Vancomycin Pharmacokinetics, Dosing & Therapeutic Drug Monitoring

Inpatient Pharmacy Education
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Nebraska Medicine

Objectives

List the mechanism of action, spectrum of activity, PK/PD, and adverse effects of vancomycin

Describe vancomycin-induced nephrotoxicity and it's risk factors

Explain vancomycin dosing and therapeutic monitoring strategies at Nebraska Medicine

Background

Reason for competency:

- Maximize clinical outcomes and minimize toxicity for patients receiving vancomycin

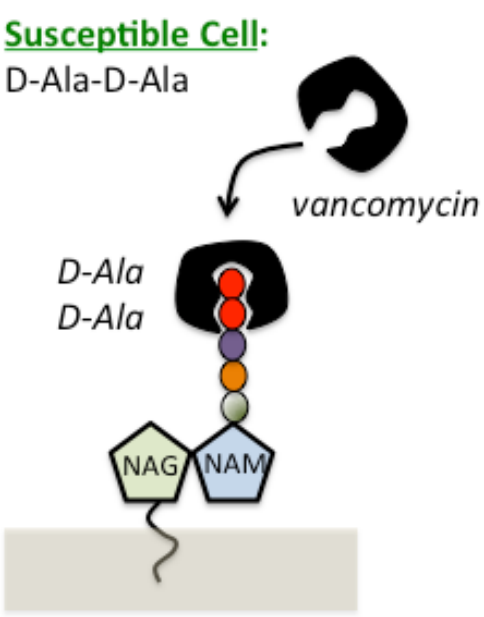
- Ensure NM pharmacists have the resources to successfully manage vancomycin dosing for patients

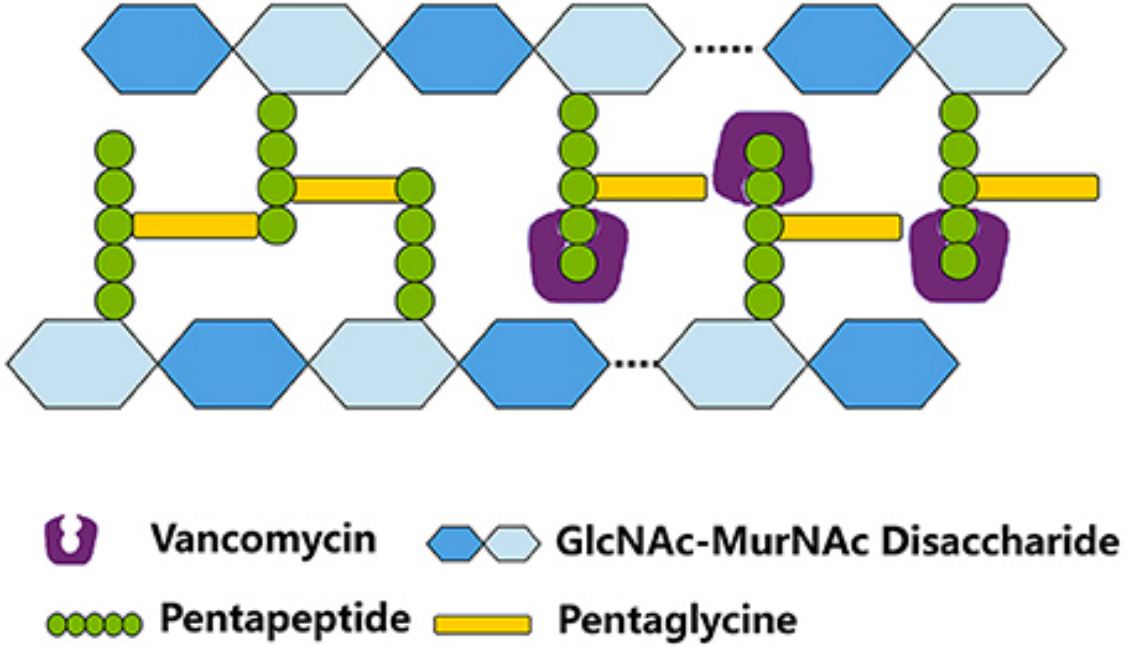
Abbreviations

IBW	Ideal body weight
ABW	Actual body weight, also known at total body weight (TBW)
DBW	Dosing body weight – this is a term used in Epic for the actual patient weight of when starting an oncology therapy plan. In should not be use as an adjusted body weight for dosing other drugs like antibiotics that have altered Vd in obesity
AdjBW	Adjusted body weight – this is the value used for dosing many antibiotics in obese patients due to their limited distribution to adipose tissue. AdjBW= IBW + 0.4(ABW-IBW)
Ke	Elimination rate constant
Vd	Volume of distribution
$t_{1/2}$	Half-life
C_{min}	Trough serum level at steady-state
AUC	Area under the concentration-time curve
SCr	Serum creatinine
MIC	Minimum inhibitory concentration
AKI	Acute kidney injury
HD	Hemodialysis

Vancomycin: Mechanism of Action

- Blocks peptidoglycan polymerization in the bacterial cell wall by changing D-ala,D-ala to D-ala,D-lac
- Results in inhibition of cell wall synthesis
- Slowly bactericidal (takes 24 hours for a 3 log kill in lab bacteria that is observed in about 4 hours with oxacillin or daptomycin)





Hu Q et al. Front Microbiol. 13 October 2016

Tulane School of Medicine. Glycopeptide Pharmacology.

Mechanism of Action

Spectrum of activity:

- Only effective against infections due to gram-positive bacteria
- No activity against gram-negative or anaerobic bacteria systemically

Clinical uses:

- Treatment of infections caused by Staphylococci, Streptococci and Enterococci including bacteremia/sepsis, pneumonia and skin among others
    - Not for definitive therapy of most infections once patient is stable or susceptibilities known
    - Alternative to beta-lactam agents for patients with resistance or a severe allergy

Pharmacokinetics

Absorption:

- Negligible oral absorption
- High colonic concentrations when given orally for *Clostridioides difficile* infection

Distribution:

- Tissue penetration varies depending on disease state/inflammation
- Enhanced CSF penetration with inflamed meninges
    - Negligible without inflammation
- Volume of distribution approximately 0.7 L/kg

Elimination:

- IV administration – primarily excreted by the kidneys
- Oral administration – primarily excreted in the feces
- Half-life = ~6-7 hours (normal renal function), can be 12 hours in typical hospitalized patients

Adverse Effects

Infusion-related reaction: “Red-man syndrome”

- Non-immunological histamine reaction causing redness, flushing and itching
    - Not a true allergy, can still receive the med if needed
- Slow down infusion to avoid, can give diphenydramine
- Normally no faster than 1g/hr, but can double the duration of infusion to limit reaction
    - Standard vancomycin infusion rates at Nebraska Medicine
        - ≤1000 mg over 60 minutes, including all pediatric doses
        - 1001-1500 mg over 90 min
        - 1501-2000 mg over 120 min
        - 2001-2500 over 150 min (rarely dose this high)
        - > 2,500 mg over 180 min (very rarely needed)

Adverse Effects

Ototoxicity

- 2% incidence, higher in elderly (6%)
- May be associated with elevated serum concentrations, but no specific threshold identified
- Manifested by vestibular damage and/or cochlear damage leading to sensory hearing loss and tinnitis (reversible)

Neutropenia

- More common with prolonged use, but reversible

Steven's Johnson Syndrome

- Uncommon, yet possible. Do not re-challenge if suspected

Forouzesh A. Antimicrob Agent Chemother. 2009

Vancomycin Use & Nephrotoxicity

Stages of vancomycin purity from 1956 to 1981

- Approved in 1958, named in reference to the word “Vanquish”
- Impurities = “Mississippi Mud” → toxicity?
- Now 90-95% pure
- From 2006-2012 → vancomycin use increased by 32%
- Use currently as prevalent as 14.4% of all inpatients

Reynolds LA, Tansey T. Superbugs and Superdrugs: A History of MRSA. 2008
CDC. *Antibiotic Use in the US.* 2017.
Magill et al. *JAMA.* 2014 Oct 8;312(14):1438-46

2009 Vancomycin Guidelines

Vancomycin is a **concentration-independent** killer of gram-positive pathogens

- AUC/MIC is the most useful PK/PD parameter to predict efficacy

Trough serum vancomycin concentrations considered most practical method for monitoring

- Drawn at steady state, just before 4th dose

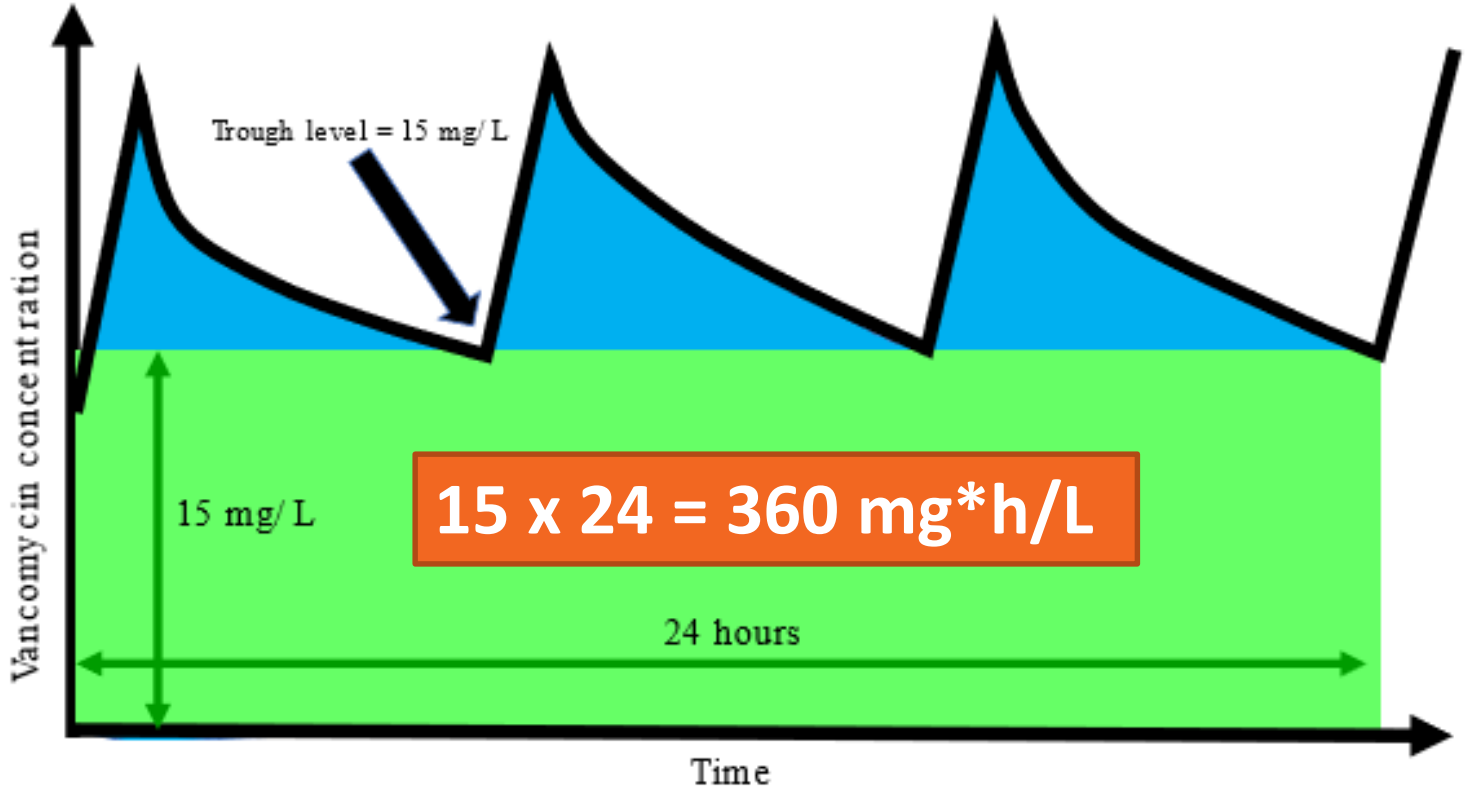
Trough concentration of 15-20 mg/L increases probability of obtaining optimal drug exposure

- Trough of 15 mg/L easiest way to ensure **AUC > 400 mg*hr/L**

Rybak et al. *Am J Health Syst Pharm.* 2009

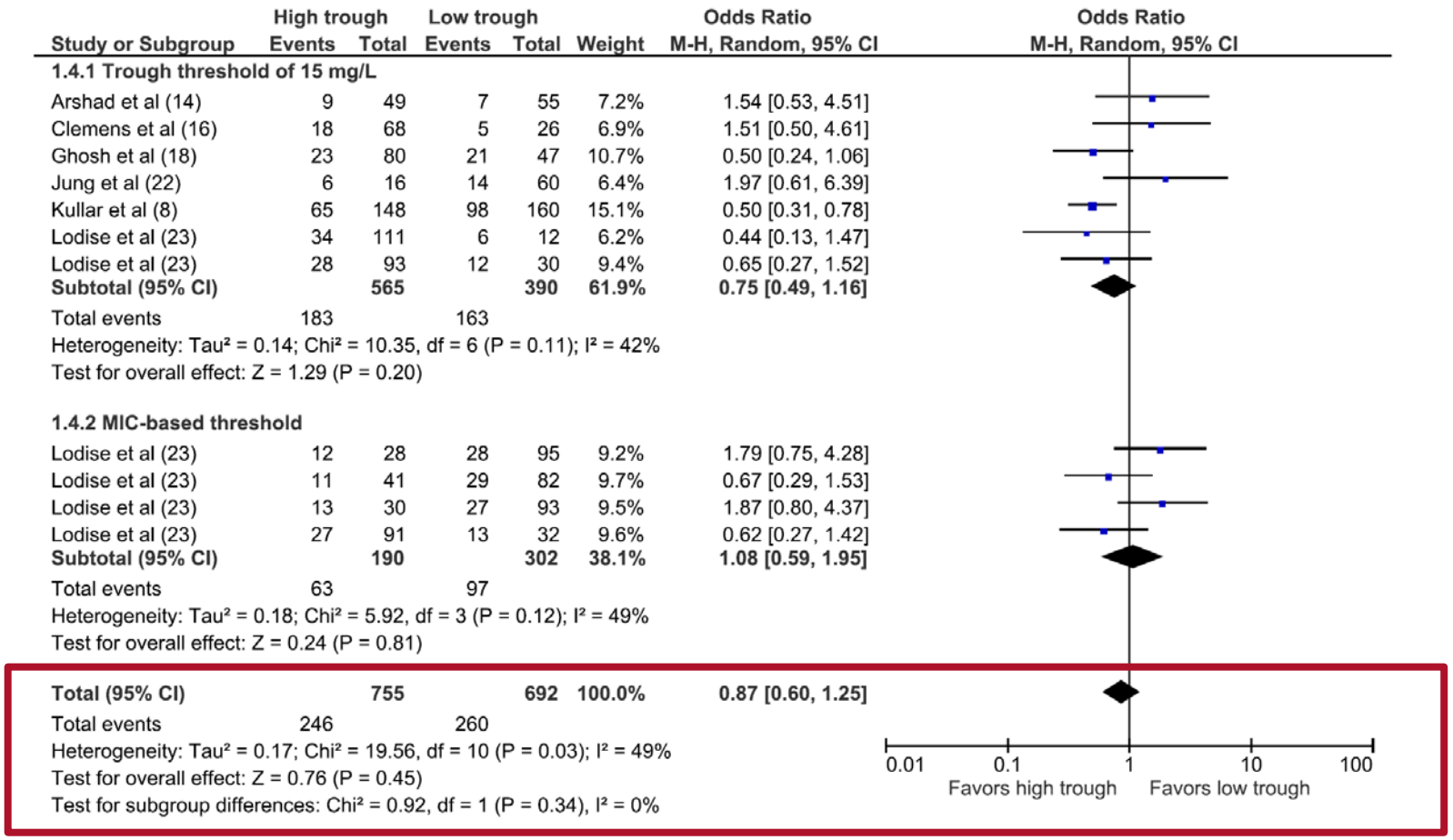
Rationale for trough-based dosing

- Trough of 15 mg/L = minimum AUC of 360
- AUC of 400 mg ~ C_{avg} 17 mg/L



Farkas, J https://emcrit.org/pulmcrit/vanco/

Efficacy by Trough

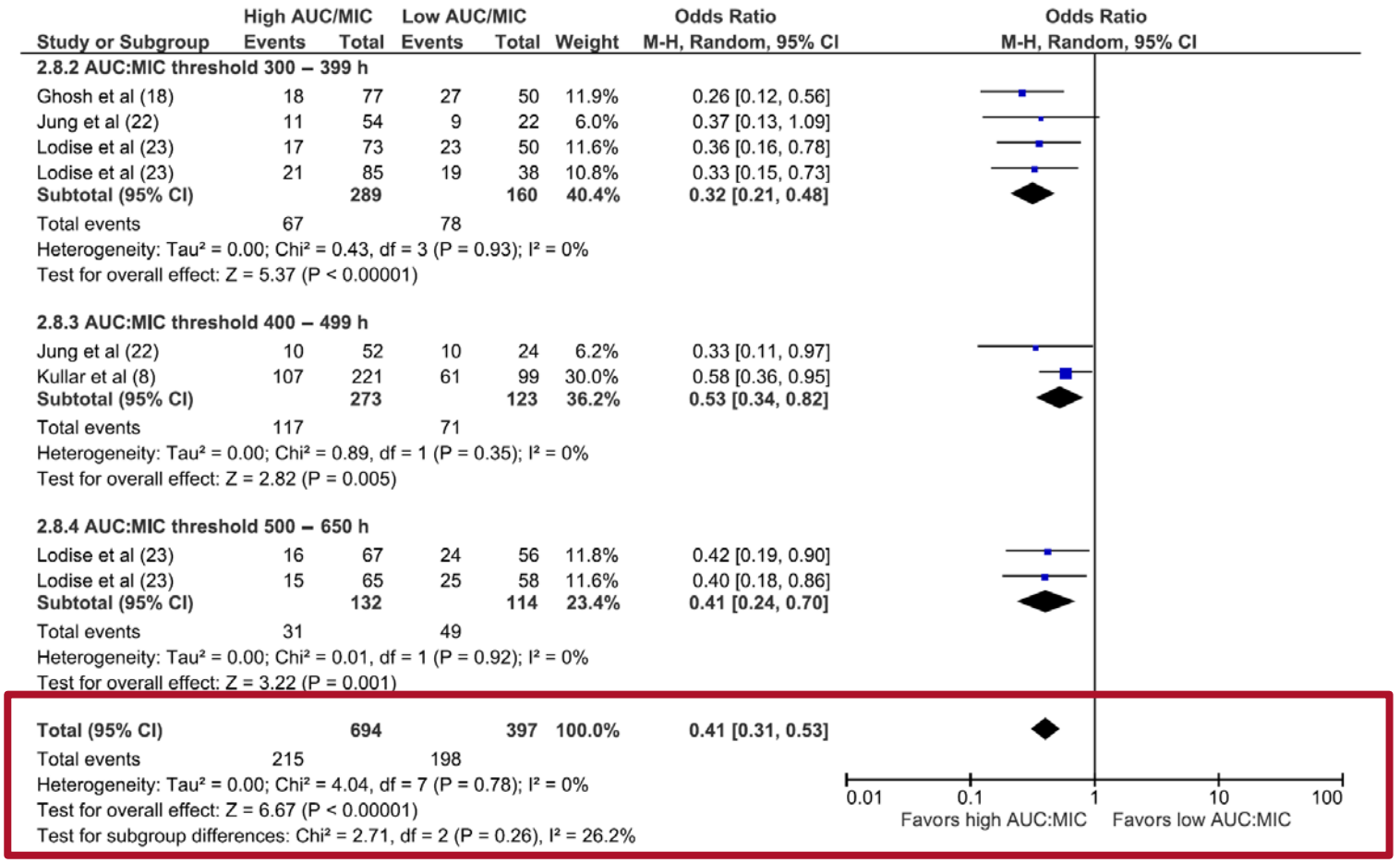


Study or Subgroup	High trough Events	Total	Low trough Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.4.1 Trough threshold of 15 mg/L						
Arshad et al (14)	9	49	7	55	7.2%	1.54 [0.53, 4.51]
Clemens et al (16)	18	68	5	26	6.9%	1.51 [0.50, 4.61]
Ghosh et al (18)	23	80	21	47	10.7%	0.50 [0.24, 1.06]
Jung et al (22)	6	16	14	60	6.4%	1.97 [0.61, 6.39]
Kullar et al (8)	65	148	98	160	15.1%	0.50 [0.31, 0.78]
Lodise et al (23)	34	111	6	12	6.2%	0.44 [0.13, 1.47]
Lodise et al (23)	28	93	12	30	9.4%	0.65 [0.27, 1.52]
Subtotal (95% CI)		**565**		**390**	**61.9%**	**0.75 [0.49, 1.16]**
Total events	183		163			
Heterogeneity: Tau² = 0.14; Chi² = 10.35, df = 6 (P = 0.11); I² = 42%						
Test for overall effect: Z = 1.29 (P = 0.20)						
1.4.2 MIC-based threshold						
Lodise et al (23)	12	28	28	95	9.2%	1.79 [0.75, 4.28]
Lodise et al (23)	11	41	29	82	9.7%	0.67 [0.29, 1.53]
Lodise et al (23)	13	30	27	93	9.5%	1.87 [0.80, 4.37]
Lodise et al (23)	27	91	13	32	9.6%	0.62 [0.27, 1.42]
Subtotal (95% CI)		**190**		**302**	**38.1%**	**1.08 [0.59, 1.95]**
Total events	63		97			
Heterogeneity: Tau² = 0.18; Chi² = 5.92, df = 3 (P = 0.12); I² = 49%						
Test for overall effect: Z = 0.24 (P = 0.81)						
Total (95% CI)		**755**		**692**	**100.0%**	**0.87 [0.60, 1.25]**
Total events	246		260			
Heterogeneity: Tau² = 0.17; Chi² = 19.56, df = 10 (P = 0.03); I² = 49%						
Test for overall effect: Z = 0.76 (P = 0.45)						
Test for subgroup differences: Chi² = 0.92, df = 1 (P = 0.34), I² = 0%						

Higher vancomycin trough levels not associated with reduced risk of treatment failure (OR 0.87, 95% CI 0.60–1.25)
Trough values not associated with reduced risk of persistent bacteremia;
No association between trough goals & mortality

Prybylski. *Pharmacotherapy.* 2015;35(10):889–898

Efficacy by AUC



Higher AUC:MIC had a significantly reduced risk of treatment failure (OR 0.41,95% CI 0.31–0.53, p<0.0001)
Risk of mortality was significantly less in the high AUC:MIC cohort (OR 0.47, 95% CI 0.33–0.65)

Prybylski. *Pharmacotherapy.* 2015;35(10):889–898

Outcomes by AUC

AUC:MIC cutoffs from a sample of studies

- >345 mg*hr/L improved efficacy for pneumonia
  - Clinical success 23% vs. 78% (Moise-Broder 2000)
- >398.5 mg*hr/L MRSA bacteremia
  - Treatment failure 45% vs 25% (Jung 2014)
- <515 mg*hr/L had best composite outcome of no clinical failure or toxicity in prospective trial (Lodise 2019)

Vancomycin and Nephrotoxicity

Before 2009 Guidelines

- It was thought that higher troughs of 15-20 mg/L would improve efficacy by consistently achieving an AUC > 400 mg*hr/L without a subsequent increase in nephrotoxicity

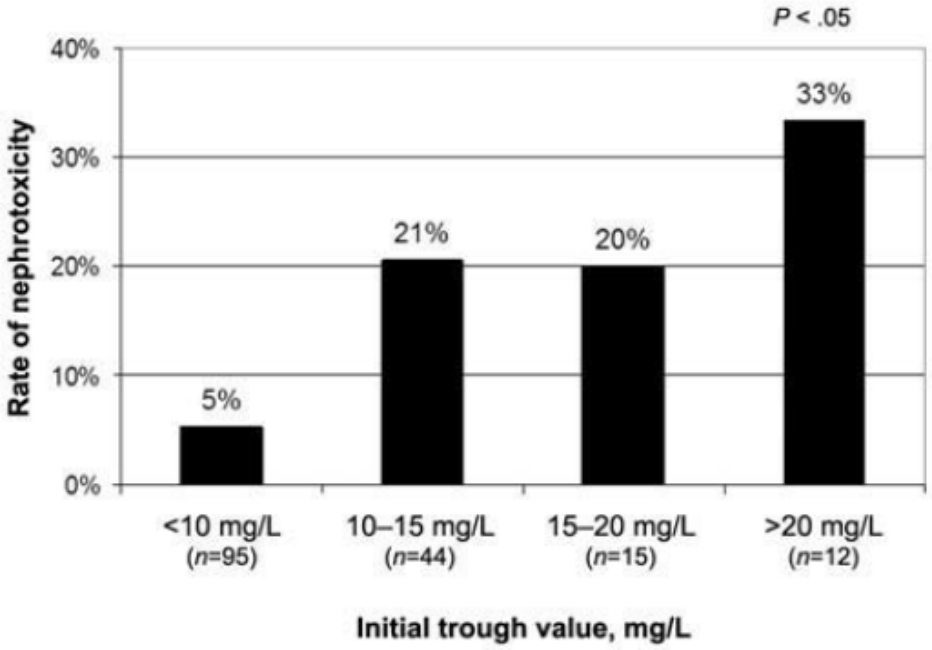


Figure 1. Bar graph showing the relationship between the initial vancomycin trough value and the rate of nephrotoxicity for the 166 patients who met the inclusion criteria.

Lodise et al. *Clin Infect Dis* 2009

Initial Vancomycin Trough and Nephrotoxicity

After 2009 Guidelines

- As the number of patients with higher troughs increased, nephrotoxicity also increased significantly - but efficacy was not substantially improved

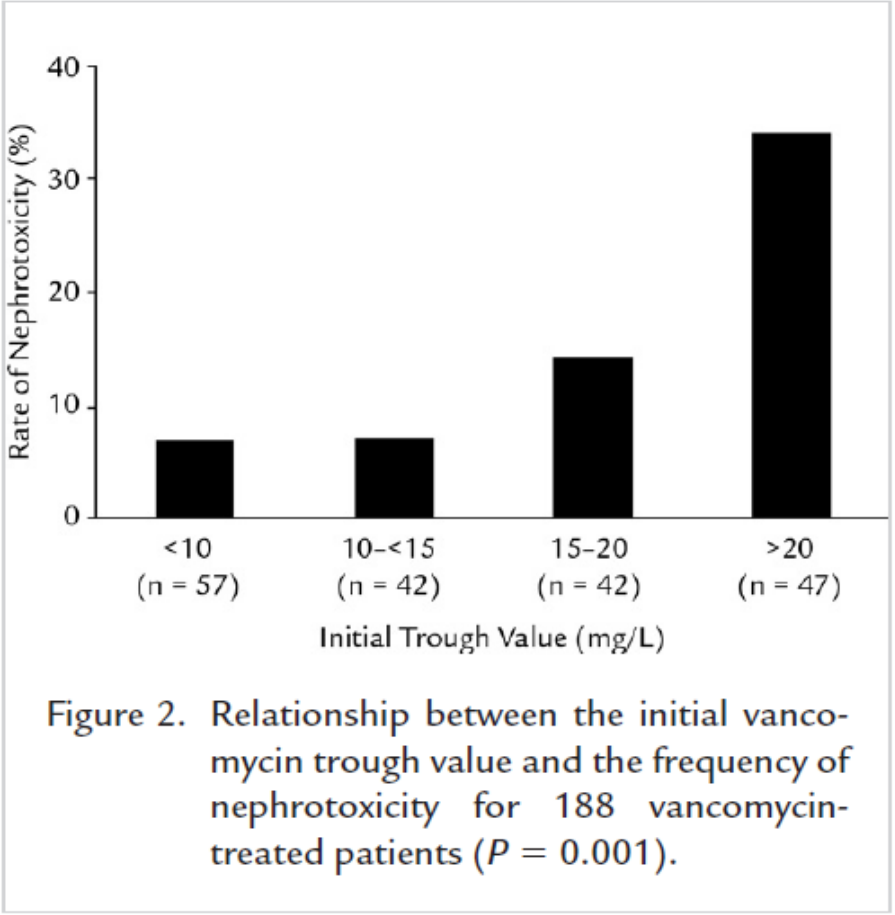
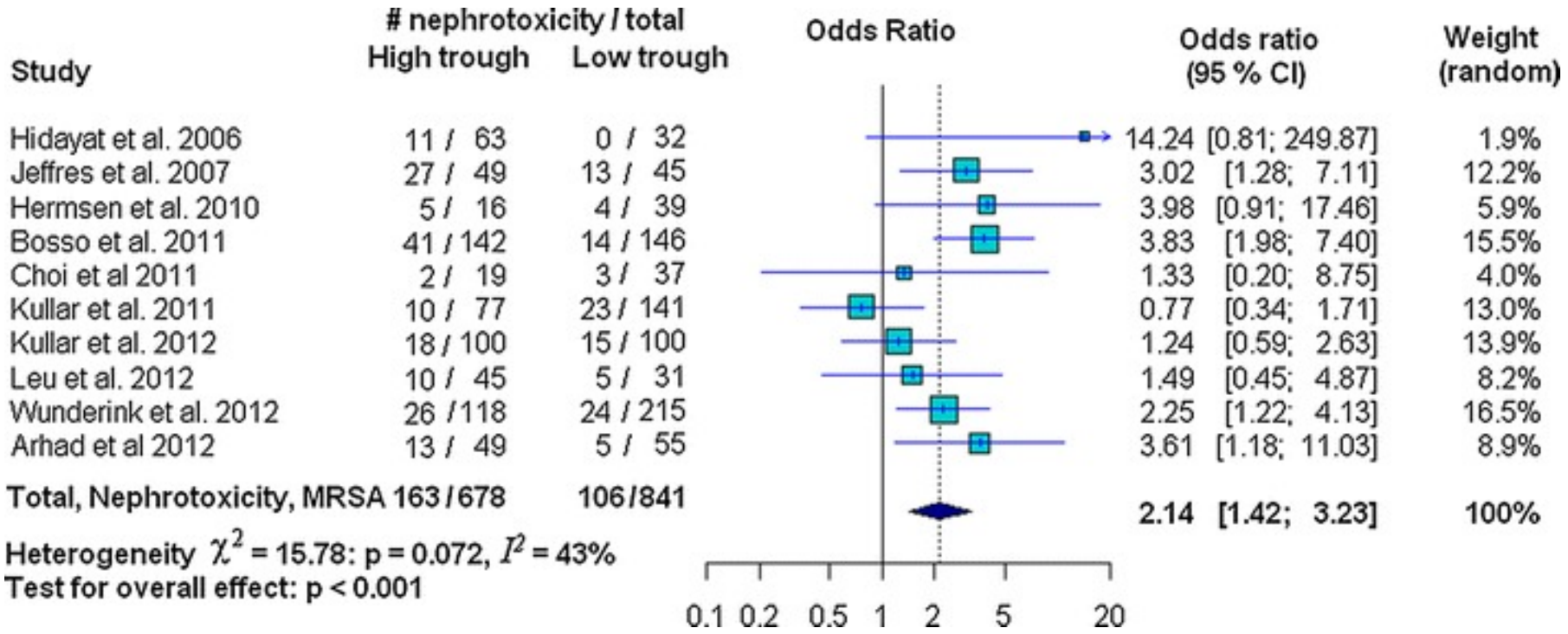


Figure 2. Relationship between the initial vancomycin trough value and the frequency of nephrotoxicity for 188 vancomycin-treated patients ($P = 0.001$).

Cano et al. *Clin Ther* 2012

Nephrotoxicity

We now understand that high trough goals more than double the risk of acute kidney injury (AKI)

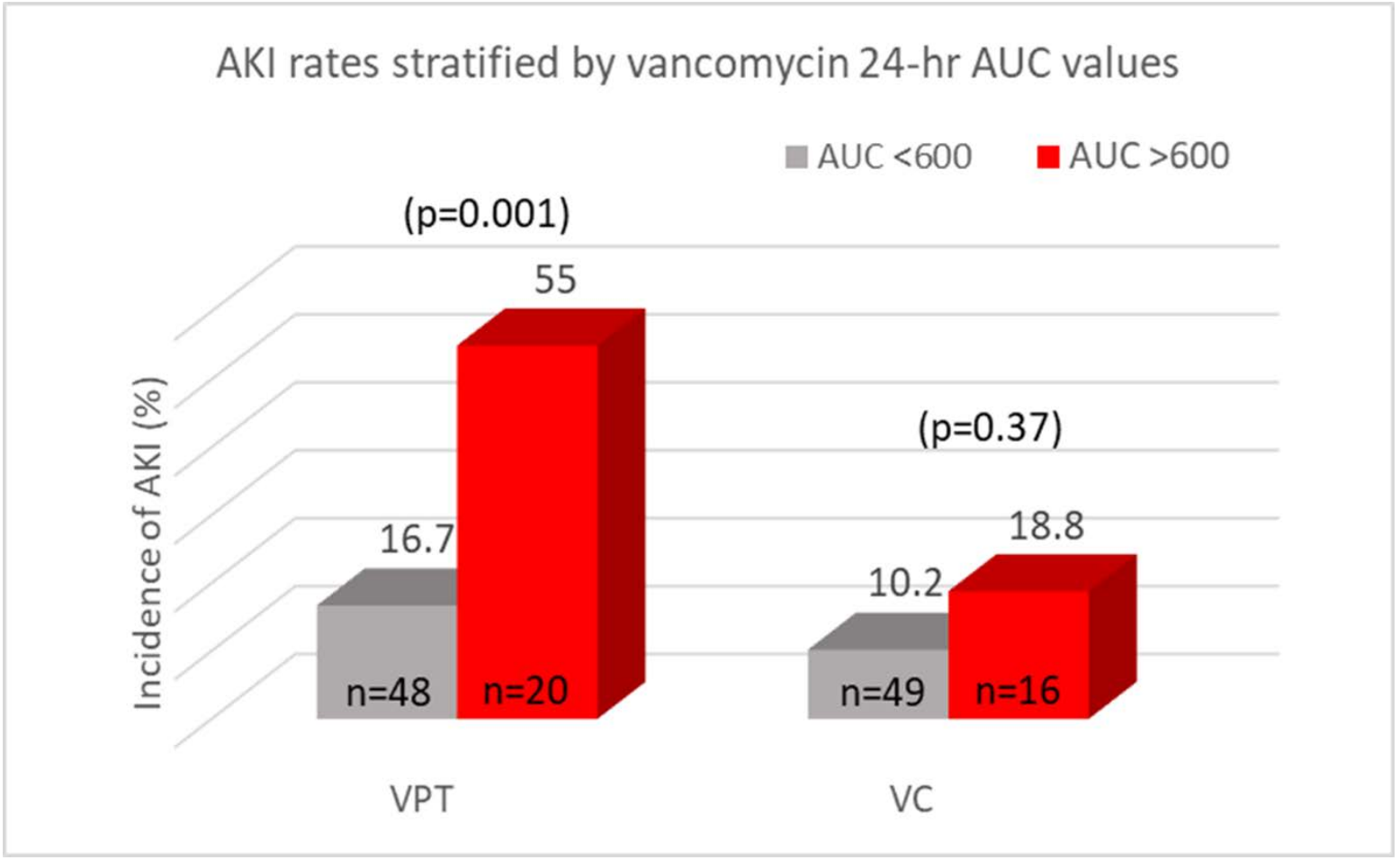


Tongai et al. *BMC Res Notes.* 2016; 9: 455.

Nephrotoxicity

- 5-7% incidence historically
    - <10% rate of AKI should still be our goal
- Reports of increased nephrotoxicity (20-30%) since targeting higher trough concentrations of 15-20 mg/L
- Related to acuity of illness, higher total daily dose, area under the curve and duration of therapy
  - Doses >4 g/d are a risk factor, likely due to high AUC
  - Onset typically occurs 4-17 days into therapy
- Up to 29-43% reported with concomitant nephrotoxins
  - Piperacillin-tazobactam now recognized as causing synergistic toxicity

Local vancomycin nephrotoxicity with piperacillin-tazobactram (VPT) 29% in 2017 vs. 13% with cefepime (VC) in 2018



5% of patients in this study grew MRSA

Glass JP, et al. Am College Clin Pharm. 2019

Nephrotoxicity Summary

Vancomycin trough values strongly correlated with nephrotoxicity

Trough > 15 mg/L = ↑ risk of nephrotoxicity based on elevated AUC in many patients

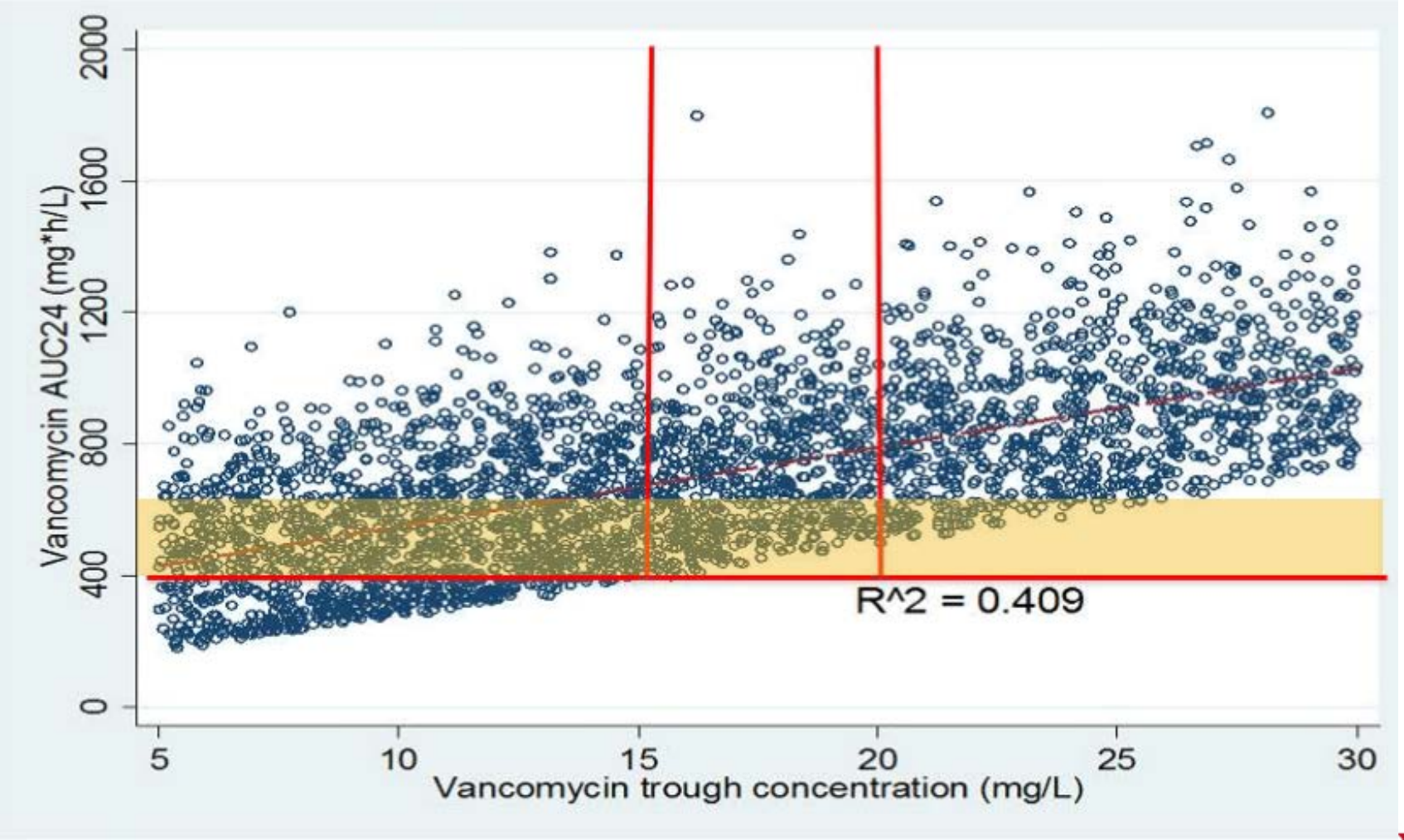
AUC threshold for increased nephrotoxicity recently recognized as **> 563 - 650 mg*hr/L**

Incidence of toxicity increases as a function of combined risk factors

Prolonged therapy duration, ICU status, concomitant nephrotoxins including piperacillin-tazobactam

Van Hal et al. *Antimicrob Agents Chemother.* 2013;57(2):734-744
Chavada et al. *Antimicrob Agents Chemother.* 2017;61(5)
Aljefri et al. *Clin Infect Dis.* 2019; e-pub ahead of print

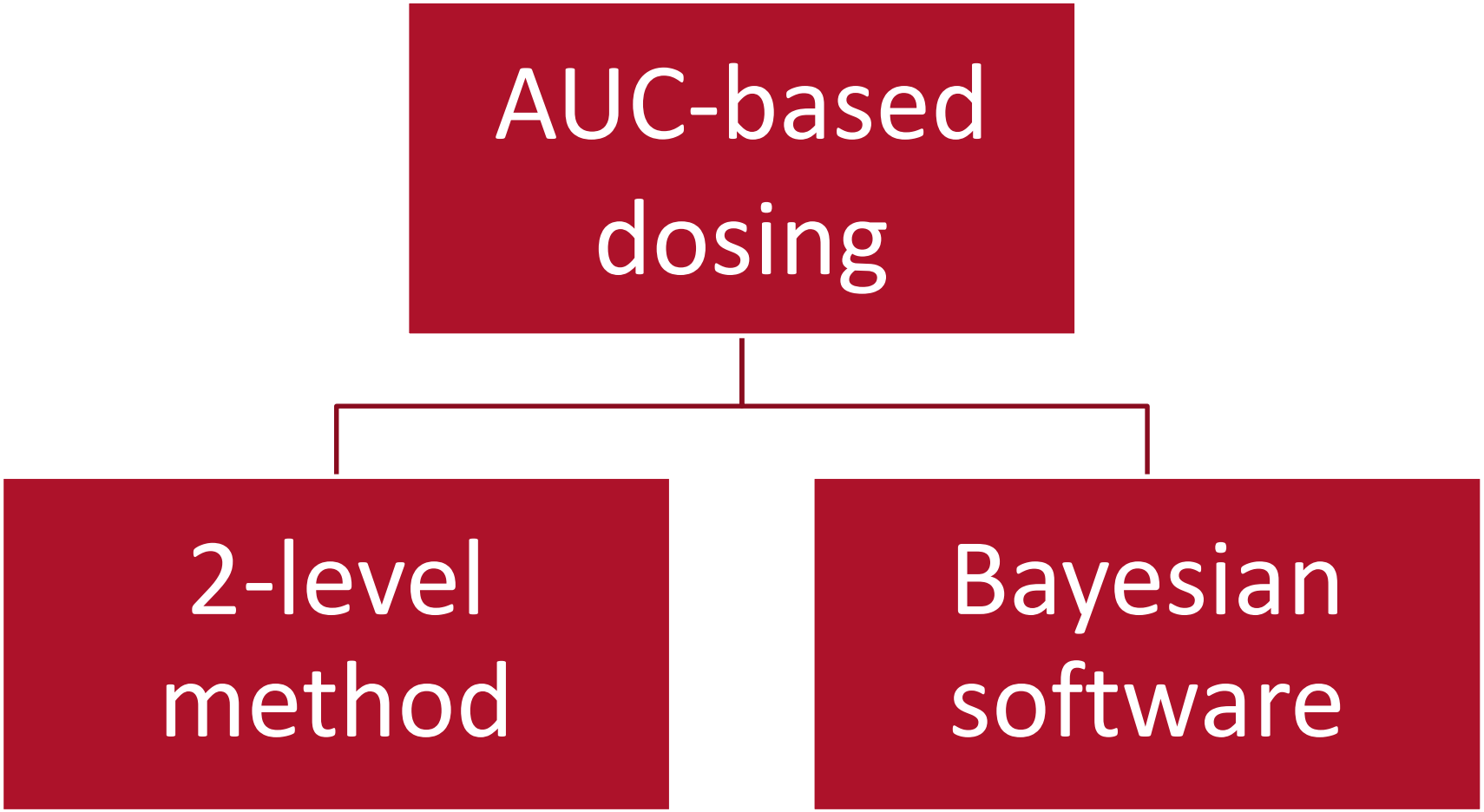
Relationship between vancomycin trough & $AUC_{0\text{-}24h}$



Simulation of 5,000 patients with different characteristics receiving vancomycin 1g q8h

Pai MP *Adv Drug Deliv Rev.* 2014 Jun 5

Implementation



Real World Experience #1

Detroit Medical Center: 2-level method of AUC dosing

- C_{min} routinely 2-3 mg/dL lower than trough-guided dosing

Bayesian estimated vancomycin exposure profile subgroup analysis

Variable	Values for the following groups[a]:		*P* value
	Trough concn-guided dosing group (*n* = 150)	AUC-guided dosing group (*n* = 150)	
C_{min24} (mg/liter)	12.7 (8.9–16.6)	10.0 (5.7–13.4)	<0.001
C_{min48} (mg/liter)	14.2 (10.3–19.5)	12.5 (8.3–16.7)	0.003
$AUC_{0–24}$ (mg · h/liter)	705 (540–883)	474 (360–611)	<0.001
$AUC_{24–48}$ (mg · h/liter)	663 (538–857)	532 (406–667)	<0.001

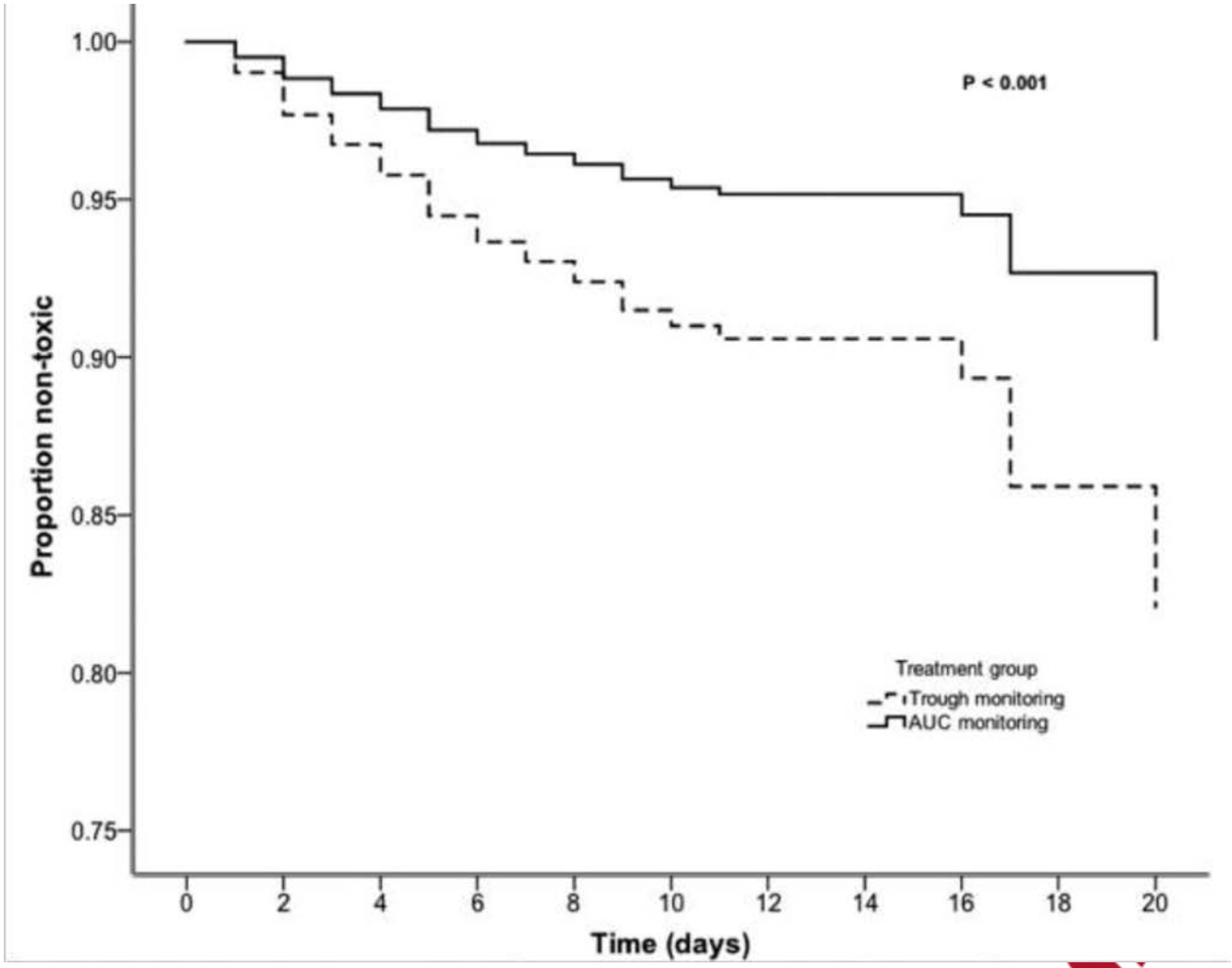
[a]Data represent the median (IQR).

Finch et al. *Antimicrob Agents Chemother.* 2017 Nov 22;61(12).

Real World Experience

Detroit Medical Center

- **Nephrotoxicity significantly less** in AUC-guided dosing group
- Patients had proven MRSA bloodstream infection where benefit > risk

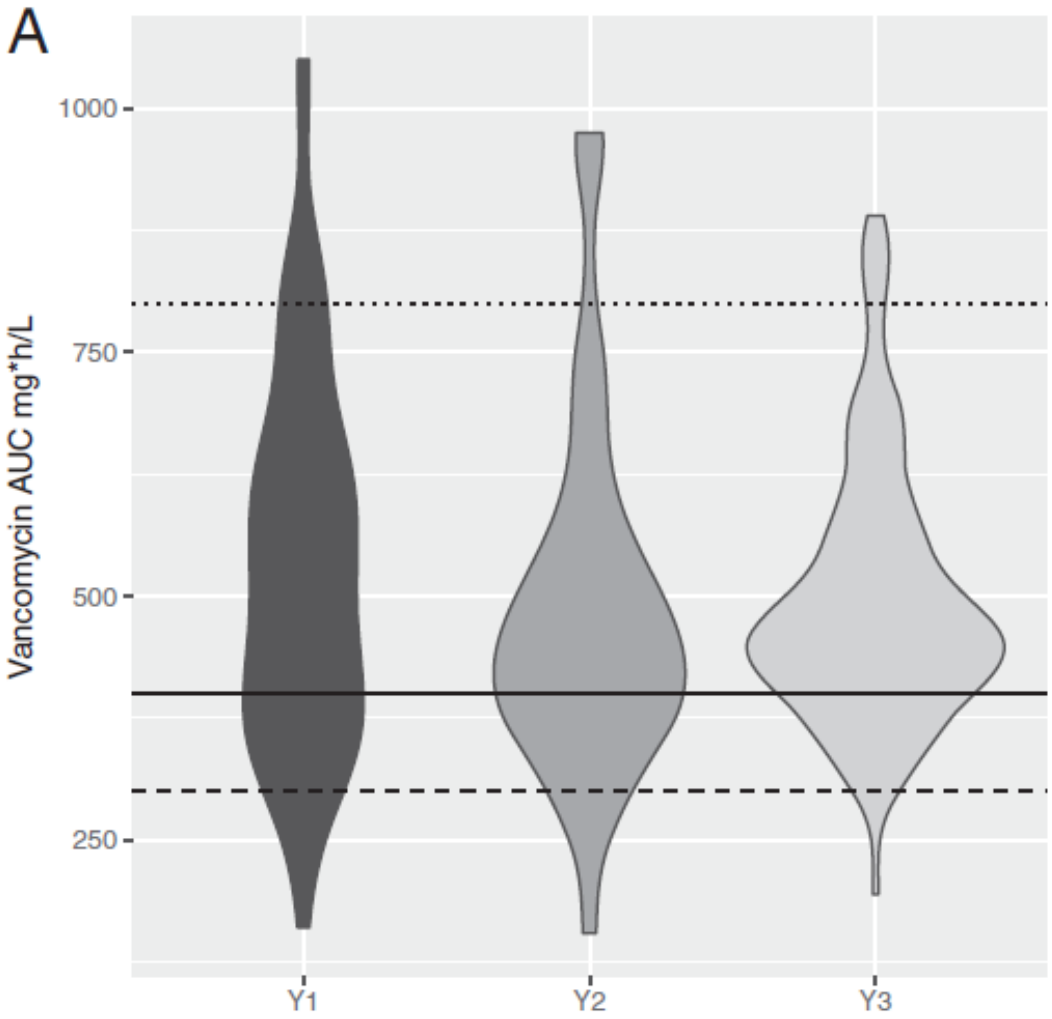


Finch et al. *Antimicrob Agents Chemother.* 2017 Nov 22;61(12).

Real World Experience #2

University of Southern California

- Using Bayesian software limited the number of patients out of range in year 2 & 3
- The violin plots show distribution of AUCs
- Solid line is their goal of AUC 400 mg*hr/L
- Dotted lines are 300 for the lower limit of efficacy and 800 for the maximum tolerated



Neely et al. *Antimicrob Agents Chemother.* 2018 25;62(2).

Real World Experience #2

University of Southern California

- Efficacy remained the same while toxicity was minimized after the switch to AUC-based dosing in year 2

Therapeutic outcomes of vancomycin therapy			
	No. (%) of Subjects		
Outcome	Yr 1 (n=75)	Yr 2 (n=88)	Yr 3 (n=89)
Resolved	59 (71)	60 (67)	66 (74)
Relapsed	1 (1)	0	0
Failure	0	0	0
Death	0	0	0
De-escalation	7(8)	5(6)	6(7)
Not indicated	8(10)	9(10)	9(10)
Transferred	6(7)	16(18)	9(10)

Resolved: Marked improvement or disappearance of signs and symptoms (s/sx) of acute infection and cessation of vancomycin therapy;

Relapses: Return of s/sx of same infection within 72h of stopping vanco therapy;

Failure: Persistence of s/sx despite vancomycin for defined treatment for vanc-susceptible infection;

Death: All-cause mortality within 72h of stopping vancomycin.

De-escalation: Step down occurred to narrower-spectrum IV antibiotics or to oral therapy

Not indicated: Infections were from organisms defined as resistant to vancomycin (e.g. GNR)

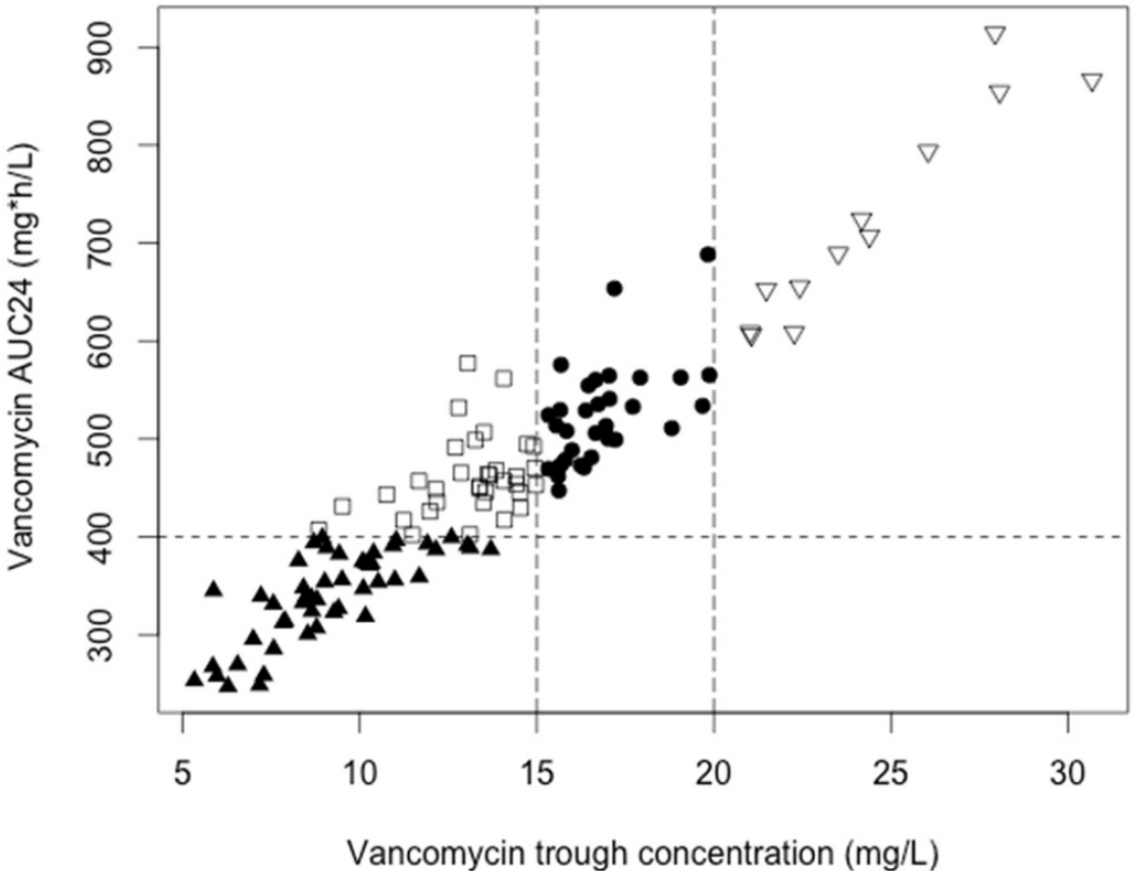
Transferred: Patient left to another facility while still receiving vanco so unable to assess outcome

Experience with Bayesian-estimated AUC

Australia: MRSA bacteremia

- 10 out of these 117 patients had AKI
- 8 of those 10 had a high AUC

- A trough of 10-15 mg/L is appropriate for a majority of patients, but 15-20 can be safe when AUC is known

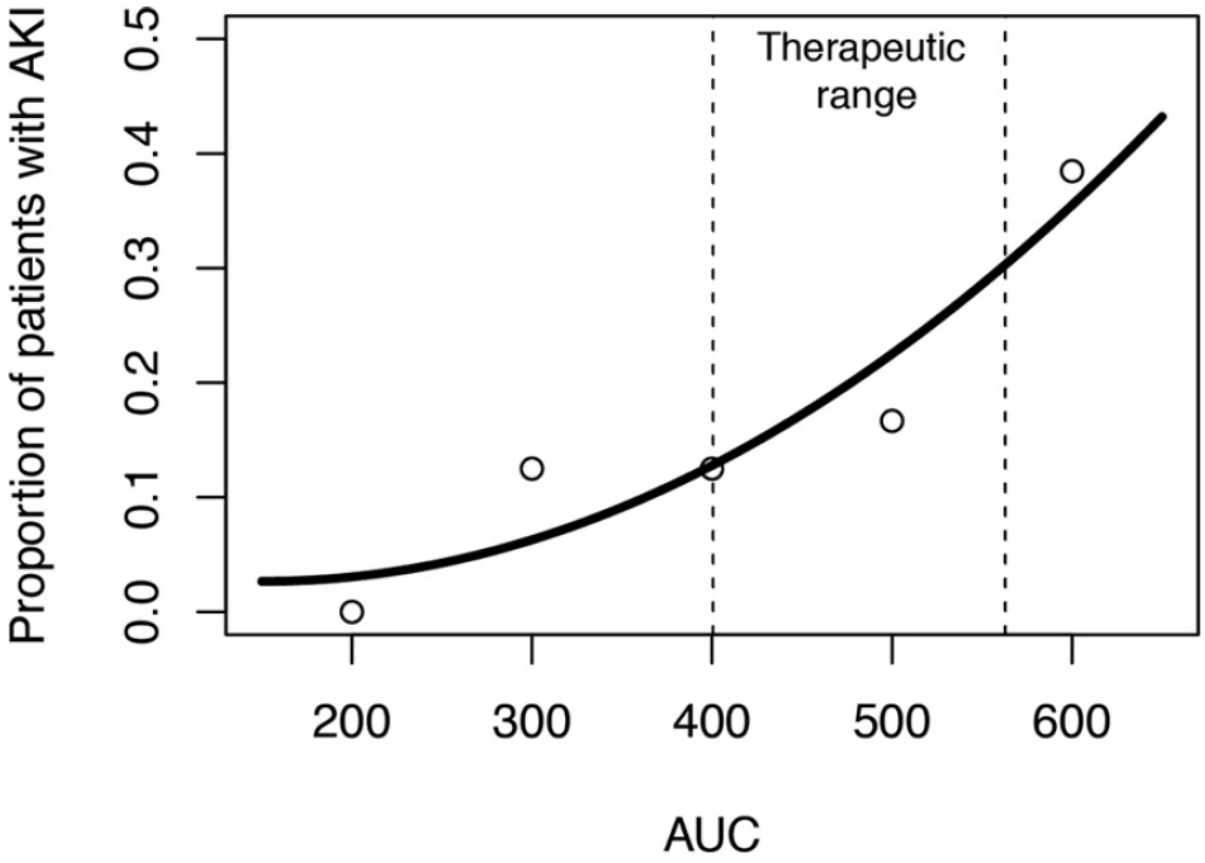


Chavada et al. *Antimicrob Agents Chemother*. 2017; 61(5)

AUC and nephrotoxicity

Australia: MRSA bacteremia

- 20 patients out 117 overall had a high AUC
- 8 of those 20 had AKI = 40%
- Risk ratio 5.0 for AKI with an elevated AUC



Chavada et al. *Antimicrob Agents Chemother*. 2017; 61(5)

2020 Vancomycin Guideline

Trough-based dosing is no longer the standard of care

AUC goal of **400-600** mg*hr/L over 24 hours (AUC_{24}) should be used to optimize efficacy and reduce nephrotoxicity

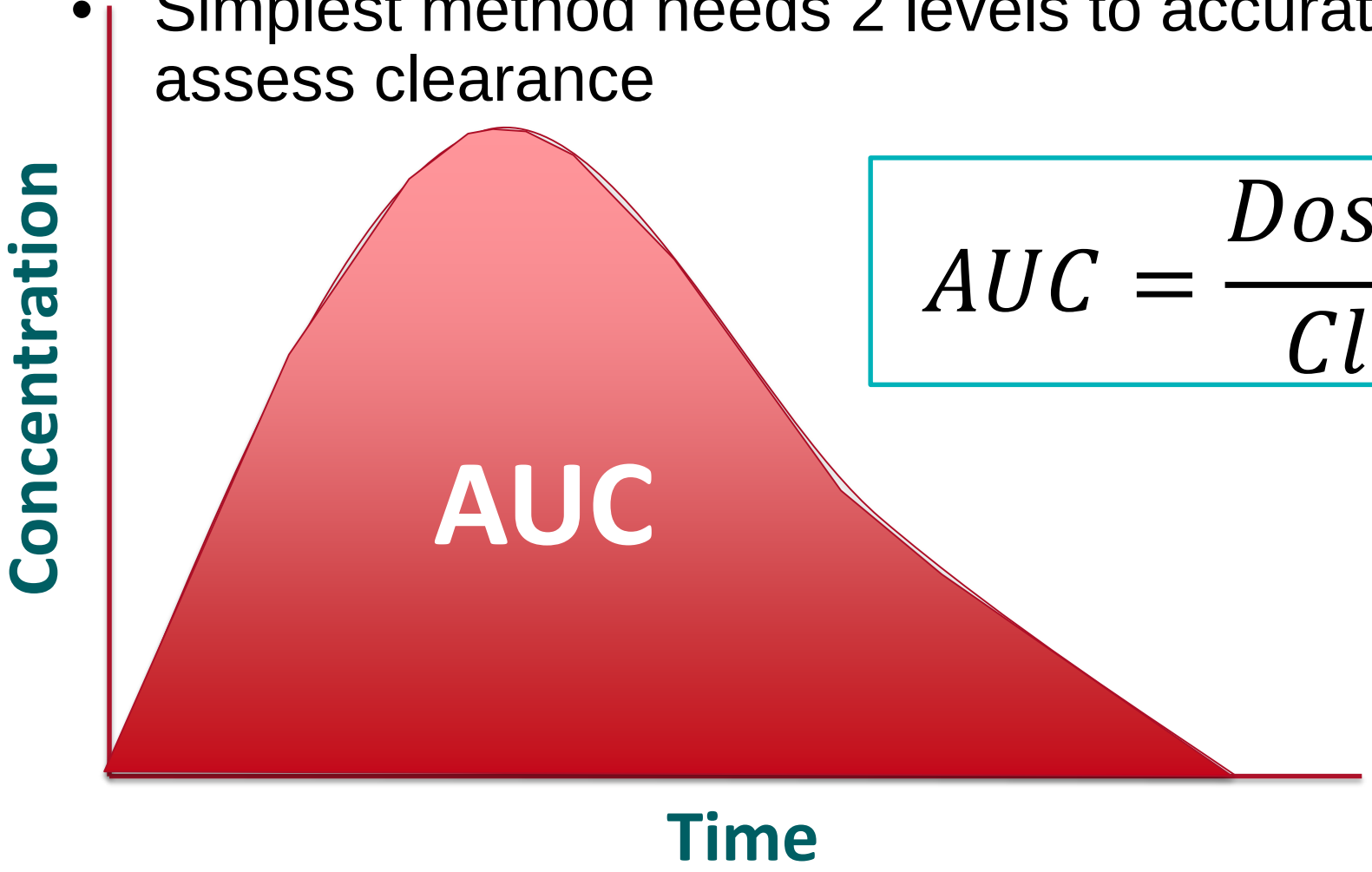
Implement by calculating AUC with 2 levels after standard dosing or using Bayesian software

https://academic.oup.com/ajhp/article/77/11/835/5810200

ASHP, IDSA, PIDS, and SIDP. Rybak et al. 2020

Measuring AUC

- Simplest method needs 2 levels to accurately assess clearance

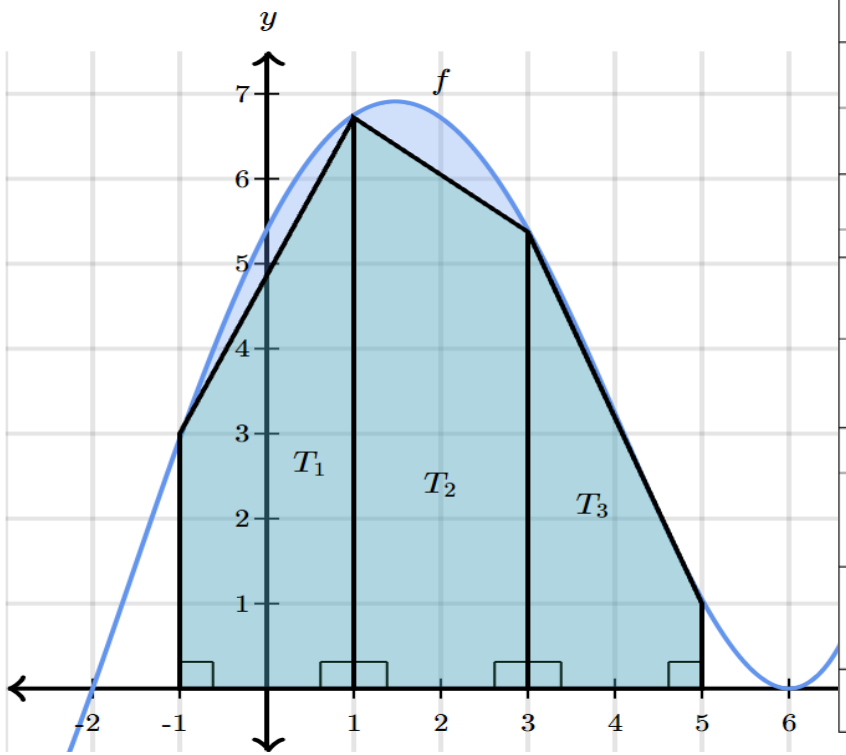


$$AUC = \frac{Dose}{Cl}$$

Khan Academy. Accessed September 10, 2019. https://www.khanacademy.org.

Trapezoidal Method (FYI)

- More accurate estimate of AUC, but calculation has many steps and still requires 2 levels

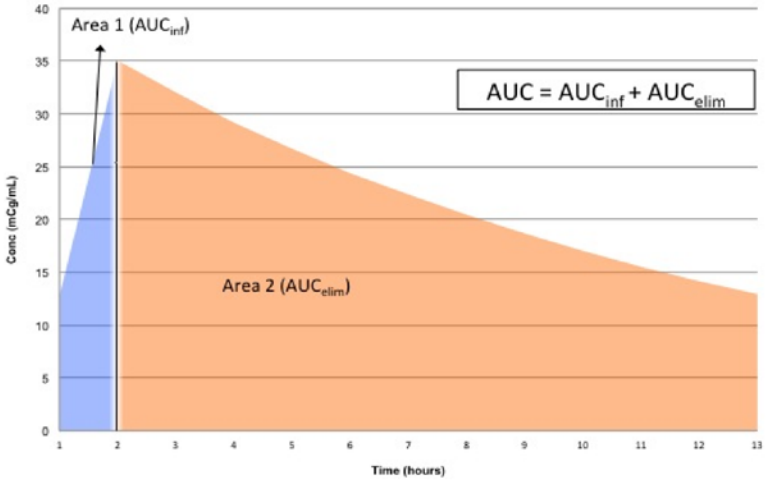


1. Verify that the doses prior to the concentrations were on time and drawn appropriately.	
2. Calculate patient's true k_e from two measured concentrations.	$k_e = \frac{\ln (C_1/C_2)}{(t_2 - t_1)}$
3. Calculate patient's true $t_{1/2}$.	$t_{1/2} = \frac{0.693}{k_e}$
4. Calculate patient's true C_{max}.	$C_{max} = \frac{C_1}{(e^{-k*\Delta T})}$ *ΔT=time between end of infusion and time level drawn*
5. Calculate patient's true C_{min}. Skip step if only 1 dose received.	$C_{min} = C_{max} * (e^{-k_e*(Tau-t)})$
6. Calculate patient's Vd.	
- If patient has received only 1 dose:	$Vd = \frac{Dose}{t} * \frac{(1 - e^{-kt})}{(k_e * C_{max})}$
- Steady-state condition:	$Vd = \frac{MD}{t} * \frac{(1 - e^{-kt})}{k_e * (C_{max} - [C_{min} * e^{-kt}])}$
7. Calculate actual vancomycin clearance (Cl_{van}).	$Cl_{van} = Vd * k_e$
8. If C_{min} concentration obtained is high, calculate time needed to reach desired range.	$T = \frac{\ln \left({C_{min}}/{C_{des}} \right)}{k_e}$
9. Calculate the new Tau.	$\text{Tau} = \frac{\ln \left({C_{max,des}}/{C_{min,des}} \right)}{k_e} + t$
10. Estimate total daily dose (TDD) needed to achieve target AUC_{24}.	$TDD\ (mg) = Cl_{van} * Desired\ AUC_{0-24}$

Trapezoidal Method, continued

- Levels should be from same dose at steady state
- Several hospitals have built these equations into spreadsheet calculators

11. Calculate new MD.	$MD = \frac{TDD}{\left(\frac{24}{Tau}\right)}$
12. Calculate predicted steady-state C_{max} for new dosing regimen.	$C_{max} = \frac{\left(\frac{Dose}{Vd}\right)}{(1 - e^{-k*Tau})}$
13. Calculate predicted steady-state C_{min} for new dosing regimen.	$C_{min} = C_{max} * (e^{-k*(Tau-t)})$
14. Calculate predicted steady-state AUC_{24} based on new dosing regimen. (see figure below)	
a. Use linear trapezoidal rule to calculate AUC during infusion.	$AUC_{inf} = \frac{(C_{max} + C_{min})}{2} * t$
b. Use logarithmic trapezoidal rule to calculate AUC during elimination.	$AUC_{elim} = \frac{(C_{max} - C_{min})}{k_e}$
c. Sum areas from above and multiply by # doses / 24 hours.	$AUC_{0-24} = (AUC_{inf} + AUC_{elim}) * \left(\frac{24}{\text{Tau}}\right)$



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}.

Note: the estimated AUC should be expected to change in proportion to dosing changes (e.g. a 50% increase in TDD will lead to ~50% increase in AUC_{24}).

- Clincalc.com/vancomycin or Vancopk.com can be used with 1 level

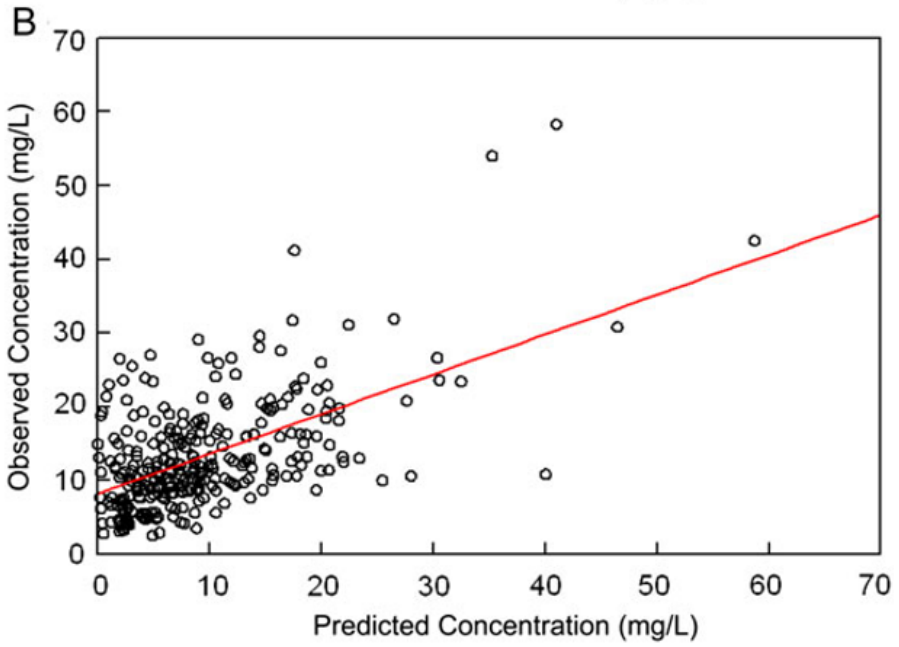
Meng L et al. Pharmacotherapy. 2019;39(4):433-442
Heil EL, et al. AJHP. 2018. 75(24):1986-1995

Bayesian Method

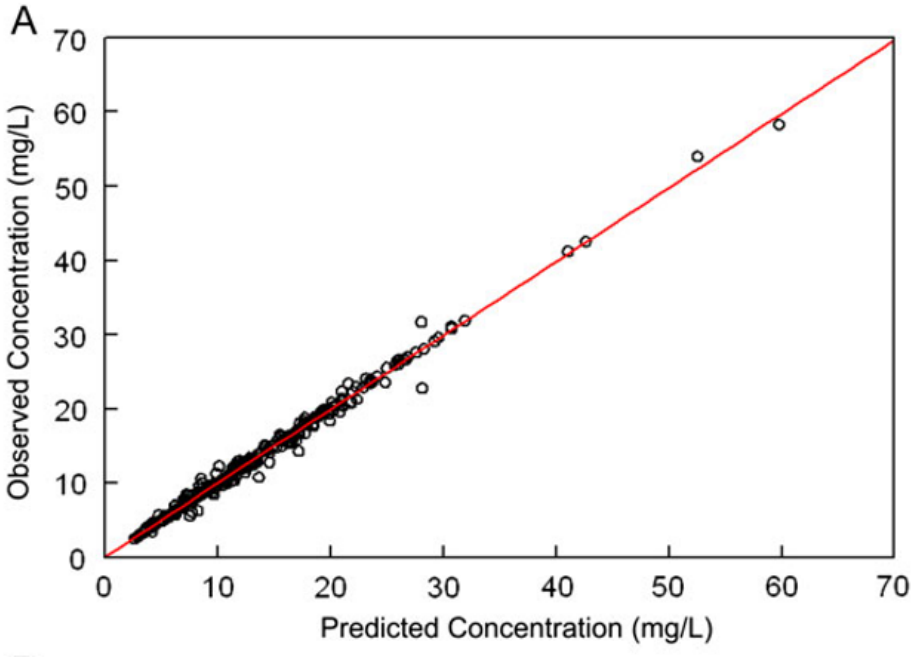
- Based on Bayes' Theorem, estimates patient's PK parameters using population database (Bayesian prior)
- Revises probability distribution using exact dosing and concentration data plus certain patient characteristics (Bayesian conditional posterior)
- Software calculates optimal dosing regimen based on specific patient's exposure profile
- Can use 1 level to adjust, even if not at steady state

Accuracy

Formula-Based Approach



Bayesian Method



Lodise et al. *Clin Infect Dis* 2014;59(5):666–75

Bayesian Method

Fewer blood samples per subject

Reduced nephrotoxicity

Similar efficacy

Potential cost savings

University of Southern California

Neely et al. *Antimicrob Agents Chemother*. 2018; 62(2)

Traditional Dosing

Weight-based dosing for comparison

- Adult: 15-20 mg/kg IV every 12 hours
  - Interval adjusted based on renal function
    - Q8h for patients under 40 years with CrCl > 100 mL/min
    - 10-15mg/kg q24h if CrCl 20-50 ml/min
    - Dose based on levels if <20 mL/min
  - Use adjusted body weight for obese
  - Assess benefit vs. risk if total dose > 4g/d
- Pediatric: 15-20 mg/kg IV every 6-8 hours

Using AUC-based dosing & Bayesian software will reduce the doses needed for most patients compared to targeting a trough 15-20 mg/L

- Some patients may require higher doses, but you can feel more confident in their safety when AUC_{24} remains < 600 mg*hr/L

Is a Loading Dose Important?

Not necessarily

- Loading doses achieve the PK/PD goal faster, but have not been proven to improve outcomes
- In one study of MRSA bacteremia, initial doses ≥1750 mg predicted protection from treatment failure
    - However, this was a post-hoc analysis and did not correlate with mg/kg
    - Keep in mind <1% of patients on vancomycin have MRSA bloodstream infections
- While higher total daily doses have been associated with nephrotoxicity, loading doses have not

Ortwine JK et al. *Inf Dis Ther.* 21 Oct 2019

Is a Loading Dose Important?

Guidelines continue to recommend a loading dose for patients who are critically ill

- 25-30 mg/kg IV x 1 dose, max of 3 g
- Actual body weight used out of convenience
- In obesity, volume is not linear with weight
    - 20-25 mg/kg is more reasonable
- Our software does not use loading doses in it's recommendations
    - They are not routinely needed, especially in floor patients
    - Remember it is the AUC that is important, not the peak or trough

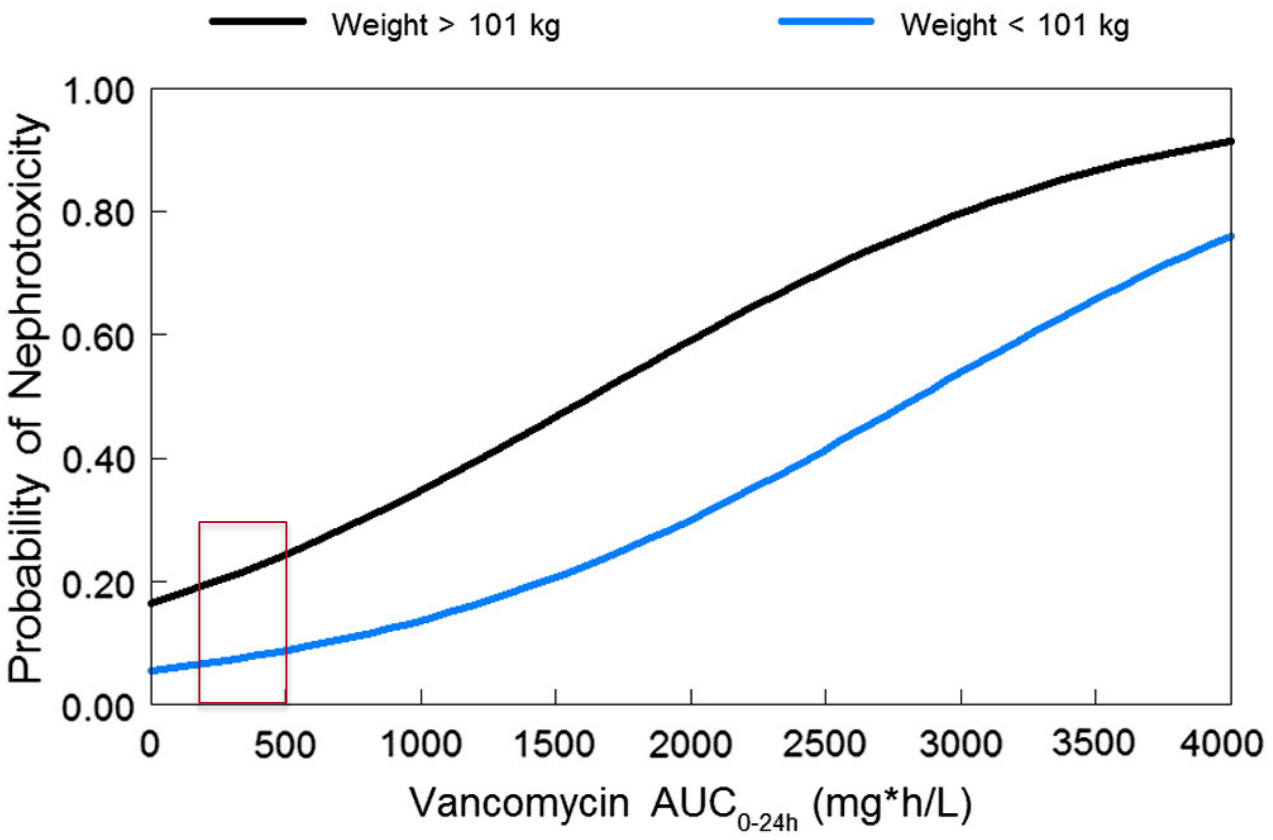
Is a Loading Dose Important?

- If choosing to give a one-time dose to get started in ED or ICU, 20-25mg/kg is reasonable for most patients with suspected MRSA bloodstream infection/sepsis
  - This will result in ≥1750 mg for most patients
- It has not been our practice to administer doses >2g
  - For doses over 2g, consider splitting up the load
  - For example, give 2g x1 and then start maintenance 6-12h later (after Scr known) rather than waiting 12-24h
- After the loading dose is administered, our software will incorporate that into it's calculations and you can change the start time to see how your maintenance regimen will perform

Denetclaw TH et al. *Annals of Pharmacother. 2015*

Relationship between vancomycin AUC nephrotoxicity and weight

- Weight >101 kg is a risk factor for AKI
- Even with software, vancomycin is hard to dose in obese patients
  - o Different models and equations exist, but none are perfect
- **Aim for AUC closer to 400 mg*hr/L**
- Be cautious and monitor obese patients more closely
  - – twice weekly labs



Pai MP *Adv Drug Deliv Rev.* 2014

Therapeutic Drug Monitoring

•Check past doses by searching “My iVents” for patient

•Adipose tissue can create an extra compartment that releases drug, especially in the obese later in course

- Monitor levels closely in overweight patients

•Q8h regimens may be necessary in these and younger patients, but should be rare overall

- Check labs twice weekly, including a trough at least until stable

Troughs

- Typical range: 10-15 mg/L meets goal of AUC 400-600 mg*h/L
- Reasonable to think about drawing at steady state with 4th dose in patients expected to continue on therapy
  - May choose to draw earlier in select patients with abnormal features
- Can be drawn anytime prior to a dose being administered.
  - Timing will be less important with software readily available to interpret

Therapeutic Drug Monitoring

- Once comfortable with software dosing recommendations, not every patient on empiric vancomycin will need a level drawn
- Evaluate whether therapy should be continued before ordering
- For example, don't get level with 4th dose if cultures negative and vancomycin unlikely to benefit patient
    - Ask if vancomycin can be discontinued instead
- For those with risk factors such as concomitant nephrotoxins think about assessing the serum concentration on day 2-3
- For those continuing therapy, draw at least 1 level each week to monitor for accumulation and ensure stable renal function
    - Although renal function usually improves in the first few days of hospital admission following hydration, vancomycin levels almost always rise after the first week of therapy

Therapeutic Drug Monitoring

Peaks, Not routinely recommended, but…

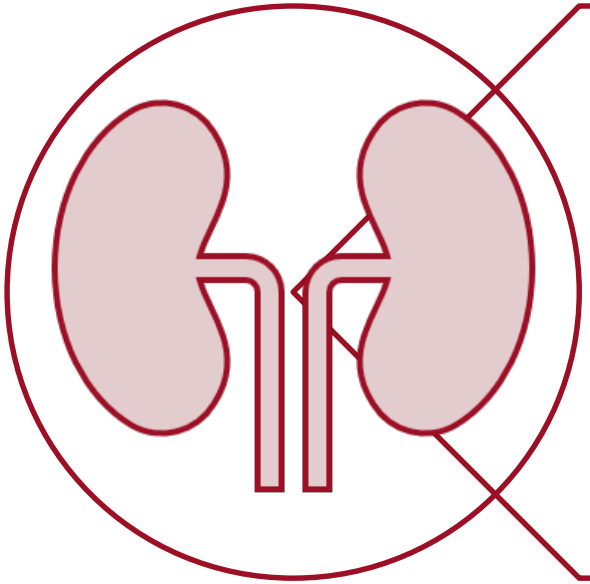
- A 2nd level at anytime can improve the fit of models
  - Useful for patients that have altered kinetics such as those in ICU with fluid shifts, cystic fibrosis, or morbidly obese
  - Two-compartment model might be a better fit for critically ill patients
- When drawn: at least 1 hour after end of infusion
- Typical range: 25-40 mg/L

Future direction: One “Random” level with AM labs can be sufficient monitoring for most standard patients on vancomycin when used with Bayesian software

Therapeutic Drug Monitoring

- Bayesian software is a tool to help you decide a dose for your patient with more precise information
    - You still need to use your clinical judgement: computers do not replace sound reasoning skills
- Keep in mind the studies confirming efficacy of AUC have been done in patients with MRSA bacteremia and pneumonia
- It is reasonable to think the drug will work the same for other organisms and infections
    - By default, our AUC target is set to 450 mg*hr/L
    - For patients with less severe infections or tenuous renal function, 400 is sensible as a goal

Limitation to Implementation



Dosing software is not validated for patients with Scr > 3 mg/dL or on dialysis at this time

- Continue to dose based on current protocols

Hemodialysis

- Almost no vancomycin is cleared in between dialysis sessions in patients with ESRD on HD
- ~30-40% vancomycin removed with each standard HD session of 3-4 hours (~ 10%/hr)
- Dosing for HD patients:
  - Recommend using Nephrology's preferred strategy (also known locally as Plumb's protocol)
  - Load, and then provide maintenance dose after HD
  - Alternative for critically ill patients with fluctuating dialysis needs
    - Can check random level after dialysis ("peak"), but needs to be drawn >4 hours post-HD to allow time for fluid redistribution
    - When <15 mg/L, re-dose with 7 mg/kg

Ariano RE et al. *Am J Kidney Dis.* 2005
Pai AB, Pai MP. *Am J Health-Syst Pharm.* 2004

Nephrology Dosing Strategy

- Indicated for adult patients with end stage renal disease receiving chronic hemodialysis
- Pre-HD target concentrations: 15-20 mcg/mL
- Loading dose: 20 mg/kg IV once (min. 1 g, max. 2 g)
- Maintenance dosing: 750 mg with each dialysis
  - Administer after each HD session until dosage changed or discontinued
  - Can be administered during the last hour of dialysis (more common as outpatient), but expect additional drug removal
  - For obese patients, it is reasonable to start with 1g for a maintenance dose (based on 7-10mg/kg)

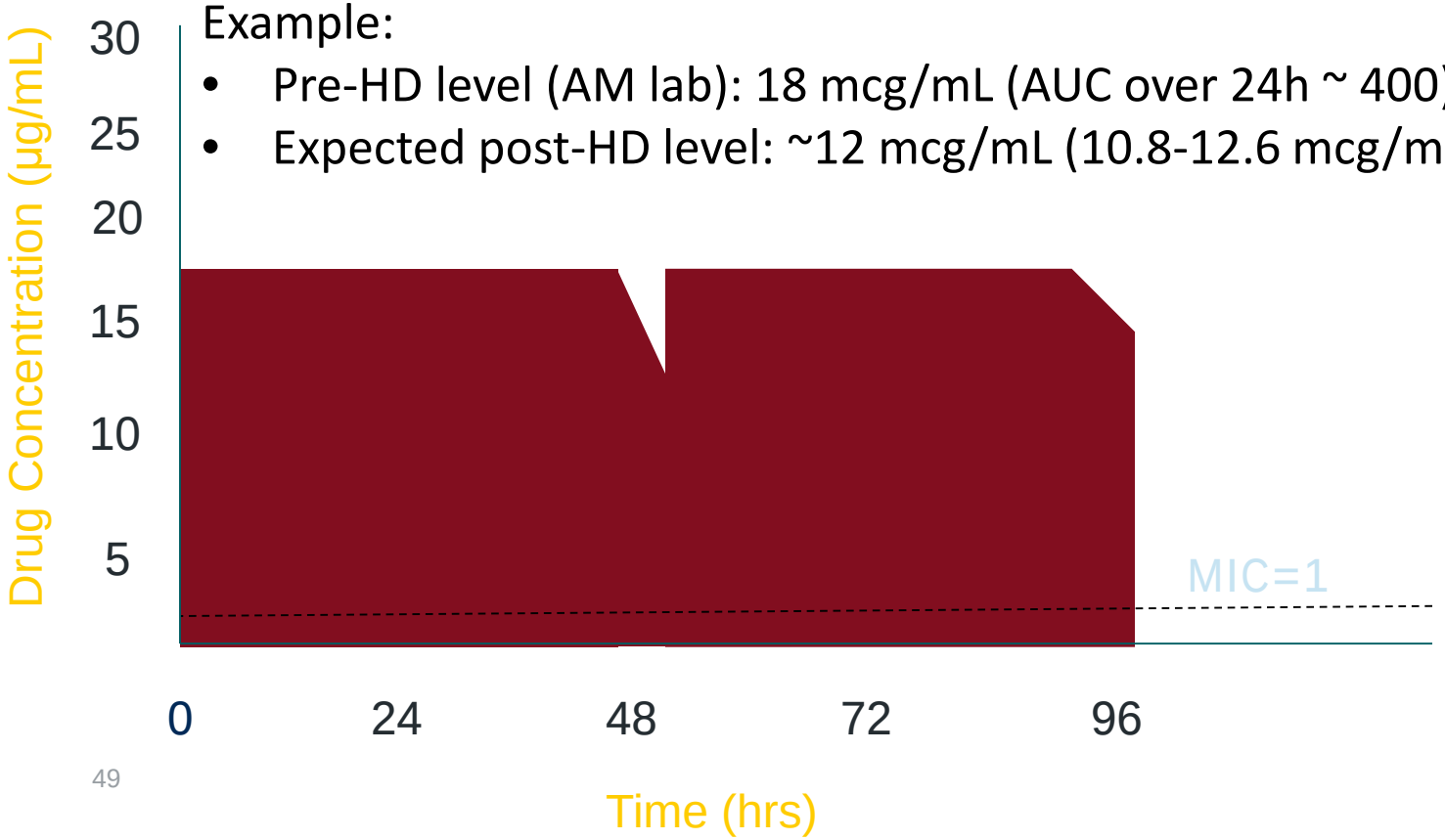
Zelenitsky SA et al. *Clin Infect Dis.* 2012
Crew PC et al. *Am J Health-Syst Pharm.* 2015

Dialysis Dosing Strategy

- Volume of distribution in dialysis patients is increased to approx. 1 L/kg
- Therefore **Load of 20 mg/kg =** initial serum concentration of ~ 20 mg/L
- **Maintenance dose of 750mg** (7-10mg/kg) TIW administered after each dialysis will replace what was removed (30-40%)

Example:

- Pre-HD level (AM lab): 18 mcg/mL (AUC over 24h ~ 400)
- Expected post-HD level: ~12 mcg/mL (10.8-12.6 mcg/mL)



Nephrology Strategy

Prior to the 2nd HD session post-load:

- Check pre-HD trough level (goal 15-20 mcg/mL)
- Continue maintenance dose based upon the level:

Pre-HD Concentration	Dialysis Dose
> 20 mcg/mL	500 mg
15-20 mcg/mL	750 mg
< 15 mcg/mL	Lesser of 15 mg/kg or 1000 mg

- Remember, studies show improved outcomes starting at AUC 345 mg*hr/L which is C_{avg} 14.5

Nephrology Strategy

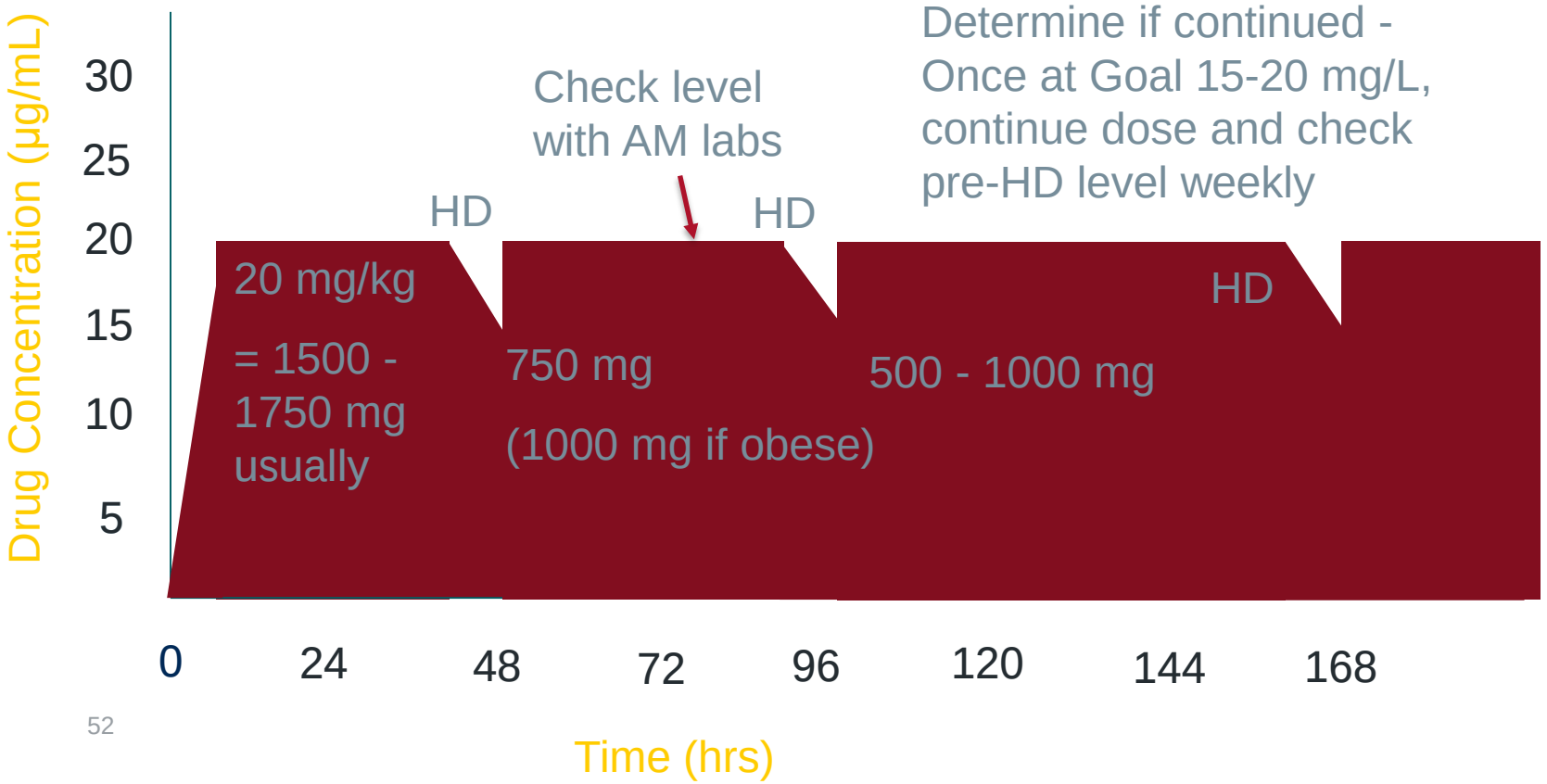
Prior to the 3rd dose post-load HD session:

- Draw another pre-HD vancomycin trough if not at goal of 15-20 mcg/mL originally, or any part of care/ schedule is abnormal following initiation
- If level is within range, continue current dose and draw a weekly vancomycin level prior to dialysis
  - Mon-Thur levels preferred to avoid changes going into weekend, especially if continuing at discharge

- Following dose adjustment, a pre-HD vancomycin level should be checked prior to next 1-2 dialysis session(s) to ensure level is stable, then weekly

Dialysis Dosing Example

Goal AUC of 400 mg*hr/L = C_{avg} 17 mg/L x 24 hours
and an AUC of 600/24 hr = C_{avg} 25 mg/L



What about the organism MIC?

Studies showing efficacy of AUC > 400 based on MIC ≤1

>90% MRSA isolates have MIC ≤1 mg/L

Exact MIC values largely unknown until ~day 3 of treatment

Continue therapy based on clinical response

What if the MIC is 2?

Meta-analysis of *Staphylococcus aureus* bacteremia studies from Kalil, et al (UNMC)

- No statistically significant difference in risk of death with high vancomycin MIC (≥1.5 mg/L) vs low vancomycin MIC (<1.5 mg/L)

Treat the patient not a number -
Keep in mind the variability of MIC results

- Standard of error in lab is ±1 doubling dilution (0.5<-1->2 mg/L)
- There is also a difference between methods used in studies
- MicroScan (prompt method) overcalled MIC of 1 mg/L by 74.1% vs gold standard broth microdilution

Kalil et al. *JAMA*. 2014; 312(15):1552-1564

Rybak et al. *J Clin Microbiol*. 2013; 51(7):2077-2081

Conclusions

Vancomycin AUC is linked to efficacy & safety

Goal AUC_{24} = 400-600 mg*hr/L

Troughs 15-20 mg/L can increase AKI risk

Bayesian Dosing = preferred strategy

Resources

- Nebraska Medicine Antimicrobial Stewardship Program Website – Pharmacokinetics
  - www.unmc.edu/intmed/divisions/id/asp/pharmacokinetics/index.html
  - Pager 888-0349
- ASHP/IDSA/PIDSA/SIDP Guidelines on Vancomycin Dosing and Monitoring
  - https://www.idsociety.org/practice-guideline/vancomycin/
  - American Journal of Health-System Pharmacy, Vol 77 (Issue 11): 1 June 2020; Pages 835-864
    - https://academic.oup.com/ajhp/article/77/11/835/5810200

Vancomycin Pharmacokinetics, Dosing & Therapeutic Drug Monitoring

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