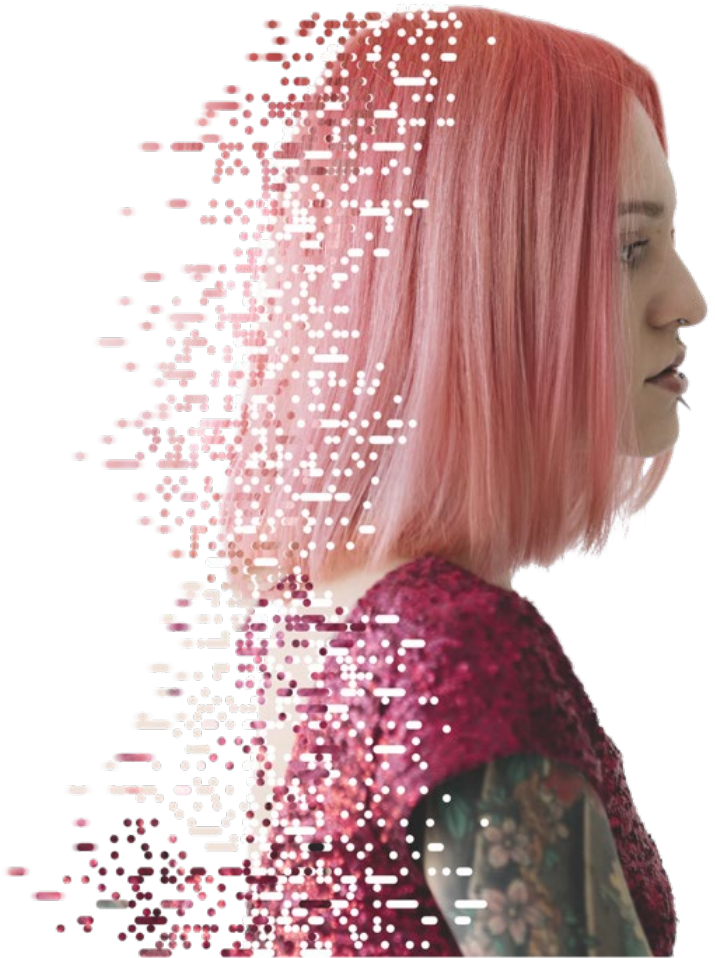

DoseMeRx™

Vancomycin Dosing
Implementing the 2020 Guidelines

Webinar

June 3, 2020

Today's Moderator

Kristi Kuper

PharmD, BCPS

Director of Clinical Pharmacy, DoseMeRx
Tabula Rasa HealthCare

Presenters

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PharmD, PhD

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Cedars-Sinai Medical Center

Implementing the 2020 Vancomycin Guidelines
What You Need To Know

Thomas Lodise, Pharm.D., Ph.D.

Professor, Albany College of Pharmacy and Health Sciences

Clinical Pharmacist, Stratton VA Medical Center

Albany, New York

Recommendations for Vancomycin Dosing and Therapeutic Drug Monitoring (Simplified)

- In patients with suspected or definitive serious MRSA infections, an individualized target **AUC/MIC$_{BMD}$ ratio of 400 to 600 (assuming a vancomycin MIC$_{BMD}$ of 1 mg/L)** should be advocated to achieve clinical efficacy while improving patient safety (A-II).
- **Given the importance of early, appropriate therapy, vancomycin targeted exposure should be achieved early during the course of therapy, preferably within the first 24 to 48 hours (A-II).**
- When the MIC$_{BMD}$ >1 mg/L, the probability of achieving an AUC/MIC target of ≥400 is low with conventional dosing; higher doses may risk unnecessary toxicity, and the decision to change therapy should be based on clinical judgment.
- When the MIC$_{BMD}$ <1 mg/L, we do not recommend decreasing the dose to achieve the AUC/MIC target.

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This information was presented at the "Implementing The New Vancomycin Guidelines: What You Need To Know" webinar held on June 3, 2020

Rybak MJ et al. Am J Health Syst Pharm. 2020 May 19;77(11):835-864. doi: 10.1093/ajhp/zxaa036.

Recommendations for Vancomycin Dosing and Therapeutic Drug Monitoring (Simplified 2)

- Trough-only monitoring, with a target of 15 to 20 mg/L, is no longer recommended, based on efficacy and nephrotoxicity data in patients with serious infections due to MRSA (A-II).
- There is insufficient evidence to provide recommendations on whether trough-only or AUC-guided vancomycin monitoring should be used among patients with noninvasive MRSA or other infections.

Rybak MJ et al. Am J Health Syst Pharm. 2020 May 19;77(11):835-864. doi: 10.1093/ajhp/zxaa036.

Relationship between Troughs and Outcomes among Patients with Invasive MRSA Infections

- The clinical benefits of maintaining vancomycin trough values in 15-20 mg/L have not been well described.[1-7]
- Link between clinical success and vancomycin trough values only observed in one study among MRSA bacteremic patients.[3]
  - Failure among patients with troughs < 15 mg/L: **61%**
  - Failure among patients with troughs between 15-20 mg/L: **40%**
  - Failure rate among patients with trough > 20 mg/L: **50%**

1. Hidayat LK, et al. Archives of internal medicine. Oct 23 2006;166(19):2138-2144. 2. Lodise TP et al. Antimicrob Agents Chemother. Sep 2008;52(9):3315-3320. 3. Kullar R et al. Clinical Infectious Diseases. Apr 15 2011;52(8):975-981. 4. Chung J et al. Anaesthesia and Intensive Care. Nov 2011;39(6):1030-1037. 5. Hermsen ED, et al. Expert Opinion on Drug Safety. Jan 2010;9(1):9-14. 6. Kralovicova K et al. .Journal of Chemotherapy. Dec 1997;9(6):420-426. 7. Zimmermann AE et al. Pharmacotherapy. Jan-Feb 1995;15(1):85-91.

Vancomycin-Induced Nephrotoxicity in “15-20 mg/L” Trough Era: A Systematic Review and Meta-Analysis

Study or Subgroup	Troughs ≥ 15 mg/L Events	Troughs ≥ 15 mg/L Total	Troughs < 15 mg/L Events	Troughs < 15 mg/L Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosso et al (3)	42	142	13	146	10.7%	4.30 [2.19, 8.43]
Cano et al (4)	22	89	7	99	8.1	4.32 [1.74, 10.69]
Chung et al (7)	12	25	16	48	7.4	1.85 [0.69, 4.96]
Hermsen et al (19)	5	16	4	39	4.3	3.98 [0.91, 17.46]
Hidayat et al (20)	11	63	0	32	1.4	14.24 [0.81, 249.87]
Jeffres et al (24)	27	49	13	45	8.6	3.02 [1.28, 7.11]
Kralovicova et al (26)	21	60	29	138	10.7	2.02 [1.04, 3.96]
Kullar et al (27)	27	139	23	141	11.5	1.24 [0.67, 2.28]
Kullar et al (28)	8	116	1	84	2.4	6.15 [0.75, 50.13]
Lodise et al (36)	7	27	14	139	7.1	3.13 [1.12, 8.69]
McKamy et al (38)	16	57	8	110	8.0	4.98 [1.98, 12.52]
Minejima et al (40)	17	72	25	155	10.5	1.61 [0.80, 3.21]
Prabaker et al (49)	7	54	24	294	8.2	1.68 [0.68, 4.11]
Zimmerman et al (63)	8	12	0	33	11.3	126.56 [6.19, 2585.90]
Total (95% CI)		921		1,503	100.0%	2.76 [1.94, 3.93]
Total events	230		177			
Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 23.80$, df = 13 (P = 0.03); $I^2 = 45\%$						
Test for overall effect: Z = 5.66 (P < 0.00001)						

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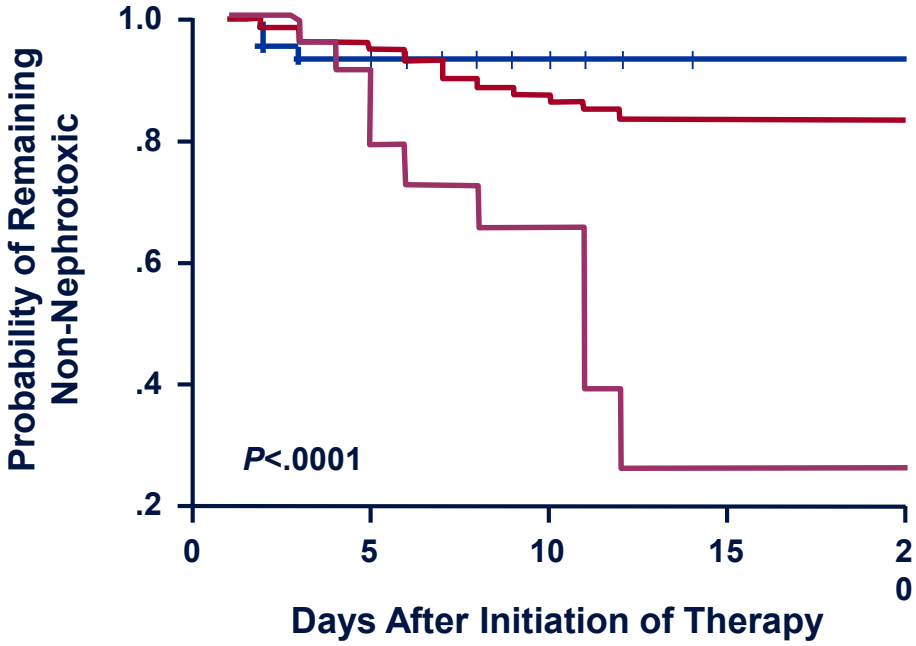
van Hal SJ, Paterson DL, Lodise TP. Antimicrob Agents Chemother. Antimicrob Agents Chemother. 2013 Feb;57(2):734-44.

Larger Vancomycin Doses Are Associated With An increased Incidence of Nephrotoxicity



Stratum 0, linezolid

Stratum 1, standard-dose vancomycin (<4 g/day)

Stratum 2, high-dose vancomycin (≥4 g/day)

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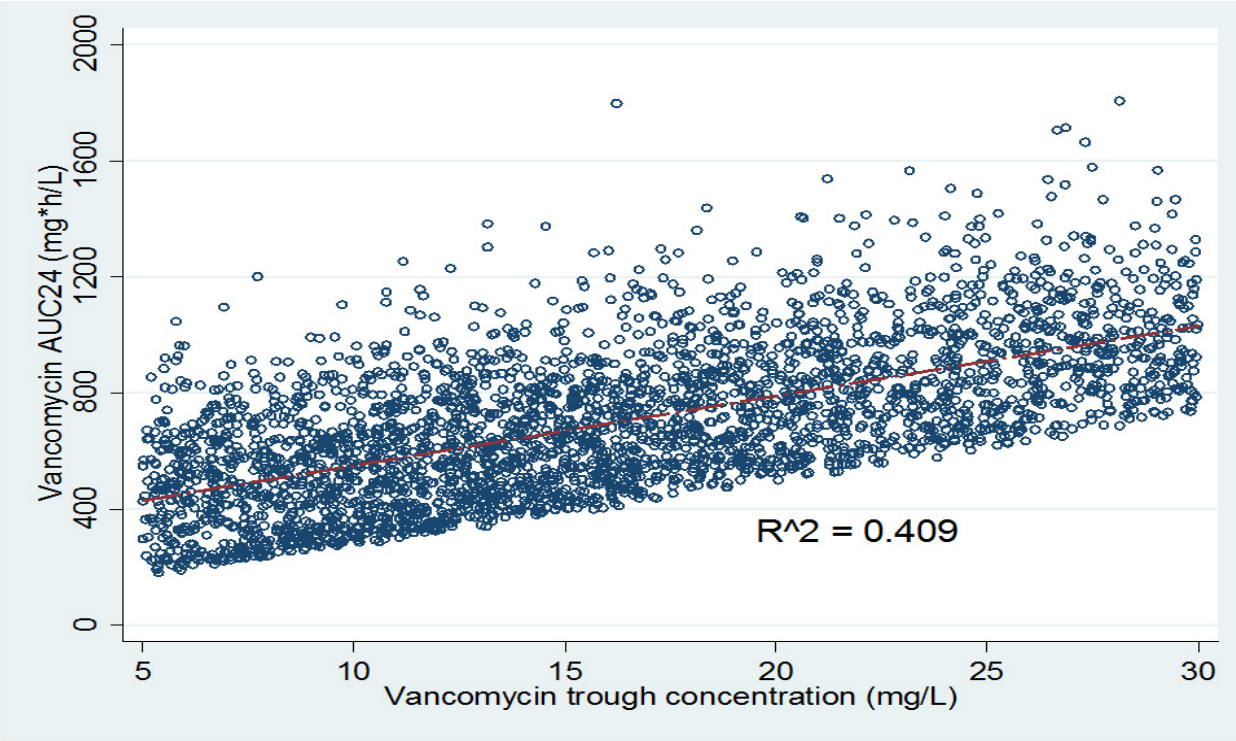
Lodise TP, Lomaestro B, Graves J, Drusano GL.. Antimicrob Agents Chemother. 2008;52:1330-1336.

Trough Value Alone is a Poor Surrogate of AUC



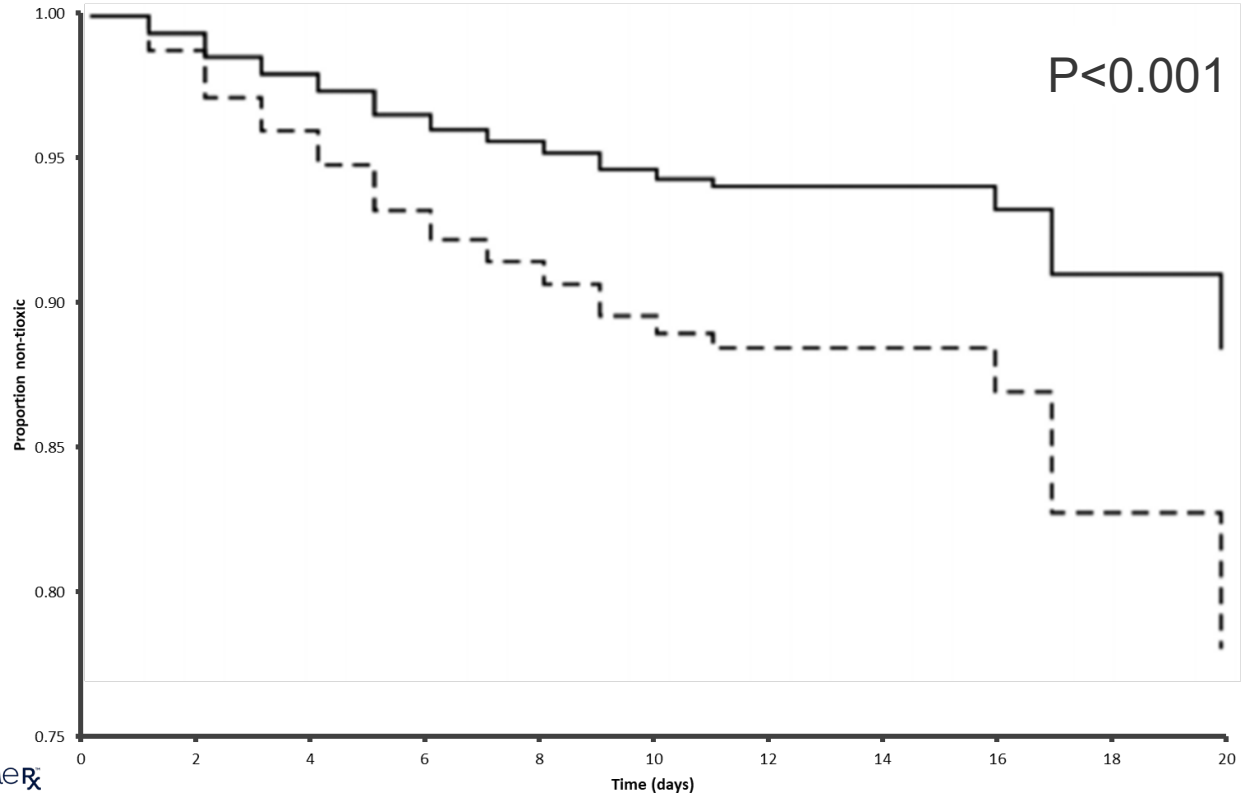
Pai MP, Neely M, Rodvold KA, Lodise TP. Approaches to Optimizing the Delivery of Vancomycin in Individual Patients. Adv Drug Deliv Rev. 2014 Jun 5. pii: S0169-409X(14)00128-8

The VAN AUC Threshold for Toxicity

Reference	Population	Breakpoints for Nephrotoxic Outcomes
Lodise 2009	Retrospective – all infection types	Nephrotoxicity risk ↑ 2.5-fold if **AUC ≥ 1,300** Nephrotoxicity risk ↑ 1.13-fold every 1 mg/L trough ↑
Suzuki 2012	Retrospective – MRSA LRTI	Nephrotoxicity: **AUCs 600-800** (most patients) Non-Nephrotoxicity: AUCs 400-600 (most patients)
Le 2015	Retrospective – all infection types	Nephrotoxicity risk ↑ 3.7-fold if **AUC ≥ 800** Nephrotoxicity risk ↑ 2.5-fold if **trough ≥ 15**
Finch 2017	Retrospective – all infection types	Nephrotoxicity risk ↓ ~2-fold using AUC-guided dosing AUC-guided cohort: median AUC 474 (360–611) Trough-guided cohort: median **AUC 705 (540–883)**
Lodise 2019	Multi-center, prospective, observational – MRSA BSI	Risk of nephrotoxicity highest when **AUC ≥793**
Neely 2018	Prospective – all infection types	Nephrotoxicity: median **AUC 625** | median **trough 15.7** Non-nephrotoxicity: median AUC 423 | median trough 8.7
Zasowski 2018	Retrospective – BSI, LRTI	Nephrotoxicity ↑ 3-4-fold if: **AUC ≥ 677** or **trough ≥ 18.8**

1. https://www.ashp.org/-/media/assets/policy-guidelines/docs/draft-guidelines/draft-guidelines-ASHP-IDSA-PIDS-SIDP-therapeutic-vancomycin.ashx?la=en&hash=8126CEE49F401CDEE5DB49712225F0A4518DB94B.

Impact of Area Under the Curve-Targeted Dosing on Vancomycin-Associated Nephrotoxicity



Treatment Group

--- Trough Monitoring

___ AUC Monitoring

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Finch NA et al. Antimicrob Agents Chemother. 2017 Nov 22;61(12). pii: e01293-17.

Bayesian Estimated Vancomycin Exposure Profile

	Trough-guided dosing group (*n* = 150)	AUC-guided dosing group (*n* = 150)	*P* value
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 NA et al. Antimicrob Agents Chemother. 2017 Nov 22;61(12). pii: e01293-17.

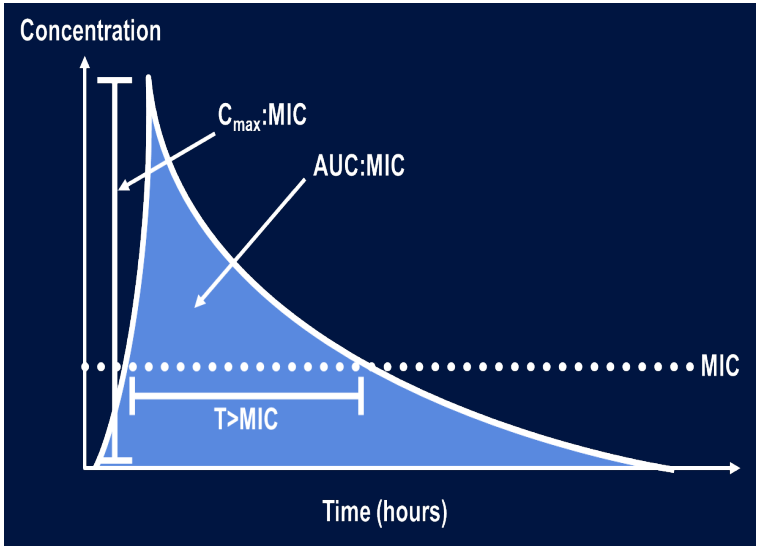
Consequences of Vancomycin-Associated Acute Kidney Injury

- For most patients, vancomycin-associated AKI (VA-AKI) is mild and resolves within one week after discontinuation of therapy.
- However, even mild cases of VA-AKI have been linked to a variety of adverse outcomes including increased in-hospital mortality, length of stay (LOS) and healthcare resource utilization.
- Data suggest that AKI is often accompanied by remote organ dysfunction, which increases a patient's susceptibility to a number of conditions (e.g., cardiovascular events, infections due to immunosuppression, etc.) over time

van Hal SJ, et al. Antimicrob Agents Chemother 2013; 57(2): 734-44. Jeffres MN et al. Clin Ther 2007; 29(6): 1107-15. Cano EL et al. Clin Ther 2012; 34(1): 149-57. Kullar R et al. Clin Infect Dis 2011; 52(8): 975-81. Minejima E et al. , Antimicrob Agents Chemother 2011; 55(7): 3278-83. Patel N et al. Patients with Acute Bacterial Skin and Skin Structure Infections. Clin Drug Investig 2018; 38(10): 935-43.

Vancomycin Exposure Profile and Outcomes Among Patients with Serious MRSA Infections

- Limited clinical data in support of the AUC/MIC ratio > 400 target among patients with infections due to MRSA.[1-3]
- Most published vancomycin exposure-response clinical evaluations[1-3] used a simple formula based on total daily vancomycin dose and estimated renal function to estimate the AUC.
  - It is nearly impossible to generate valid estimates of exposure variables in a given individual based on glomerular filtration estimation formulas alone due to the presence of wide inter-patient exposure variability.



AUC = Area under the concentration–time curve
C_{max} = Maximum plasma concentration

1. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Clinical pharmacokinetics. 2004;43(13):925-942.
2. Kullar R, Davis SL, Levine DP, Rybak MJ. Clinical Infectious Diseases. Apr 15 2011;52(8):975-981.
3. Holmes NE, Turnidge JD, Munckhof WJ, et al. Antimicrob Agents Chemother. Apr 2013;57(4):1654-1663.

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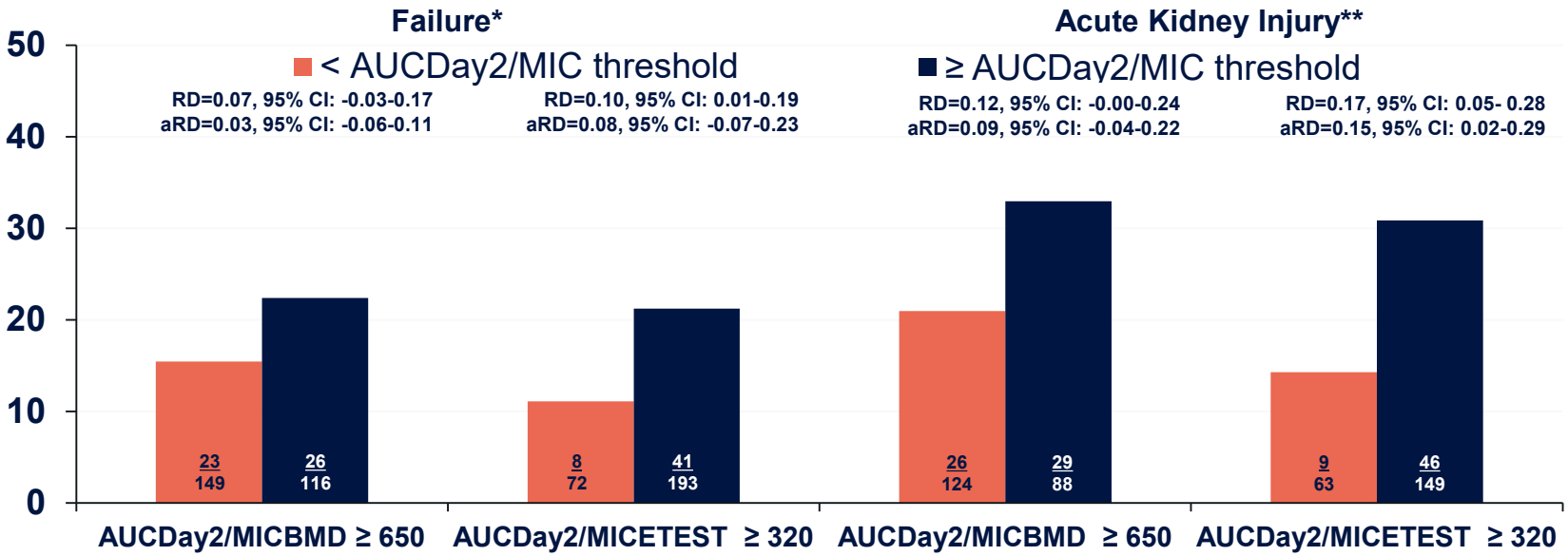
Prospective Observational Evaluation of the Association between the Day 2 Vancomycin Exposure and Failure Rates among Adult, Hospitalized Patients with MRSA Bloodstream Infections (PROVIDE)

- Study Design
  - Prospective, multi-center, observational study of adult patients with confirmed MRSA bloodstream infections treated with vancomycin.
    - A validated Bayesian method will be used to estimate the vancomycin exposure profile with limited blood concentration data[1]
- Primary Study Objectives[2]
  - To estimate the difference in failure rates among "evaluable" patients who have vancomycin AUC_{DAY2}/MIC_{BMD} ratios ≥ 650 relative to those with AUC_{DAY2}/MIC_{BMD} ratios < 650.
  - To estimate the difference in failure rates among "evaluable" patients who have AUC_{DAY2}/MIC_{ETEST} ratios ≥ 320 relative to those with AUC_{DAY2}/MIC_{ETEST} ratios <320.
- Sample size: 250 evaluable subjects
  - Sufficient power (>80%) at a two-sided alpha of 0.05 to detect a ~15-20% difference in failure rates between dichotomous AUC_{DAY2}/MIC exposure variables.

Definition: Failure defined as death within 30 days of index MRSA blood culture OR persistent bacteremia ≥7 days after initiation of vancomycin therapy and before therapy completion. Abbreviations: AUC: area under the curve; MICBMD: minimum inhibitory concentration values by broth microdilution method; MICETEST: minimum inhibitory concentration value by ETEST™ method.

1. Neely MN et al. Antimicrob Agents Chemother 2014;58:309-16. 2. Lodise TP et al. Clin Infect Dis. 2014 Sep 1;59(5):666-75.

Comparisons of Outcomes between AUCDAY2/MIC Exposure Groups



Abbreviations: AUC: area under the curve; MIC; minimum inhibitory concentration; RD: risk difference; aRD: adjusted risk difference; BMD: broth microdilution.

*All variables associated with failure at P ≤ 0.1 and considered at model entry included: prior receipt of vancomycin, type of MRSA infection (community vs. hospital/healthcare), "other" source of infection, pre-existing valvular heart disease, heart failure, APACHE, age, creatinine clearance at baseline, infective endocarditis, and presence of prosthetic material.

**Patients with Baseline Serum Creatinine (< 2.0 mg/dL). All variables associated with acute kidney injury at P ≤ 0.1 and considered at model entry included: race, prior surgery, urinary source, prior hospital length of stay, creatinine clearance baseline, and prior vancomycin.

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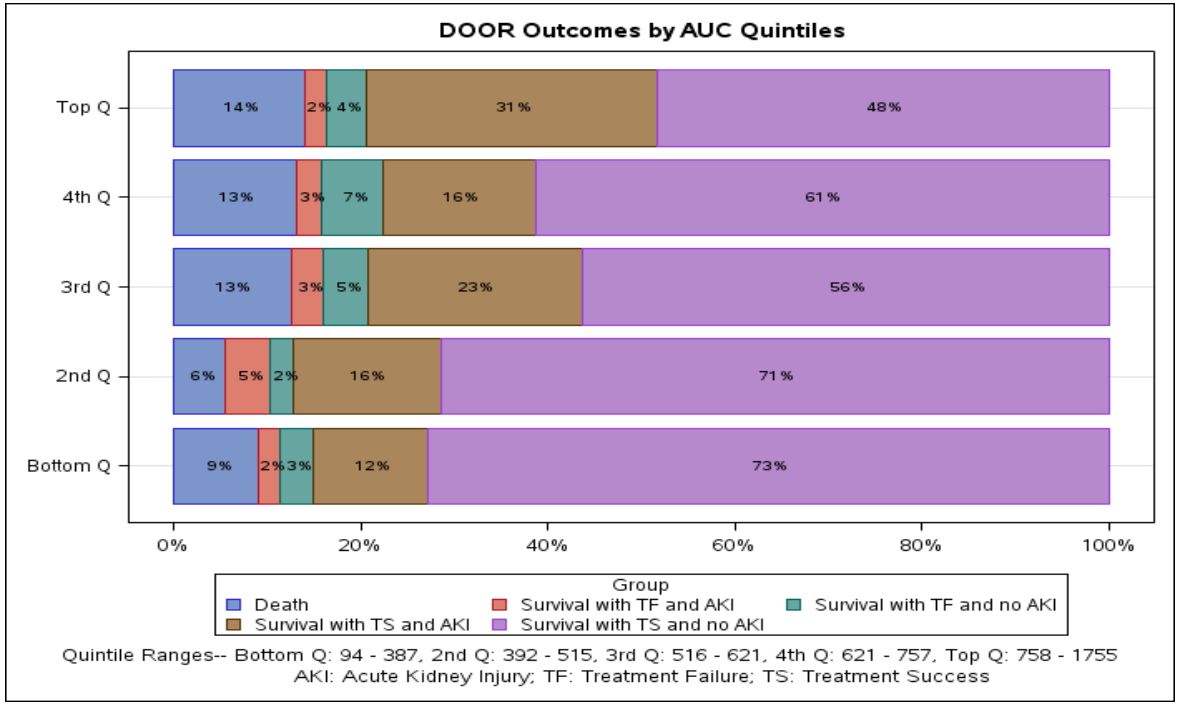
This information was presented at the "Implementing The New Vancomycin Guidelines: What You Need To Know" webinar held on June 3, 2020

Lodise TP et al,. Clin Infect Dis. 2020 Apr 10;70(8):1536-1545.

Desirability of outcome ranking (DOOR) analysis



Study findings suggest that daily 2 AUCs should be maintained between 400-515 to maximize efficacy and minimize the likelihood of AKI

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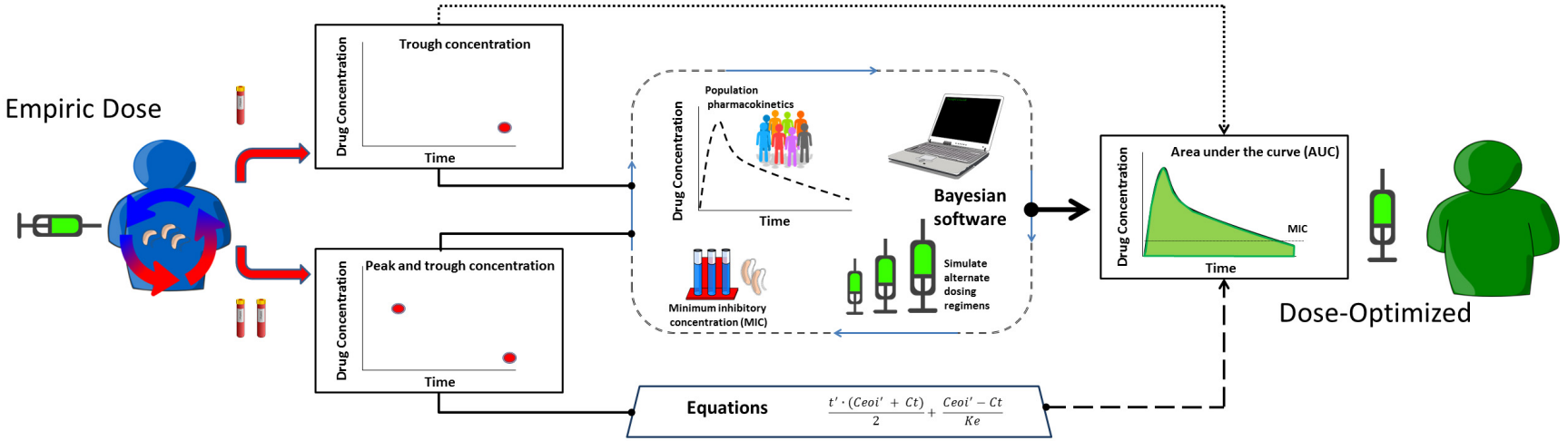
Lodise TP et al,. Clin Infect Dis. 2020 Apr 10;70(8):1536-1545.

AUC vs. AUC/MIC guided dosing

- The MIC value is of less importance for several reasons.
  - There is a narrow range of vancomycin MIC values by broth microdilution (the gold standard) among contemporary MRSA isolates (observed here and in other studies), with values of 0.5 or 1 mg/L in most institutions.
  - There is inherent imprecision of MIC measurement, with a range of accuracy of ± 1 log2 dilutions.
  - MIC values are typically not available within the first 72 hours of index culture collection.
  - There is a high degree of variability between MIC testing methods typically used in health care institutions relative to the broth microdilution MIC method.

Rybak MJ et al. Am J Health Syst Pharm. 2020 May 19;77(11):835-864. Jones RN. Clin Infect Dis, 2006;42 Suppl 1:S13-24. Farrell DJ, Castanheira M, Mendes RE, Sader HS, Jones RN. Clin Infect Dis, 2012;55 Suppl 3:S206-214. Rybak MJ, Vidaillac C, Sader HS, et al. J Clin Microbiol, 2013;51:2077-2081. Kruzel MC, Lewis CT, Welsh KJ, et al. J Clin Microbiol, 2011;49:2272-2273. Lodise TP et al,. Clin Infect Dis. 2020 Apr 10;70(8):1536-1545.

Bayesian and Equation-Based Approaches to Estimating the AUC



Pai MP, Neely M, Rodvold KA, Lodise TP. Adv Drug Deliv Rev. 2014 Jun 5. pii: S0169-409X(14)00128-8

Bayesian Approach to AUC Estimation

- Bayesian software only requires four specific components
  - Structural mathematical model that best describes the pharmacokinetics of a given agent
  - Density file, which contains the parameter estimates and their associated dispersion for the embedded structural PK model (Bayesian prior)
  - Patient file that contains their drug dosing and collected PK data
  - Patient “target” file which contains the target exposure profile and initial estimates of future dosing regimens
- With this information, the Bayesian dose optimization software calculates a Bayesian posterior parameter value file or that patient.
  - The dose optimization software then calculates the optimal dosing regimen based on the specified exposure profile in the target file

Pai MP, Neely M, Rodvold KA, Lodise TP. Adv Drug Deliv Rev. 2014 Jun 5. pii: S0169-409X(14)00128-8

Advantages of Bayesian Approach to AUC Estimation

- Innovative treatment schemas such as front-loading doses with a transition to a lower maintenance dosing regimen can be designed to rapidly achieve target concentrations within the first 24 to 48 hours among critically ill patients.
- Concentration-time information does not need to be collected at “steady-state” (after the 3rd or 4th dose).
- Ability to include covariates, such as CL_{CR}, in the structural PK models (Bayesian prior density file) that account for the pathophysiological changes that readily occur in critically ill patients.
- It is preferred to obtain 2 PK samples to estimate the AUC with the Bayesian approach (A-II).
  - A trough concentration alone may be sufficient to estimate the AUC with the Bayesian approach in some patients, but more data across different patient populations are needed to confirm the viability of using trough-only data (B-II).

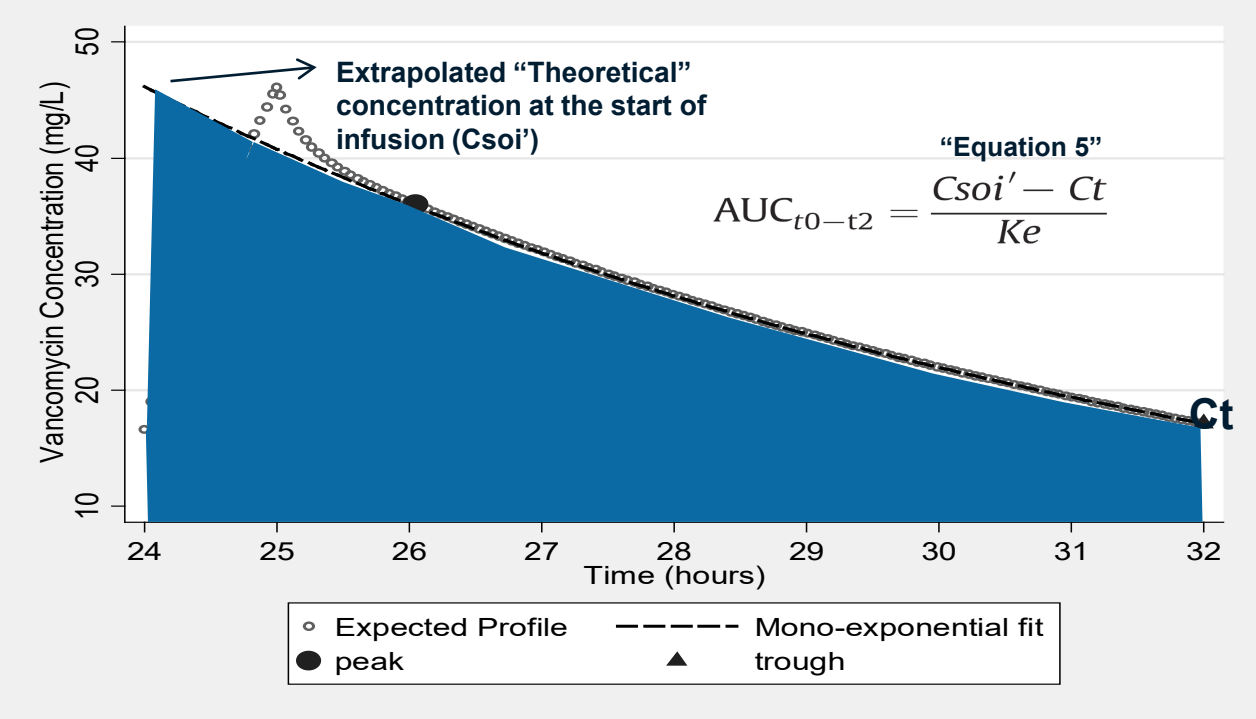
Rybak MJ et al. Am J Health Syst Pharm. 2020 May 19;77(11):835-864 . Pai MP, Neely M, Rodvold KA, Lodise TP. Adv Drug Deliv Rev. 2014 Jun 5. pii: S0169-409X(14)00128-8

Equation-Based Approach to AUC Estimation

- Use of a post-distributional peak (1-2 hours post infusion) and trough concentrations can be used to determine the daily AUC value with reasonable precision and low bias with simple first-order PK formulas.
- Simple to use and can be programmed into electronic medical system to automatically compute the AUC.
- Disadvantages
  - Highly preferably to have concentration time data over same dosing interval (peak and trough data).
  - Can only provide a snapshot of the AUC for the sampling period.
  - May provide unreliable estimates when drug is not near steady-state conditions.

Pai MP, Neely M, Rodvold KA, Lodise TP. Adv Drug Deliv Rev. 2014 Jun 5. pii: S0169-409X(14)00128-8

Equation-Based Approach to AUC Estimation



Pai MP, Neely M, Rodvold KA, Lodise TP. Adv Drug Deliv Rev. 2014 Jun 5. pii: S0169-409X(14)00128-8

Valid Estimation of the Vancomycin AUC with Trough only Data using Bayesian Estimation Software

AUC Estimation Method	Number of Samples	AUC (mg*h/L)	Ratio of computed AUC to reference AUC	R^2
Bayesian	All	250 [84.1, 688]	Reference	Reference
Bayesian	**Trough only**	**259 [82.9, 573]**	**1.0 [0.74, 1.28]**	**0.948**
Equation-based method 1	Peak and Trough	239 [90.6, 662]	0.99 [0.83, 1.16]	0.971
Equation-based method 2	Peak and Trough	247 [100, 675]	1.02 [0.85, 1.22]	0.987

Neely MN, Youn G, Jones B, et al. Are vancomycin troughs adequate for optimal dosing? Antimicrob Agents Chemother 2014;58:309-16.
Pai MP, Neely M, Rodvold KA, Lodise TP. Approaches to Optimizing the Delivery of Vancomycin in Individual Patients. Adv Drug Deliv Rev. 2014 Jun 5. pii: S0169-409X(14)00128-8

Evaluation of a Bayesian Approach to Estimate Vancomycin Exposure in Obese Patients with Limited Pharmacokinetic Sampling: A Pilot Study

Model	AUC_{FULL} (95% CI)	AUC_{PT} (95% CI)	Ratio to AUC_{FULL} (95% CI)	R^2	AUC_T (95% CI)	Ratio to AUC_{FULL} (95% CI)	R^2
1	437 (296 – 617)	393 (275 – 576)	**0.91 (0.87 – 0.95)**	0.997	574 (379 – 725)	**1.30 (1.19 – 1.40)**	0.986
2	478 (305 – 683)	456 (300 – 659)	**0.96 (0.93 – 0.99)**	0.998	511 (336 – 682)	**1.04 (0.97 – 1.13)**	0.982
3	469 (314 – 628)	489 (274 – 620)	**0.99 (0.94 – 1.04)**	0.997	401 (275 – 482)	**0.87 (0.77 – 0.97)**	0.974
4	489 (309 – 604)	412 (308 – 613)	**0.93 (0.84 – 1.01)**	0.990	520 (278 – 735)	**1.13 (0.81 -1.44)**	0.851
1	437 (296 – 617)	393 (275 – 576)	**0.91 (0.87 – 0.95)**	0.997	574 (379 – 725)	**1.30 (1.19 – 1.40)**	0.986
2	478 (305 – 683)	456 (300 – 659)	**0.96 (0.93 – 0.99)**	0.998	511 (336 – 682)	**1.04 (0.97 – 1.13)**	0.982

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Carreno JJ, Lomaestro B, Tietjan J, Lodise TP. Antimicrob Agents Chemother. 2017 Apr 24;61(5).

Conclusions

- Despite its subsequent widespread integration in clinical practice, the clinical benefits of maintaining higher vancomycin trough values have not been well described.
- Revise consensus guidelines recommend AUC-guided dosing.
  - Bayesian software and first-order PK calculator can be used to reliable estimate the AUC with limited PK samples.
- Stewardship teams play a critical role in implementation and assessment of vancomycin AUC-guided dosing programs.

Developing an AUC-Based Dosing Implementation Plan and Defining a New Vancomycin Dosing Protocol

The Who, What, When, Where, Why, How

Ethan A. Smith, PharmD, BCIDP
Program Coordinator – Antimicrobial Stewardship
Cedars-Sinai Medical Center

Cedars Sinai

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This was presented at the "Implementing The New Vancomycin Guidelines: What You Need To Know" webinar held on June 3, 2020

Some ~~Food~~… Vanco For Thought

- GP is a 32 year old, healthy male, no past medical history
- Presents with 3-day history of left thigh pain/redness
- Vitals in the emergency department
  - HR: 120 beats/min | BP: 100/60 mmHg
  - Temp: 102°F (38.9 °C) | WBC: 18,000/mm^3 | SCr: 0.7 mg/dL
- Blood cultures drawn, GP admitted
- Vancomycin 1,000 mg Q8h + Ceftriaxone 2,000 mg Q24h

Some ~~Food~~… Vanco For Thought

- Blood cultures @ 12 hours = MRSA by rapid diagnostics
- GP has clinically stabilized, VAN trough due before 5th dose
  - Trough goal per protocol = 15-20 mg/L
  - GP's trough = 13.6 mg/L

Poll Question #3

- What should be done?
  a) Continue 1,000 mg Q8h
  b) Increase to 1,250 mg Q8h
  c) Need more information
  d)  …change to daptomycin (hint: no)

Some ~~Food~~… Vanco For Thought

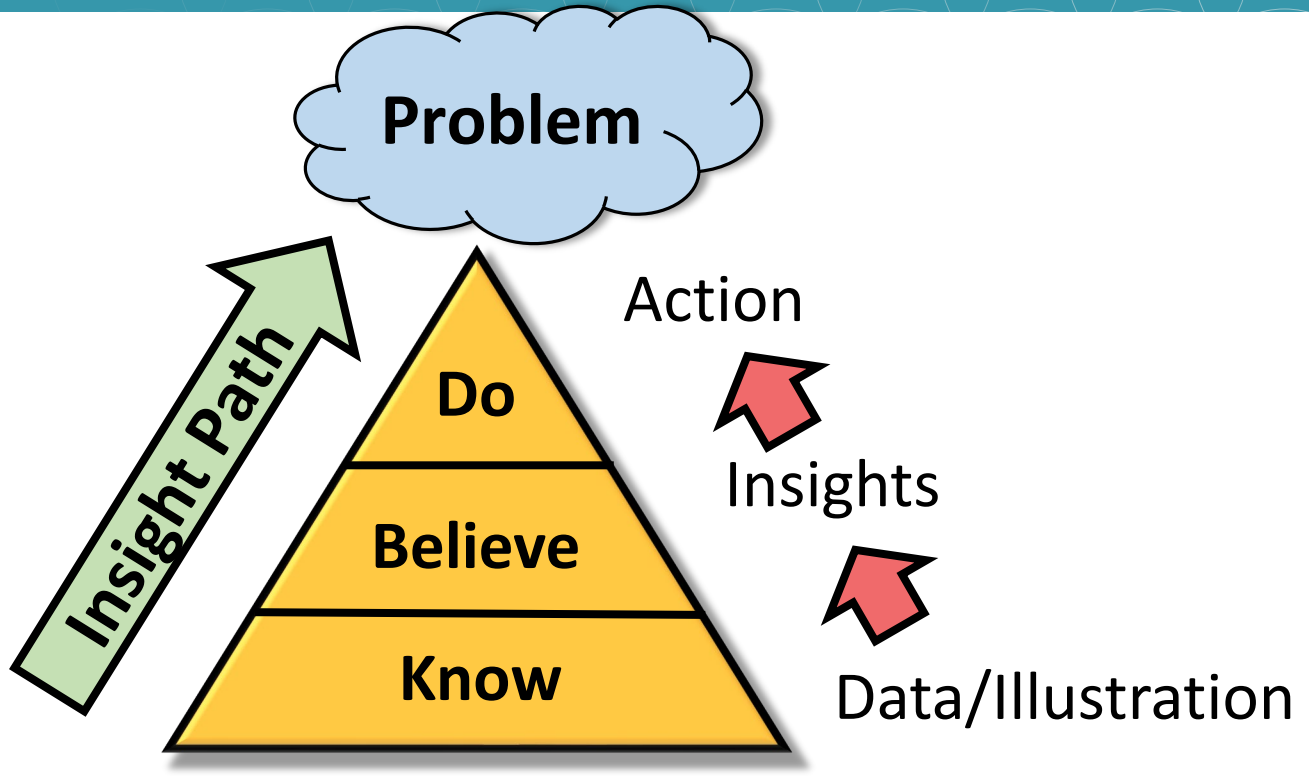
- Blood cultures @ 12 hours = MRSA by rapid diagnostics
- GP has clinically stabilized, VAN trough due before 5th dose
  - Trough goal per protocol = 15-20 mg/L
  - GP's trough = 13.6 mg/L
- What should be done?
  a) Continue 1,000 mg Q8h
  b) Increase to 1,250 mg Q8h
  c) Need more information
  d)  …change to daptomycin (hint: no)

Some ~~Food~~… Vanco For Thought

- Additional information reveals…
- **<u>Continue 1,000 mg Q8h (trough 13.6mg/L):</u>**
  - Calculated $AUC_{0\text{-}24}$ = **582 mg•hr/L**
  - ***Therapeutic $AUC_{0\text{-}24}$ = 400-600 mg•hr/L***
- **<u>Increase to 1,250 mg Q8h:</u>**
  - Estimated trough $\frac{13.6\ mg/L}{1{,}000\ mg} = \frac{X\ mg/L}{1{,}250 mg}$ ➔ x = 17 mg/L
  - Corresponding $AUC_{0\text{-}24}$ = **748 mg•hr/L**
  - Nephrotoxicity ↑ if $AUC_{0\text{-}24}$ > 700-800 mg•hr/L

1. https://www.ashp.org/-/media/assets/policy-guidelines/docs/draft-guidelines/draft-guidelines-ASHP-IDSA-PIDS-SIDP-therapeutic-vancomycin.ashx?la=en&hash=8126CEE49F401CDEE5DB49712225F0A4518DB94B.

Oratium – “The Pyramid Guys”



18. The Compelling Communicator. Consider House Press; 2016.

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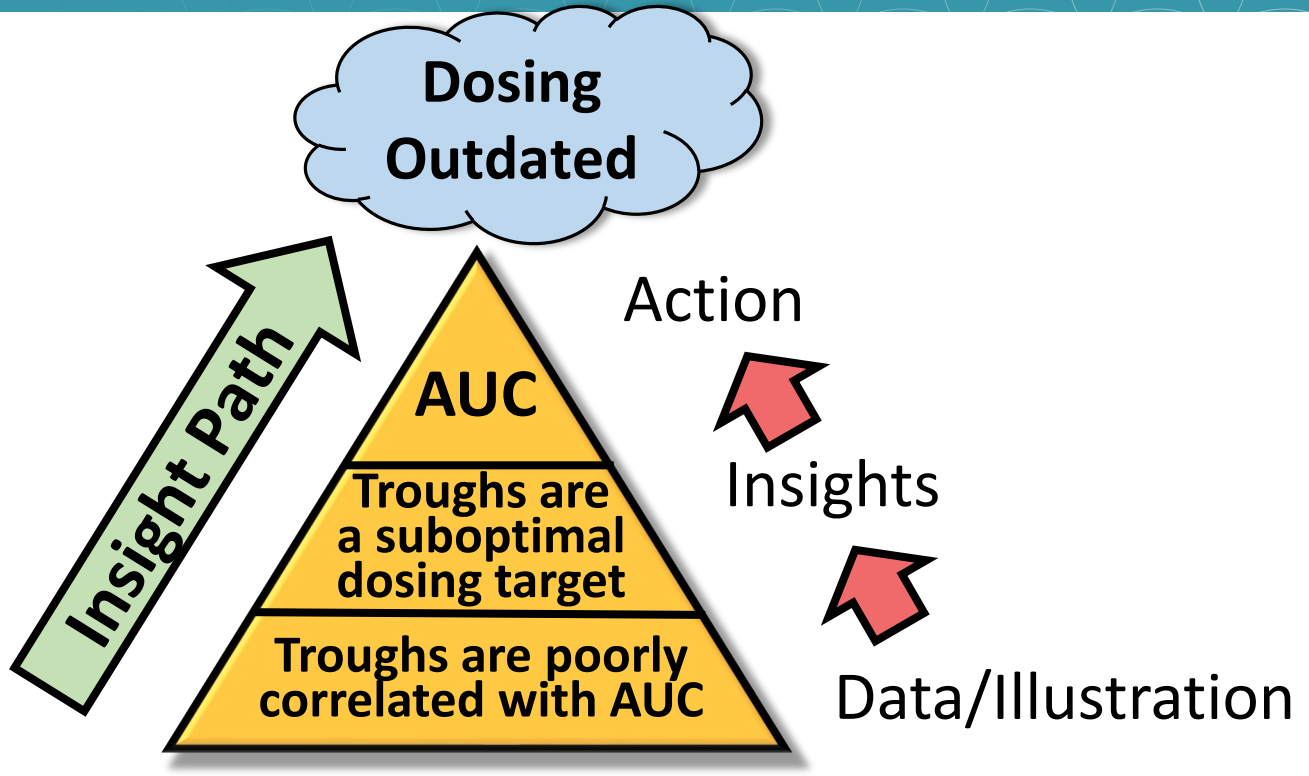

18. The Compelling Communicator. Consider House Press; 2016.

Step 1 – Identify The Scope of the "Problem"

- **What are the current vancomycin (VAN) dosing processes?**
  - Trough-based or AUC-based?
  - What calculators or nomograms are being used?
  - Who is dosing vancomycin (physicians, pharmacists, other)?
- **What are the barriers to implementing a new process?**
  - *How do we break the 15-20 mg/L trough goal habit?*
  - Staff familiarity, adaptability?
  - What financial resources are available?
  - What computer/technical resources are available?
  - Who is available to take the lead?

Step 2 – Determine How AUC is Calculated

- **"Home-Grown" Excel® Calculator**
  - What equations are going to be used?
  - Who has the expertise to program/validate the calculator?
  - Where will this calculator be available?
  - What processes need to be in place if calculator crashes?
- **3rd-Party Bayesian Software**
  - What models are needed and is a test-platform available?
  - How many users are required?
  - Which program is most cost-effective?
  - Will EHR integration be desired?

To Bayesian, or not to Bayesian

- Must make a determination what is most practical & budget-friendly for each institution

Parameters	First-Order Equations	Bayesian Methods
Model	Patient-Specific	Population + Patient-Specific
Formulas	Simple	Complex
Flexibility	Static	Predictive/Adaptive
Levels Needed	Peak/Trough **Required**	Trough-Only **OR** Peak/Trough
Obtaining Levels	Steady-State	First 24-48 Hours
Level Timing	Precise Timing **Required**	Timing "Agnostic"

1. https://www.ashp.org/-/media/assets/policy-guidelines/docs/draft-guidelines/draft-guidelines-ASHP-IDSA-PIDS-SIDP-therapeutic-vancomycin.ashx?la=en&hash=8126CEE49F401CDEE5DB49712225F0A4518DB94B.
2. *Pharmacotherapy*. 2018;38(12):1174-83.

Justifying the $$$ for Bayesian Software

- **Nephrotoxicity & AUC Dosing – Detroit Medical Center**
  - Pre-implementation: nephrotoxicity rate = 6%
  - Post-implementation: nephrotoxicity rate = 3%

  } **50% Relative Reduction**

- **Hypothetical Medical Center** (1,500 courses of VAN/year)
  - 1,500 x 0.06 = 90 cases of nephrotoxicity/year
  - 90 x $15,639* = $1,407,510/year
  - 50% reduction = 45 cases of nephrotoxicity prevented
  - 45 x $15,639* = $703,755/year due to toxicity avoided
  - Bayesian software: $5,000-$30,000/year
  - **Cost avoidance: $675,000+**

*2003 study – cost adjusted for inflation

19. *Am J Health-Syst Pharm.*2018;75(24):1986-95.
20. *Drugs.* 2017;77:1143.54.

Step 3 – Buy-in from Key Stakeholders

- **Who are the key players?**
  - Pharmacist expert/champion?
  - Physician expert/champion?
  - What committees/divisions need to approve?
  - Timeline for IT review of 3rd-party software?
  - Timeline for legal to review 3rd-party software contracting?
- **How to present the information?**
  - Improved safety/efficacy (patient outcomes)
  - Potential for reduction in costs (reduction in AKI / level monitoring)

Step 4.1 – Revise VAN Dosing Policies

- **Determine who is excluded from AUC-based dosing**
  - VAN for surgical prophylaxis
  - Peritoneal dialysis patients
  - Hemodialysis patients (if not using Bayesian)
  - Continuous Renal Replacement Therapy (CRRT)
    - Depending on ability to do continuous infusion
  - Others?
- **Provide guidance on organism and MIC**
  - Assume MIC = 1 mg/L for *S. aureus*
  - Don't lower AUC goal if MIC < 1 mg/L
  - For non-*S. aureus* – AUC goal 400-600 mg•hr/L or trough 15-20 mg/L?

Step 4.2 – Revise VAN Dosing Policies

- **Provide guidance on choosing a Bayesian dosing model**
  - Will vary depending on models purchased
  - Definitions for obesity
  - When to use 1-compartment vs. 2-compartment model
- **Provide guidance on trough-only or peak-trough TDM**
  - 2020 guidelines recommend 2-level TDM
  - What is the likelihood that 2-level TDM can be broadly implemented?
  - Is there any data supporting single-level TDM?
  - What happens when patients go home on vancomycin?

2 Points to Draw a Line, Right?

- Bayesian software was able to reliably estimate AUC with trough-only PK sampling
  - Trough-only PK = calculated AUCs ≈ 80-100% of reference
  - If aiming for AUC in middle of goal range (~500), the slight variation in calculated AUC is unlikely to substantially impact target attainment
  - Single-level AUC estimation = improvement over trough goals 15-20
  - Two-level AUC estimation further improved accuracy of calculated AUCs (≈ 90-100% of reference) consider 2 levels for:
    - Hemodynamic instability or dynamic renal function
    - Critical illness or severe infection

2. *Pharmacotherapy*. 2018;38(12):1174-83.

Step 5.1 – Implementation

- **After necessary approvals have been secured**
  - Determine a practical “go-live date”
  - Assign roles/responsibilities for aspects of implementation
  - Develop staff training packet/reference
  - Consider local CE presentation/inservice(s)
  - If using Bayesian software, training may be included from vendor
  - Develop case-based competency, users to pass competency prior to using new dosing processes
- **Arrange provider-oriented education**
  - Residents, ID providers, high-volume hospitalists

Step 5.2 – Implementation

- **Consider utilizing "superuser" process**
  - Identify interested pharmacists
  - Choose pharmacists from different areas/shifts
  - Superusers to serve as experts for their areas
  - Develop a more comprehensive training process (essential reading materials, more in-depth/live training)
  - Encourage superusers to answer questions/consults prior to staff reaching out to coordinators/managers
  - Consider those who volunteered for superuser in yearly evaluations/career ladders

Step 5.3 – Implementation Checklist

- **Tying steps 5.1 and 5.2 together**
  - The “playbook” or “roadmap” for ensuring the transition goes smoothly and to hold participants accountable
  - Break down larger tasks into smaller goals
  - Establish deadlines for each aspect to meet go-live date
  - Schedule times for training(s)/inservice(s)
  - Re-present at division/committee meetings closer to the go-live date as a reminder
  - Ensure ample time for staff to review and pass competencies and ask questions

Step 6.1 – Post-Implementation

- **Vancomycin rounds**
  - Daily opportunity for front-line staff to “ask the expert”
  - Encourage staff to submit interesting/challenging cases, disseminate to all staff
  - Identify opportunities to revise dosing policies/workflows (if needed)
- **Staff resources**
  - Develop a “living” FAQ document that is updated on a regular basis
  - Post educational materials in a location that is easily accessible, so front-line staff can revisit as necessary
  - Consider a “how-to” video series on a regular basis

Step 6.2 – Post-Implementation

- **METRICS!!**
  - How will you define your success?
  - Rates of creatinine increase?
  - First level(s) in therapeutic range?
  - Time to therapeutic AUC?
  - What baseline metrics do you have – can you directly compare?
  - Are there any automated reports you can leverage?
  - What groups of key-stakeholders need to see data?
  - Track as a stewardship metric for accreditation (e.g. Joint Commission)

Conclusions

- **No one-size-fits-all approach to calculate AUCs**
  - Depends on many factors, including hospital demographics
  - Avoidance of toxicity is key in justifying costs
- **An exercise in change management vs. clinical application**
  - The clinical *why* is easily justified, the *how* presents the biggest challenge
  - Breaking old habits is hard
  - Cannot extrapolate assumptions of traditional trough-based dosing to AUC-based dosing (particularly a Bayesian approach)
  - Utilize high-performers as superusers

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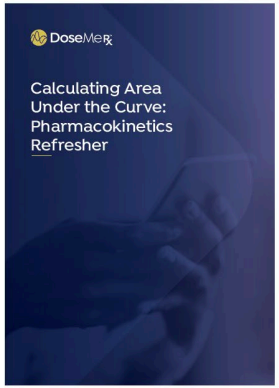
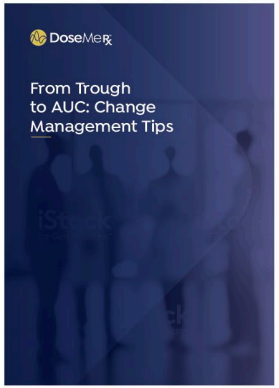
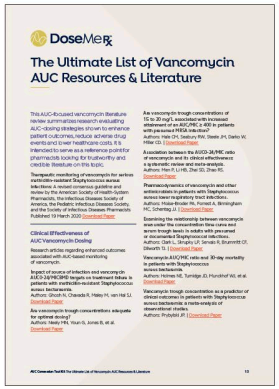
Resources







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