C1}{C2})}{T\prime}$

$$t_{1/2} = \frac{\ln(2)}{k}$$

$$k = \frac{\ln(\frac{42}{19})}{8} = 0.099\ hr^{-1}$$

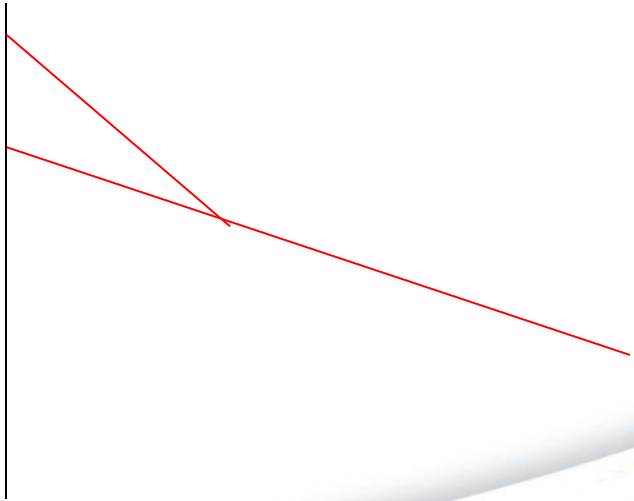
$$t_{1/2} = \frac{\ln(2)}{0.099\ hr^{-1}} = 7\ hrs$$

Calculate C_{max}

$$C_{max} = \frac{C_1}{e^{-k(\Delta T)}}$$

$$C_{max} = \frac{42}{e^{-0.099(2)}}$$

$$C_{max} = 51.2 \frac{mg}{L}$$



Volume of Distribution

Simple:

$$V_d = \frac{Loading\ Dose}{C_{max}}$$

$$V_d = \frac{1750\ mg}{51.2\ mg/L}$$

$$V_d = 34.2\ L\ (0.53\ \text{L per kg})$$

$$V_d = \frac{Loading\ Dose}{Infusion\ Time} x \frac{1 - e^{-kt}}{k\ x\ C_{max}}$$

$$V_d = \frac{1750\ mg}{2\ hrs} x \frac{1 - e^{-0.099(2)}}{0.099\ x\ 51.2}$$

$$V_d = 31.0\ \text{L}\ (0.48\ \text{L per kg})$$

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Clearance & TDD Required

$$Cl = k \; x \; V_d$$

$$Cl = 0.099 \; (31.0)$$

$$Cl = 3.07 \; L \; per \; hr$$

$$TDD = Cl \; x \; AUC_{goal}$$

$$TDD = 3.07 \; (500)$$

$$TDD = 1535 \; mg \; per \; day$$

Maintenance Dosing

- $$\tau = \frac{\ln(\frac{C_{max,desired}}{C_{tr,desired}})}{k} + t$$

$$\tau = \frac{\ln(\frac{40}{10})}{0.099} + 1$$

τ = ~15 hrs

$$MD = \frac{TDD}{\frac{24}{\tau}}$$

$$MD = \frac{1500}{\frac{24}{12}} = 750 \text{ mg q12h}$$

Calculate Estimated PK Parameters With This Regimen

$$Predicted\ C_{max} = \frac{\frac{MD}{V_d}}{1-e^{-k\ \tau}}$$

$$Predicted\ C_{max}\ x\ e^{-k(\tau-t)}$$

$$Predicted\ C_{min} =$$

$$Predicted\ C_{max} = \frac{\frac{750}{31.0}}{1-e^{-0.099\ (12)}}$$

$$Predicted\ C_{min} = 34.8\ x\ e^{-0.099(12-1)}$$

$$Predicted\ C_{max} = 34.8\ mg/L$$

$$Predicted\ C_{min} = 11.7\ mg/L$$

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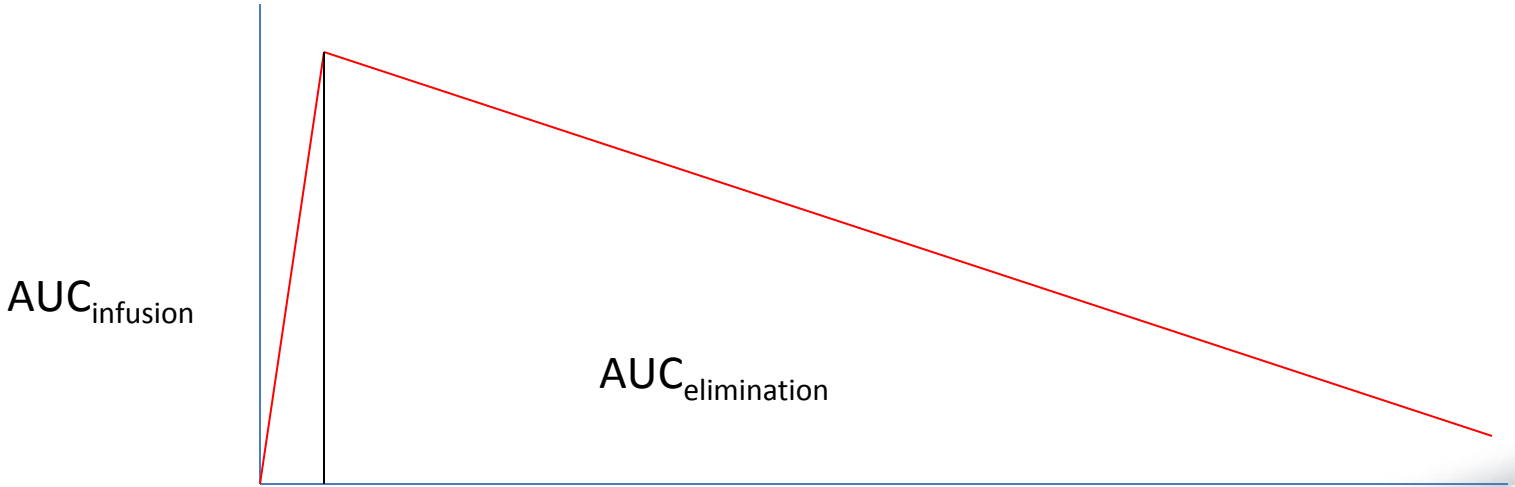
Anatomy of AUC: Oversimplified



Estimate AUC of Proposed Regimen: Infusion

$$AUC_{infusion} = \frac{(Predicted\ C_{max} + Predicted\ C_{min})}{2} x\ t$$

$$AUC_{infusion} = \frac{(34.8 + 11.7)}{2} x\ 1$$

$$AUC_{infusion} = 23.3$$

Estimate AUC of Proposed Regimen: Elimination

$$AUC_{elimination} = \frac{Predicted\ C_{max} - Predicted\ C_{min}}{k}$$

$$AUC_{elimination} = \frac{34.8-11.7}{0.099} = 233.3$$

$$AUC_{0-24} = (AUC_{infusion} + AUC_{elimination})\ x\ (\frac{24}{\tau})$$

$$AUC_{0-24} = (23.3+233.3)\ x\ (\frac{24}{12})$$

$$AUC_{0-24} = 513.2\ \text{mg·hr/L}$$

Alternative Estimation of AUC

- $AUC_{0-\infty} = \frac{Dose}{Cl}$

$$AUC_{0-24} = \frac{Total\ Daily\ Dose}{Cl}$$

$$AUC_{0-24} = \frac{1500\ mg}{3.07\ L/hr} = 488.6\ \text{mg·hr/L}$$

Assessing AUC at Steady State

Patient Case #2

63 y/o (weight=75kg) in MICU admitted for VAP (MRSA; MIC 1)

Renal function stable at 1.1 mg/dL

On vancomycin 1000 mg q24h infused over 1 hour @ 0800

Trough @ 0730 = 18 mg/L

Peak @ 1100 = 42 mg/L

Calculate Elimination Rate Constant (k)

- $$k = \frac{ln\frac{C_{peak}^{ss}}{C_{trough}^{ss}}}{T'}$$

T' = Determined by subtracting the time difference b/t C_{pk} and C_{tr} from τ

$$k = \frac{ln\frac{42}{18}}{24-(0.5+1+2)}$$

$$t_{1/2} = \frac{\ln(2)}{k}$$

$$k = 0.041\ hr^{-1}$$

$$t_{1/2} = \frac{\ln(2)}{0.041} = 16.8\ \text{hrs}$$

Back Extrapolate for C_{max} and C_{min}

$$C_{max} = \frac{C_{pk,as\ drawn}}{e^{-kt'}}$$

$$C_{max} = \frac{42}{e^{-0.041(2)}}$$

$$C_{max} = 45.6\ \text{mg/L}$$

$$C_{min} = C_{tr,as\ drawn}\ x\ e^{-kt'}$$

$$C_{min} = 18\ x\ e^{-0.041(0.5)}$$

$$C_{min} = 17.6\ \text{mg/L}$$

Assess AUC

$$AUC_{infusion} = \frac{(C_{max} + C_{min})}{2} x\ t = 31.6$$

$$AUC_{elimination} = \frac{C_{max} - C_{min}}{k} = 683$$

$$AUC_{0-24} = (AUC_{infusion} + AUC_{elimination})\ x\ (\frac{24}{\tau}) = 714.6\ \text{mg·hr/L}$$

Based on the AUC, I would:

A. Continue current dosing
B. Change dosing to q12h to minimize peak concentration
C. Decrease dosing
D. Increase dosing

Dose Changes Using AUC

- Assume linear pharmacokinetics:

$$TDD_{new} = \frac{TDD_{current}}{AUC_{current}} x AUC_{goal}$$

$$TDD_{new} = \frac{1000mg}{714.6} x500 = 700\,mg$$

Benefits of V_d Calculation

$$V_d = \frac{MD}{t} \text{ x } \frac{(1-e^{-kt})}{k(C_{max}-[C_{min} x\ e^{-kt}])} = 34.1 \text{ L (0.46 L/kg)}$$

$$Cl = k\ x\ V_d = 0.041\ (34.1) = 1.40 \text{ L/hr}$$

$$AUC_{0-24} = \frac{Total\ Daily\ Dose}{Cl} = 714 \text{ mg·hr/mL}$$

May use to model new regimen if desired

Continuous Infusion

Using Continuous Infusion

- Initial dosing:

$$Dose = \frac{TDD}{24\ hours}$$

AUC Calculations at Steady State

- $AUC_{0-24} = Vancomycin\ level\ at\ steady\ state\ x\ 24$

$$R_{in} = C_{ss} x\ Cl$$

A patient on continuous infusion vancomycin has a steady state level of 24 mcg/mL. What is the $AUC_{0\text{-}24h}$?

A. 420 mg·hr/L
B. 500 mg·hr/L
C. 576 mg·hr/L
D. 626 mg·hr/L

Nephrotoxicity Risk of Continuous Infusion Vancomycin

- Meta-analysis: Continuous associated with ↓ nephrotoxicity
  - RR = 0.61, 95% CI 0.47-0.80
- No significant differences in treatment failure or mortality

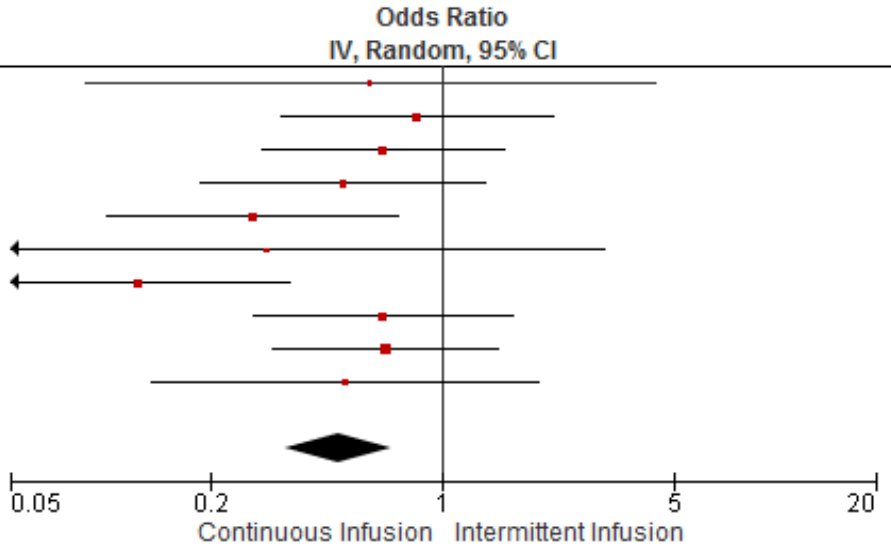
Int J Antimicrob Agents. 2016 Jan;47(1):28-35

Focus on Those at Highest Risk? Critically Ill Patients

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Wysocki 1995	-0.5008	1.01	3.3%	0.61 [0.08, 4.39]	1995
Wysocki 2001	-0.1767	0.481	12.0%	0.84 [0.33, 2.15]	2001
Hutschala 2009	-0.411	0.431	14.2%	0.66 [0.28, 1.54]	2009
Akers 2012	-0.6872	0.5038	11.2%	0.50 [0.19, 1.35]	2012
Saugel 2013	-1.316	0.5123	10.9%	0.27 [0.10, 0.73]	2013
Schmelzer 2013	-1.2164	1.188	2.4%	0.30 [0.03, 3.04]	2013
Hanrahan 2014	-2.1046	0.535	10.2%	0.12 [0.04, 0.35]	2014
Hong 2015	-0.412	0.4574	13.0%	0.66 [0.27, 1.62]	2015
Tafelski 2015	-0.3971	0.397	16.0%	0.67 [0.31, 1.46]	2015
Duszynska 2016	-0.6773	0.682	6.8%	0.51 [0.13, 1.93]	2016
Total (95% CI)			**100.0%**	**0.49 [0.33, 0.70]**	

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 11.18$, df = 9 (P = 0.26); $I^2 = 19\%$

Test for overall effect: Z = 3.80 (P = 0.0001)



Flannery AH. Presented at ACCP Annual Meeting, 2017

Acute kidney injury

Pros and Cons of Continuous Infusions

Pro:

- AUC calculations easier and fewer assumptions
- Associations with less nephrotoxicity
- Reduced lab cost

Con:

- IV access issues & compatability
- Logistical level issues
- Phlebitis concerns

Antimicrob Agents Chemother. 2015 Feb;59(2):930-4

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Practical Experience: 2 Centers

- Calculators pivotal to success
- Working with 2 levels after first dose
- Education
- Don’t forget: you already (sort of) know how to dose vancomycin

Key Takeaways

- Key Takeaway #1
  - Vancomycin AUC can be estimated with 2 levels using varying approaches in clinical practice
- Key Takeaway #2
  - Continuous infusion vancomycin may be associated with reduced nephrotoxicity, but a number of confounders present in the literature significantly limit any conclusions
- Key Takeaway #3
  - AUC monitoring is capable of being implemented—but be prepared to learn to adapt approach

Questions or Discussion?

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Clinical Meeting & Exhibition

Vancomycin: Teaching an Old Dog New Tricks

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