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(292-L01) Contemporary Considerations: Cutting-Edge Advances in Vancomycin Therapy

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Thomas Lodise, PharmD, PhD
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Disclosure

The program chair and presenters for this continuing education activity have reported no relevant financial relationships, except:

- **Manjunath (Amit) Pai** - Astellas Pharma, Inc.: Consultant; Melinta Therapeutics: Consultant; Theravance Biopharma: Board Member/Advisory Panel

- **Marc Scheetz** - Merck: Grant/Research Support; Premier; Speaker's Bureau

Start Time	End Time	Presentation	Presenters
8:00 AM	8:25 AM	Updates to literature and research surrou...	Marc H. Scheetz, Pharm.D., M.Sc., BCPS-AQ ID
8:25 AM	8:50 AM	Understand the updates to Vancomycin Ph...	Thomas Lodise, PharmD, PhD
8:50 AM	9:15 AM	Interactive Debate: Vancomycin is Clinically...	Michael J. Rybak, Pharm.D., MPH, FCCP
9:15 AM	9:40 AM	Interactive debate. Vancomycin is clinically ...	Manjunath (Amit) Pai, PharmD
9:40 AM	9:45 AM	QA	Marc H. Scheetz, Pharm.D., M.Sc., BCPS-AQ ID;T...

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Vancomycin: PK/PD Toxicity. A Focus on Nephrotoxicity.

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Disclosure

- **I submit the following disclosures:**
  - **I have received honoraria for speaking by Premier, Inc.**
  - **I am a currently a funded study investigator for the NIH (multiple studies) and the CARE Foundation.**
  - **I have previously received salary support from Merck/Cubist (2015) for an antimicrobial stewardship study and the State of Illinois for an organism virulence study (2016).**
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- **The views offered in the presentation are not necessarily the views of Midwestern University, Northwestern Memorial Hospital, or any other affiliated organizations.**

Overview

- Historical Review
  - Clinical and Laboratory Data
- Returning to ‘Pre’- Clinical Data
- Minimization of Toxicity, Dosing Strategies?

Does vancomycin cause nephrotoxicity?

- A Yes, it causes kidney damage.
- B No, it is correlated with damage, but those studies are flawed.
- C No, I have given this drug thousands of times and havenever seen nephrotoxicity.

Historical Review

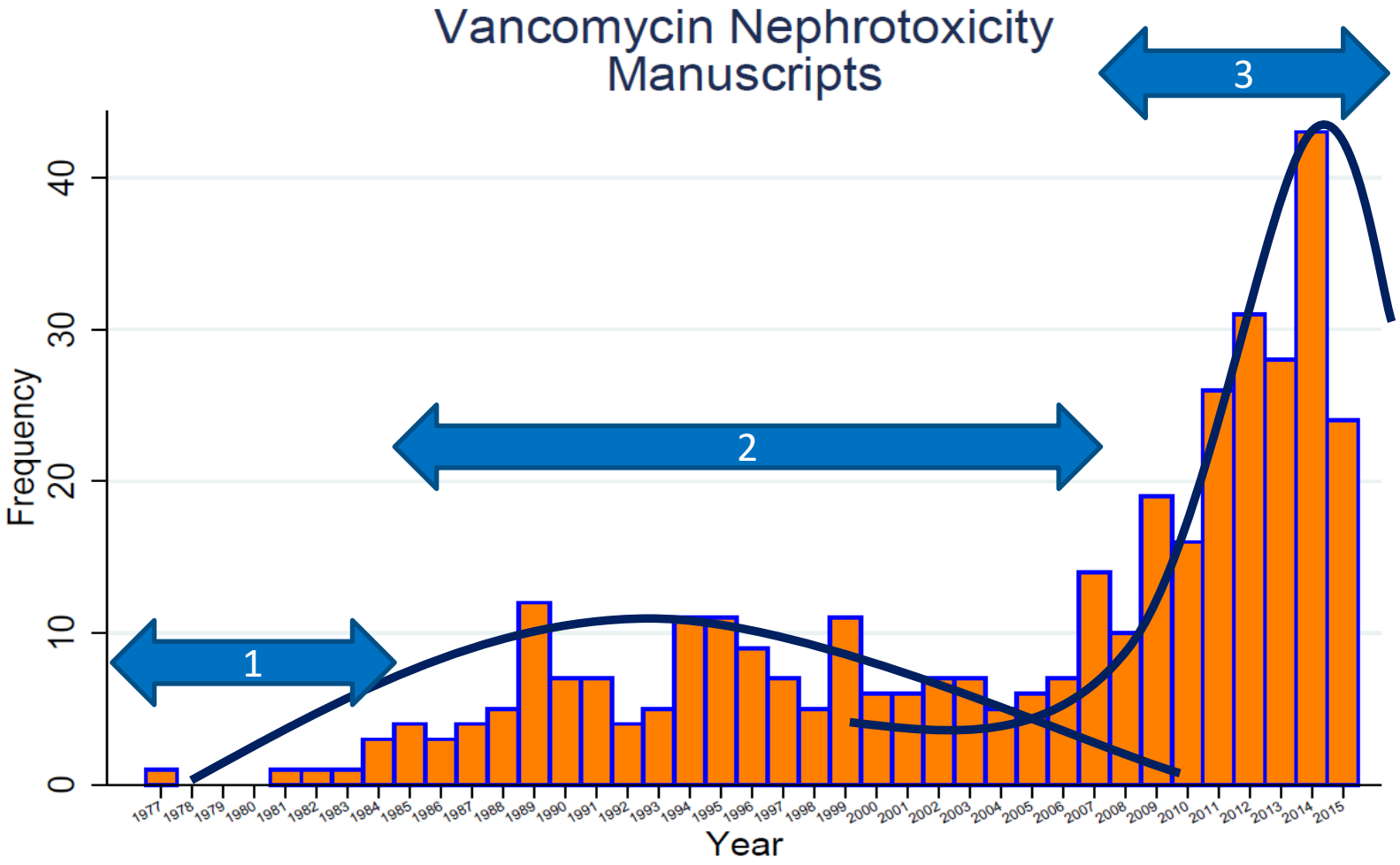
Vancomycin and Toxicities

- Ototoxicity
- Neurotoxicity

- Nephrotoxicity… where we will spend our time.
  - Acute kidney injury (AKI) is a significant and preventable cause of excess morbidity.
  - AKI prevalent among critically ill, hospitalized patients
  - Of approximately 1.8 million persons affected annually, ~20% AKI cases are thought to be drug-related.
  - AKI associated with increased mortality, greater LOS

Young MP, et al. Eff Clin Pract. 2000;3(6):284-9.
Bagshaw SM, et al. Nephrol Dial Transplant. 2008;23(4):1203-10.
Uchino S, et al. JAMA. 2005;294(7):813-8.

Vancomycin and Kidney Injury… 1950's to current.



Scheetz MH. Pubmed Search 071715. Keywords "Vancomycin" and "Nephrotoxicity"

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Circa 1950s

- MRSA non-existent
  - Quickly shelved…. Semi-synthetic penicillins treat PCN-resistant *S.aureus*
- New drug. Impure
  - "A **pyrogen reaction** with chills and high fever occurred not infrequently with the early batches of vancomycin, and often this reaction appeared just 1 hour after the injection. This type of reaction was relatively infrequent with later batches of vancomycin." [1]
- Early realizations. Partially correct.
  - "In patients with azotemia or renal insufficiency vancomycin should be used with caution and in smaller doses, and **therapy should be guided by repeated serum assays**.... This is to insure that high serum levels of vancomycin do not develop in these patients…. **Assays need NOT be done in young patients with normal renal function**….We think the level should be kept below 30 to 40mcg/mL except in unusual circumstances."[1]
  - Concern for cochleotoxicity and vestibulotoxicity
  - Out of 85 patients, all suffered some phlebitis. [1]

1. Geraci JE, et al. Arch Intern Med. 1962

Circa 1980 – 2005. MRSA!

- Vancomycin is now crystalline and pyrogen-free
- Nephrotoxicity is infrequent (~5%); concomitant nephrotoxins (e.g. aminoglycosides potentiate ~35% [1])
- Rat study: up to 400 mg/kg SQ over 28 days without kidney damage, however, histological changes are seen in dose dependent fashion. [2]
  - Serum concentrations were not obtained
- Second study corroborates SQ rat data and low kidney injury, but…. [3]
  - Dogs: LD_{50} is 292 mg/kg IV, secondary to renal failure (allometry equivalent: 162 mg/kg).
  - Dogs: Long term studies show slight renal damage in 4/22 dogs receiving 50 mg/kg IV (allometry equivalent: 28 mg/kg)

1. Farber B, and Moellering R. Antimicrob Agents Chemother 1983.
2. Aronoff GR. Antimicrob Agents Chemother. 1981.
3. Wold JS, Turnipseed SA. Rev Infect Dis. 1981.

The Original "Eli Lilly" Data: Intra-Peritoneal

Evaluation of renal function in rats given combinations of vancomycin and tobramycin.

Insignificant

Significant (i.e. p<0.05)

Vancomycin (mg/kg)	Tobramycin (mg/kg)	BUN (mg/dl)	Serum creatinine (mg/dl)	Gluconeogenesis (µg/g per hr)	NAG (µmoles substrate/ min)	Relative kidney weight (g/100g of body weight)
0	0	**21 ± 1**	**0.5 ± 0.1**	18 ± 2	2.3 ± 1.2	**0.90 ± 0.02**
75	0	**19 ± 1**	**0.6 ± 0.0**	23 ± 3	8.9 ± 2.5	**0.97 ± 0.04**
150	0	**26 ± 3**	**0.7 ± 0.1**	18 ± 2	14.4 ± 4.7	**1.20 ± 0.09**
0	60	25 ± 1	0.4 ± 0.0	22 ± 5	24.6 ± 3.7	0.98 ± 0.02
75	60	32 ± 3	0.6 ± 0.3	17 ± 2	45.2 ± 5.5	1.15 ± 0.04
150	**60**	**151 ± 31***	**4.0 ± 1.0***	**7 ± 4***	**123 ± 43***	**1.31 ± 0.04***

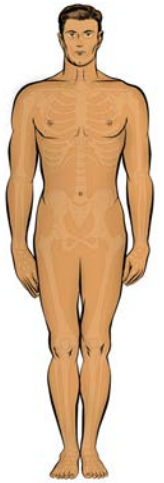
150/6.2 =24.2 mg/kg

NOTE: Vancomycin doses were administered IP BID x 4D ; tobramycin was given SC BID x 4 days.

BUN = blood urea nitrogen; NAG = N-acetyl-ß-glycosaminidase.

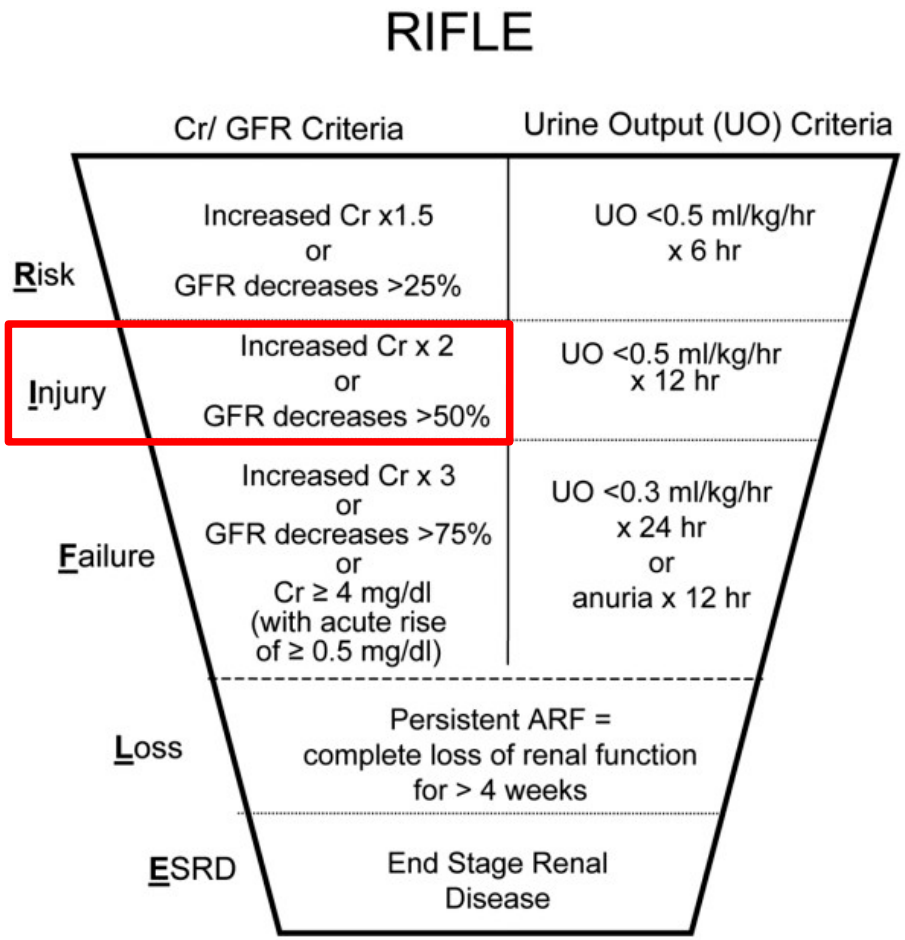
The Doubt?

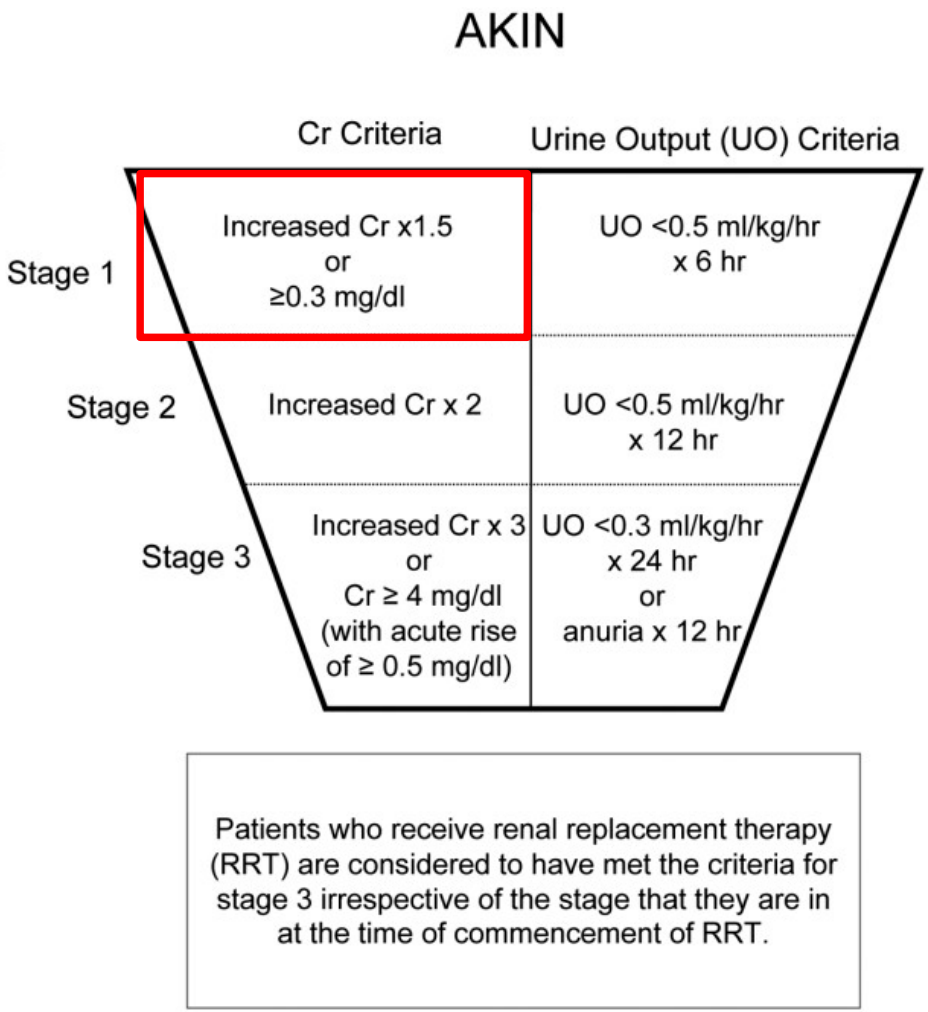
- Vancomycin causes very little nephrotoxicity?
  - Cantu et al.[1] Summarizes 82 cases in the literature.
    - 41 receiving concomitant aminoglycosides
    - 20 had other explanatory reasons for injury
    - 18 did not sufficiently detail if other potential causes were present
    - Only 3 patients received vancomycin monotherapy. [1]
- Chicken or the Egg? Which came first, nephrotoxicity or high troughs?
- It is realized that prospective studies are needed.



1. Cantu T, et al. Clinical Infectious Diseases. 1994.

Defining Nephrotoxicity





Patients who receive renal replacement therapy (RRT) are considered to have met the criteria for stage 3 irrespective of the stage that they are in at the time of commencement of RRT.

Cruz et al. Critical Care 2009

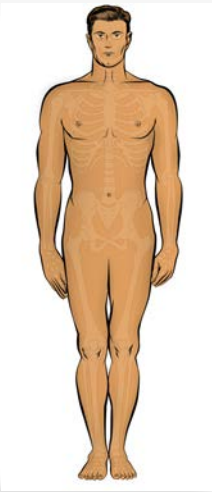
Vanco Circa 2009: Time for a Change

Paraphrasing the "Expert Panel Recommendations for Vancomycin Therapeutic Drug Monitoring (TDM)"

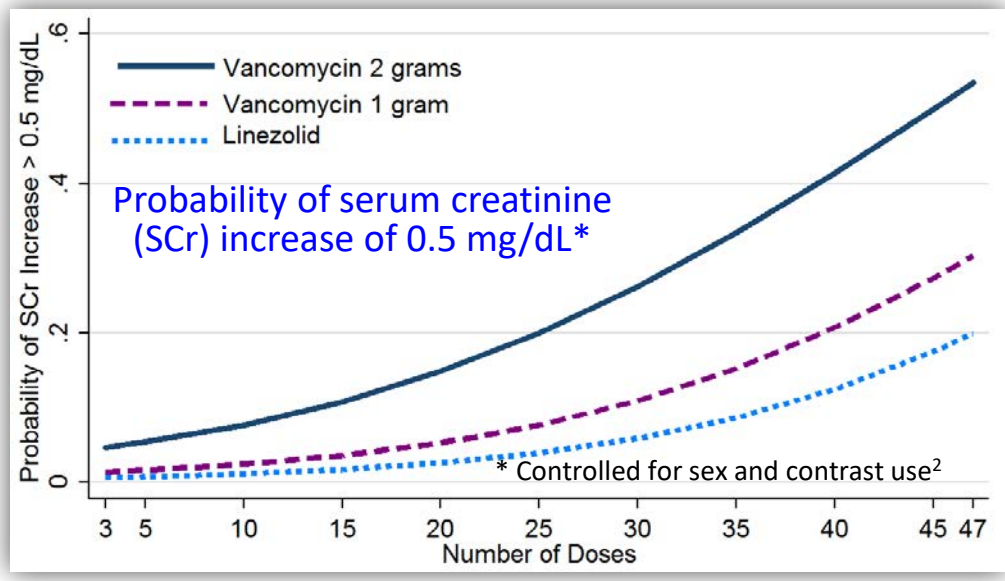
Variable	Recommendations	Level of Evidence and Grade of Recommendation
TDM for Vancomycin-Induced Nephrotoxicity Definition	>2 consecutive increases in serum creatinine concentrations (defined as an increase of 0.5 mg/dL or a ≥50% increase from baseline) after several days of vancomycin therapy.	IIB
Criteria for monitoring	Data do not support using peak serum vancomycin concentrations to monitor for nephrotoxicity.	IIB
	Trough monitoring is recommended	IIIB
Frequency of monitoring	Frequent monitoring is not recommended.	IIB
	All patients receiving >3 days should have at least one steady-state trough concentration obtained.	IIB
	There are limited data supporting the safety of sustained trough concentrations of 15-20 mg/L. Once-weekly monitoring is recommended of hemodynamically stable patients. More frequent or daily trough monitoring is advisable in patients who are hemodynamically unstable.	IIIB

Am J Health-Syst Pharm—Vol 66 Jan 1, 2009

Modifiers of Vancomycin Kidney Injury… many papers, similar answers.



Odds ratios nephrotoxicity[1]			
Parameter	aOR	95% CI	P value
Vancomycin ≥4 g/day	4.4	1.7-11.8	0.003
Wt of ≤101.4 kg	3.4	1.5-7.9	0.004
CrCl level of ≤86.6 ml/min	3.7	1.2-11.5	0.020
ICU residence	2.2	1.1-4.6	0.045



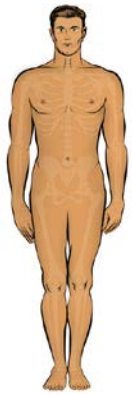
1. Lodise T, AAC 2008.
2. Bosch K, Scheetz M, et al. Int J Antimicrob Agents. 2014

Initial Clinical PK / Ptoxicity Evaluations

Bivariate Analysis: Vancomycin and Nephrotoxicity

	Nephrotoxicity (n = 21)	No Nephrotoxicity (n = 145)	*P*
Initial mean vancomycin trough (mg/L) ± SD	14.6 ± 8.3	9.6 ± 5.1	0.014
Initial vancomycin trough value, ≥9.9 mg/L	16 (76.2)	56 (38.6)	0.001
$AUC_{0\text{-}24ss}$ value, mean mg x h/L ± SD	1318.4 ± 1147.2	898.5 ± 475.9	0.11
$AUC_{0\text{-}24ss}$ value >1300 mg x h/L	7 (33.3)	20 (13.8)	0.05

NOTE: $AUC_{0\text{-}24ss}$, vancomycin area under the curve from 0-24 h at steady state



Logistic Regression, Nephrotoxicity

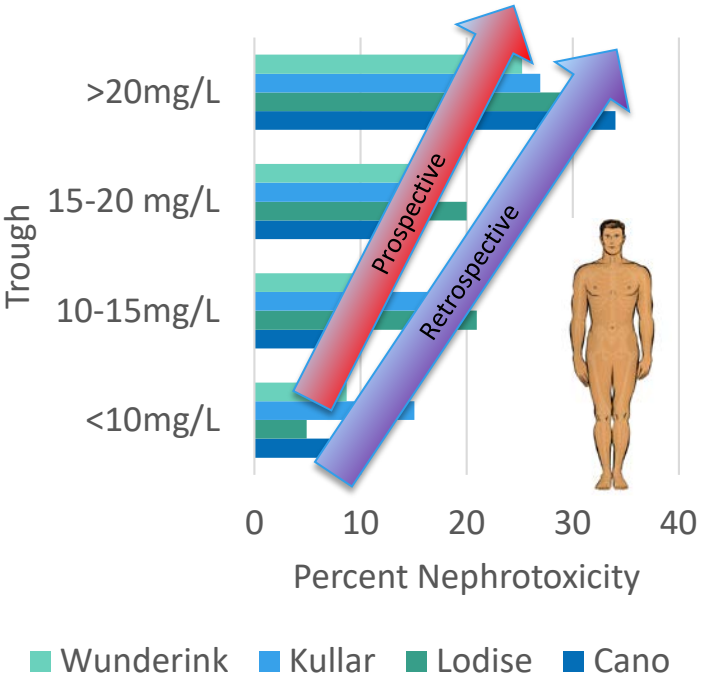
Parameter	**aOR (95% CI)**	***P***
Initial trough value	1.13 (1.05-1.21)	0.001
ICU	3.25 (1.18-8.97)	0.023

Lodise et al. Clinical Infectious Diseases 2009

Change Realized. Dose:Response

META-ANALYSIS: Nephrotoxicity rate is between 5 and 43%

Study or Subgroup	High troughs ≥15mg/L Events	Total	Low trough <15 mg/L Events	Total	Odds Ratio 95% CI
Bosso et al. (21)	42	142	13	146	4.30 [2.19, 8.46]
Cano et al. (22)	22	89	7	99	4.32 [1.74, 10.69]
Chung et al. (23)	12	25	16	48	1.85 [0.69, 4.96]
Jeffres et al. (15)	27	49	13	45	3.02 [1.28, 7.11]
Kullar et al. (32)	8	116	1	84	6.15 [0.75, 50.13]
Kullar et al. (8)	27	139	23	141	1.24 [0.67, 2.28]
Lodise et al. (36)	7	27	14	139	3.13 [1.12, 8.69]
Zimmermann et al. (51)	8	12	0	33	126.56 [6.19, 2585.90]
Total (95% CI)		599		735	3.12 [1.81, 5.37]
Total Events	153		87		



1. Van Hal SJ, Paterson D, Lodise, T. AAC 2013.

A Prospective Look

- Study **took 5.5 yr**; **1,255 patients randomized** to get to: **172 linezolid and 176 vancomycin patients** (Per Protocol analysis)
- Arguments about the baseline differences between the groups will be endless… but they were reasonably well matched.
- Vancomycin troughs at day 3 and pharmacists prospectively dosed and adjusted doses for patients based on renal function.
- Nephrotoxicity: 8.4% of Linezolid patients and 18.2% of vancomycin patients.
- Attributable vancomycin nephrotoxicity: ~10%
  - This assumes that we follow Historical Dosing Methods!

Baeline Demographics and Clinical Characteristics of the Per-Protocol Population

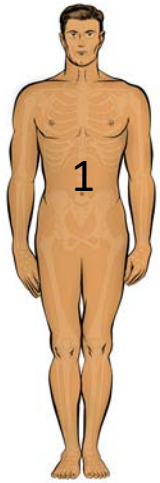
CHARACTERISTIC	LINEZOLID (n = 172)	VANCOMYCIN (n = 176)
Preexisting condition, No. (%)		
Diabetes mellitus	62 (36.1)	74 (42.5)
Pulmonary	117 (68.0)	118 (67.1)
Kidney	48 (27.9)	65 (36.9)
Cardiac	97 (56.4)	106 (60.2)
Age, years, mean (SD)	60.7 (18.0)	61.6 (17.7)
Weight, kg, mean (SD)	78.1 (23.3)	76.5 (21.8)
Mechanical ventilation, No. (%)	115 (66.9)	130 (73.9)
Type of pneumonia, No. (%)		
Healthcare-associated[a]	26 (15.1)	30 (17.1)
Nosocomial	146 (84.9)	146 (83.0)
Ventilator-assocaited[b]	104 (60.5)	117 (66.5)
Bacteremia, No. (%)	9 (5.2)	20 (10.8)
APACHE II score		
Mean (SD)	17.2 (6.4)	17.4 (6.0)
Modified CPIS (maximal score 17)[c]		
Mean (SD)	9.7 (2.1)	9.4 (2.3)
Vancomycin serum trough levels, median (interquartile range) µg/mL		
Day 3 (n=140)		12.3 (9.45)
Day 6 (n = 90)		14. 7 (10.40)
Day 9 (n = 33)		16.1 (11.30)

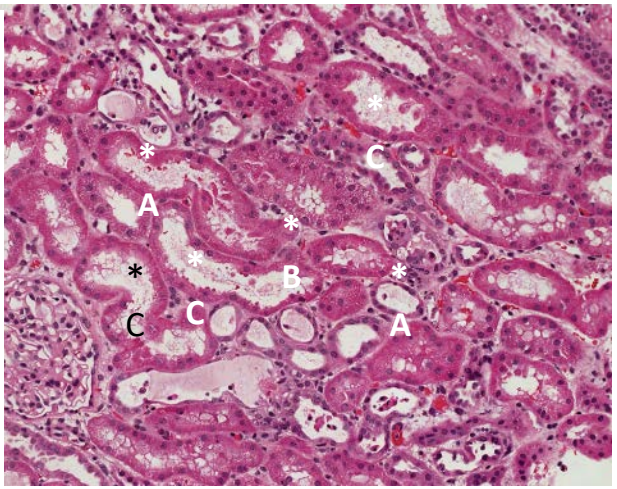
Wunderink R et al. *Clin Infect Dis*. 2012.

RETURN TO ‘PRE’-CLINICAL DATA

Mechanism Realized

- Vancomycin appears to induce oxidative stress at the renal proximal tubule; free radical scavenging and antioxidant molecules have minimized this toxicity.





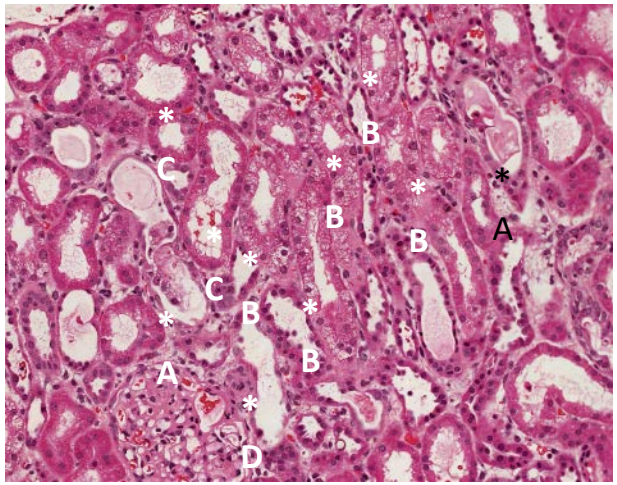
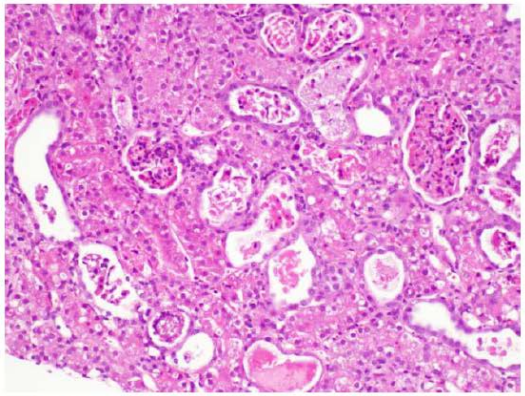


Figure. A biopsy showing tubular damage secondary to vancomycin toxicity at the location immediately above the asterix *. Some of tubules contain hyaline or epithelial casts in their lumina (*A), show vacuolization of their cytoplasm (*B), display moderate acute tubular necrosis (*C), and in one case a glomerular afferent arteriole shows swollen endothelia and an occlusive change (*D).



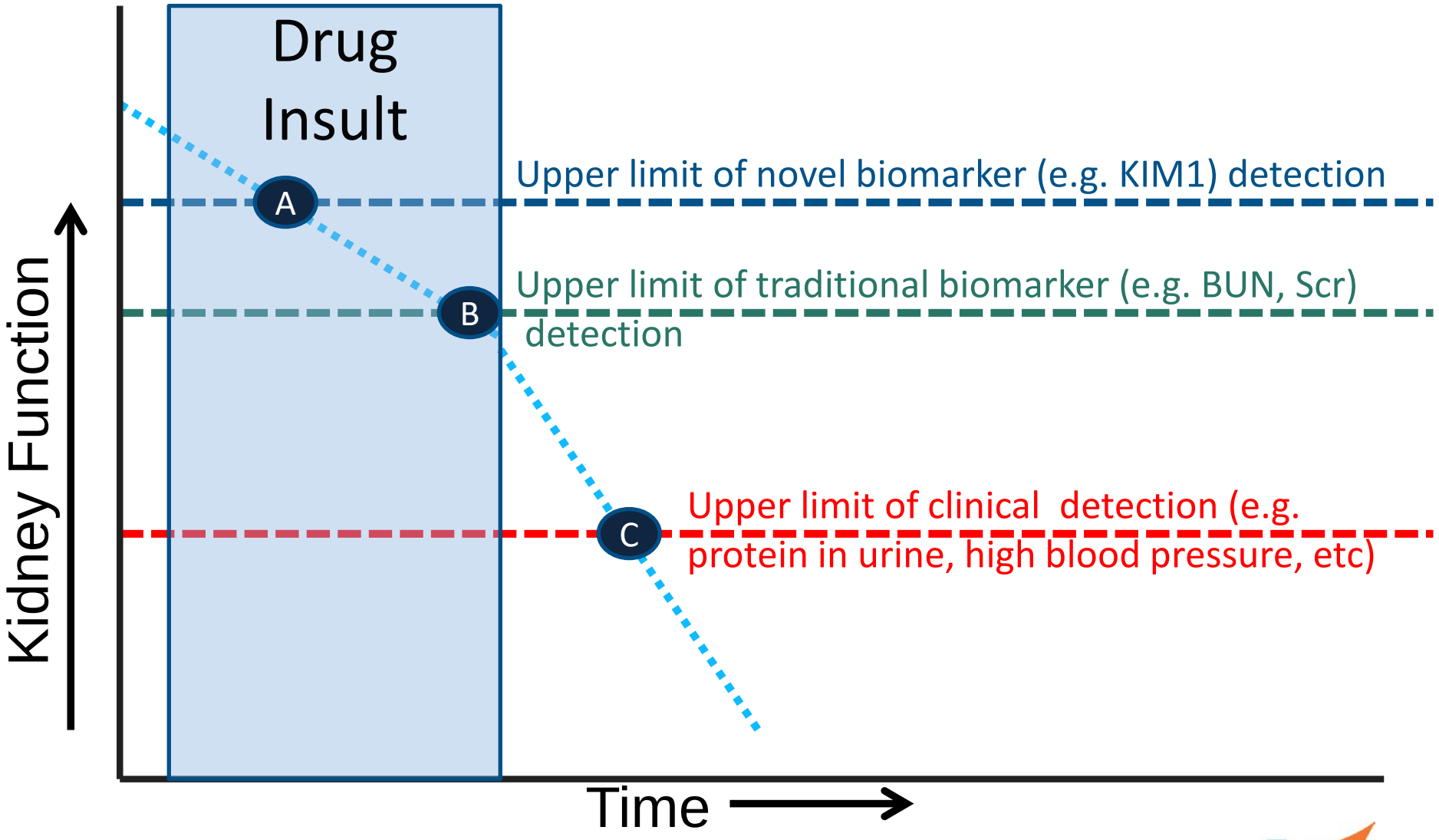
R138 400 mg/kg 400 mg/kg daily 72h

Histo Pathology Observations [Correlation]:
KIDNEY : Tubular cell regeneration; mild : Cortical and outer medulla
KIDNEY : Intratubular casts; minimal : Cortical and all of medulla
KIDNEY : Tubular cell degeneration/necrosis/ apoptosis; minimal : Cortical and outer medulla
KIDNEY : Tubular cell alteration; cortical, minimal : Sloughed cells

P4151714.jpg; R138; Group 25 of 29
Cortex with multiple tubules containing sloughed cells.

1. Shah-Khan F, et al. Int J Nephrol. 2011
2. Scheetz M, currently unpublished.

Ability to detect kidney injury according to time and method of detection

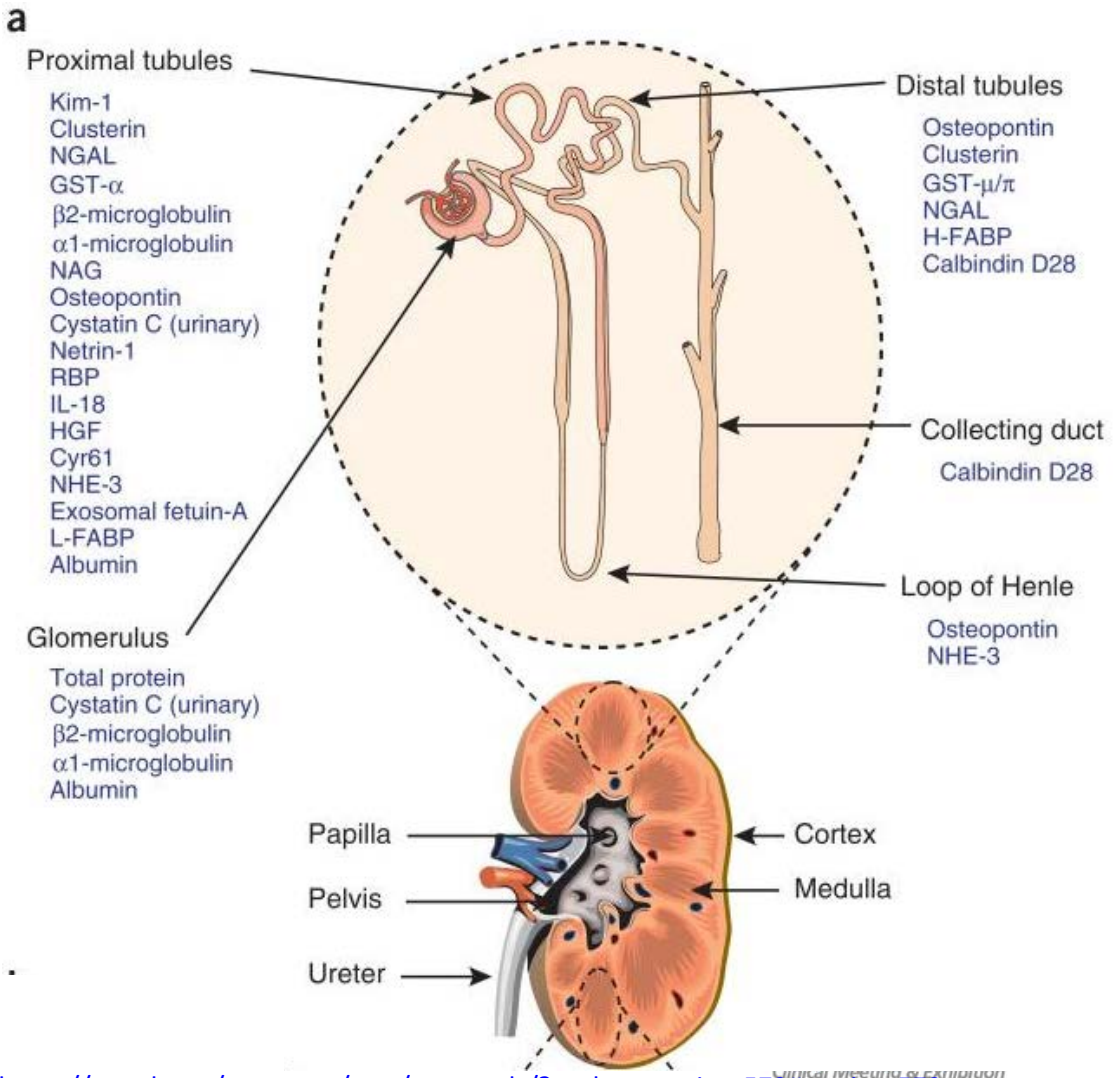


A. Point of hypothesized detection of novel biomarker abnormality
B. Point of irreversible nephrotoxic event
C. Point at which nephrotoxicity is detected with standard clinical variables

Kidney Biomarkers

PSTC Nephrotoxicity Working Group…
ideal renal safety biomarker. :

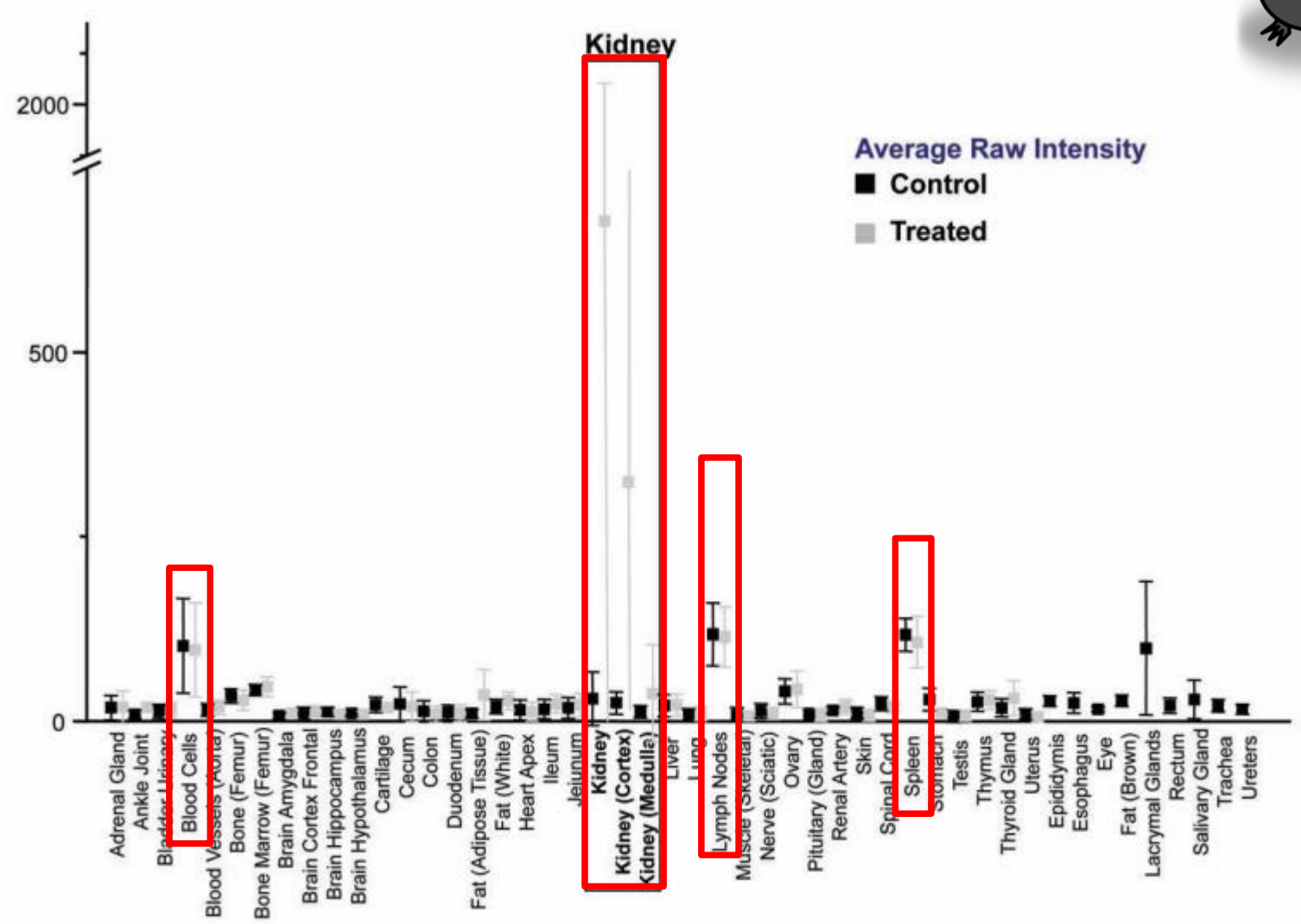
- Kidney injury identified early
- Dose response relationship with toxicity
- Applicable to various species, including humans
- Specific to kidney injury
- Is a barometer of progression of injury and recovery from damage
- Limitations well characterized
- Can easily be measured in readily available body fluids or tissues (e.g. urine).



Bonventre JV, et al. Nature biotechnology. 2010.

https://c-path.org/programs/pstc/pstc-tools/?anchor=section-572#section-572

KIM is Kidney specific



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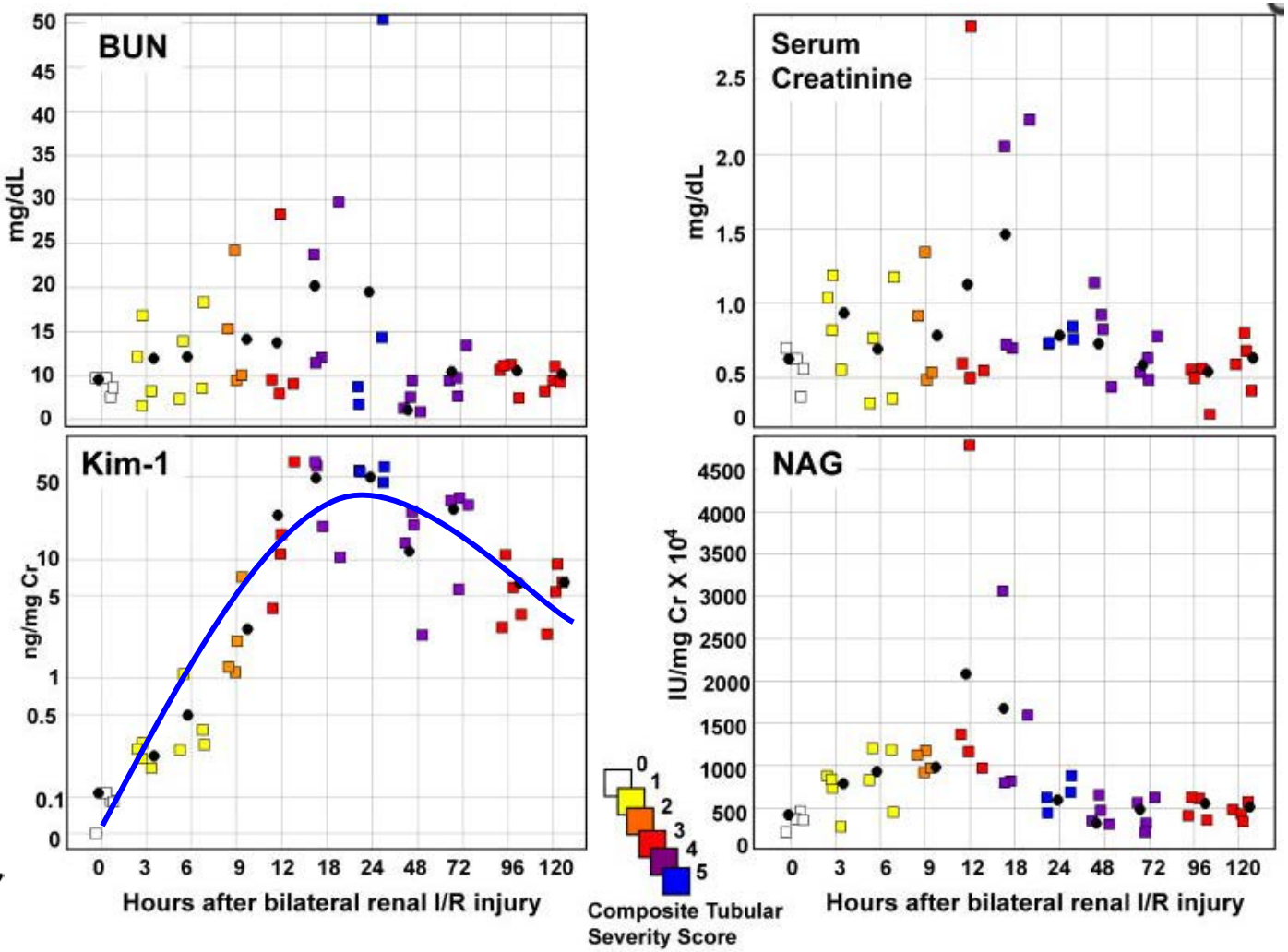
Vaidya V, et al. Nat Biotechnol. 2010

Bilateral Renal Ischemia/Reperfusion



Vaidya V, et al. Nat Biotechnol. 2010

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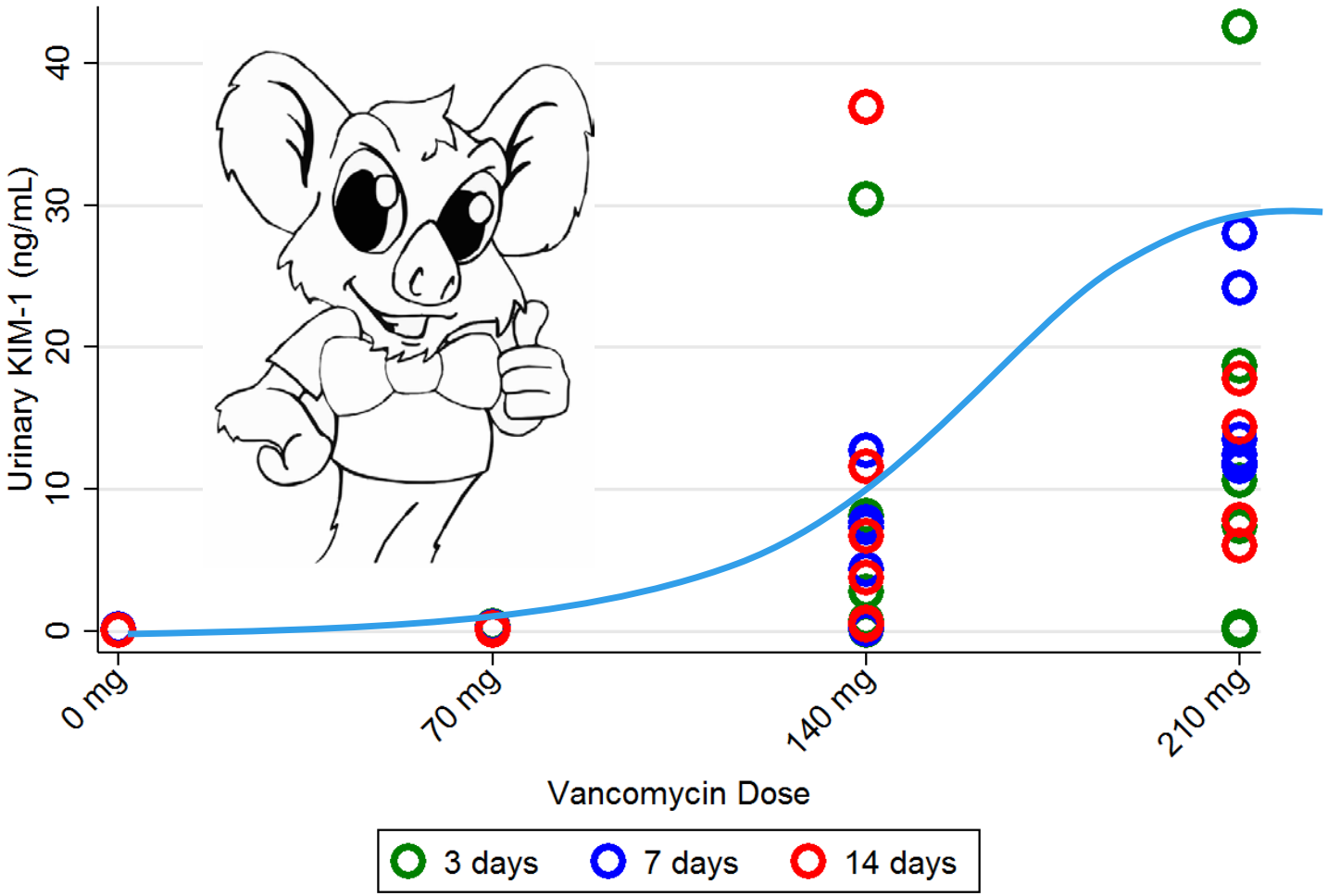
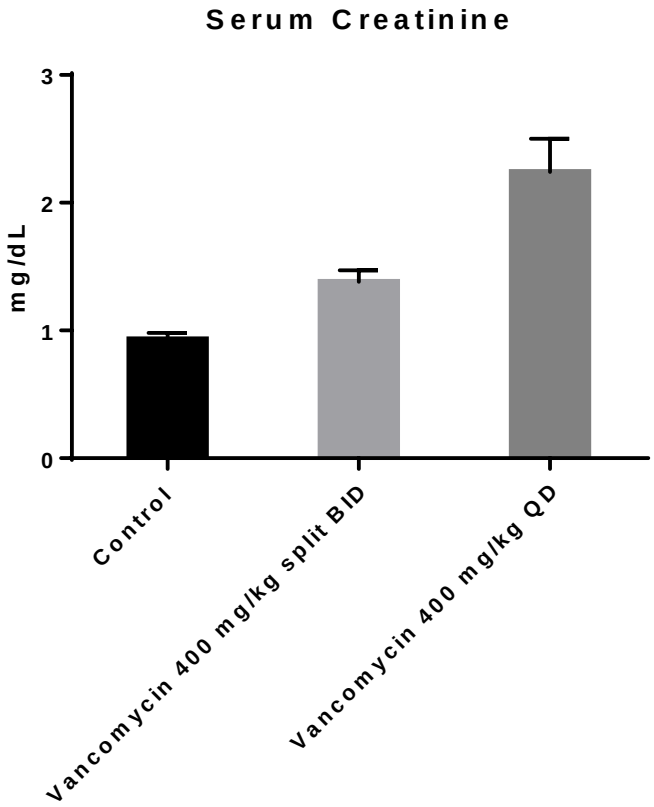
Urinary KIM-1 by Dose and Days of Therapy

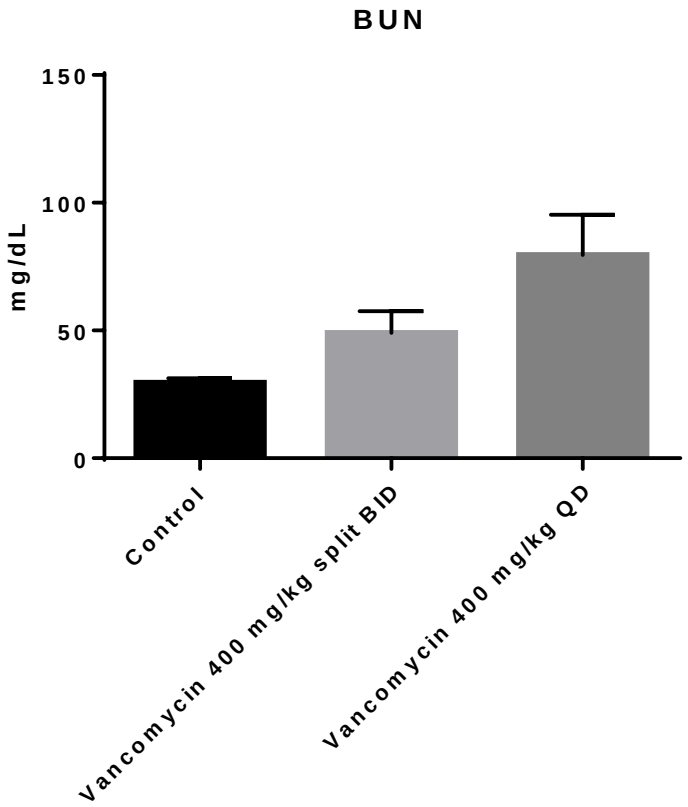


- Similar data have been shown by others[2]

1. Data abstracted from: Vaidya, et al. Nature Biotechnology. 2010.
2. Fuchs T, et al. Toxicologic Pathology. 2012

Same Vancomycin Dose x 7 days, Split v. Not



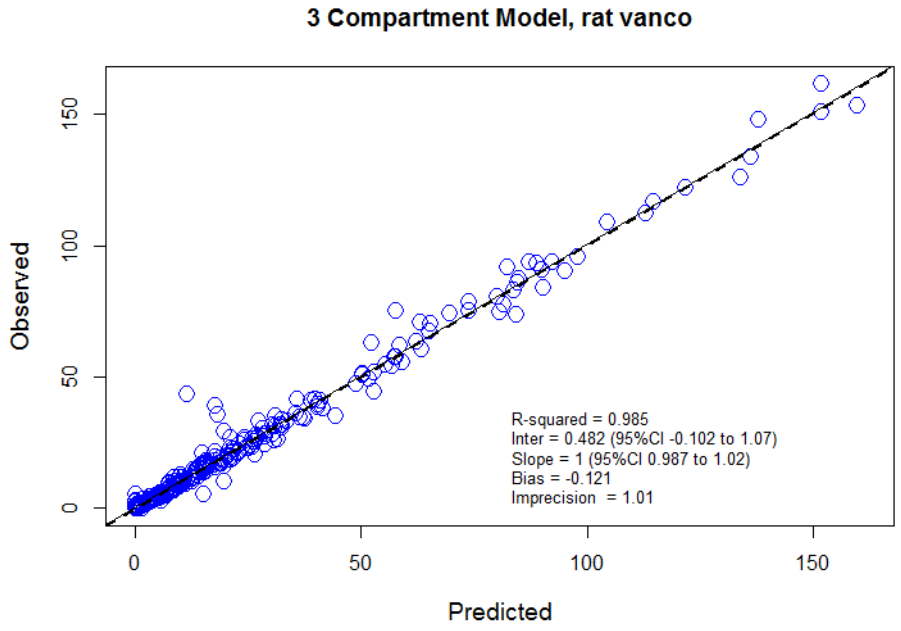


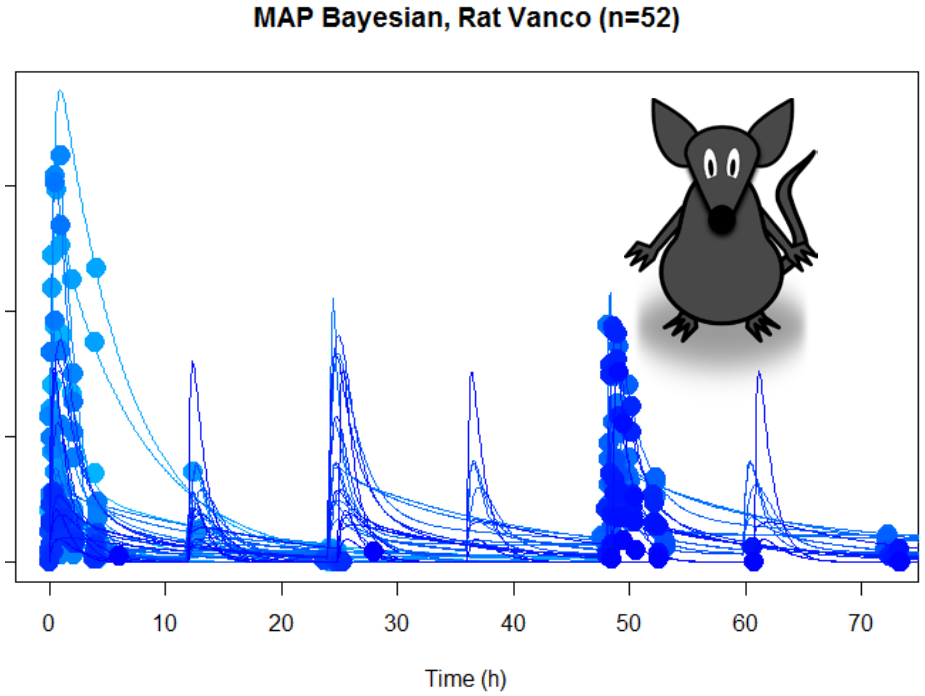
1. Konishi H, et al. J Chemother. 2013.

Gaps in the Road

- Barriers to elucidating EXPOSURE response for vancomycin-associated AKI:
  - Additional covariates (e.g. severity of illness) may obscure exposure-response relationship
  - Homogeneity of current human dosing strategies
- Need for innovative approaches to detecting AKI:
  - Use of novel urinary biomarkers may enhance detection of AKI prior to histopathological change
  - Combining animal models and novel biomarkers allows establishment of causative relationship

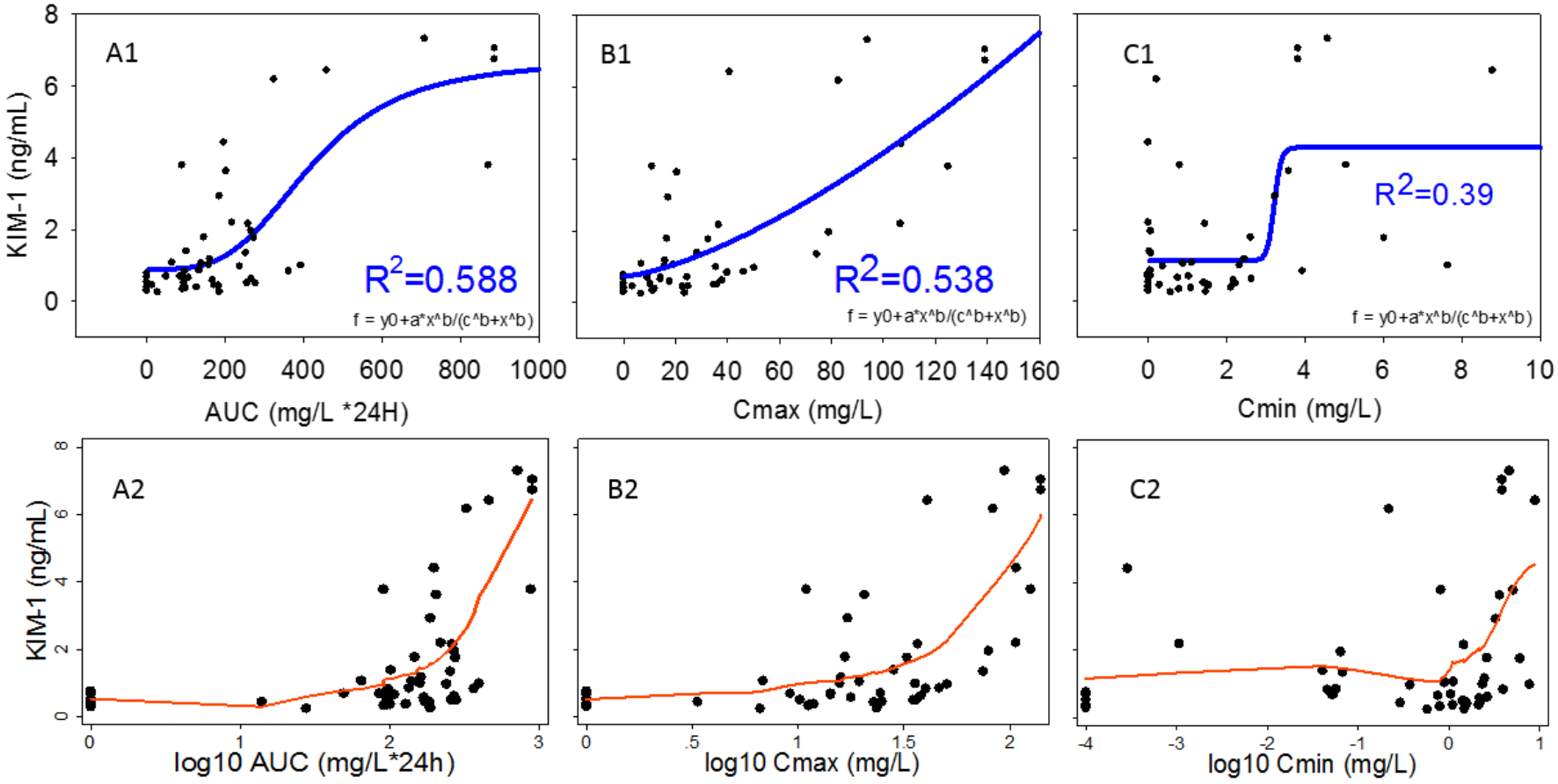
Our Group: Intraperitoneal Dosing, Vancomycin in SD Rats





Data from: Rhodes, Scheetz, et al.
AAC Accepted Manuscript Posted Online 18 July 2016
Antimicrob. Agents Chemother. doi:10.1128/AAC.00591-16

Kidney Injury Molecule 1 vs. Vancomycin PK Parameters: 24-hour dosed animals only



Scheetz et al. not yet published. NIAID R15AI105742

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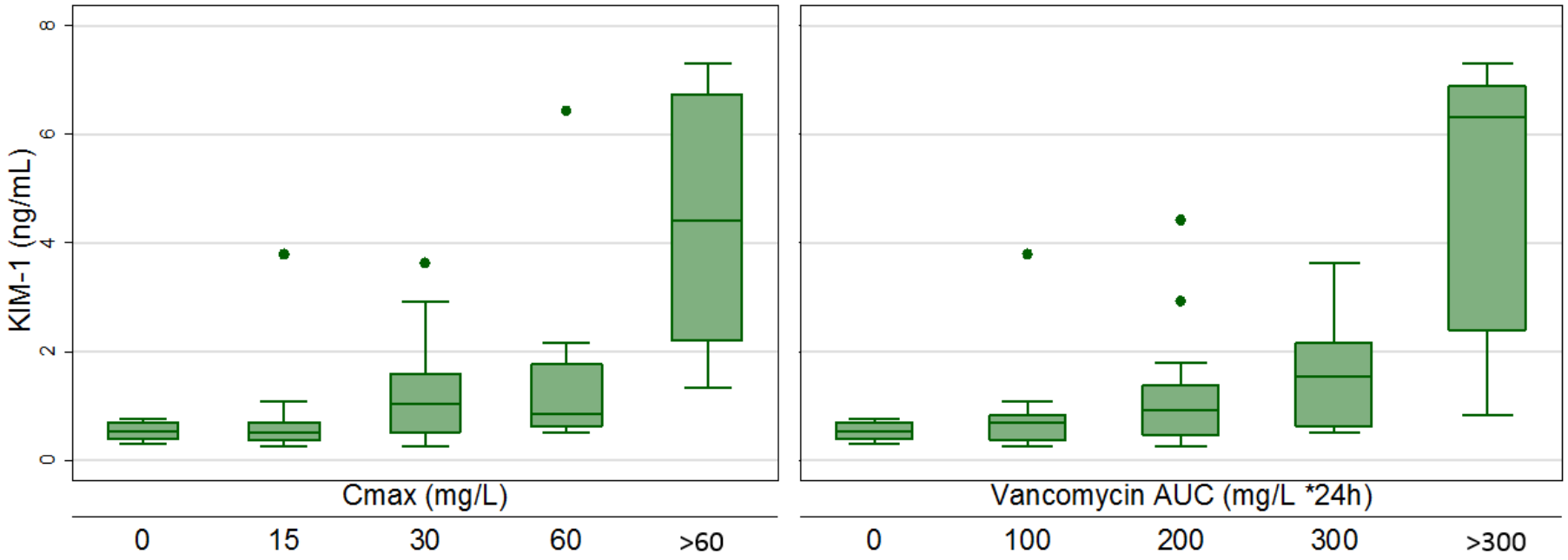
Viewed via Stratifications

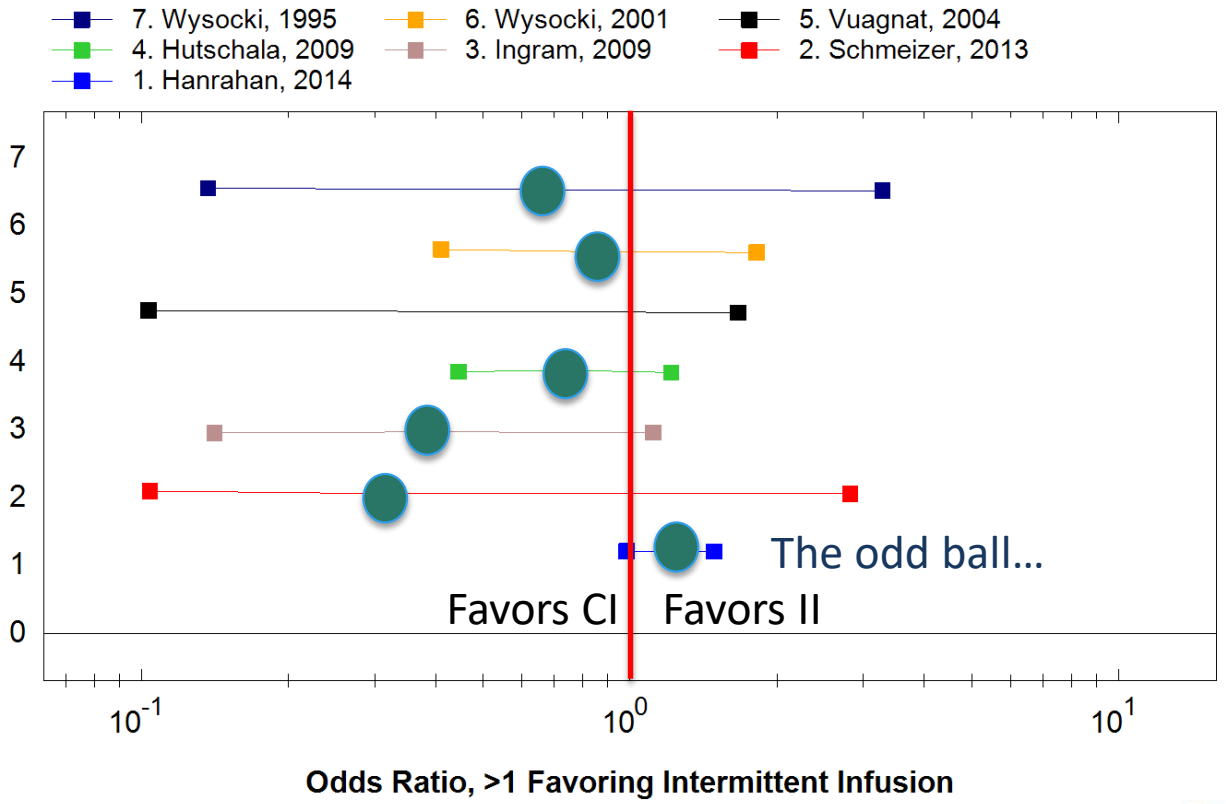


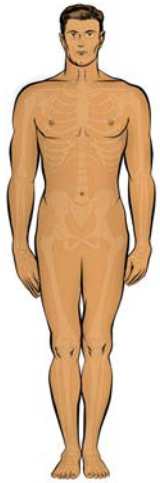
Scheetz et al. not yet published.

MINIMIZATION OF TOXICITY? GUIDED STRATEGIES.

Continuous Infusion vs. Intermittent Infusion

- Update of: Cataldo MA, et al. JAC 2012
  - Specific to Nephrotoxicity and additional studies included..





Data abstracted from: Hanrahan TP, Roberts J, et al. IJAA, 2015

So what was going on with that 'odd ball'?

1430 patients included; those with central lines received CI per hospital protocol

Summary of Patients Data Receiving Vancomycin by Infusion Method Type

Bivariates

Percent (%)	Continuous Infusion (n = 653)	Intermittent Infusion (n = 390)	Mixed (n = 221)	Unknown (n = 166)	*P*
Median serum vancomycin concentration (mg/L), medican (IQR)	18.4 (15.6-21.2)	8.8 (6.5-11.2)	15.5 (12.1-19.1)	11.9 (8.2-17.7)	< 0.001
Average vanco g/day, median (IQR)	1.7 (1.2-2.1)	1.5 (0.9-2.2)	1.7 (1.2-2.1)	2.0 (1.0-2.1)	0.003
Length of vancomycin therapy (d), median (IQR)	5.3 (3.4-10.3)	4.4 (2.5-7.3)	5.0 (2.9-9.2)	0.8 (0.4-1.2)	< 0.001
ICU mortality (%)	172 (26.3)	49 (12.6)	31 (14.0)	36 (21.7)	< 0.001
Nephrotoxicity	161 (24.7)	77 (19.7)	44 (19.9)	18 (10.8)	0.001

Multi-Variate

*Intermittent Infusion is associated with **aOR=8.2, p<0.001** risk of nephrotoxicity after controlling for vasopressors, duration of therapy, and interaction between serum concentrations and infusion scheme*

Hanrahan TP, et al. CCM 2014.

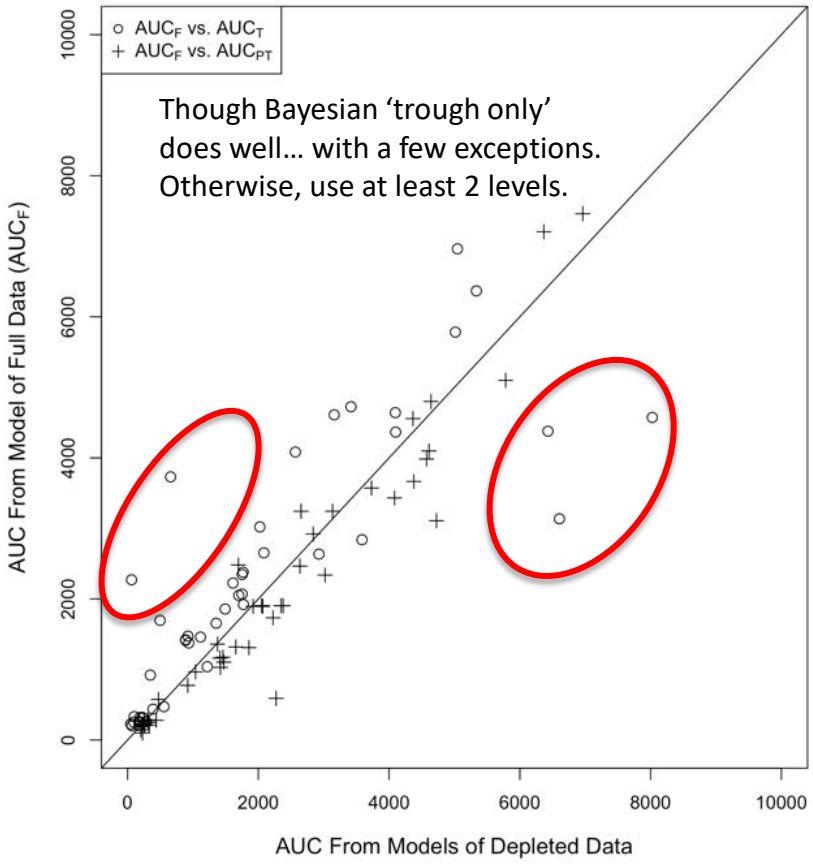
So Let's Say it is AUC…

What does this mean for our patients?

High variability with standard dosing!

Vancomycin exposures of simulated profiles with two doses given by 1-h intravenous infusion every 12h

Parameter	Value achieved with dose of: 1000 mg	1500 mg
Median (range) AUC_{0-24} (mg· h/liter)	343.1 (72.5-2194.0)	514.5 (109.0-3291.0)
% (no.) of patients with AUC_{0-24} (mg· h/liter)		
≥ 400	28.7 (1435)	80.1 (4005)
≥ 700	2.7 (136)	15.7 (787)
≥ 1300	0.02 (1)	0.38 (19)
Median (range) AUC_{0-24} of those with trough concn >20 mg/liter	602.0 (225.7-2194.0)	728.6 (264.8-3291.0)
% (no.) with trough concn of >20 mg/liter and AUC_{0-24} (mg· h/liter) of:		
< 400	14 (52)	3 (29)
400-700	61 (229)	41 (389)
≥ 700	26 (97)	56 (526)



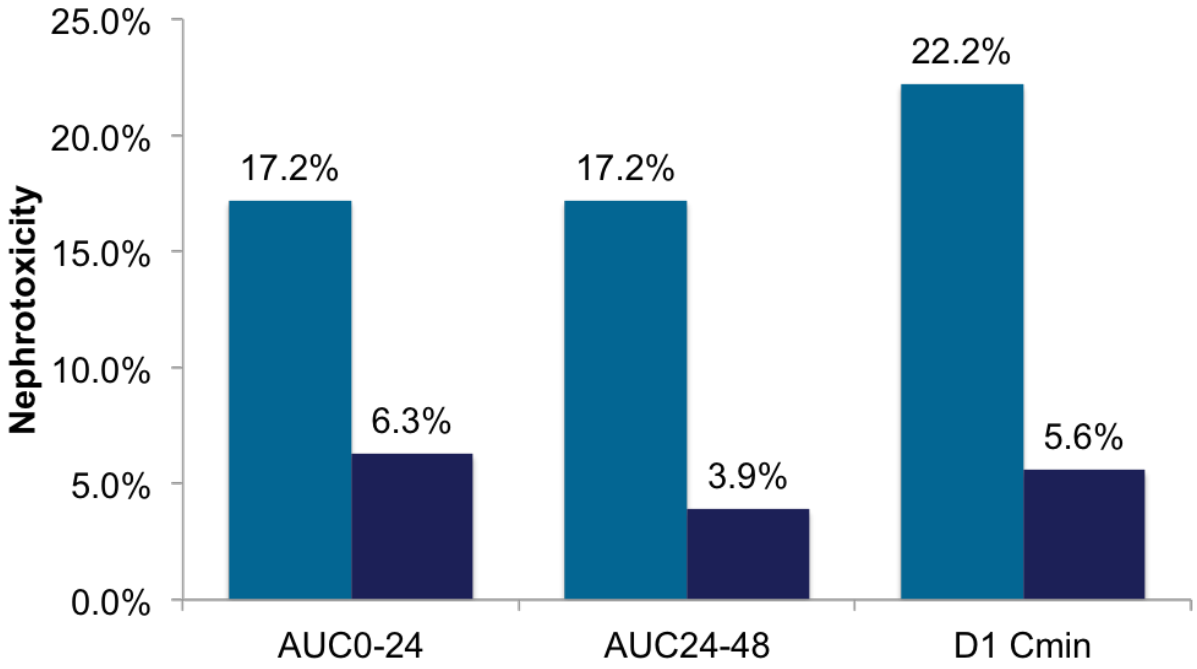
Neely M, et al. AAC 2014.

Modified Figure also courtesy Michael Neely

What is the magic AUC?

•Retrospective, single-center, observational cohort study from 2014 to 2015 at the Detroit Medical Center

•Inclusion criteria: age ≥ 18 y; ≥ 72 h of intravenous vancomycin; ≥ 1 serum vancomycin concentration during initial 96 h; bacteremia indication per pharmacy to dose order

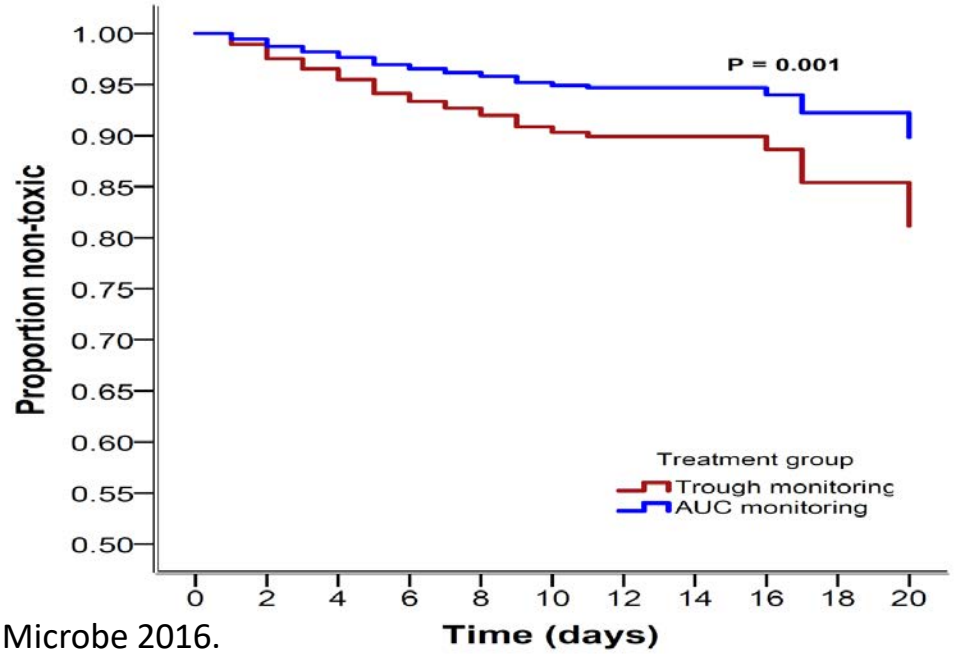


Zasowski, Murray, Trinh, Finch, Mynatt, Rybak. Microbe 2016

So Less can be More?

- Retrospective, multi-center, quasi-experimental study of patients in 2 treatment groups
  - Pre-intervention group (goal= Trough 15-20 mg/L goal)
  - Post-intervention group (goal= AUC_{24h} 400-600 mg*hr / L)
  - Bayesian exposure profiles bacteremic patients (n=160), decreased vancomycin exposure for those under AUC strategy.

Outcome (Matched Cohort) : Nephrotoxicity				
Outcome**		Trough (n=548)	AUC (n=548)	P-value
AKIN	Stage 1	108 (19.7)	86 (15.7)	0.08
	Stage 2	66 (12.0)	41 (7.5)	0.01
	Stage 3	18 (3.3)	12 (2.2)	0.27
RIFLE	Risk	101 (18.4)	90 (16.4)	0.38
	Injury	39 (7.1)	23 (4.2)	0.04
	Failure	18 (3.3)	12 (2.2)	0.27



Finch, Murray, Zasowski, Mynatt, Yost, Zhao, Pogue, Rybak. Microbe 2016.

Key Takeaways

- Key Takeaway #1
  - We learn more each day about Vancomycin induced Nephrotoxicity
- Key Takeaway #2
  - Troughs are not likely to predict Nephrotoxicity (other than after the fact or by using Bayesian modeling)
- Key Takeaway #3
  - AUC monitoring may be needed to prevent nephrotoxicity (while ensuring appropriate exposures for patients). Continuous infusion may be on the horizon.

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Vancomycin PK/PD Efficacy

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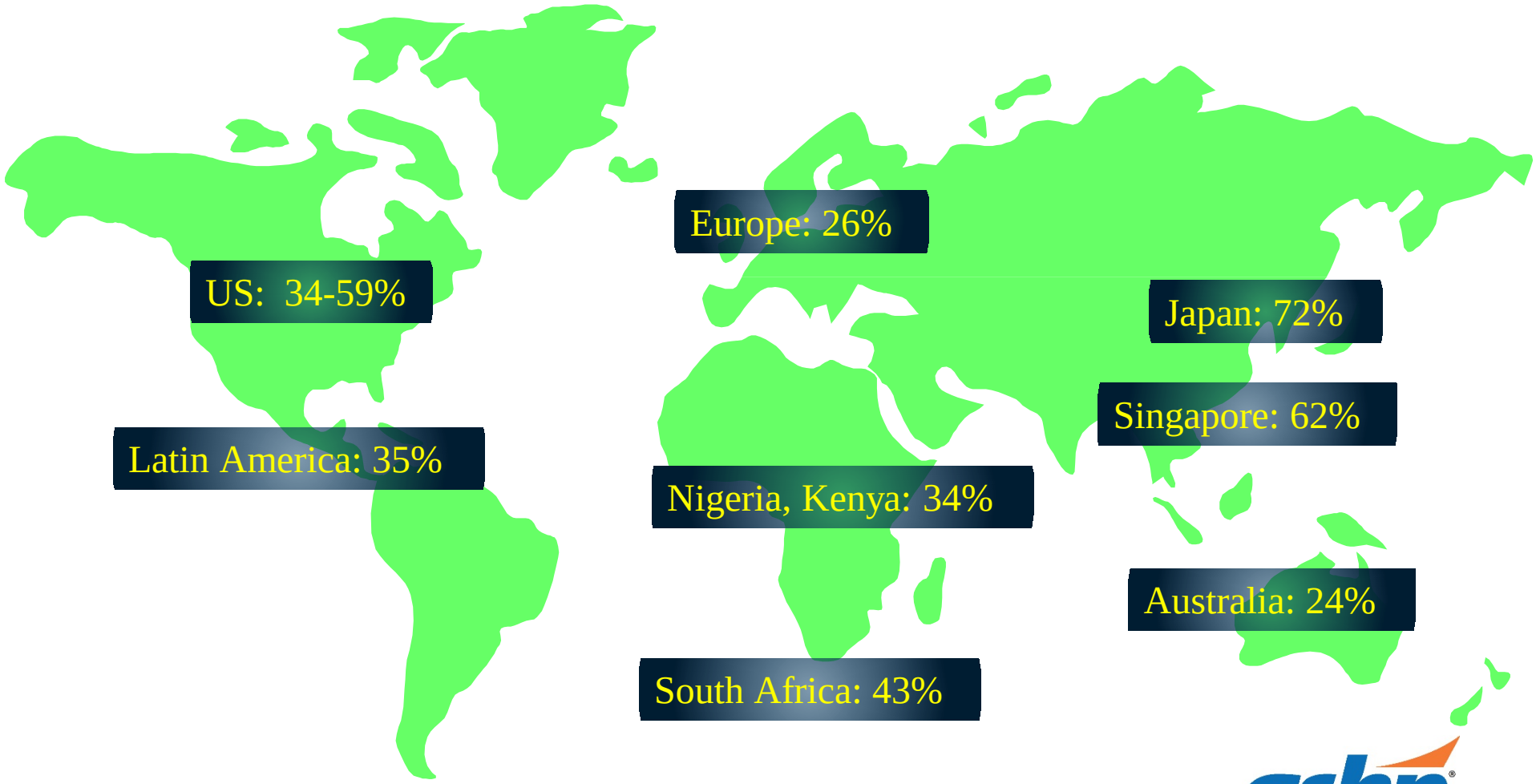
Methicillin Resistance among *S. aureus* Worldwide

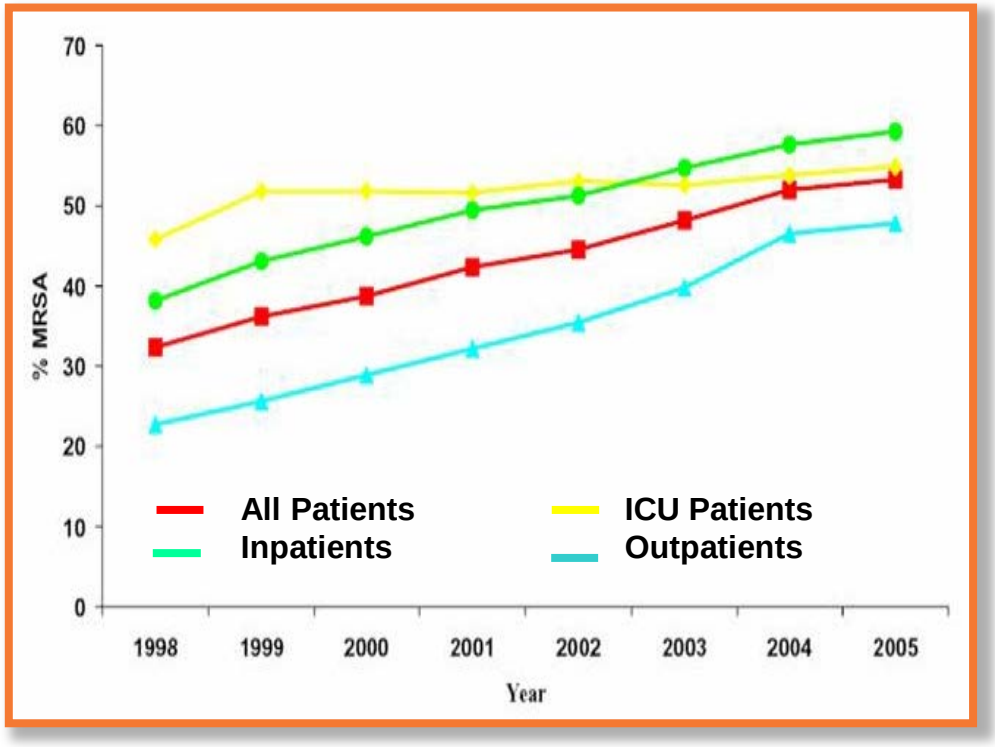


CMAJ 2002;167:885-91; Diagn Microbiol Infect Dis 2004;49:231-6
Clin Microbiol Infect 2003;9:153-6; Clin Infect Dis 2001;32:S114-32
Styers D, Sheehan DJ, Hogan P, Sahm DF. Ann Clin Microbiol Antimicrob. 2006 Feb 9;5:2.

Methicillin Resistance among *S. aureus* Surveillance Data from 300 US Labs

- Population-based studies indicate that MRSA is not limited to intensive care settings
- MRSA is now commonplace in the inpatient and outpatient settings.
- Epidemic strains of MRSA from the community have emerged as causes of hospital-acquired infections

MRSA Trends by Patient Location



Styers D et al. *Ann Clin Microbiol Antimicrob.* 2006;5:2.

Empiric Treatment of Suspected *S. aureus* Infections

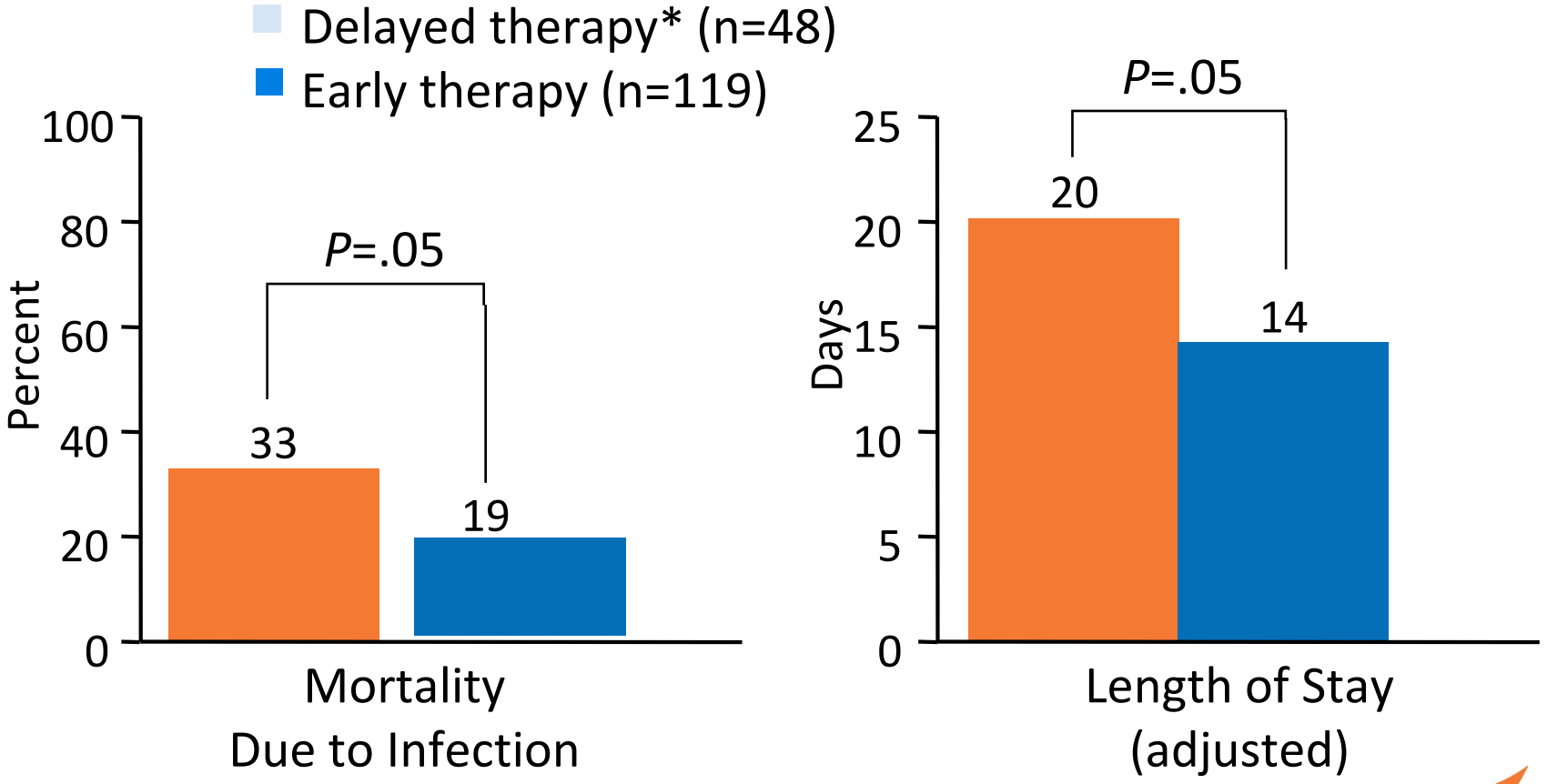
- Clinicians should consider MRSA as a potential pathogen in patients presenting with a clinical syndrome consistent with *S. aureus*
  - Endemic in healthcare institutions
    - Both intensive care unit (ICU) and non-ICU
  - Problematic in the community setting
- Important to get it right the first time

Centers for Disease Control and Prevention. National Nosocomial Infections Surveillance (NNIS) System

Lodise TP, McKinnon PS, Swiderski L, Rybak MJ. Outcomes analysis of delayed antibiotic treatment for hospital-acquired *Staphylococcus aureus* bacteremia. *Clin Infect Dis.* 2003;36:1418-1423.

Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant *S. aureus* infections among patients in the emergency department. *N Engl J Med.* 2006;355:666-674.

Delayed Therapy for *S. aureus* Bacteremia Increases Mortality and Length of Stay



*Breakpoint between early and delayed treatment was 44.75 hours.

Lodise TP et al. *Clin Infect Dis*. 2003;36:1418-1423.

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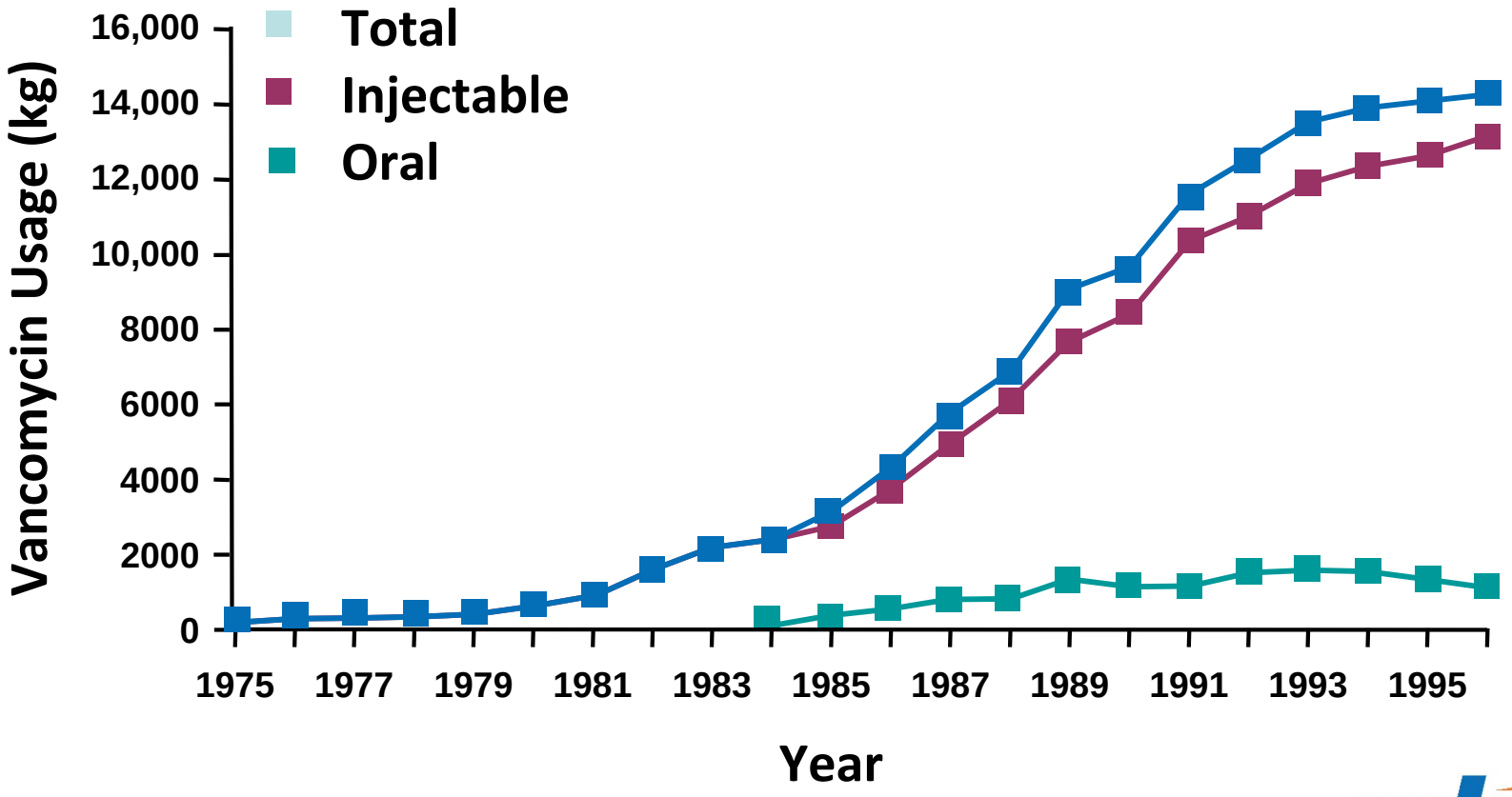
Vancomycin Utilization Over 20 Years



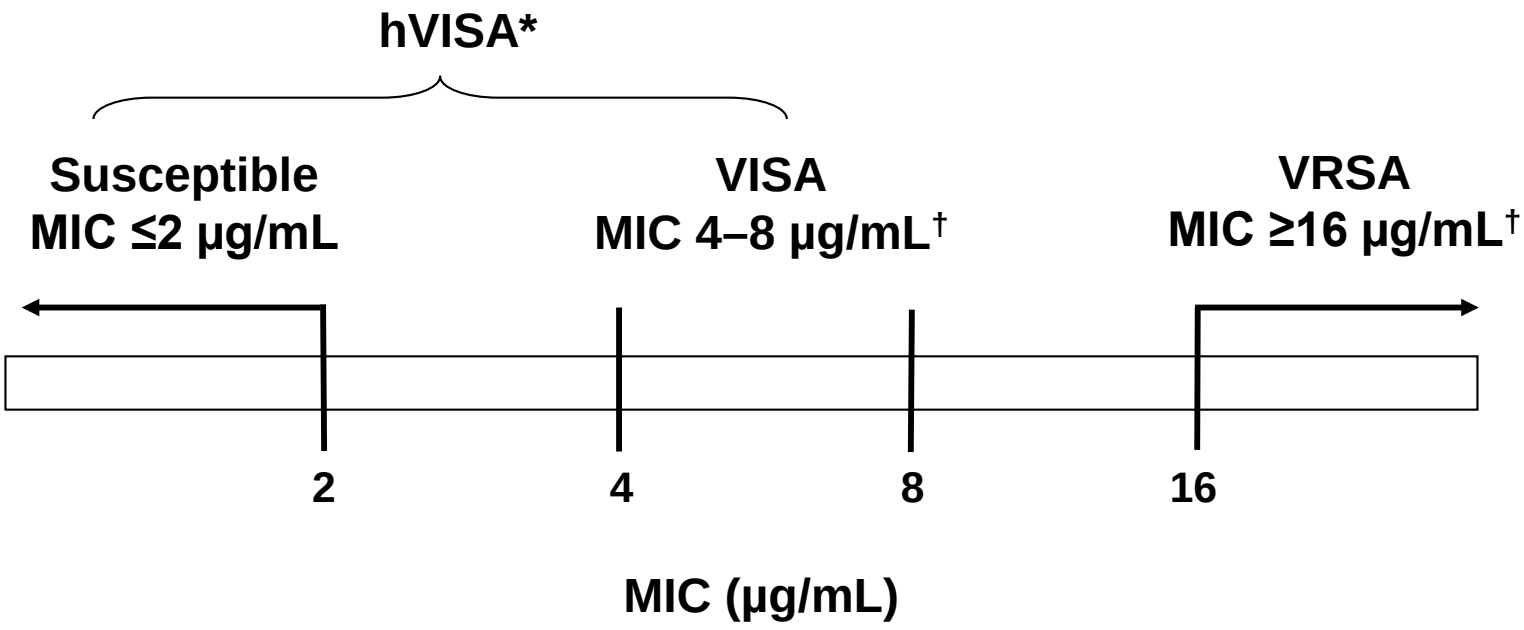
Kirst HA, Thompson DG, Nicas TI. Historical yearly usage of vancomycin. *Antimicrob Agents Chemother*. 1998;42:1303-1304.

Vancomycin Susceptibility in *S. aureus*

- Over 20 million days of vancomycin therapy are used annually in the United States alone.[1]
- Despite heavy reliance on vancomycin, MRSA infections are still nearly 100% susceptible to vancomycin as per Clinical Laboratory Standards Institute (CLSI) and FDA susceptibility breakpoints.[2,3]
  - Antibiotic susceptibility is based on the minimum inhibitory concentration (MIC)
    - MIC: lowest or minimum antimicrobial concentration that inhibits visible microbial growth in artificial media after a fixed incubation time

1. Kirst HA, Thompson DG, Nicas TI. Historical yearly usage of vancomycin. Antimicrob Agents Chemother. May 1998;42(5):1303-1304.
2. Sader HS, Fey PD, Limaye AP, et al. Antimicrob Agents Chemother. Oct 2009;53(10):4127-4132.
3. Clinical Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Twentieth Informational Supplement (June 2010 Update)" CLSI document M100-S20-U (ISBN 1-56238-729-4

S. aureus Susceptibility Defined: Vancomycin Resistant (VRSA), Vancomycin Intermediate (VISA), Heteroresistance (hVISA)



*In addition to the MIC, hVISA strains are identified by population analysis profiling (PAP), simplified PAP by BHIA-V4, simplified PAP on Mueller-Hinton agar, Etest, Disk-agar, MicroScan, and resistant mutant emergence.

†Breakpoints reflect 2006 CLSI guidelines.

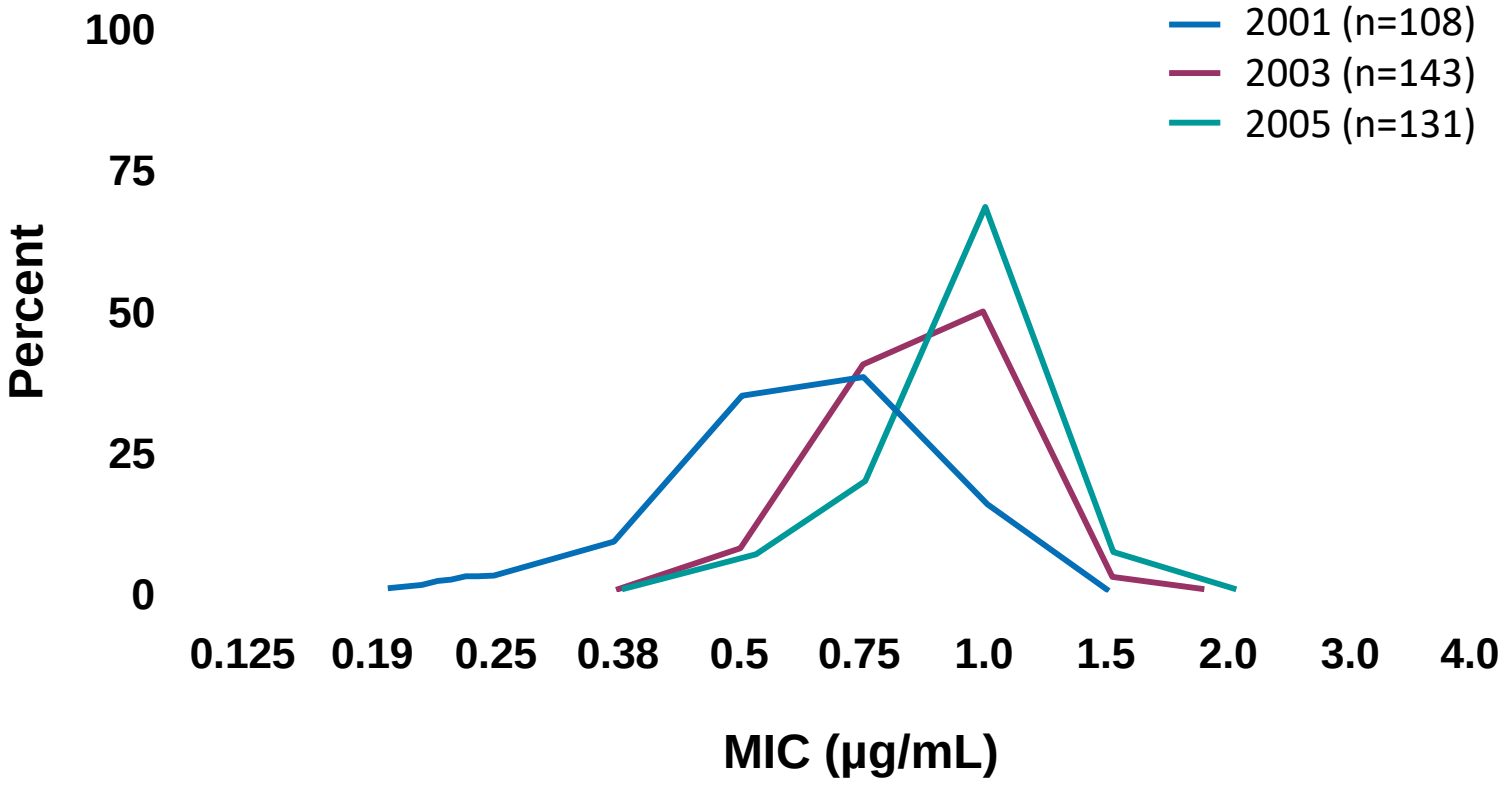
Clinical and Laboratory Standards Institute. *M100-S16, Performance Standards for Antimicrobial Susceptibility Testing; Sixteenth Informational Supplement*. Wayne, Pa: Clinical and Laboratory Standards Institute; 2006; Liu C, Chambers HF. *Staphylococcus aureus* with heterogeneous resistance to vancomycin: epidemiology, clinical significance, and critical assessment of diagnostic methods. *Antimicrob Agents Chemother.* 2003;47:3040-3045.

Lack of Vancomycin MIC Creep by Microbroth Dilution MIC Testing

Organism, year	No. of isolates tested	MIC_{50}, mg/L	MIC_{90}, mg/L	Percentage of isolates, according to MIC		
				2 mg/L	4 mg/L	8 mg/L
S. aureus						
1998	5966	1	1	5.3	0.1	0.0
1999	5011	1	1	4.8	< 0.1	0.0
2000	6346	1	1	7.8	< 0.1	<0.1
2001	5907	1	1	6.5	0.1	0.0
2002	7046	1	1	6.4	0.0	0.0
2003	5182	1	1	4.7	0.1	0.0

Jones, R. N. 2006. Microbiological features of vancomycin in the 21st century: minimum inhibitory concentration creep, bactericidal/static activity, and applied breakpoints to predict clinical outcomes or detect resistant strains. Clin. Infect. Dis. 42(Suppl. 1):S13-S24

Vancomycin MIC Population Distribution for MRSA: 2001–2005



Clinical MRSA blood isolates collected at a single tertiary care center

Steinkraus G, White R, Friedrich L. Vancomycin MIC creep in non-vancomycin-intermediate *Staphylococcus aureus* (VISA), vancomycin-susceptible clinical methicillin-resistant *S. aureus* (MRSA) blood isolates from 2001–05. *J Antimicrob Chemother.* 2007;60(4):788–794.

Relationship between vancomycin MIC and outcomes for serious MRSA infections

Study	Study Population	Primary Outcome	MIC Testing Methodology MIC Range (mg/L)	Low MIC Outcomes	High MIC Outcomes	Difference in Outcomes	*P* -value
Maclayton et al.	Adult hemodialysis patients with MRSA bacteremia	Mortality	Vitek ≤ 0.5 (n=33) 2 (n=17)	24%	35%	**11%**	NS at <0.05 <0.001
Hidayat et al.	Adult patients with MRSA infection	Treatment Failure	Etest ≤ 1 (n=40) 2 (n=39)	15%	38%	**23%**	0.02
Soriano et al.	Adult patients with MRSA bacteremia	30-Day Mortality	Etest 1 (n=38) 1.5-2 (n=40)	15.8%	39.8%	**24%**	<0.05
Hsu et al.	Adult patients with MRSA infection	Treatment Failure	Etest ≤ 1 (n=38) > 1 (n=45)	11%	38%	**27%**	0.034
Lodise et al.	Adult patients with MRSA bacteremia	Treatment Failure	Etest < 1.5 (n=26) ≥ 1.5 (n=66)	15.4%	36.4%	**21%**	0.049
Musta et al.	Adult patients with MRSA bacteremia	Mortality	Etest ≤ 1.5 (n=429) ≥ 2 (n=60)	25.7%	47.6%	**21.9%**	0.03
Wang et al.	Adult patients with MRSA bacteremia	30-Day Mortality	BMD = 2 (n=26) < 2 (n=97)	27.8%	50%	**22.2%**	0.057

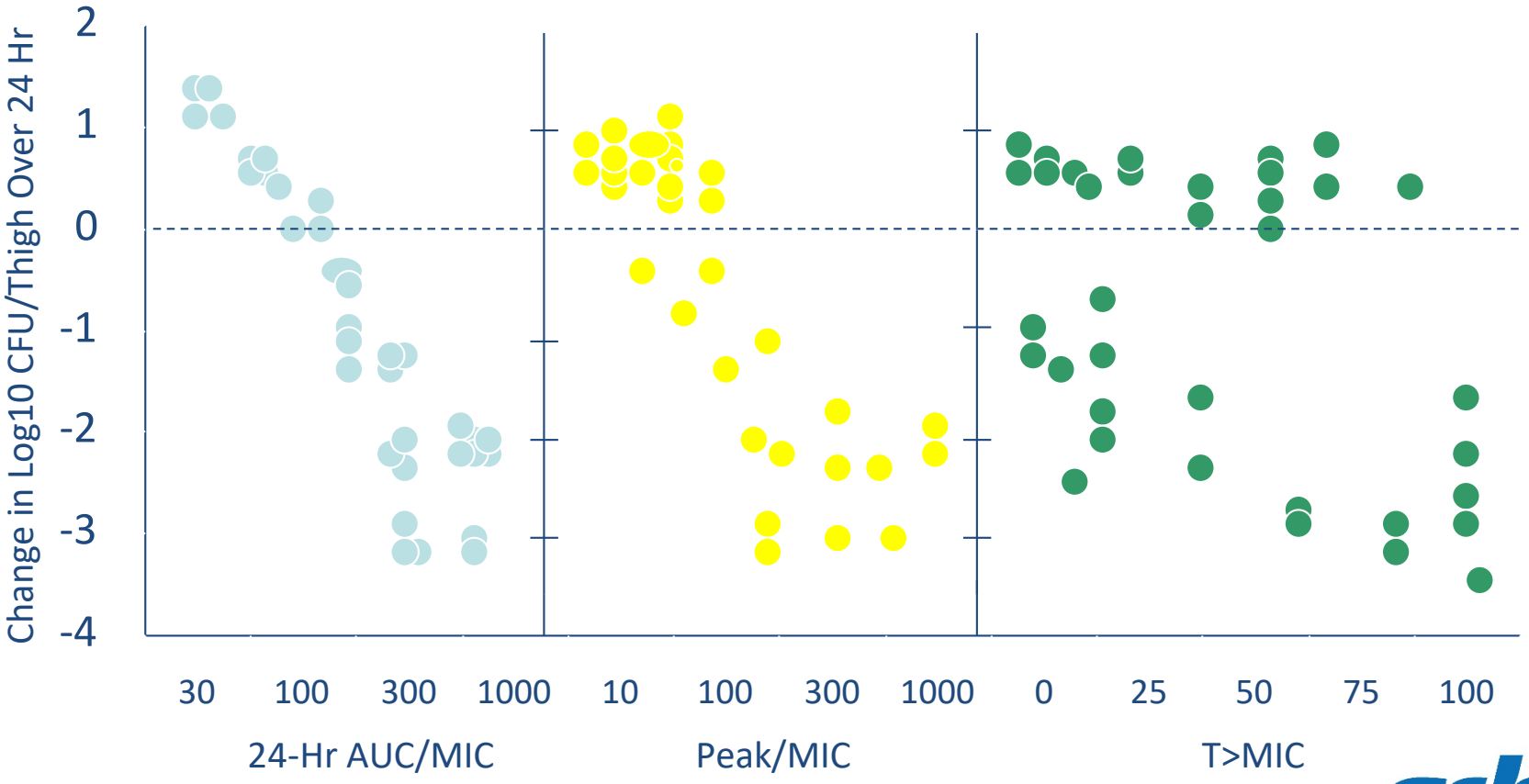
Adapted from van Hal SJ, Lodise TP, Paterson DL. Clin Infect Dis. 2012. Mar;54(6):755-71.

AJHP 2009 Consensus Review on the Therapeutic Monitoring of Vancomycin

- The AUC/MIC is the pharmacodynamic parameter best associated with vancomycin efficacy against *Staphylococcus aureus*.
- An AUC/MIC ratio of 400 has been advocated as a target to achieve clinical effectiveness with vancomycin
  - An AUC/MIC ratio of 400 is unachievable with conventional dosing in patients if MIC is ≥ 2 mg/L.
- Total troughs serum vancomycin concentrations of 15-20 mg/L are recommended for complicated infections.
  - AUCs are not determined in clinical practice due to the perceived difficulty in calculating AUC/MIC values.

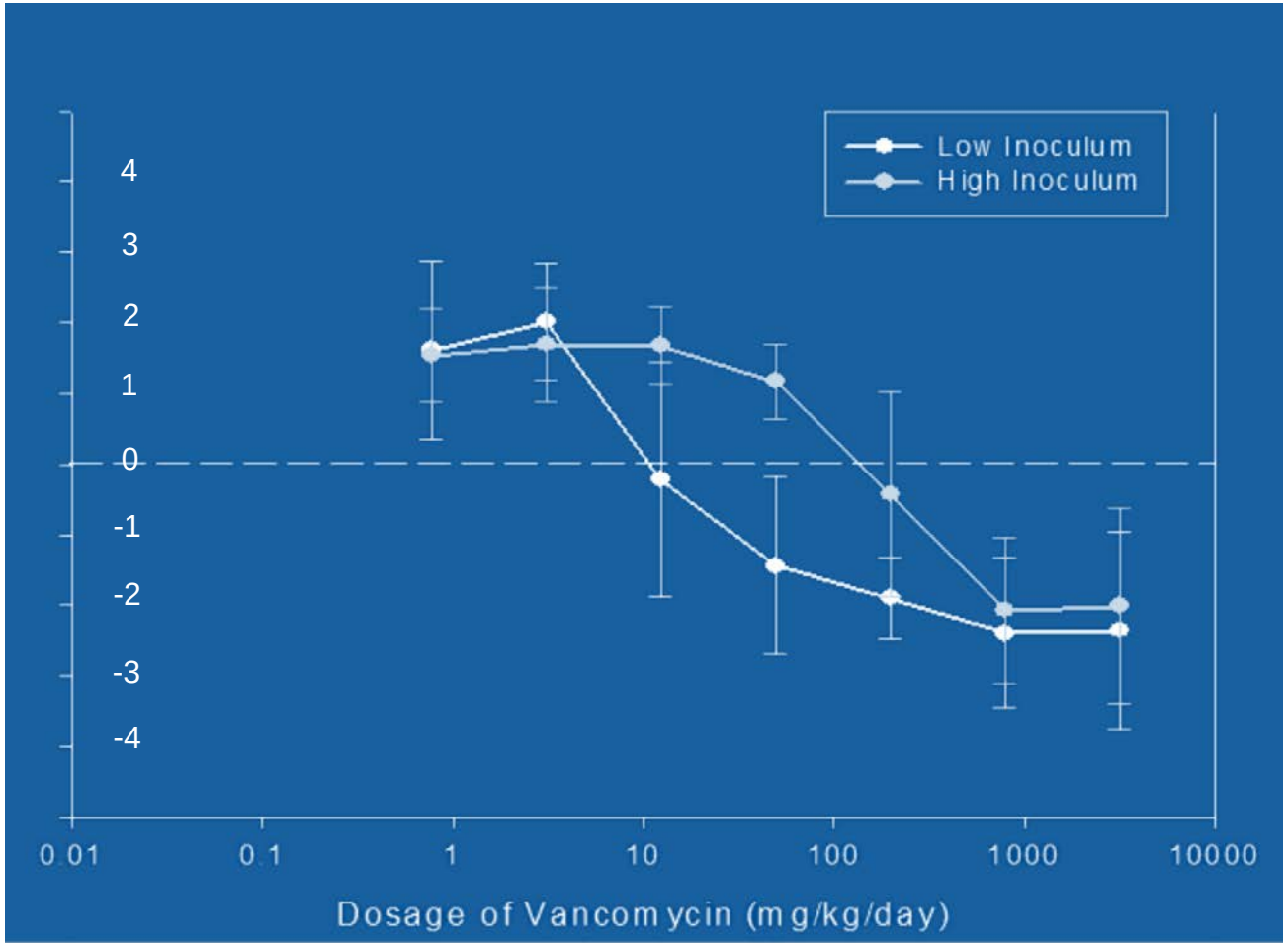
Rybak et al. *Am J Heath-Syst Pharm* 2009; 66:82-98

Pharmacodynamic Indices and *in-vitro* Activity for Vancomycin: Murine Thigh Infection Model



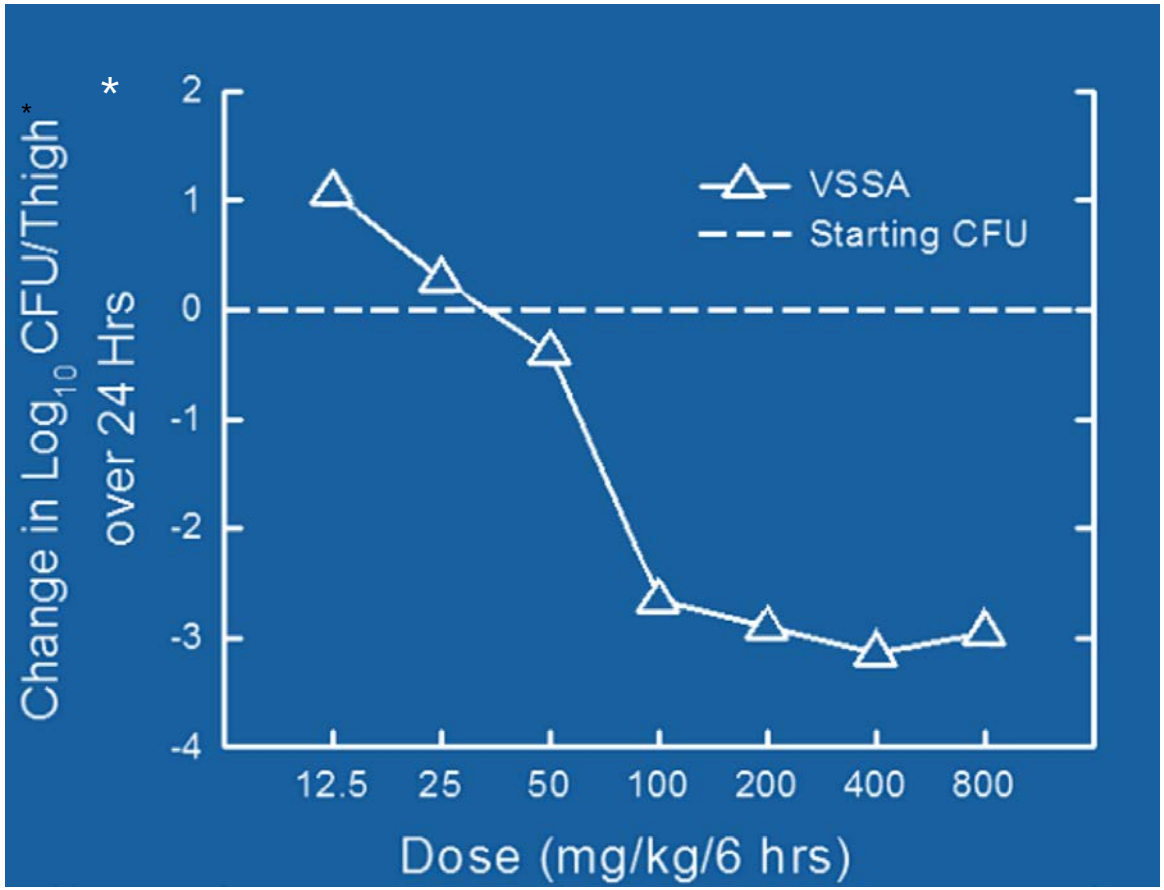
Ebert S. In vitro cidal activity and pharmacokinetic parameters for vancomycin against methicillin-susceptible and resistant *S. aureus* [abstract 439]. In: Program and abstracts of the 27th Interscience Conference on Antimicrobial Agents and Chemotherapy (New York). Washington, DC: American Society for Microbiology; 1987.

Inoculum Effect of Vancomycin with *Staphylococcus aureus* in neutropenic mice at 10^5 and 10^7 CFU, opposite thighs



D. Lee, Y. Murakami, T. Stamstad, K. Marchillo, J. Ashbeck, D. R. Andes, W. A. Craig. Abstract # A-37. ICAAC 2007

In Vivo PD of Vancomycin against VSSA: Neutropenic Murine Thigh-Infection Model



*Starting inoculum $10^{6.1\text{-}6.9}$ CFU/thigh

Free drug $AUC_{0\text{-}24}$/MIC for a Static Effect with Various Staphylococci

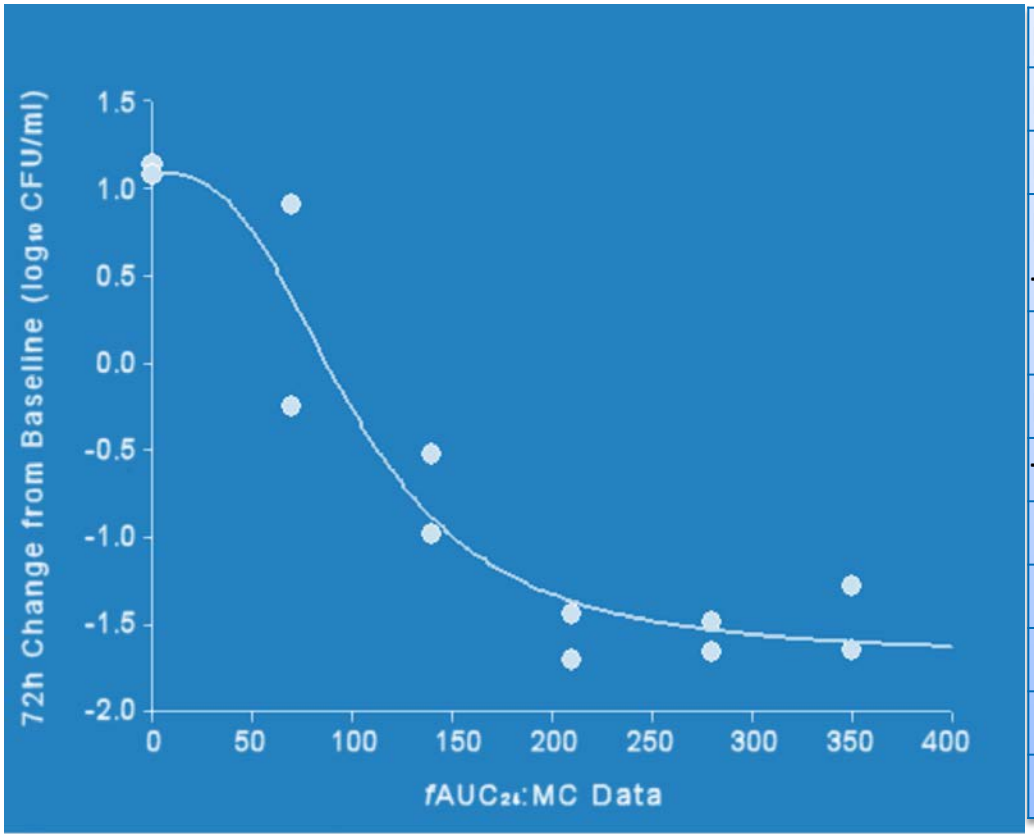
VSSA*	**157-263**

- fAUC/MIC upwards of 400-500 were required for a 2-log reduction

Similar does-response studies performed with 2 of 3 strains at a 1.0 to 1.3 log lower inoculum: 46-87% reduction in the magnitude of the static dose.

Craig WA, Andes DR..Abstract A-64. 46th ICAAC.San Francisco, CA: 2006 Sep.

Vancomycin PK-PD Targets in in Vitro PD Model against MRSA*

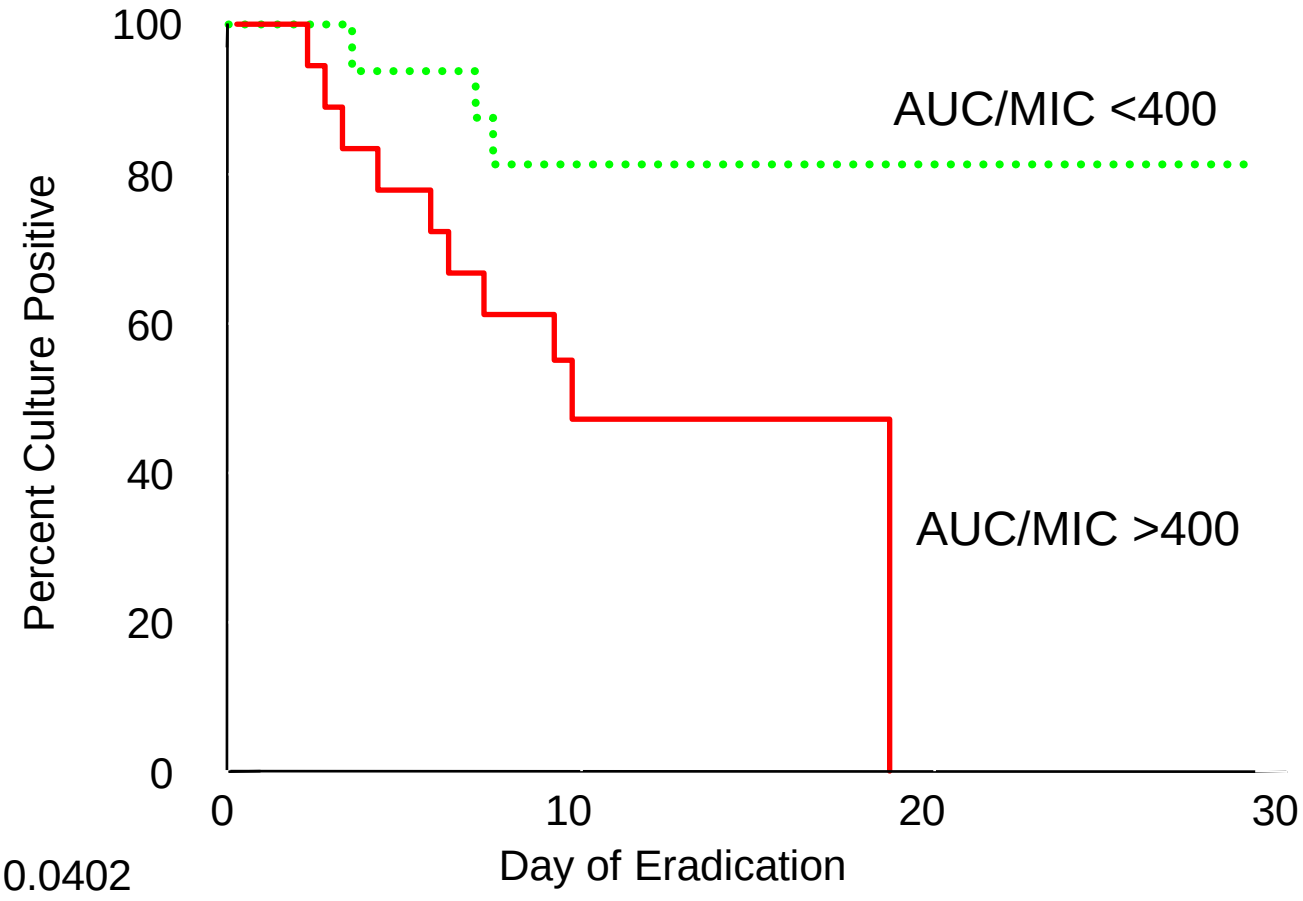


Model Fit Parameter	Estimate
Effect at 0 mg/L*h	2.28
Hills Constant (Slope)	2.81
Maximal Effect (Change from Control)	-2.77
PK-PD TARGET	
fAUC:MIC to achieve:	
-0.5 Log_{10} CFU/ml	113
-1.0 Log_{10} CFU/ml	151
-1.5 Log_{10} CFU/ml	260
-2.0 Log_{10} CFU/ml	Not Achievable
-3.0 Log_{10} CFU/ml	Not Achievable

*Two agr-functional, group II MRSA clinical isolates obtained from patients with a bloodstream infection (MIC 1.0 mg/liter) at a high inoculum of 10^8 CFU/ml.

Harigaya Y, Bulitta JB, Forrest A, Sakoulas G, Lesse AJ, Mylotte JM, Tsuji BT. *Antimicrob Agents Chemother.* 2009 Sep;53(9):3894-901.

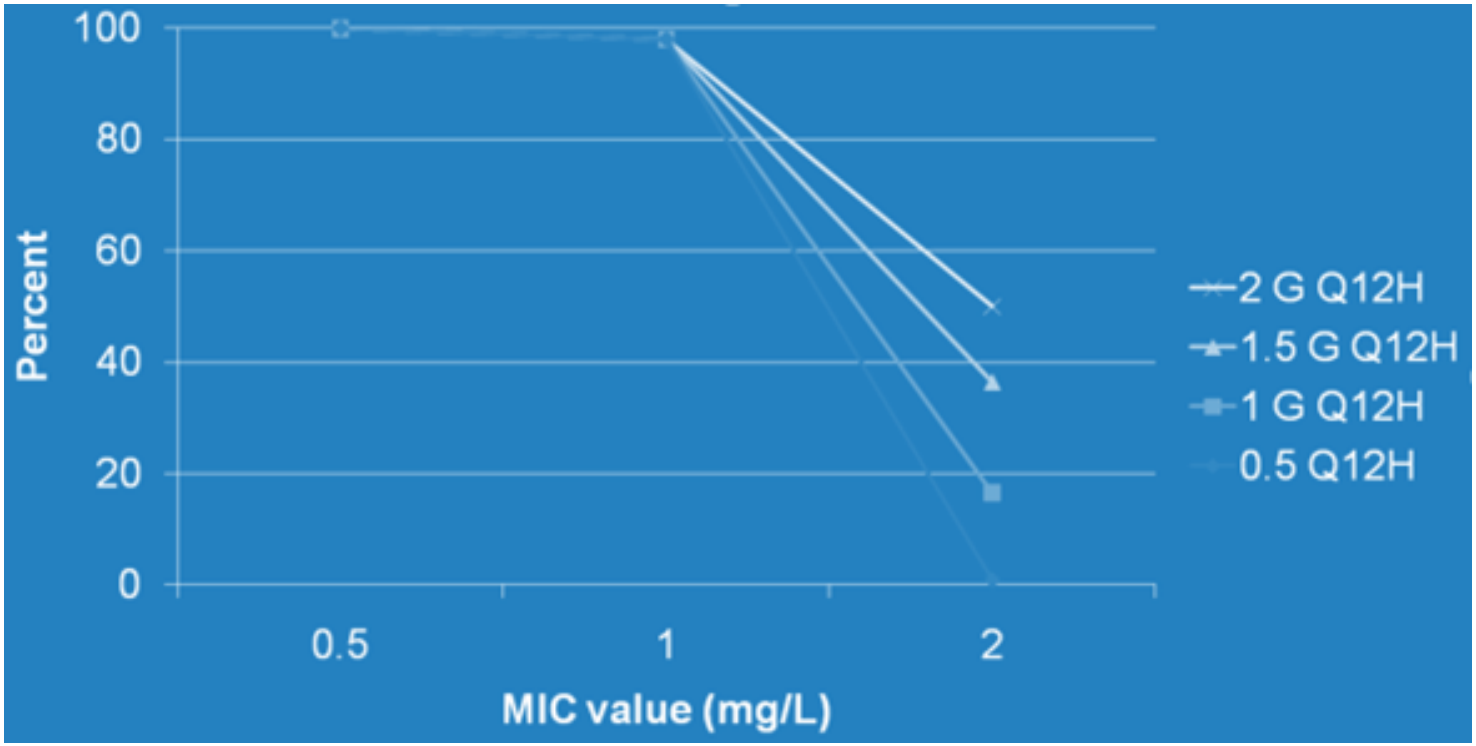
Vancomycin Pharmacodynamics in Patients with *S. aureus* Pneumonia



P = 0.0402

Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. *Clin Pharmacokinet.* 2004;43:925-942.

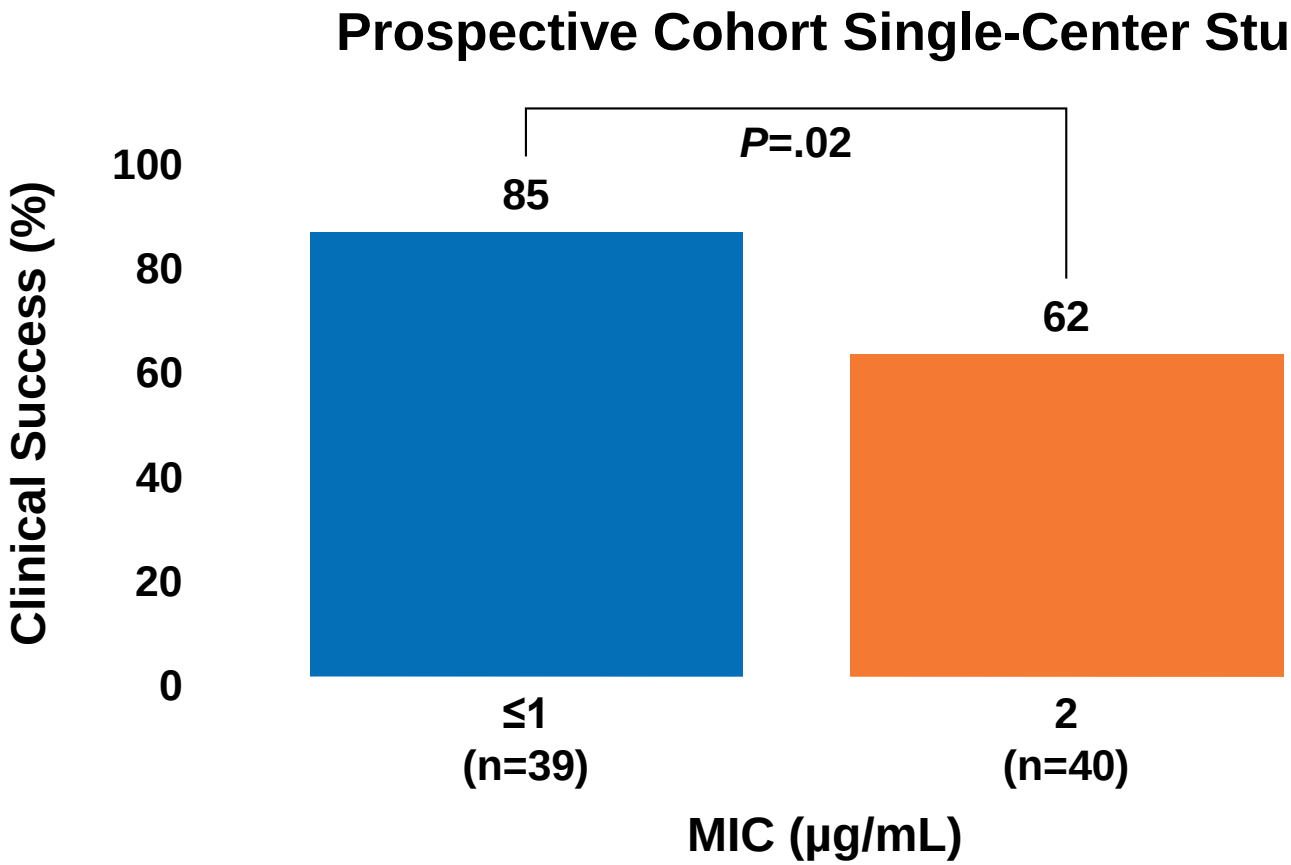
Probability of AUC/MIC ratio ≥ 400 for vancomycin regimens of varying intensity when Cmin is between 15 and 20 mg/L



Among the 9,999 subjects simulated, the total number of subjects with Cmin values 15 – 20 mg/L were: a) 406 subjects(0.5G Q12h); b) 1100 subjects (1G Q12h); c) 1190 subjects (1.5G Q12h); d) 1096 subjects (2G Q12h)

Patel N et al. *Clin Infect Dis*. 2011 Apr 15;52(8):969-74

Increasing the Dose of Vancomycin to Reach Higher Trough Levels May Not Improve Clinical Outcomes



Target vancomycin trough levels, 15 to 20 µg/mL

Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections. *Arch Intern Med*. 2006;166:2138-2144.

Relationship between Troughs and Outcomes: Invasive MRSA Infections

- The clinical benefits of maintaining higher vancomycin trough values 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%
- A growing number of studies have found increased rates of acute kidney injury with the use of intensive vancomycin regimens aimed at achieving trough in excess of 15 mg/L.[8]

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

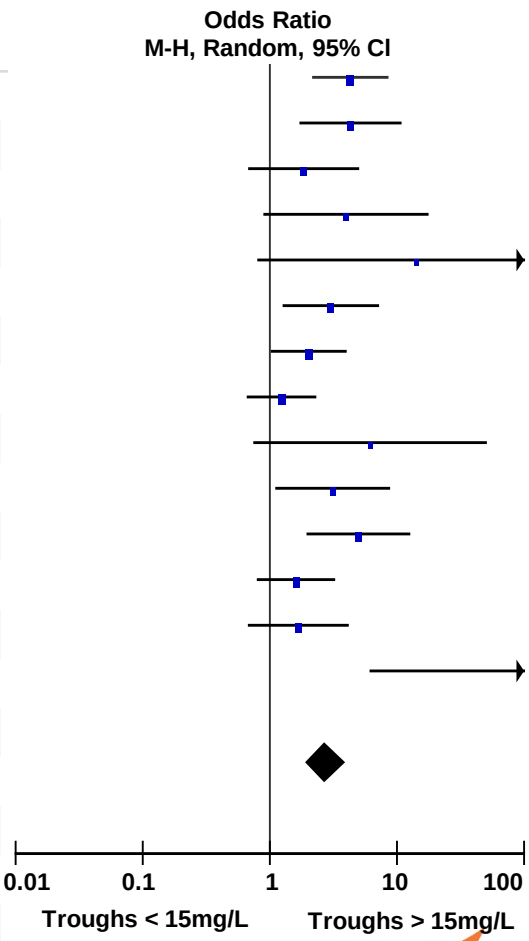
Vancomycin-Induced Nephrotoxicity

In the "15-20 mg/L" Trough Era: A Systematic Review and Meta-Analysis

	Troughs ≥15 mg/L		Troughs < 15 mg/L			Odds Ratio M-H, Random, 95% CI
Study or Subgroup	Events	Total	Events	Total	**Weight**	
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			

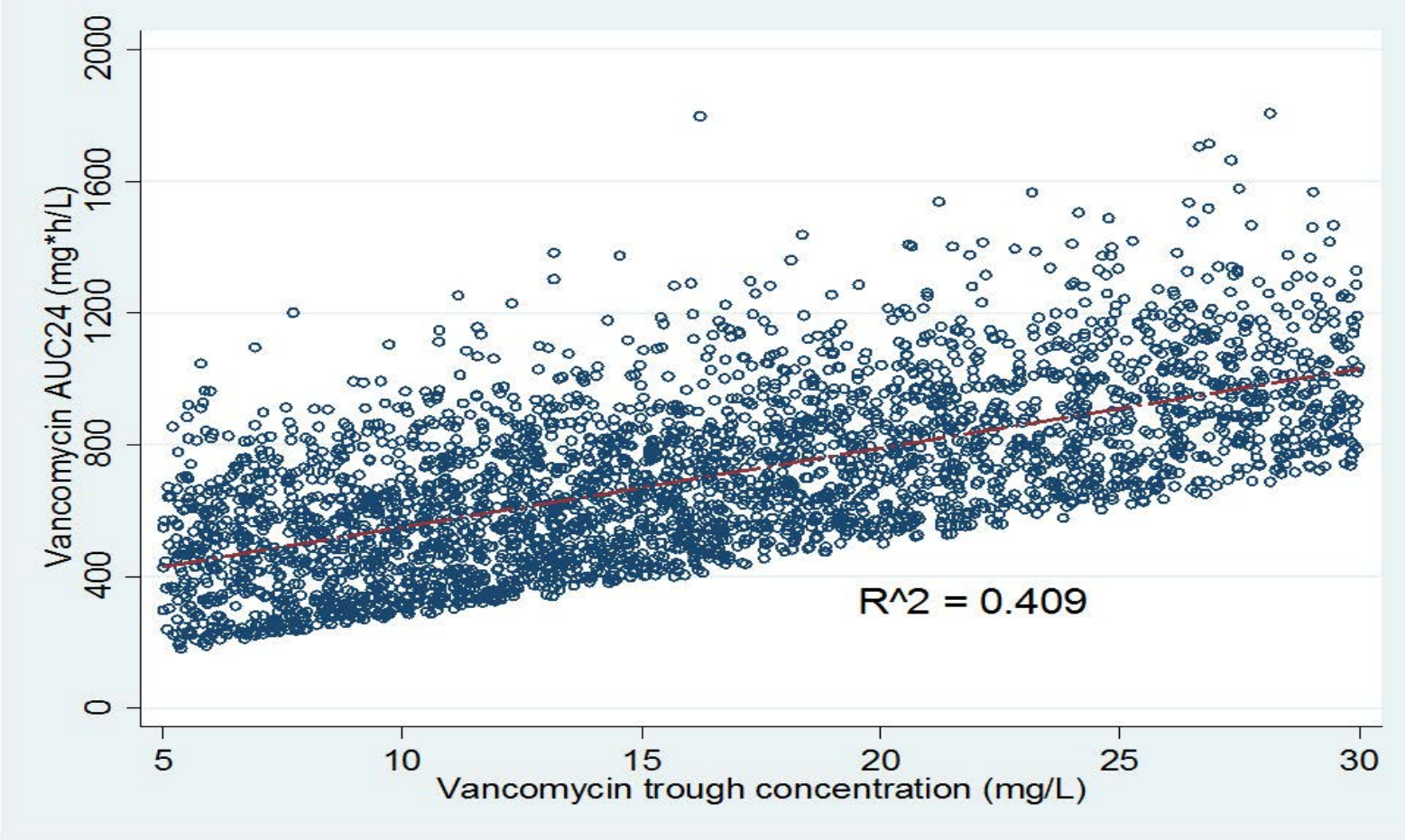
Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 23.80$, df = 13 (P = 0.03); $I^2 = 45\%$

Test for overall effect: Z = 5.66 (P < 0.00001)



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

Relationship between the Vancomycin Trough Value and $AUC_{0\text{-}24hours}$



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*

Limited Data in Support of AUC/MIC ratio of ≥ 400

- Data, albeit limited, from the neutropenic mouse thigh infection model indicate that the bactericidal activity of vancomycin is maximized when AUC/MIC > 400.[1]
  - It is unclear if data from this pre-clinical infection model is predictive of patient outcomes for bloodstream infections.
- Limited clinical data in support of the AUC/MIC ratio > 400 target among patients with invasive infections due to MRSA.[2-4]
- Importantly, most published vancomycin exposure-response clinical evaluations[2-4] 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.

1. Craig WA. *Infect Dis Clin North Am*. Sep 2003;17(3):479-501. 2. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. *Clinical pharmacokinetics.* 2004;43(13):925-942. 3. Kullar R, Davis SL, Levine DP, Rybak MJ. *Clinical Infectious Diseases*. Apr 15 2011;52(8):975-981. 4. Holmes NE, Turnidge JD, Munckhof WJ, et al. *Antimicrob Agents Chemother.* Apr 2013;57(4):1654-1663.

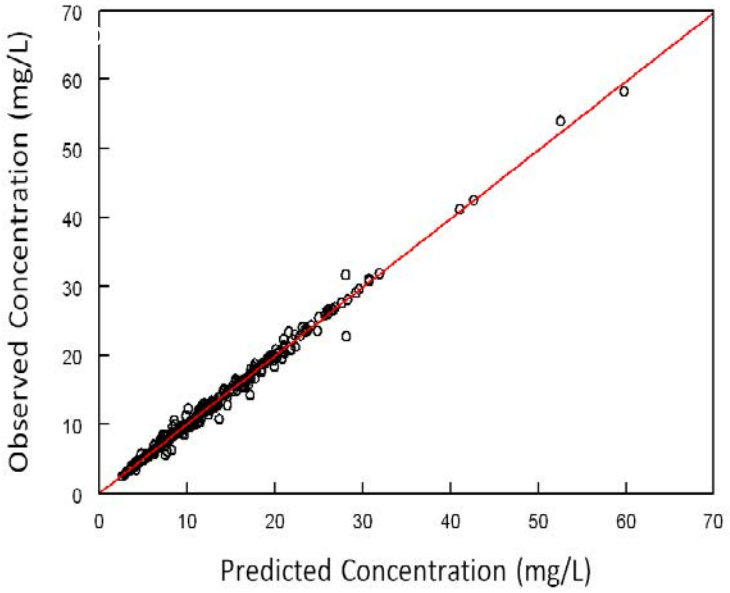
Effect of the Vancomycin Exposure Profile on the Outcomes of Patients with MRSA Bloodstream Infections

- Using a validated Bayesian method to estimate the vancomycin exposure profile with limited vancomycin blood concentration data[1], Lodise and colleagues evaluated the relationship between vancomycin exposure and failure among a retrospective cohort of hospitalized, adult patients with MRSA bloodstream infections at an academic medical center.[2]
- Given the time-critical nature of the first 48 treatment hours for MRSA bloodstream infections[3], they assessed the relationships between day 1 and day 2 vancomycin exposure variables (Cmin/AUC and AUC/MIC) and failure.
  - Considered both broth micro-dilution MICs and ETEST™ MICs
  - Failure defined as any one of the following: 30-day mortality, bacteremia > 7 days, or recurrence <60 days of completing therapy

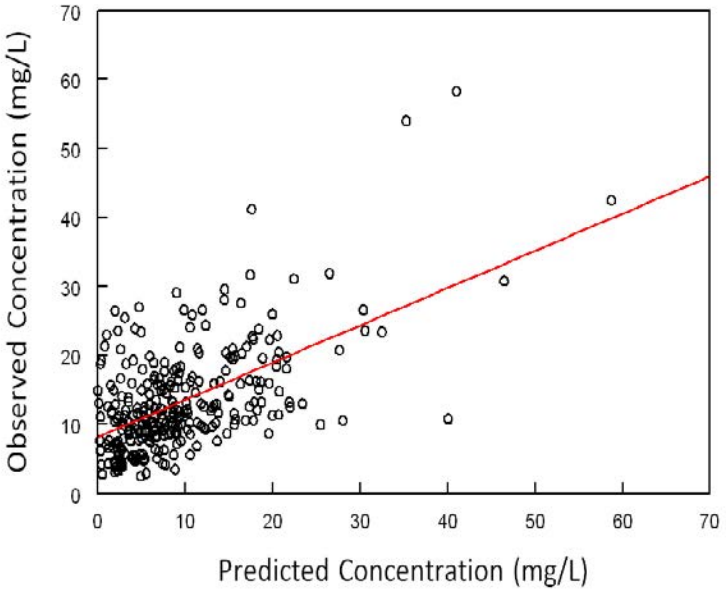
1. Neely MN, Youn G, Jones B, et al. Are vancomycin troughs adequate for optimal dosing? *Antimicrob Agents Chemother* 2014;58:309-16. Lodise TP, McKinnon PS, Swiderski L, Rybak MJ. Clin Infect Dis 2003 Jun 1;36(11):1418-23. Lodise TP, McKinnon PS, Swiderski L, Rybak MJ. *Clin Infect Dis* 2003;36:1418-23.

Observed vs. Predicted Plots for MAP-Bayesian and Formula-Based Estimation Approaches

MAP-Bayesian Approach

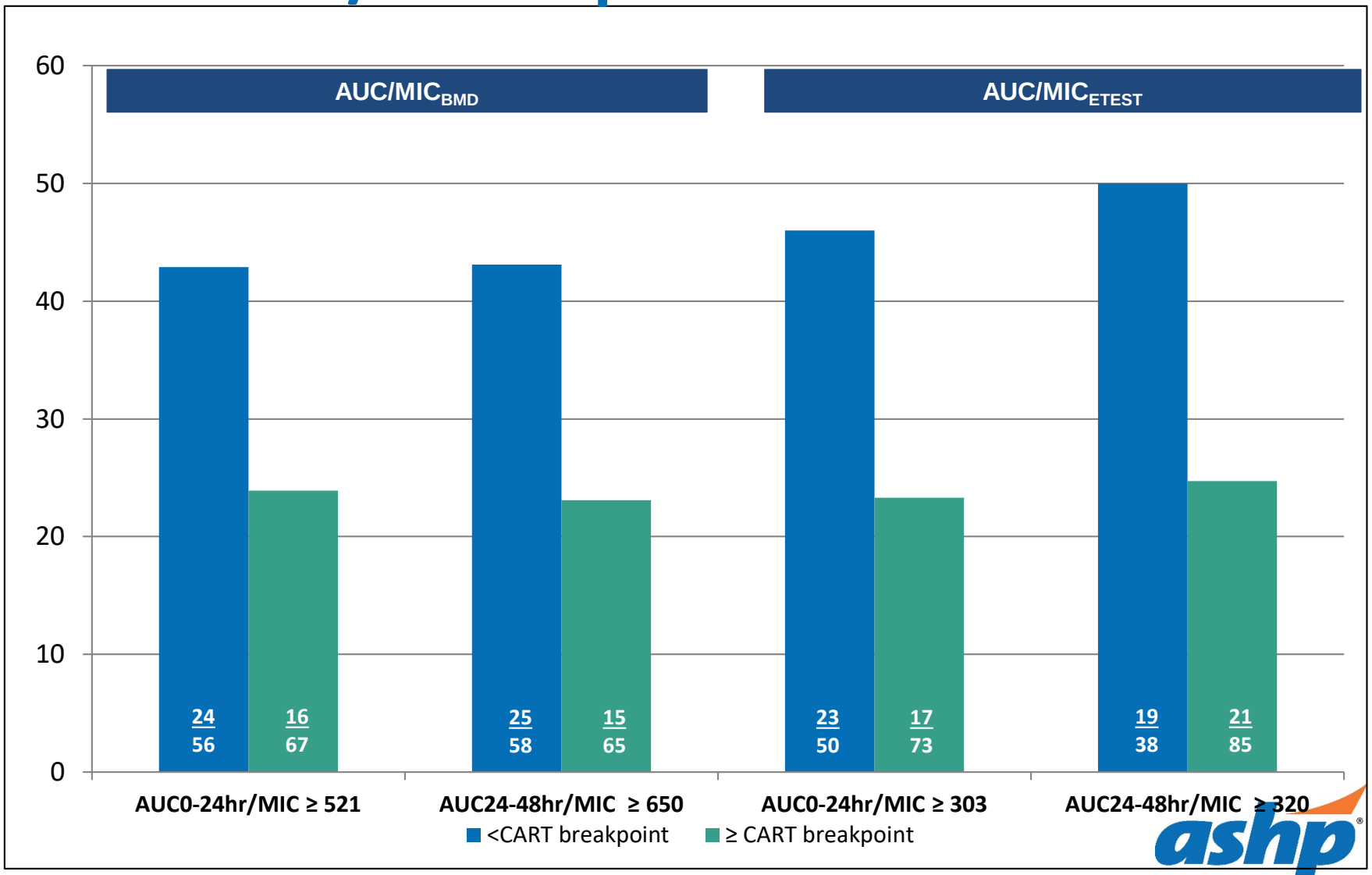


Formula-Based Approach



Lodise TP, Drusano GL, Zasowski E, Dihmess A, Lazariu V, Cosler L, McNutt LA. *Clin Infect Dis. 2014 Sep 1;59(5):666-75*

Bivariate Rel. CART-Derived Day 1 and Day 2 AUC/MIC Exposures and Failure



Lodise TP, Drusano GL, Zasowski E, Dihmess A, Lazariu V, Cosler L, McNutt LA. *Clin Infect Dis. 2014 Sep 1;59(5):666-75*

Rel. between CART-Derived AUC Exposure Variables and Outcomes: Poisson Regression

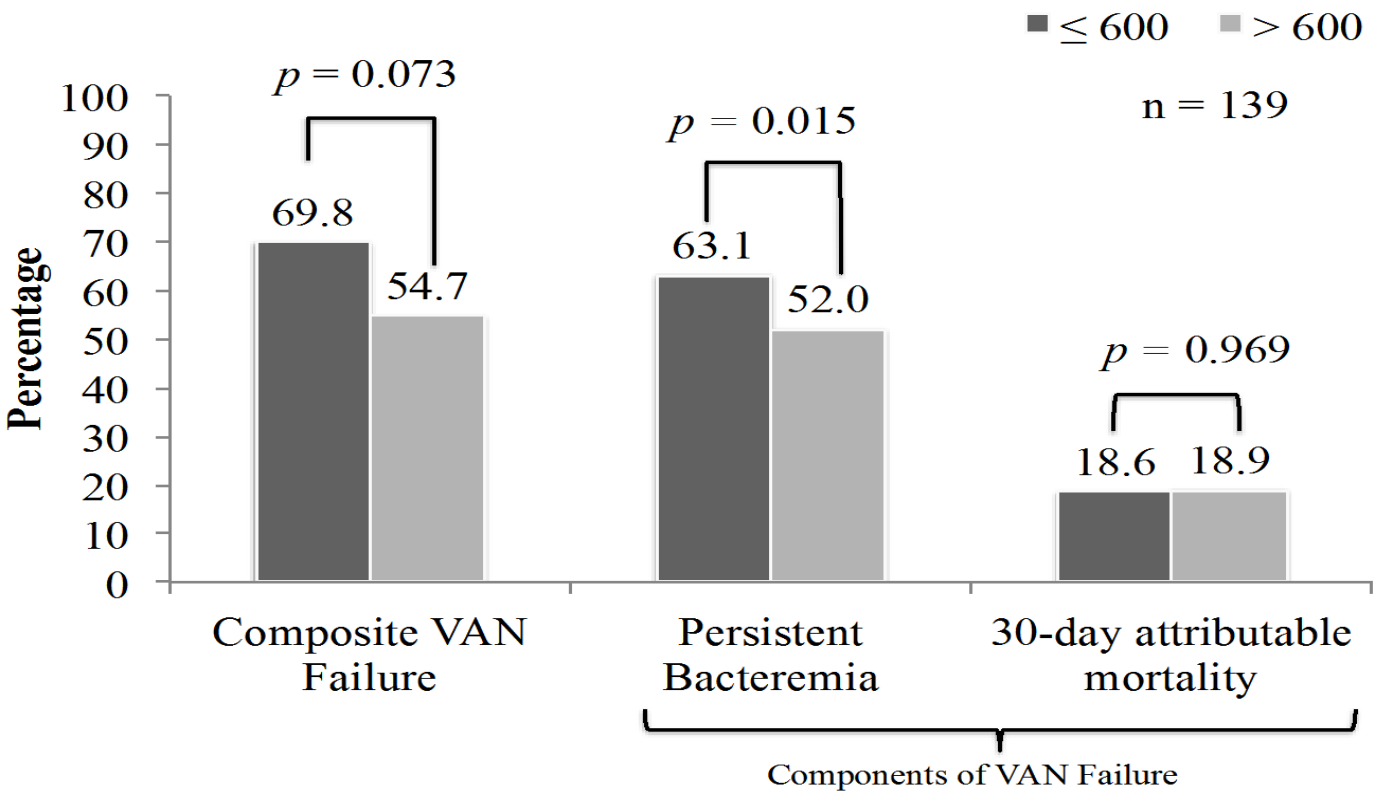
	Exposure	Overall Failure*			30-Day Mortality**		
		RR	95% CI	P-value	RR	95% CI	P-value
Day 1	$AUC_{0\text{-}24hr}$ / MIC_{BMD} ≥ 521	0.54	0.32-0.91	.02	0.43	0.20-0.90	.03
	$AUC_{0\text{-}24hr}$ / MIC_{ETEST} ≥ 303	0.48	0.29-0.78	.003	0.32	0.16-0.64	.001
Day 2	$AUC_{24\text{-}48hr}$/MIC_{BMD} ≥ 650	0.58	0.34-0.99	.05	0.50	0.25-1.02	.06
	$AUC_{24\text{-}48hr}$/MIC_{ETEST} > 320	0.53	0.32-0.88	.01	0.49	0.24-0.98	.04

*All variables associated with failure at P ≤ 0.2 and considered at model entry included: P-value ≤ 0.2 included: APACHE-II score, chronic obstructive pulmonary disease, diabetes mellitus, malignancy, recent prior surgery, MIC_{ETEST} ≥ 1.5 mg/L, and cumulative number of reduced vancomycin susceptibility phenotypes.

** Baseline covariates associated with 30-day mortality at P ≤ 0.2 and considered at model entry included: Baseline covariates associated with 30-day mortality at a P-value ≤ 0.2 included: APACHE-II Score, malignancy, MIC_{ETEST} ≥ 1.5 mg/L, MIC_{BMD} ≥ 1 mg/L, and MBC/MIC ratio > 4.

Lodise TP, Drusano GL, Zasowski E, Dihmess A, Lazariu V, Cosler L, McNutt LA. *Clin Infect Dis. 2014 Sep 1;59(5):666-75*

The Association between the Vancomycin Day 1 AUC and Outcomes Among Patients with MRSA Infective Endocarditis

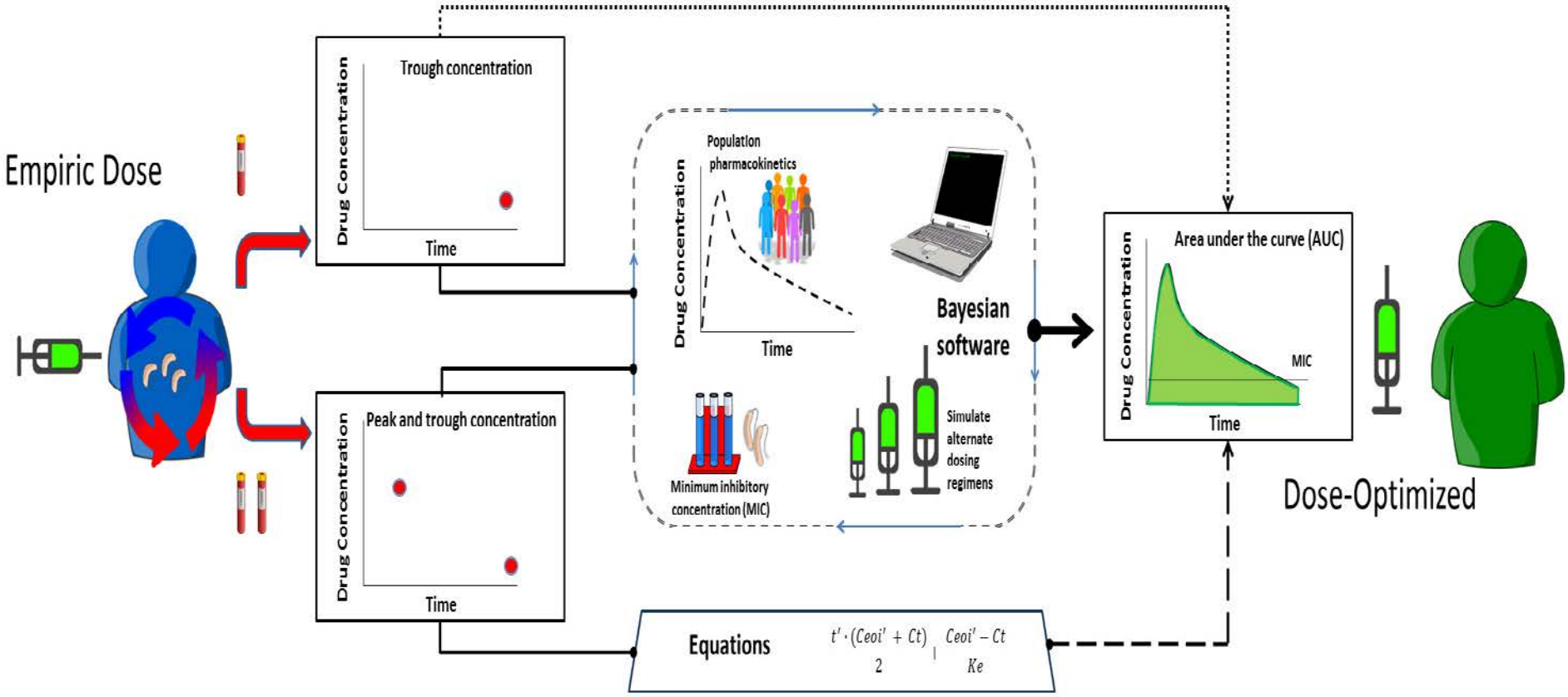


Casapao AM, Lodise TP, Davis SL, Claeys KC, Kullar R, Levine DP, Rybak MJ . *Antimicrob Agents Ch* 2015 Jun;59(6):2978-85.

Vanco PK/PD Targets from Clinical Evaluations using Bayesian AUC Estimation

- Brown, J. et al. *AAC* 2012
  - 50 Patients with MRSA IE/attributable mortality
    - o AUC/MIC$_{(Etest)}$ at steady state $\geq$ 211 –Bayesian???
- Jung, Y et al. *Int J Antimicrob Agents* 2014
  - 76 patients with MRSA bacteremia/30 day all cause mortality
    - o AUC/MIC$_{(BMD)}$ at steady state$\geq$ 430 –Bayesian
    - o AUC/MIC$_{(Etest)}$ at steady state$\geq$385
- Song, K, et al. *Int J Antimicrob Agents* 2015
  - 117 patients with MRSA bacteremia –composite – clearance, mortality, >7 days BS
    - o AUC/MIC$_{(BMD)}$ at steady state>392.7 – Bayesian
    - o AUC/MIC$_{(Etest)}$ at steady state >397.2
- Gawronski KM, et al. Clinical therapeutics 2013
  - 59 patients with MRSA bacteremia and MRSA osteomyelitis-time to microbiologic clearance
    - o AUC/MIC$_{(Etest)}$ at steady state >293 – Bayesian

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 (PKs) 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. Approaches to Optimizing the Delivery of Vancomycin in Individual Patients. *Adv Drug Deliv Rev. 2014 Jun 5. pii: S0169-409X(14)00128-8*

Advantages of Bayesian Approach to AUC Estimation

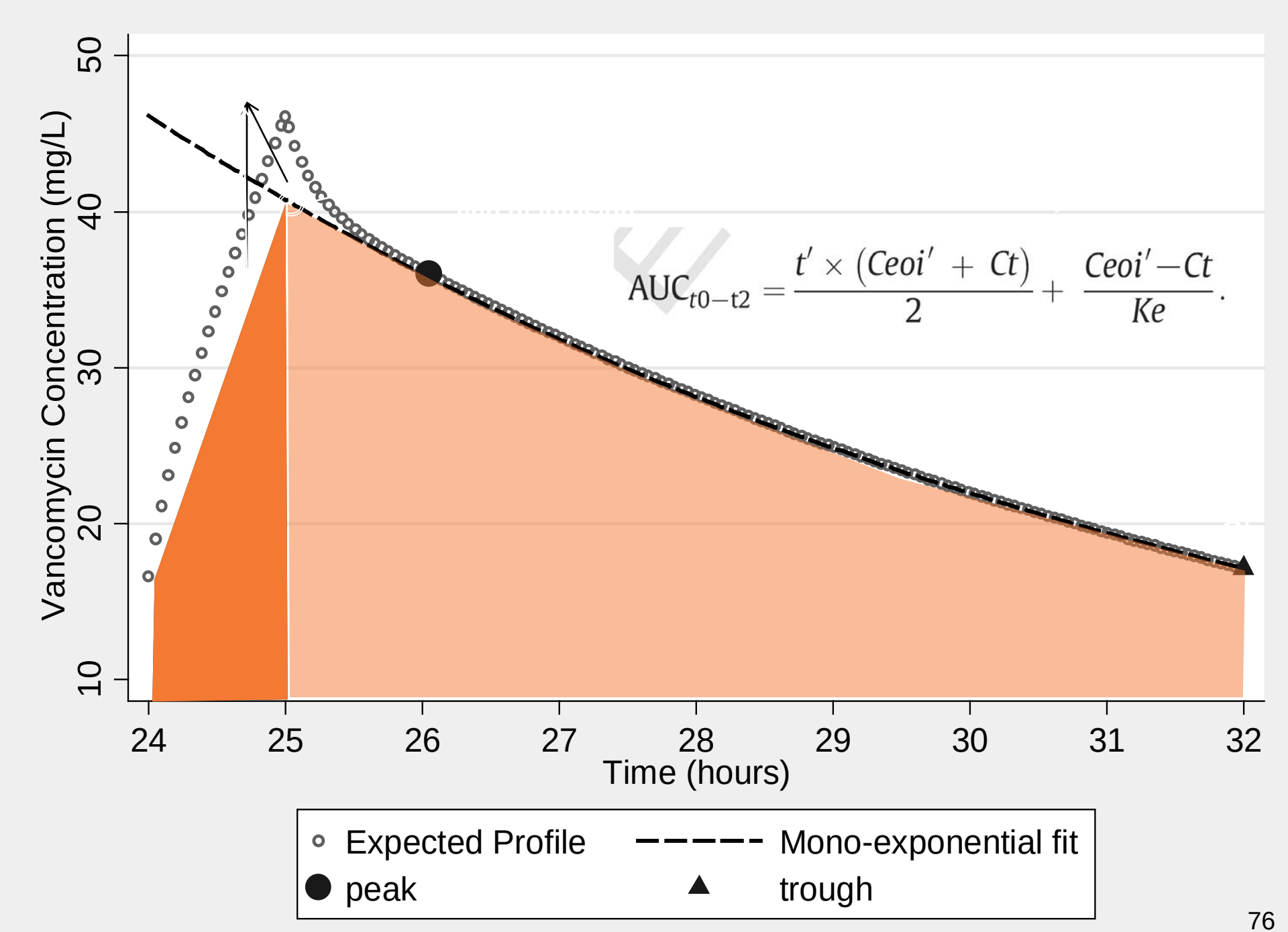
- Only requires trough data to accurately estimate the AUC.
- Innovative treatment schemas, such as front-loading doses with a transition to a lower maintenance dosing regimen, can be designed to rapidly achieve target concentrations within the first 24 to 48 hours among critically ill patients.
- Concentration-time 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.

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*

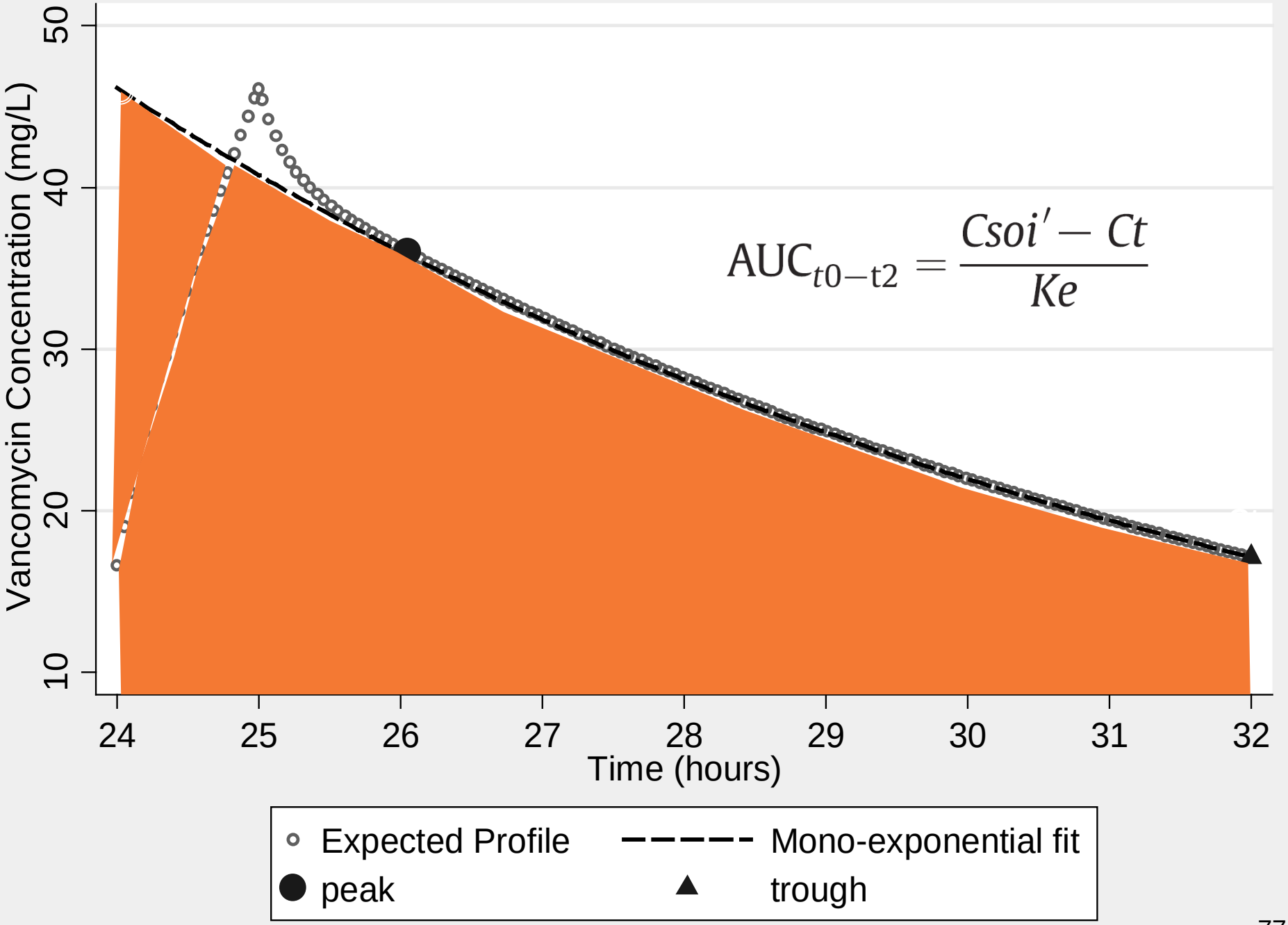
Equation-Based Approach to AUC Estimation

- Use of a post-distributional peak (1-2 hours post infusion) and trough concentrations can inform 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. Approaches to Optimizing the Delivery of Vancomycin in Individual Patients. *Adv Drug Deliv Rev. 2014 Jun 5. pii: S0169-409X(14)00128-8*



Pai MP, Neely M, Rodvold KA, Lodise TP. Adv Drug Deliv Rev. 2014 Jun 5. pii: S0169-409X(14)00128-8. doi: 10.1016/j.addr.2014.05.016.



Pai MP, Neely M, Rodvold KA, Lodise TP. Adv Drug Deliv Rev. 2014 Jun 5. pii: S0169-409X(14)00128-8. doi: 10.1016/j.addr.2014.05.016.

Valid Estimation of Vancomycin AUC with Trough-only Data using Bayesian Est. 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

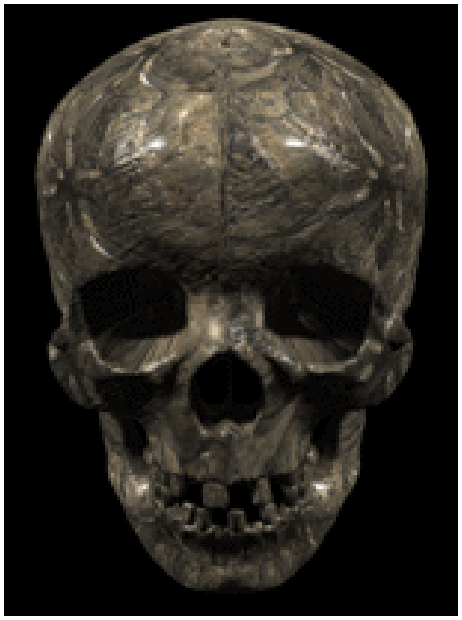
Neely MN, Youn G, Jones B, et al. Are vancomycin troughs adequate for optimal dosing? Antimicrob Agents Chemother 2014;58:309-16.
Pai MP, Neely M, Rodvold KA, Lodise TP. Approaches to Optimizing the Delivery of Vancomycin in Individual Patients. *Adv Drug Deliv Rev. 2014 Jun 5. pii: S0169-409X(14)00128-8*

Summary

- Further studies are needed to determine if optimization of vancomycin therapy can improve outcomes without subjecting patients to an increased risk of vancomycin-related toxicities
  - Must determine PK/PD targets for efficacy and toxicity to truly optimize vancomycin dosing and evaluate its PK/PD profile
- Drug entities that exploit new targets are available
- Our challenge is to appropriately place these new antimicrobials in roles that are suitable to optimize strengths, minimize weaknesses, and (hopefully) prevent emergence of resistance

Section End

Vancomycin is Clinically Dead



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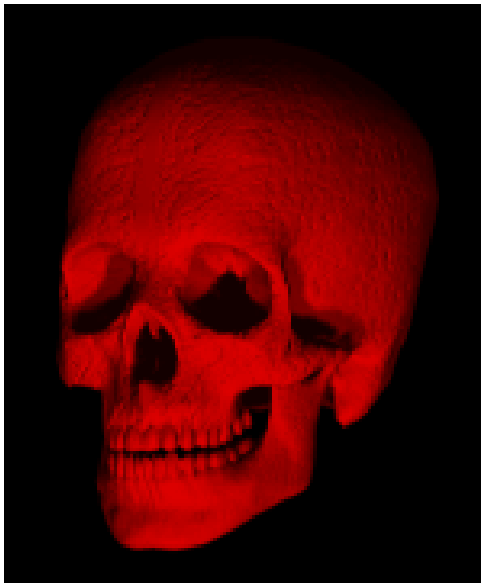


ashp
MIDYEAR2016
Clinical Meeting & Exhibition

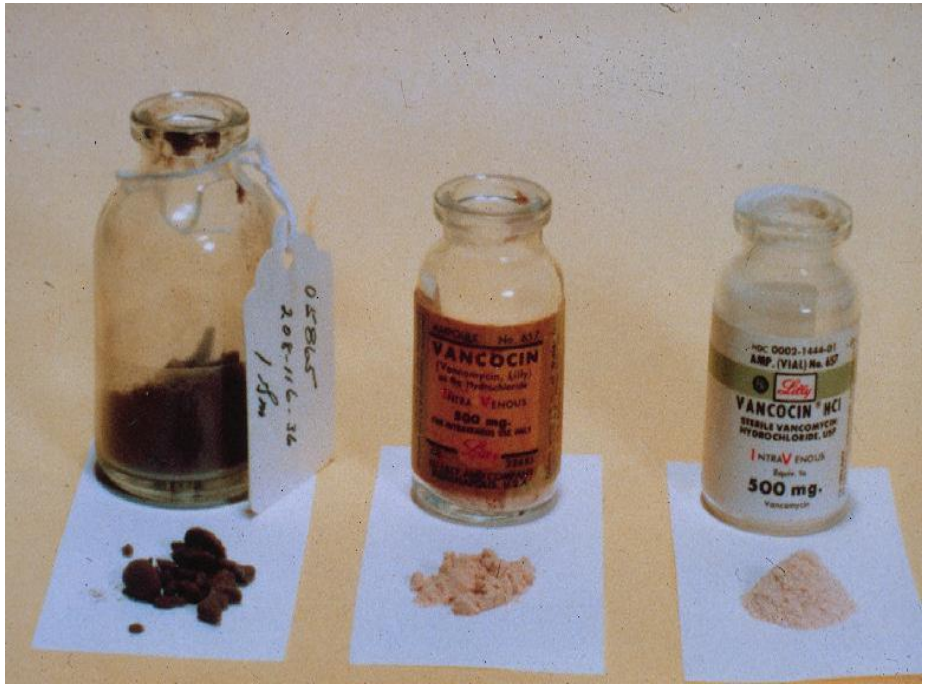
Disclosures/Acknowledgments

- Currently receiving grant support, serve as a speaker or consultant for the following:
  - Accelerated Diagnostics
  - Allergan
  - Bayer
  - Cempra
  - Melinta
  - Merck
  - The Medicine Company
  - National Institutes of Health
    - R21 AI109266-01 (PI)
    - R01 AI121400-01 (PI)
    - Contract: HHSN22201000039C (Co-Inv)
  - Theravance

Development of Vancomycin

- 1956: Screened for activity from soil sample obtained from Borneo
- Derived from *Streptomyces orientalis*
- Compound #05865 named vancomycin (derived from “vanquish”)
- Approved by FDA for clinical use in 1958
  - Limited clinical data

“Older than DIRT”



“Dubbed Mississippi Mud”

Vancomycin Historical Information

- Late 1950's-60: Broad use initially due to lack of effective therapy
- 1960's: Use decreased dramatically as semisyntheric penicillins became available and concerns over toxicity.
- 1970's-90's: Increased use due to increase in methicillin-resistant *S. aureus*

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

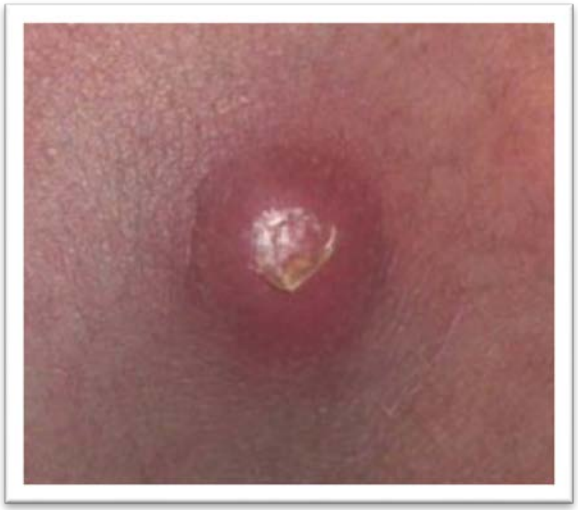
80,461
SEVERE MRSA INFECTIONS PER YEAR

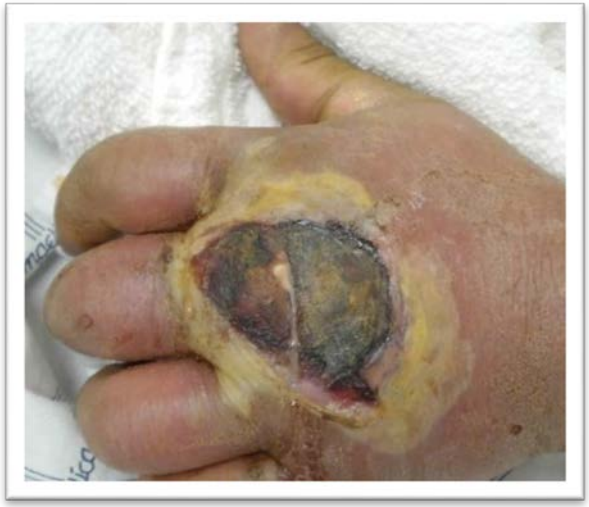
11,285
DEATHS FROM MRSA PER YEAR

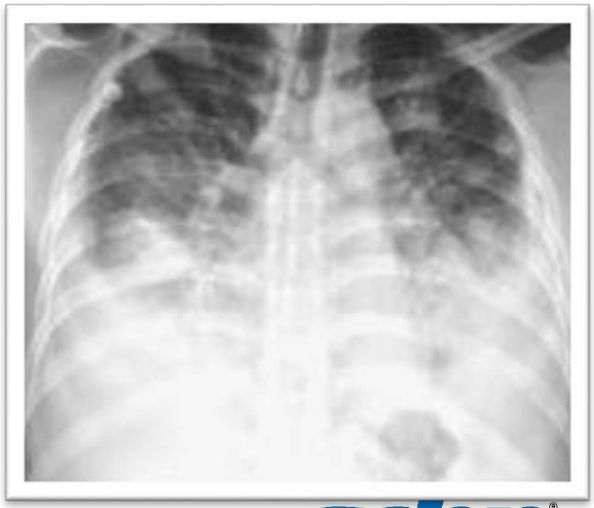
STAPH BACTERIA ARE A LEADING CAUSE OF
HEALTHCARE-ASSOCIATED INFECTIONS

THREAT LEVEL
SERIOUS

This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

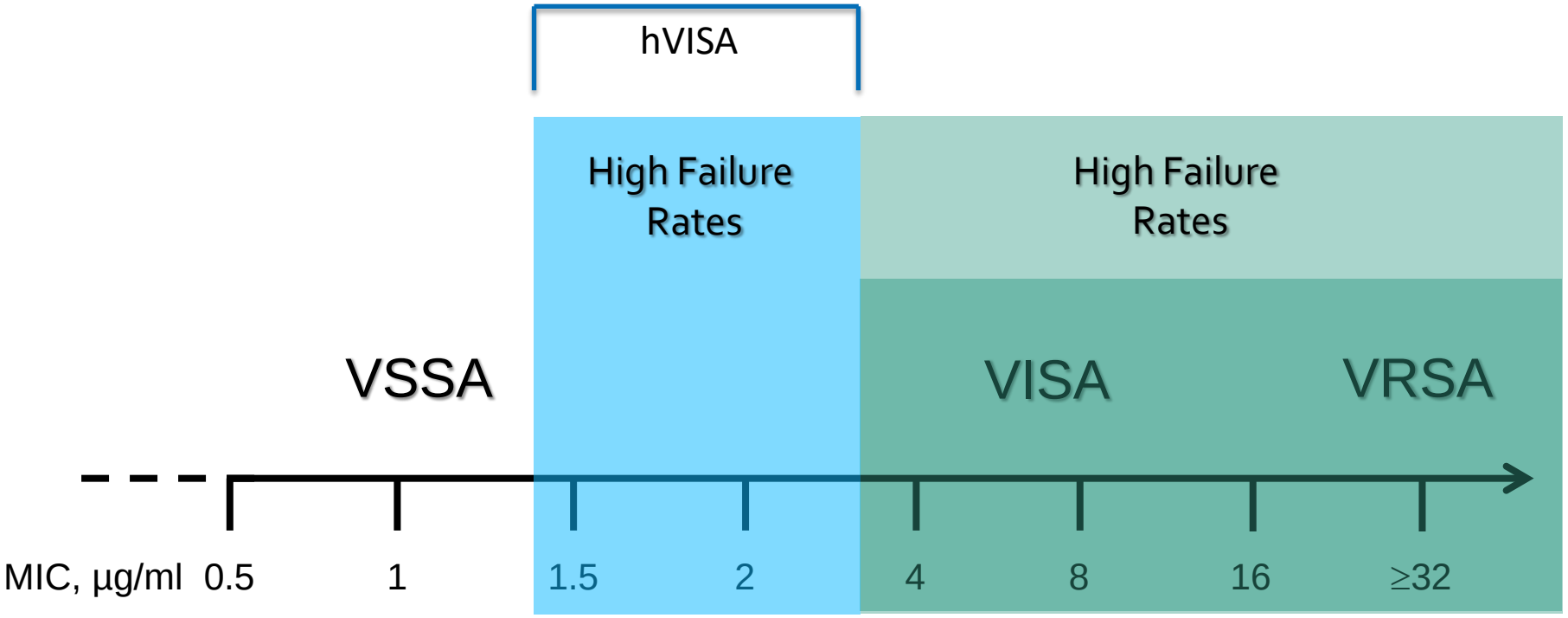






Centers for Disease Control and Prevention. Retrieved from: http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf

Vancomycin has been the Mainstay of Therapy for MRSA but it has Major Issues

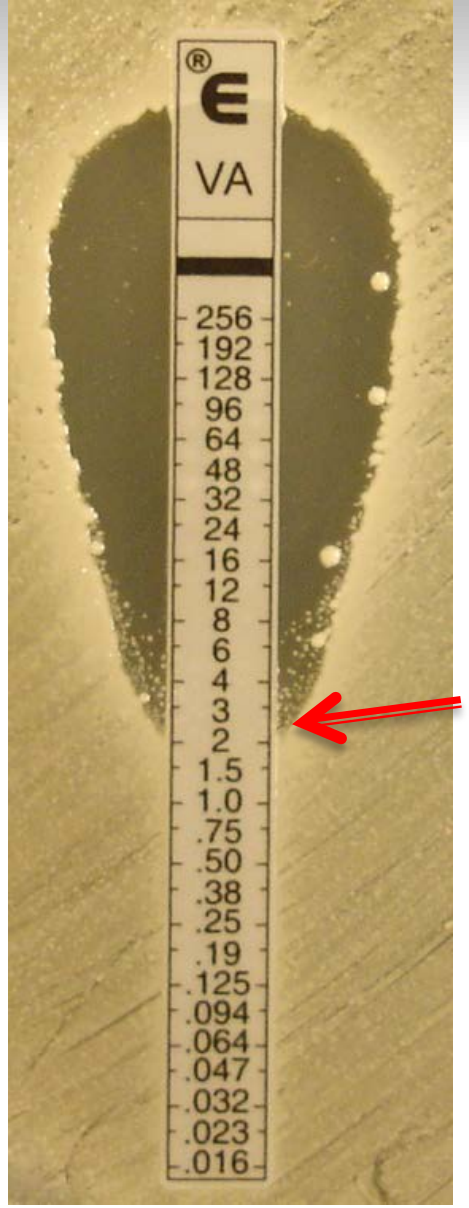


- The FDA revised vancomycin breakpoints in line with the CLSI

1. CLSI. Performance standards for antimicrobial susceptibility testing; eighteenth informational supplement. M100-S18, 2008
2. IDSA News, May 2008;18(5) (available at http://www.idsociety.org/newsArticle.aspx?id=11388)
3. Hiramatsu K. et al. J Antimicrob Chemother. 1997;40:135-6. Moore et al. *AAC* 2003;47:1262-66. Liu et al. *AAC* 2003;47:3040-45. Howden BP et al. CID 2004; 521-28. Wootton M. et al. J Clin Microbiol. 2007 Feb;45(2):329-32. Charles P.et al. CID 2004;38:448-51. Maor et al. *J Clin Microbiol*. 2007;45:1511-14. Rybak M. et al. *J Clin Microbiol*. 2008;46:2950-4. Maor Y. *J Infect Dis.* 2009;199:619-24. van Hal et al. *Antimicrob Agents Che*mother. 2011;55:405-10.

hVISA and Clinical Failure

- Low level resistance MIC = 0.5-2 mg/L
- Subpopulation analysis demonstrate
  - Growth on BHI agar 4-6 mg/L of vanco
  - Additional applied vancomycin pressure can increase the MIC further
- Not screened for by clinical laboratories
- hVISA associated with prolonged bloodstream infections & clinical failure
- Estimates rates of hVISA: 5-50.7%



Moore et al. *AAC* 2003;47:1262-66. Liu et al. *AAC* 2003;47:3040-45. Howden BP et al. CID 2004; 521-28. Wootton M. et al. J Clin Microbiol. 2007 Feb;45(2):329-32. Charles P.et al. CID 2004;38:448-51. Maor et al. *J Clin Microbiol*. 2007;45:1511-14. , Maor Y.G., et al., *J Clin Microbiol*. 2007;45:1511-14. Rybak M. et al. *J Clin Microbiol*. 2008;46:2950-54., Bae I.G., et al. *J Infect Dis*. 2009;200:1355-66., Maor Y.G., et al. J Infect Dis. 2009; 199:619-24., Musta A.C., et al. Vancomycin MIC plus heteroresistance and outcome of methicillin-resistant *Staphylococcus aureus* bacteremia: trends over 11 years. *J Clin Microbiol*. 2009;47:1640-44., van Hal S.J., *Antimicrob Agents Chemother*. 2011;55:405-10. Zhang S. et al. *Plos One* 2015; 10 (8): e0136082. Koh, YR. et al. *Ann Lab Med.* 2016; 36 (3): 235-43.

Photo courtesy of M. Rybak *ARL* WSU 2016

Clinical Outcomes in Patients with hVISA Bloodstream Infections

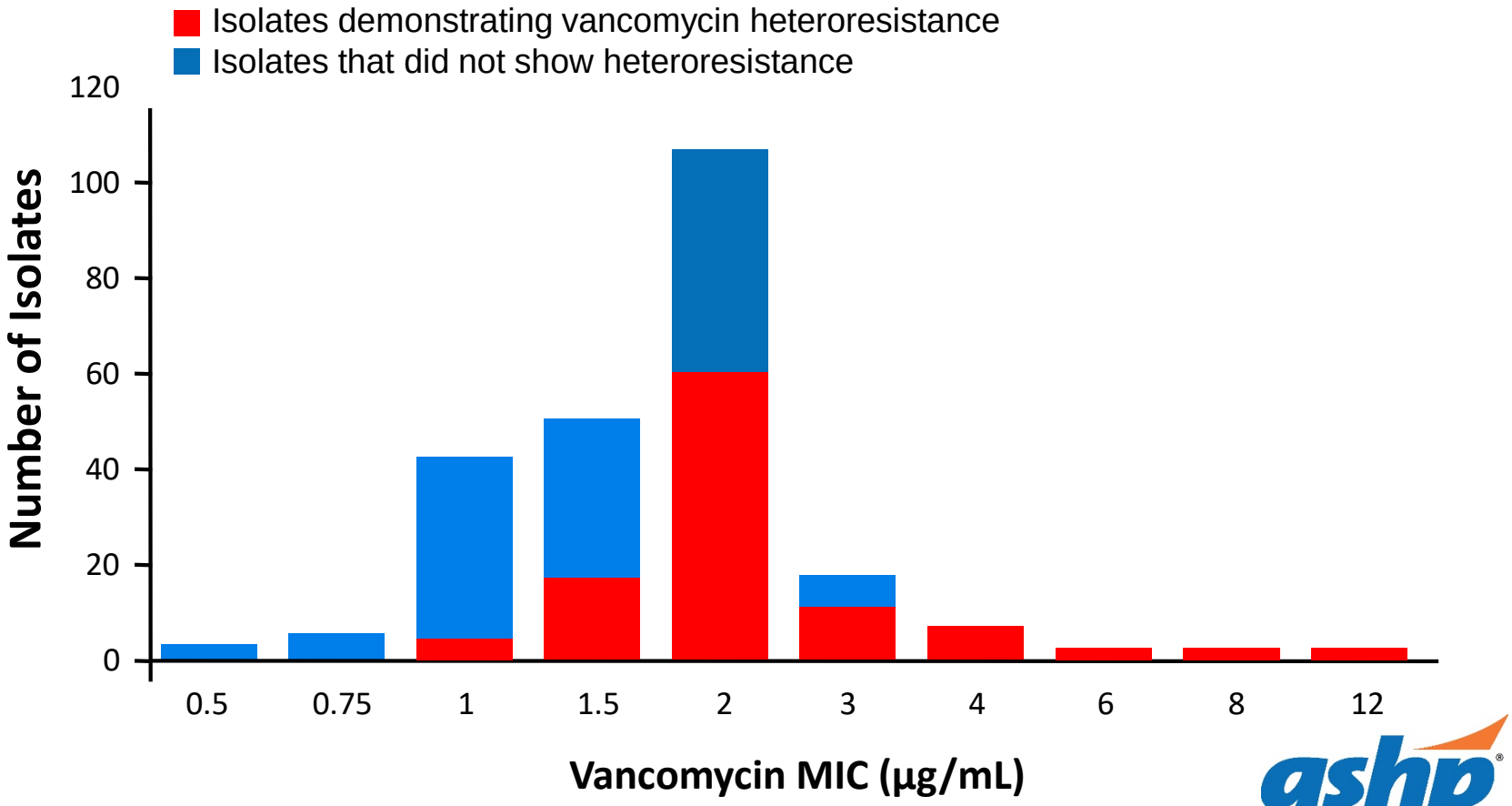
Logistic regression analysis of risk factors associated with vancomcycin treatment failure

Factor	Adjusted OR (95% CI)	P value
hVISA	11.14 (4.32-28.74)	< 0.001
Admission to ICU	4.51 (1.75-11.60)	0.002
High-risk Infection*	2.53 (1.00-6.39)	0.05

* Infection caused by infective endocarditis, pneumonia or bone & joint infection

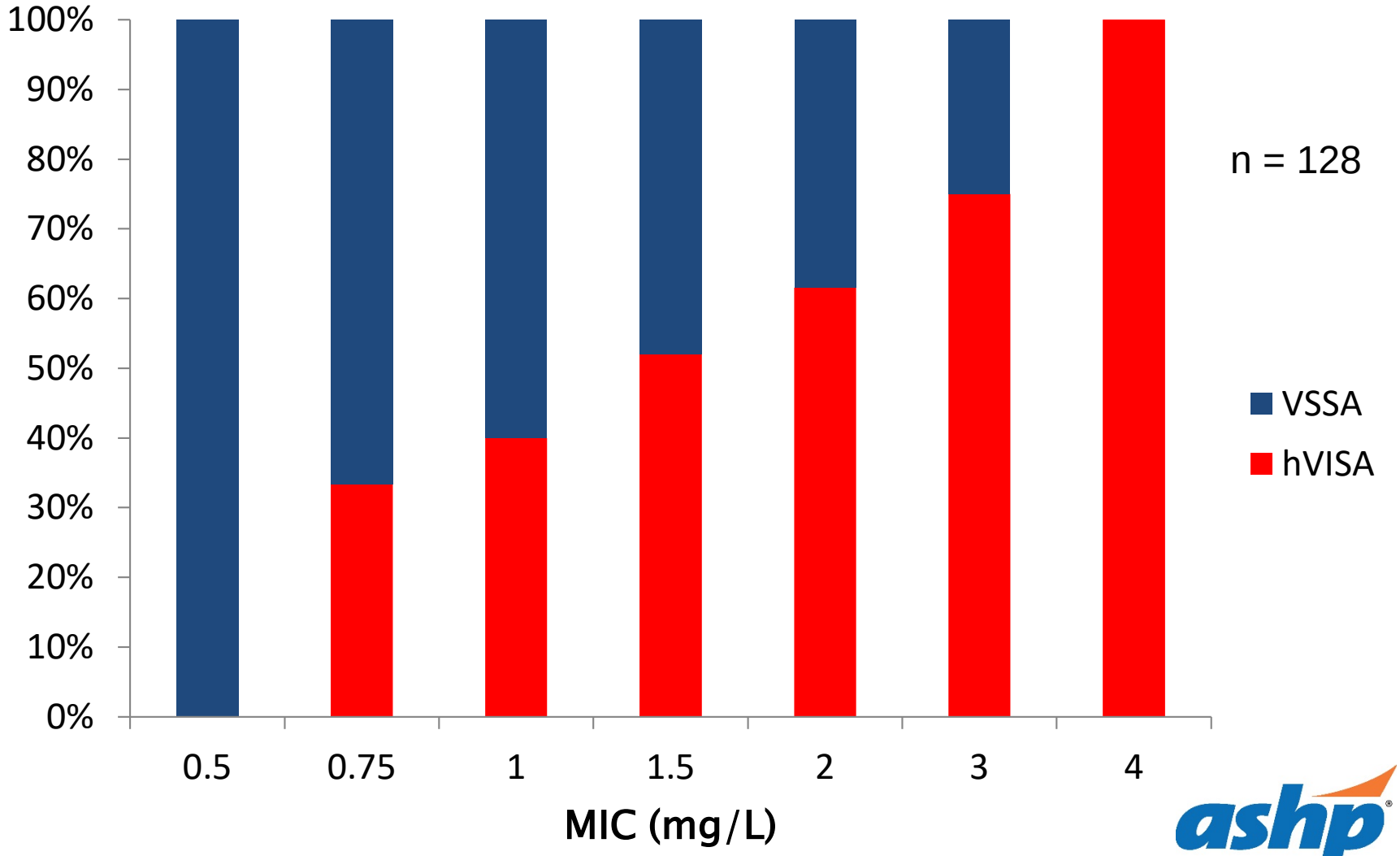
Casapao, A.M., et al. *Antimicrob Agents Chemother.* 2013; 57 (9): 4252-59.

Heteroresistance with Vancomycin in *S. aureus* is Seen with MICs as low as 1.0 µg/ml



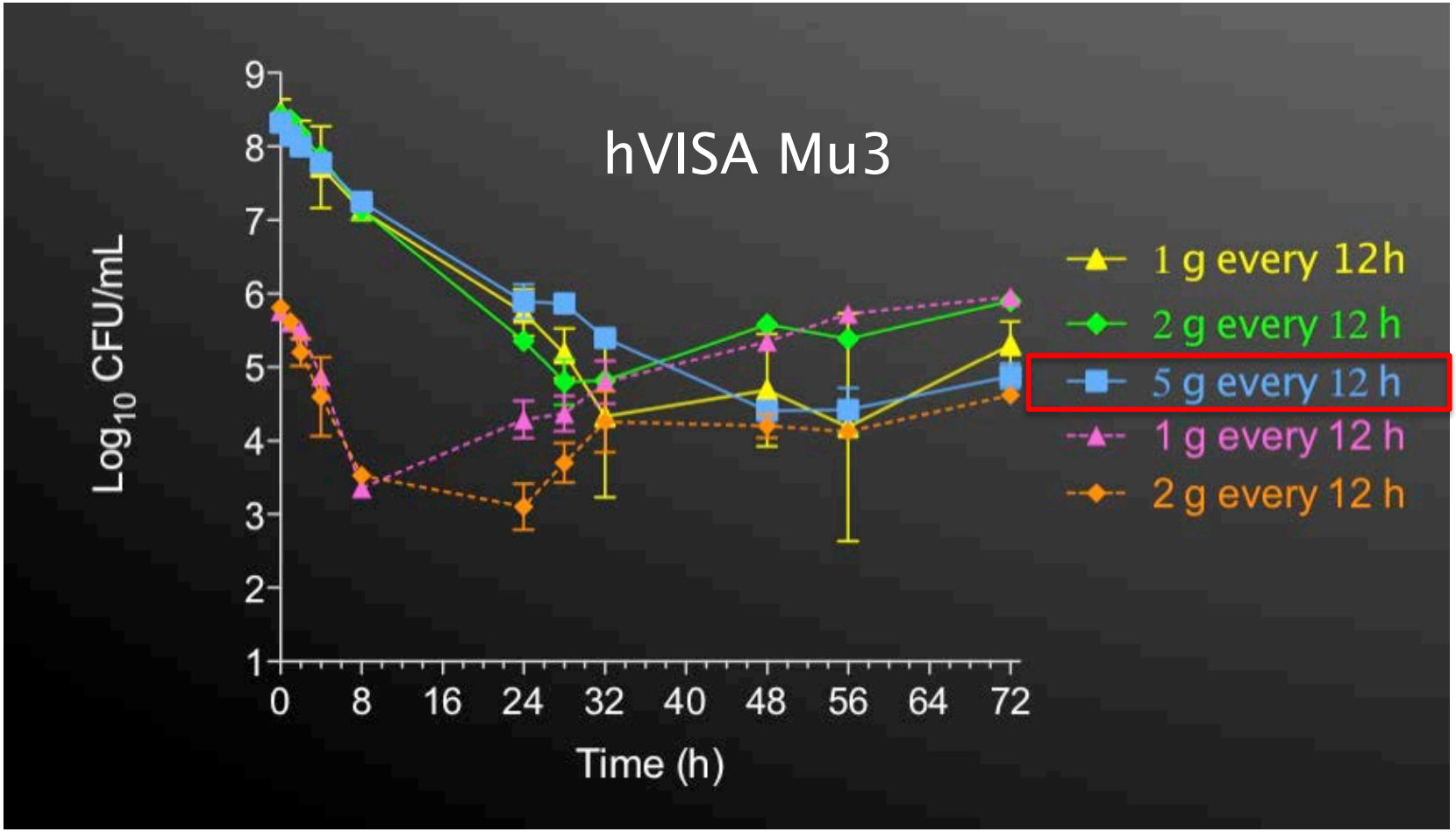
Adapted from: Tenover FC, Moellering RC.. *Clin Infect Dis.* 2007:44:1208-1215.

Etest MIC Distribution and hVISA



Casapao, A. et al. *Antimicrob Agents Chem*other. 2013,57, (9), 4252-9.

hVISA and Vancomycin Exposure

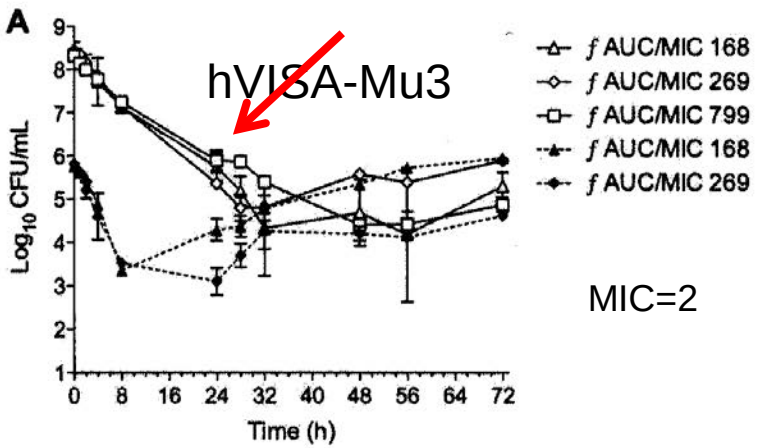


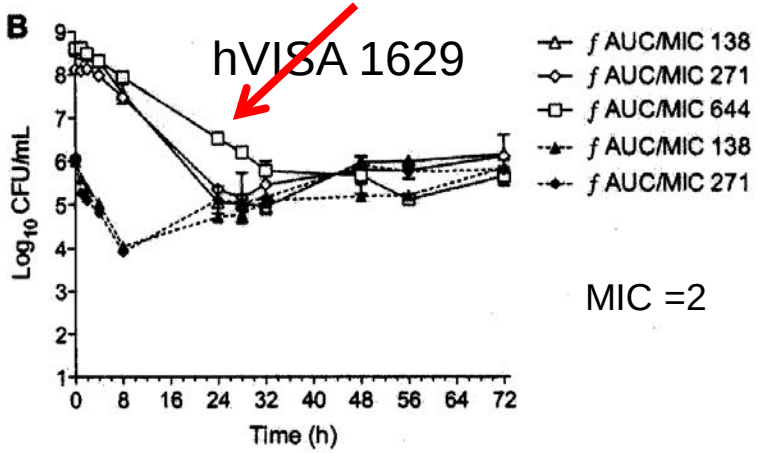
Rose WE. et al. *Antimicrob Agents Chemother*. 2009:53:805-7.

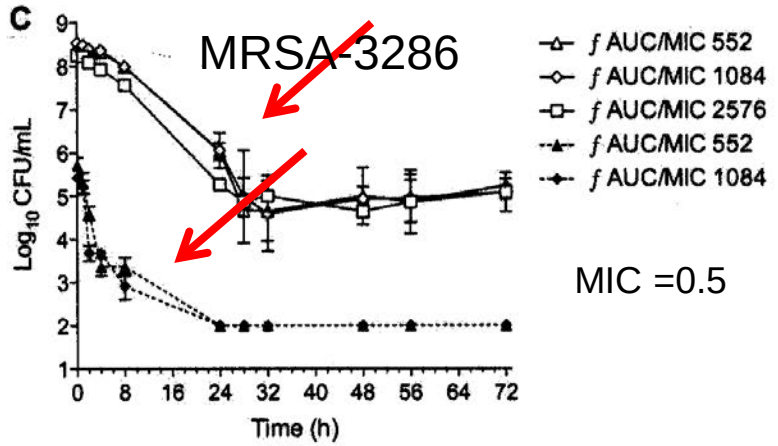
hVISA & Vancomycin

The Inoculum Impact

- Evaluated inoculum & impact of dose on vancomycin killing activity vs. hVISA
- Results:
  - Both hVISA & inoculum had a severe impact on vancomycin activity

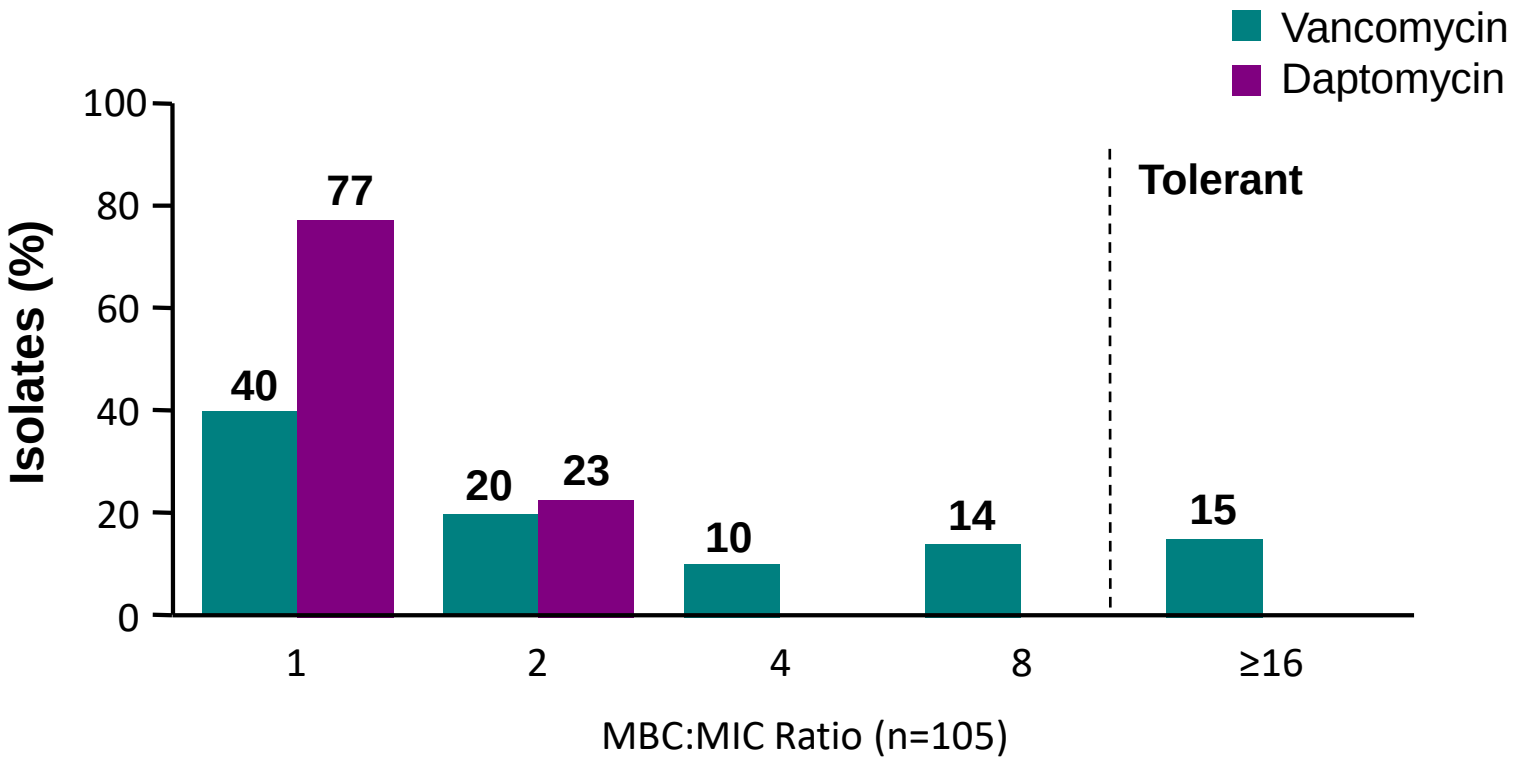






Rose WE. et al. *Antimicrob Agents Chemother*. 2009:53:805-7.

Fifteen Percent of Wildtype MRSA are Tolerant to Vancomycin

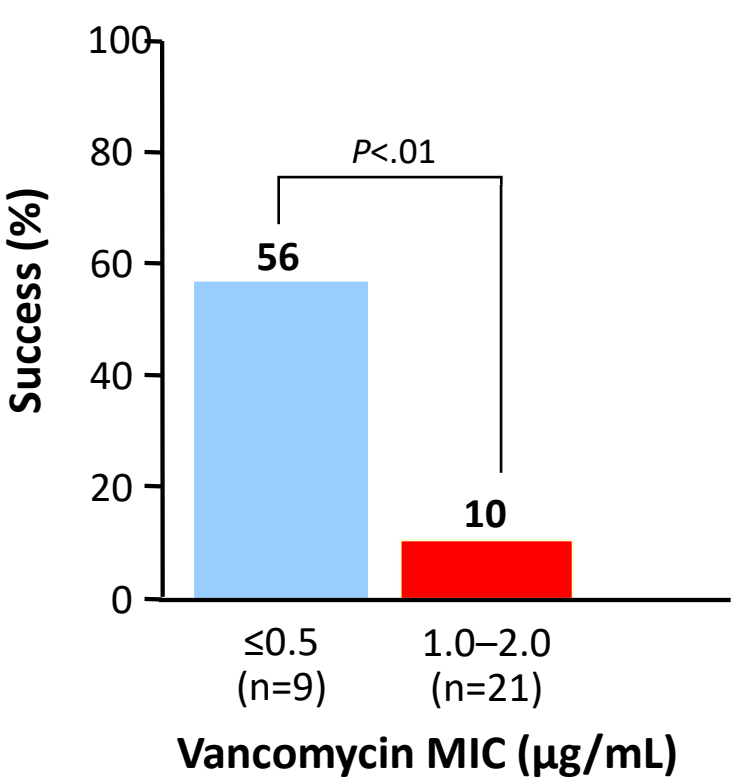


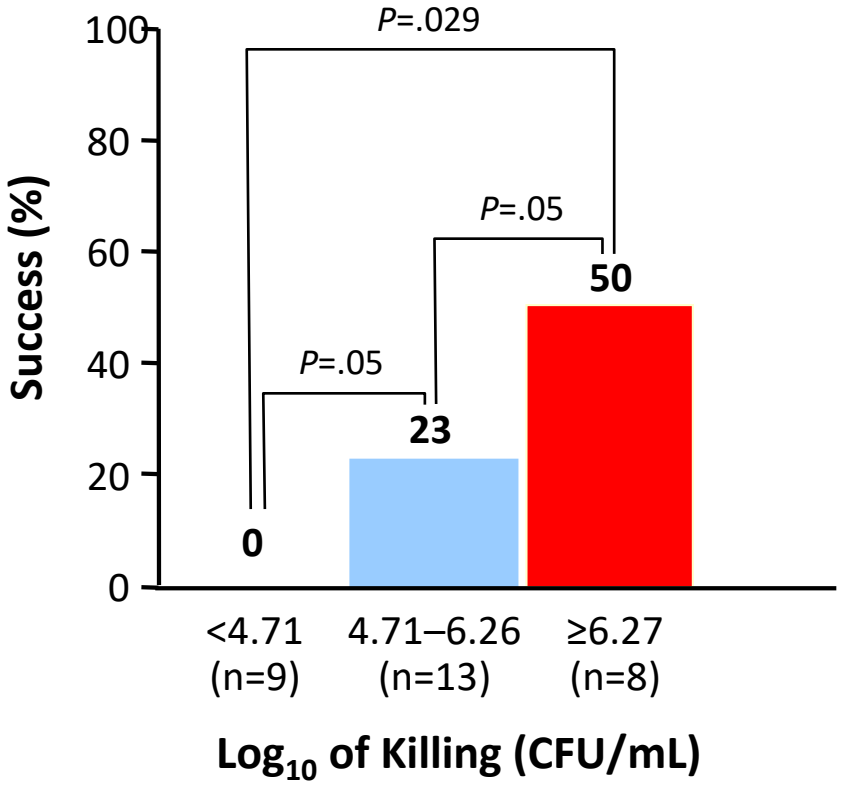
- 74% of hVISA isolates are tolerant to vancomycin

Jones et al. *Clin Infect Dis* 2006;42:S13–24

Correlation of Vancomycin MIC and Patient Outcome

Therapeutic Efficacy of Vancomycin in Relation to MIC or Bactericidal Activity



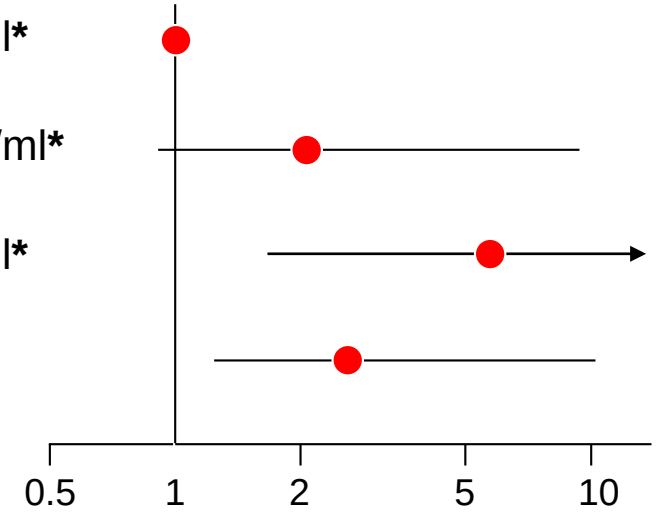


Adapted from Sakoulas et al. 2004 *J. Clin Microbiol*.42:2398-2402

Vancomycin MIC as a predictor for mortality in MRSA

n = 414

Treatment group	Risk of mortality (OR [95% CI])	*P*-value
Vancomycin MIC=1 µg/ml*	1	
Vancomycin MIC=1.5 µg/ml*	2.86 (0.87, 9.35)	0.08
Vancomycin MIC=2 µg/ml*	6.39 (1.68, 24.3)	<0.001
Inappropriate therapy†	3.62 (1.20, 10.9)	<0.001



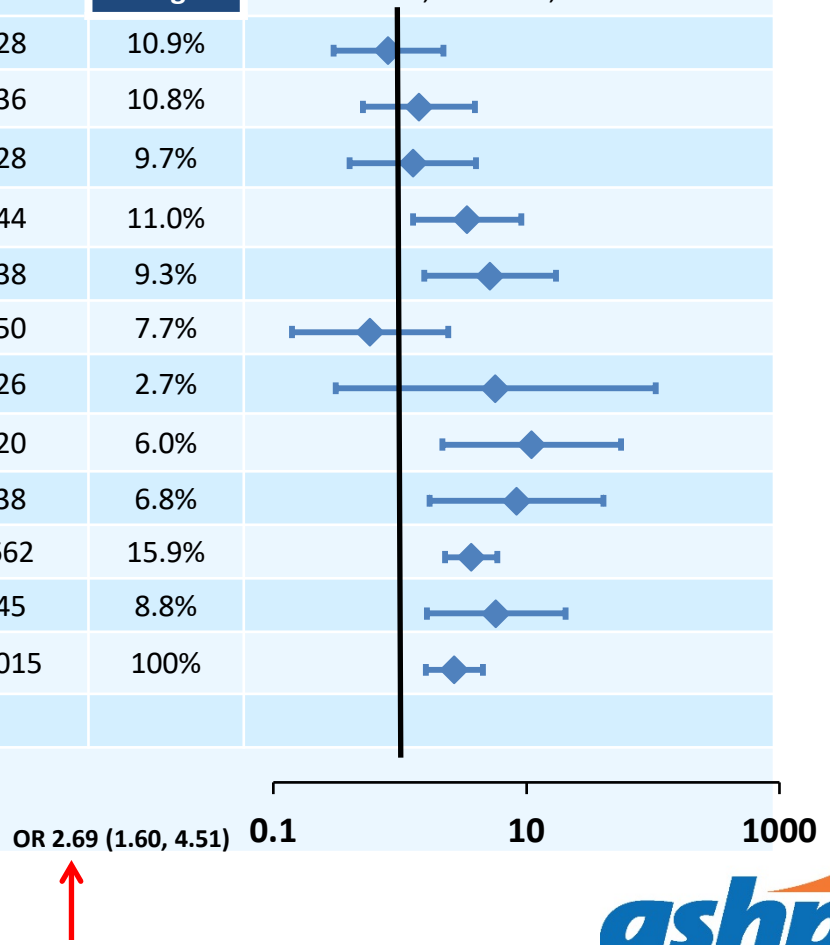
*MIC of vancomycin for first MRSA isolate determined by E-test
†Inappropriate therapy defined as empirical therapy to which the MRSA strain was resistant

Adapted from: Soriano A *et al. Clin Infect Dis* 2008;46:193–200.

Vancomycin MIC as a predictor for treatment failure in MRSA infections

Forest plot using Mantel–Haenszel analysis

Study or subgroup	High MIC ≥1.5 µg/mL Events	High MIC ≥1.5 µg/mL Total	Low MIC <1.5 µg/mL Events	Low MIC <1.5 µg/mL Total	Weight	Odds ratio M-H, Random, 95% CI
Bae et al.	14	37	12	28	10.9%	
Choi et al.	12	34	10	36	10.8%	
Ferry et al.	9	24	9	28	9.7%	
Hidayat et al.	20	51		44	11.0%	
Hsu et al.	17	45	4	38	9.3%	
Lalueza et al.	3	13	17	50	7.7%	
Lodise et al.	6	66	0	26	2.7%	
Moise et al.	11	14	5	20	6.0%	
Moise-Broder et al.	23	25	22	38	6.8%	
Takesue et al.	34	97	85	662	15.9%	
Yoon et al.	14	18	17	45	8.8%	
Total (95% CI)		424		1015	100%	
Total events	163		188			



Heterogeneity: $Tau^2 = 0.38$; $c^2 = 22.59$, df 10 (P = 0.01); $I^2 = 56\%$. Test for overall effect: Z = 3.75 (P = 0.0002)

Adapted from: Van Hal SJ *et al*. *Clin Infect Dis*. 2012;54:755–771

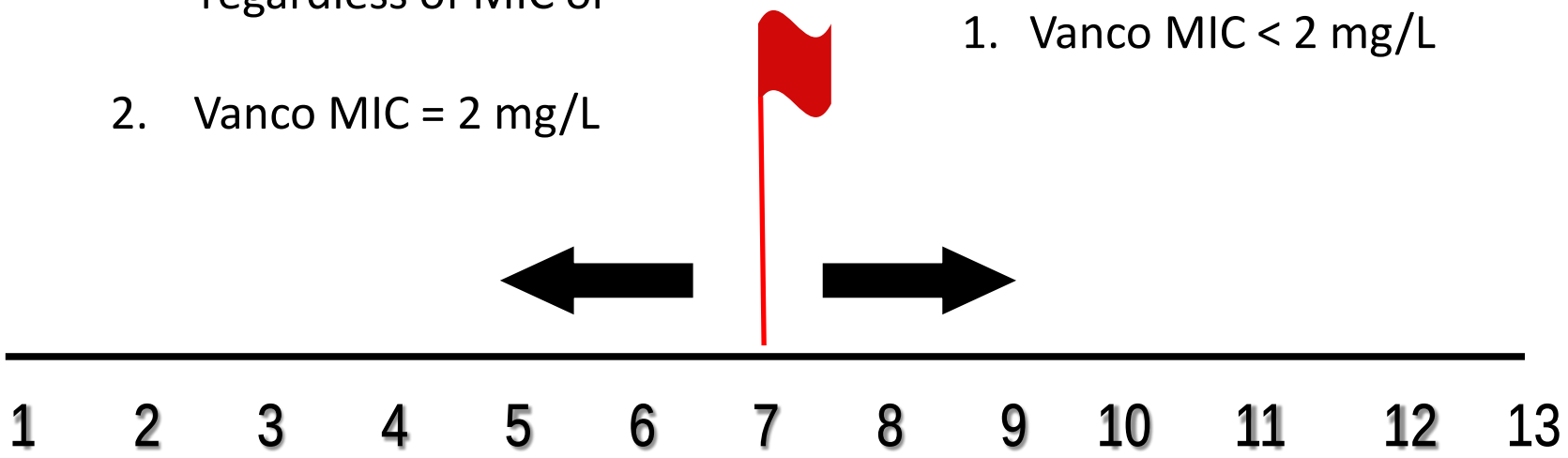
Management of Vancomycin Failure

Consider change in therapy if:

1. Unsatisfactory clinical response, regardless of MIC or
2. Vanco MIC = 2 mg/L

No change in therapy if:

1. Clinically responding and
1. Vanco MIC < 2 mg/L



Liu, C. et al., *Clin Infect Dis*. 2011;52:285-292.

INVITED ARTICLE CLINICAL PRACTICE

Ellie J. C. Goldstein, Section Editor

Avoiding the Perfect Storm: The Biologic and Clinical Case for Reevaluating the 7-Day Expectation for Methicillin-Resistant *Staphylococcus aureus* Bacteremia Before Switching Therapy

Ravina Kullar,[1] James A. McKinnell,[2,3] and George Sakoulas[4]

[1]Department of Medical Affairs, Cubist Pharmaceuticals, Lexington, Massachusetts; [2]Infectious Disease Clinical Outcomes Unit (ID-CORE), Los Angeles Biomedical Research Institute, David Geffen School of Medicine, University of California, [3]Department of Medicine, Torrance Memorial Medical Center, and [4]Division of Pediatric Pharmacology and Drug Discovery, University of California San Diego School of Medicine, La Jolla

Kullar, K. et al. *Clin Infect Dis.* 2014;59 (15): 1455-61.

Ineffective Vancomycin Therapy Negatively Impacts the Innate Immune System Response

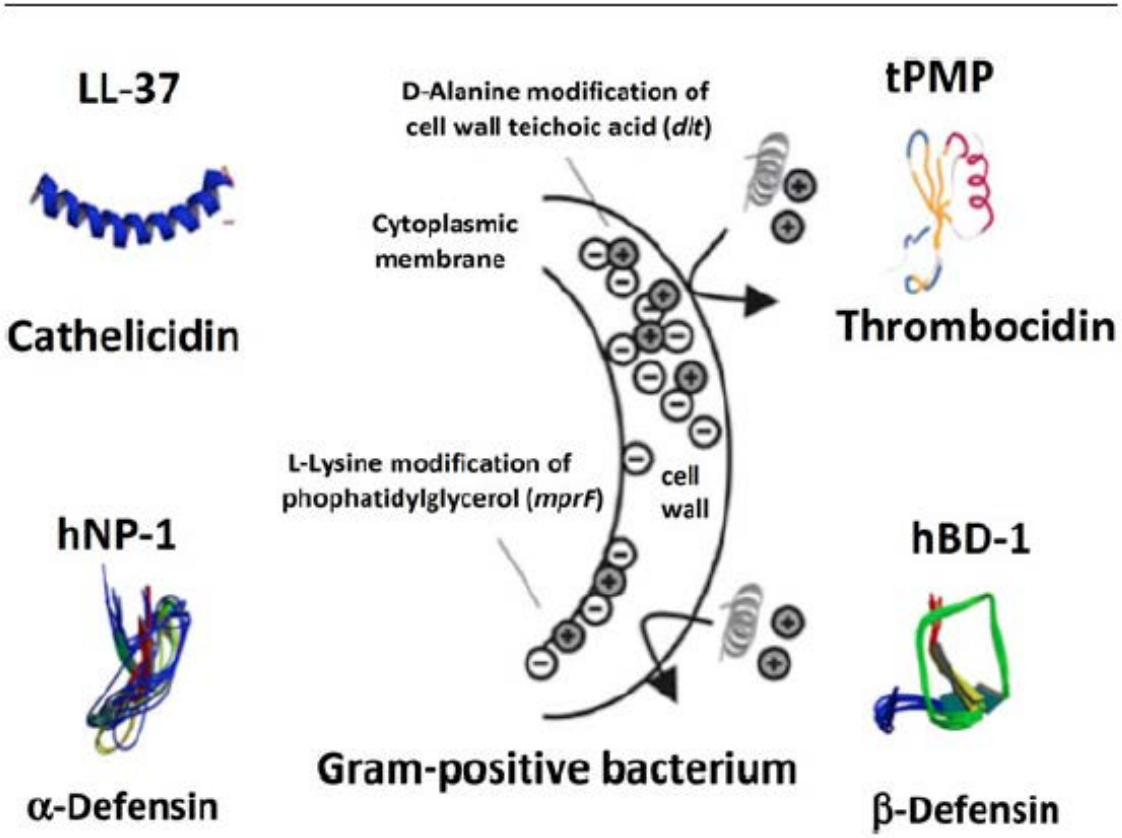


Figure 1. Examples of cationic antimicrobial host defense peptides. Abbreviations: hBD-1, human beta-defensin-1; hNP-1, human neutrophil peptide-1; mprF, multiple peptide resistance factor; tPMP, thrombin-induced platelet microbicidal protein.

Kullar, R. et al. Clin Infect Dis. 2014:59 (15): 1455-61

Vancomycin the Spoiler

Human Cathelicidin LL-37 Resistance and Increased Daptomycin MIC in Methicillin-Resistant *Staphylococcus aureus* Strain USA600 (ST45) Are Associated with Increased Mortality in a Hospital Setting

George Sakoulas,[a] Kripa Guram,[a] Katherine Reyes,[b] Victor Nizet,[a] Marcus Zervos[b]

University of California San Diego School of Medicine, La Jolla, California, USA[a]; Henry Ford Hospital, Wayne State University School of Medicine, Detroit, Michigan, USA[b]

Bacteremia caused by methicillin-resistant *Staphylococcus aureus* (MRSA) USA600 has been associated with increased patient mortality. We found that USA600 MRSA exhibited significantly increased resistance to human cathelicidin LL-37 killing and daptomycin MIC creep compared to non-USA600 MRSA. Virulent health care-associated MRSA strains may coevolve innate host defense peptide and antibiotic resistances.

Ineffective Vancomycin → **Cationic Peptide Resistance** → **Daptomycin Resistance**

Sakoulas G. et al. J Clin Microbiol. 2014;52 (6): 2172-74.

Alternative Therapy to Vancomyc for MRSA

- Ceftaroline
  - Bactericidal
  - Twice-daily administration
- Daptomycin
  - Conc-dependent killing
  - Bactericidal
  - Once-daily administration
- Linezolid
  - Bacteriostatic
  - Twice-daily administration
- Telavancin
  - Conc-dependent killing
  - Bactericidal
  - Once-daily administration
- Dalbavancin
  - Conc-dependent killing
  - Bactericidal
  - 1st and 8th day (ABSSSI)
- Oritavancin
  - Conc-dependent killing
  - Bactericidal
  - Single-dose (ABSSSI)
- Tedizolid
  - Bacteriostatic
  - Once-daily (ABSSSI)

Rybak, J.M. et al. *Expert Opin*. 2013;14 (14): 1-14.

Relationship Between Vancomycin Resistance and Daptomycin Susceptibility

- Correlation between reduced daptomycin susceptibility and vancomycin-intermediate *S aureus*[1]
- Induction of daptomycin heterogeneous susceptibility in *S aureus* by exposure to vancomycin[2]
- An association between reduced susceptibility to daptomycin and reduced susceptibility to vancomycin in *S aureus*[3]
- Association with prior vancomycin exposure and daptomycin non-susceptibility[4]

[1]Cui L et al. *Antimicrob Agents Chemother*. 2006;50:1079-1082.
[2]Sakoulas G et al. *Antimicrob Agents Chemother*. 2006;50:1581-1585.
[3]Patel JB et al. *Clin Infect Dis*. 2006;42:1652-1653.
[4]Rose W. et al *Antimicrob Agents Chemother*. 2008;52:831-36.

MAJOR ARTICLE

Early Use of Daptomycin Versus Vancomycin for Methicillin-Resistant *Staphylococcus aureus* Bacteremia With Vancomycin Minimum Inhibitory Concentration >1 mg/L: A Matched Cohort Study

Kyle P. Murray,[1] Jing J. Zhao,[1] Susan L. Davis,[3] Ravina Kullar,[3] Keith S. Kaye,[2] Paul Lephart,[4] and Michael J. Rybak[1,2,3]

[1]Department of Pharmacy, Detroit Medical Center, [2]Division of Internal Medicine, Division of Infectious Diseases, Wayne State University and Detroit Medical Center, [3]Anti-Infective Research Laboratory, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, and [4]University Laboratories, Detroit Medical Center, Detroit, Michigan

Murray, K. et al. *Clin Infect Dis*. 2013. 56; 96):1562-1569.

Predictors of Clinical Failure

Multivariate Logistic Regression

	Unadjusted OR	P	Adjusted OR	P
ICU admission	4.4 (2.2-8.9)	<0.001	5.8 (2.7-12.8)	<0.001
Vancomycin treatment	3.7 (1.9-7.4)	<0.001	4.5 (2.1-9.8)	<0.001
Intravenous drug use	2.8 (1.4-5.4)	0.002	3.0 (1.4-6.3)	0.004

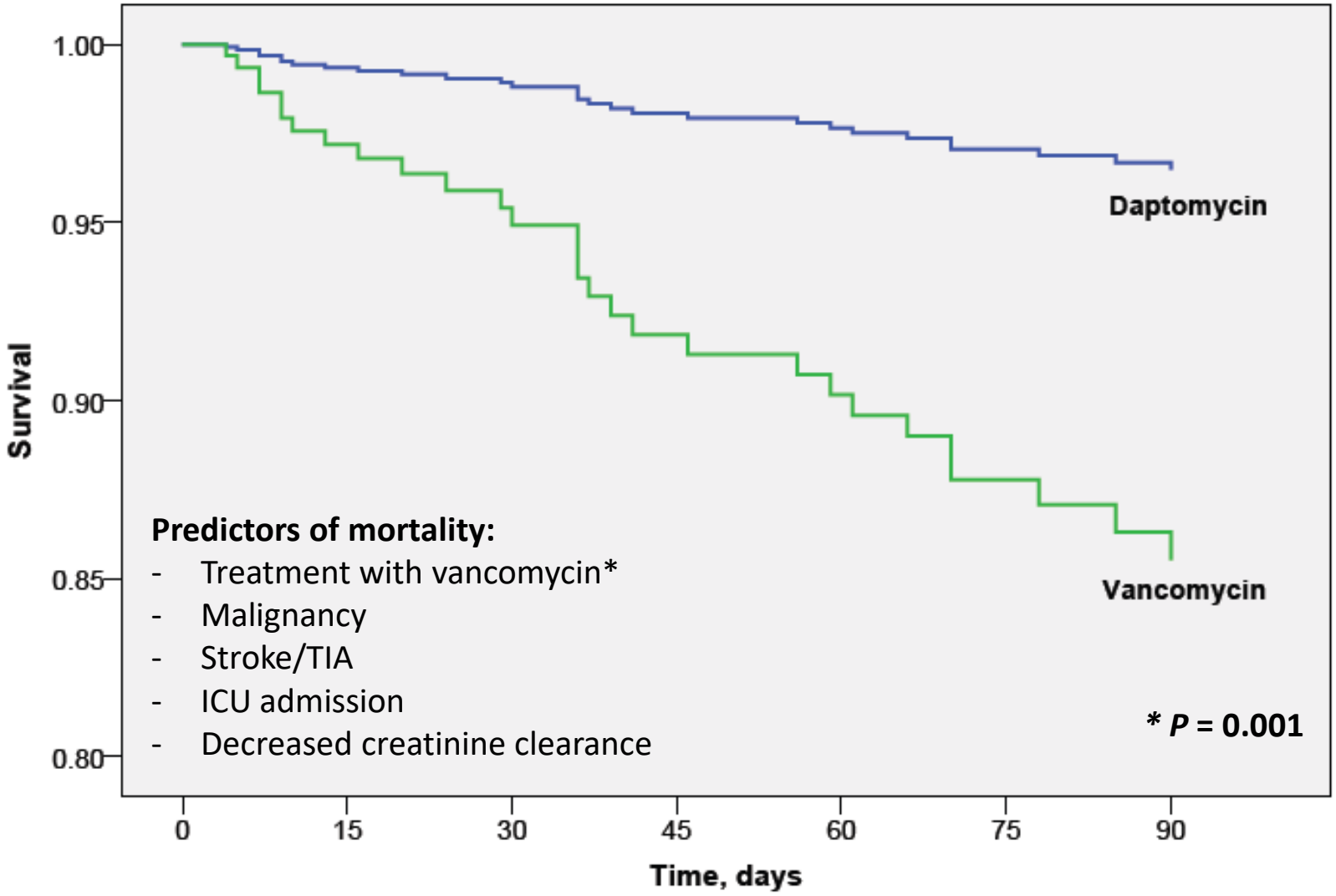
Variables with $P < 0.2$ when compared between treatment groups, and variables associated with clinical failure ($P < 0.2$) considered for inclusion.

Murray, K. et al. *Clin Infect Dis*. 2015. 56; 96):1562-1569.

Survival to 90 Days

Cox Proportional Hazards

n = 170



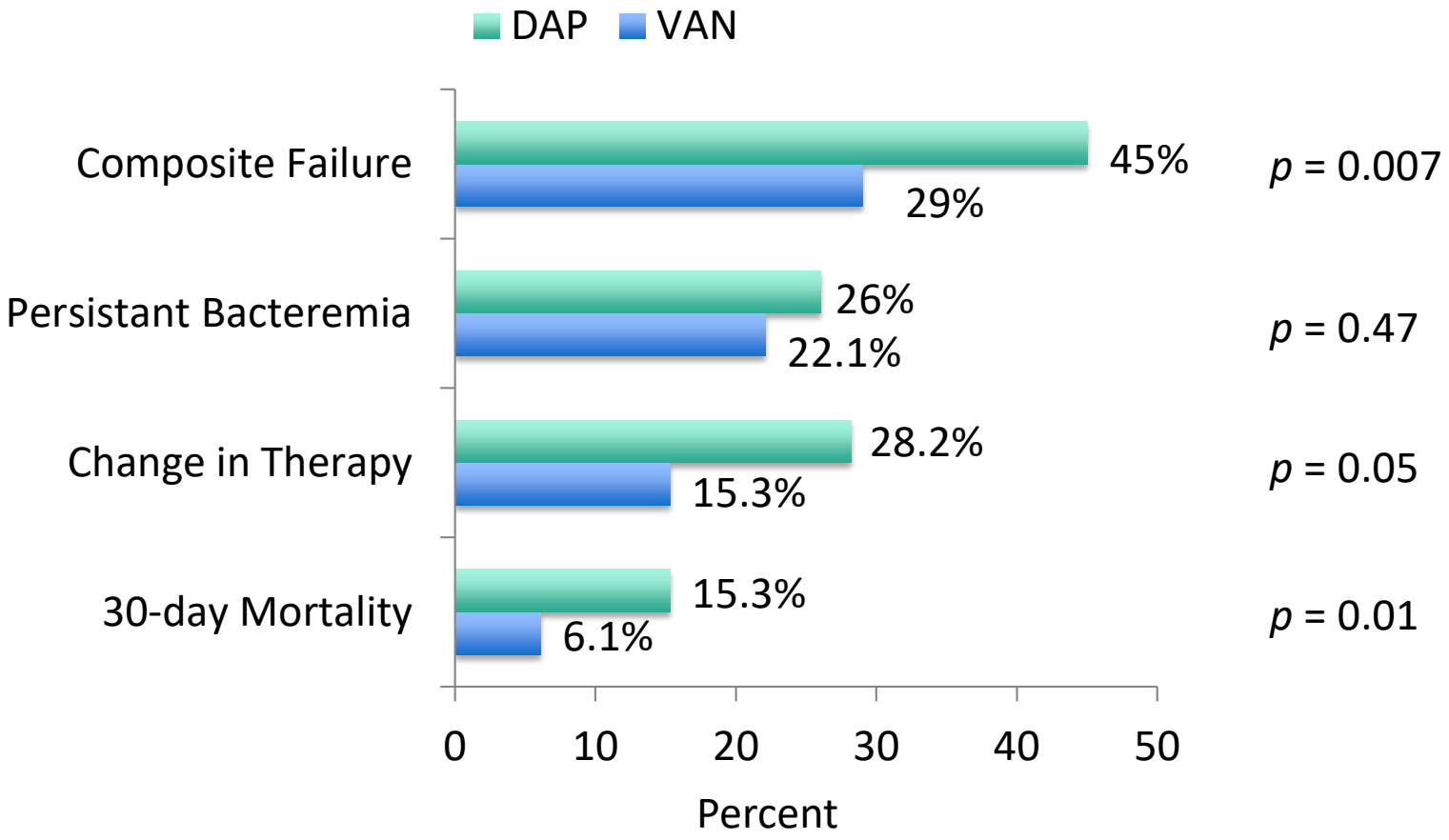
Predictors of mortality:

- Treatment with vancomycin*
- Malignancy
- Stroke/TIA
- ICU admission
- Decreased creatinine clearance

***P* = 0.001**

Adapted from: Murray, K. et al. *Clin Infect Dis*. 2013. 56; 96):1562-1569.

Daptomycin Improves Outcomes Regardless of Vancomycin MIC in a Propensity-Matched Analysis of MRSA Bacteremia



Claeys, K.C. et al. *Antimicrob Agents Chemother*. 2016; 10 (60)

ashp MIDYEAR2016 Clinical Meeting & Exhibition

Safety

	Daptomycin (n = 85)	Vancomycin (n=85)
Nephrotoxicity[a]	0.00	22 (25.9%)
CPK elevation[b]	1 (1.2%)	0.00
Emergence of resistance during treatment	2 (2.4%)	0.00

Data are no. (%) of patients.

a. Nephrotoxicity defined as increase in SCr of ≥ 0.5 mg/dL or 50% over baseline on at least 2 consecutive occasions.

b. Significant CPK elevation defined as increase > 5 ULN.

Murray, K. et al. *Clin Infect Dis*. 2013. 56; 96):1562-1569.

IDSA GUIDELINES

Vancomycin Therapeutic Guidelines: A Summary of Consensus Recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists

Michael J. Rybak,[1,2,3] Ben M. Lomaestro,[4] John C. Rotschafer,[5] Robert C. Moellering, Jr.,[6,7,8] Willam A. Craig,[9] Marianne Billeter,[10] Joseph R. Dalovisio,[11] and Donald P. Levine[3]

[1]Anti-Infective Research Laboratory, Department of Pharmacy Practice, College of Pharmacy & Health Sciences, and [2]Department of Medicine, School of Medicine, Wayne State University, and [3]Detroit Receiving Hospital & University Health Center, Detroit, Michigan; [4]Albany Medical Center, Albany, New York; [5]Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis; [6]Shields Warren-Mallinckrodt Medical Research, [7]Harvard Medical School, and [8]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts; [9]University of Wisconsin School of Medicine and Public Health, Madison; and [10]Oshsner Medical Centers and [11]Department of Infectious Diseases, Oschsner Health System, New Orleans, Louisiana

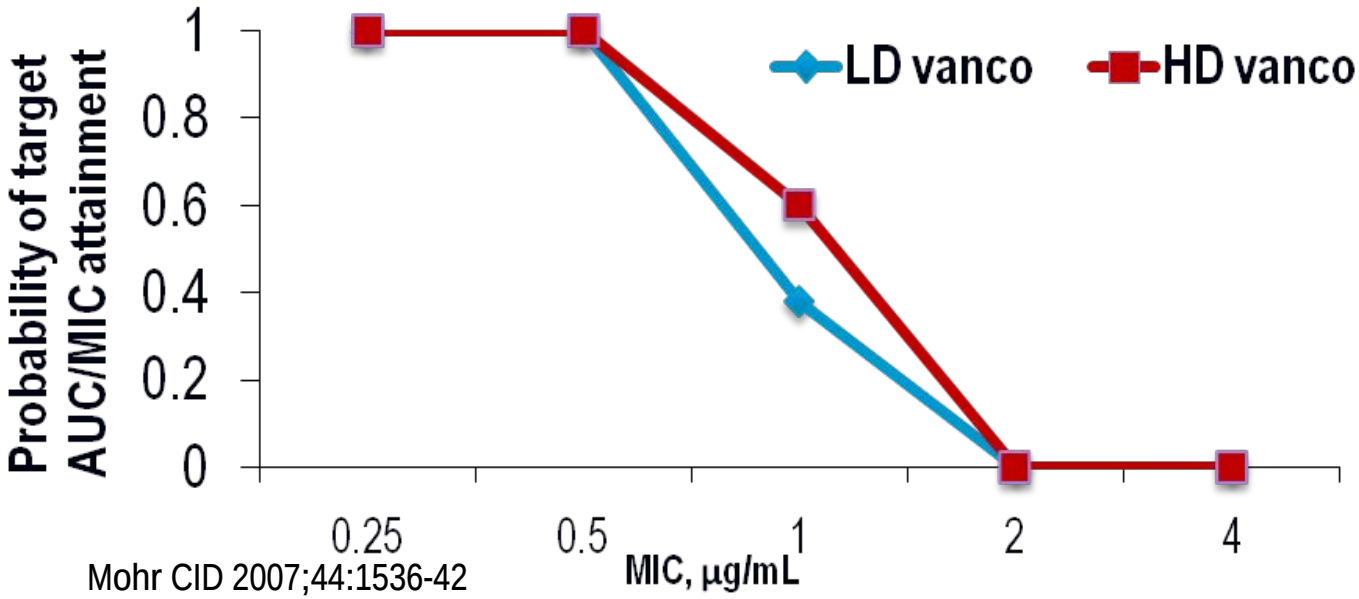
Rybak et al. *Clin Infect Dis.* 2009;49:325-327.

Vancomycin Consensus Summary

- PK/PD target is AUC/MIC
  - Target AUC/MIC ≥ 400
    - Bacteremia
    - Pneumonia
    - Meningitis
    - Endocarditis
    - Osteomyelitis
- Trough of 15-20 mg/L
  - ≈ AUC/MIC of ≥400
    - Conc. ≤ 10 mg/L encourages resistance

Rybak et al. *Am J Health-Syst Pharm*. 2009;66:82-98.
Rybak et al. *Clin Infect Dis*. 2009;49:325-327.

Achieving the Vancomycin Targets



Mohr CID 2007;44:1536-42

- Probability of achieving target AUC/ MIC is 0% if vancomycin MIC = 2 µg/mL with low or high-dose vancomycin
- Vanco MICs of 2 µg/mL associated with ↑ vanco Rx failures[1]
- "MIC creep" observed in some centers but not others[2]
  - Perhaps due to clonal dissemination or technical artifact

[1]Sakoulas *JCM* 2004;42:2398-402; Hidayat L *Arch Intern Med* 2006;166:2138-44; Lodise *AAC* 2008;52:3315-20; Maor *JID* 2009;199:619-24 [2]Alos *JAC* 2008;62:773-5; Holmes *AAC* 2008;52:757-60; Jones *CID* 2006;42:S13-24; Sader *AAC* 2009; 53:4127-32

Impact of Vancomycin Exposure on Outcomes of Patients with MRSA Bacteremia

Independent Predictors of Vancomycin Failure by Logistic Regression n= 320

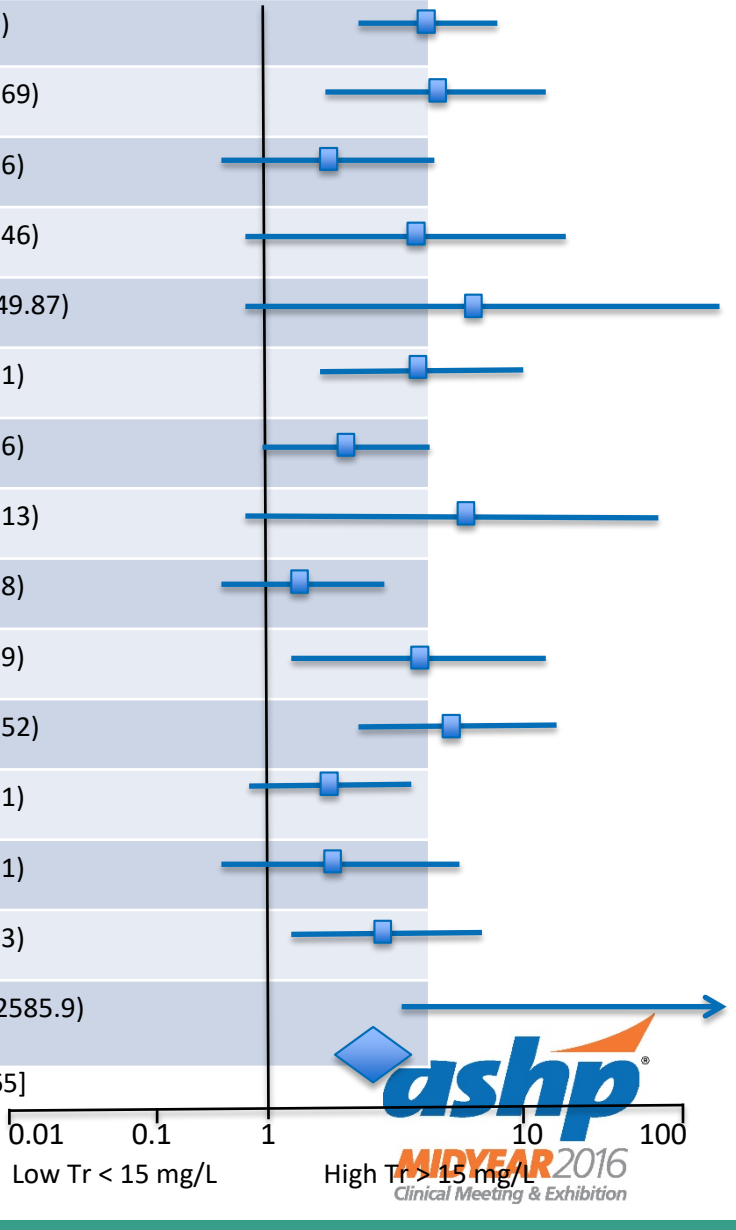
Characteristic	AOR; CI	P value
Infective endocarditis	4.55; 2.26-9.15	< 0.001
Nosocomial-acquired bacteremia	2.19; 1.21-3.97	0.009
Initial Vanco Trough Conc. < 15 mg/L	2.0; 1.25-3.22	0.004
Vanco MIC> 1 mg/L by Etest	1.52; 1.09-2.49	0.045

* AUC_{24h}:MIC ratio <421 was significantly (P=0.038) associated with failure

Kullar R., Davis SL., Levine, DP., Rybak MJ. *Clin Infect. Dis*. 2011; 52(8):975-81.

Troughs ≥ 15 are associated with Nephrotoxicity

Study Group	Tr≥15 mg/l	Total	Tr < 15 mg/L	Total	Weight	Odds Ratio, CI
Bosso et al.	42	142	13	146	9.8%	4.3 (2.19-8.43)
Cano et al.	22	89	7	99	7.2%	4.32 (1.74-10.69)
Chung et al.	12	25	16	48	6.5%	1.85 (0.69-4.96)
Hermsen et al.	5	16	4	39	3.6%	3.98 (0.91-17.46)
Hidayat et al.	11	63	0	32	1.1%	14.24 (0.81-249.87)
Jeffres et al.	27	49	13	45	7.7%	3.02 (1.28-7.11)
Kralovicova et al.	21	60	29	138	9.8%	2.02 (1.04-3.96)
Kullar et al.	8	116	1	84	2.0%	6.15 (0.75-50.13)
Kullar et al.	27	139	23	141	10.6%	1.24 (0.67-2.28)
Lodise et al.	7	27	14	139	6.2%	3.13 (1.12-8.69)
McKamy et al.	16	57	8	110	7.0%	4.98 (1.98-12.52)
Minejima et al.	17	72	25	155	9.6%	1.61 (0.80-3.21)
Prabaker et al.	7	54	24	294	7.3%	1.68 (0.68-4.11)
Wunderink et al.	26	118	24	215	10.7%	2.25 (1.22-4.13)
Zimmermann et al.	8	12	0	33	1.0%	126.56 (6.19-2585.9)
Total events = 256		1039		1718	100%	2.67 [1.95,3.65]



Van Hal, S.J. et al. *Antimicrob Agents Chemother*. 2013. 57; (2): 734-742.

Vancomycin Toxicity Issues

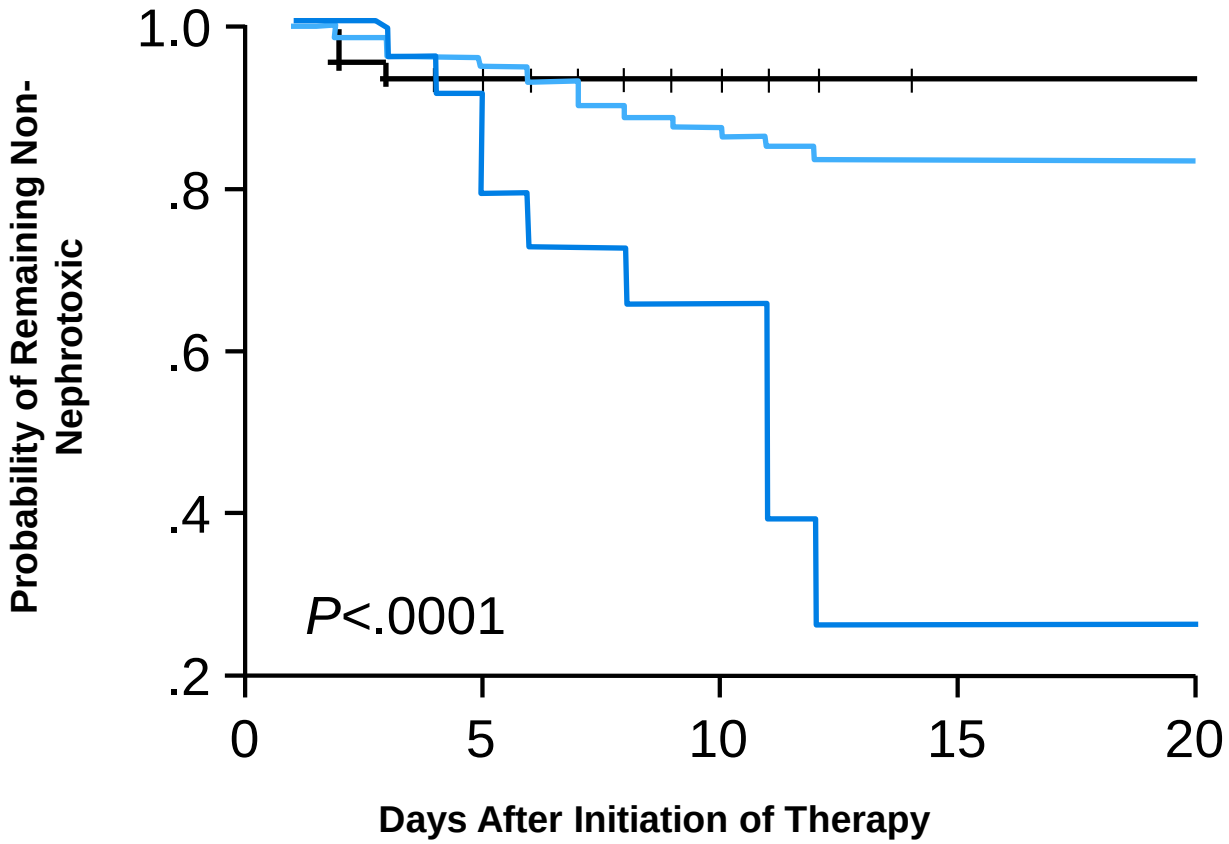
- Infusion related (based on concentration)
  - Phlebitis
  - Red Man Syndrome

- Nephrotoxicity
  - low (5-7%) at conventional doses (approximately 2 g/day
  - higher rates: up to 35% in combination with aminoglycoside
  - limited data on doses at $\geq$ 4 g/day
    - Studies suggests rates of 13-34.6%

- Ototoxicity
  - Low incidence reported in the literature
  - Not demonstrated in animal models at high dosages
    - Recent report[2] on otoxicity and higher dosages
      - Higher in older > 53 yrs, long exposure (≈ 28 days)
      - and with higher troughs (mean 19 mg/L; P<0.008)

1. Lodise T. et al. AAC 2008;52:1330-36.
2. Forouzesh A. et al. AAC 2009;53:483-6.
3. Kullar et al. CID 2011; 52(8): 975-81.

Time-to-Nephrotoxicity—Stratified Kaplan-Meier Analysis



Stratum 0, linezolid

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

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

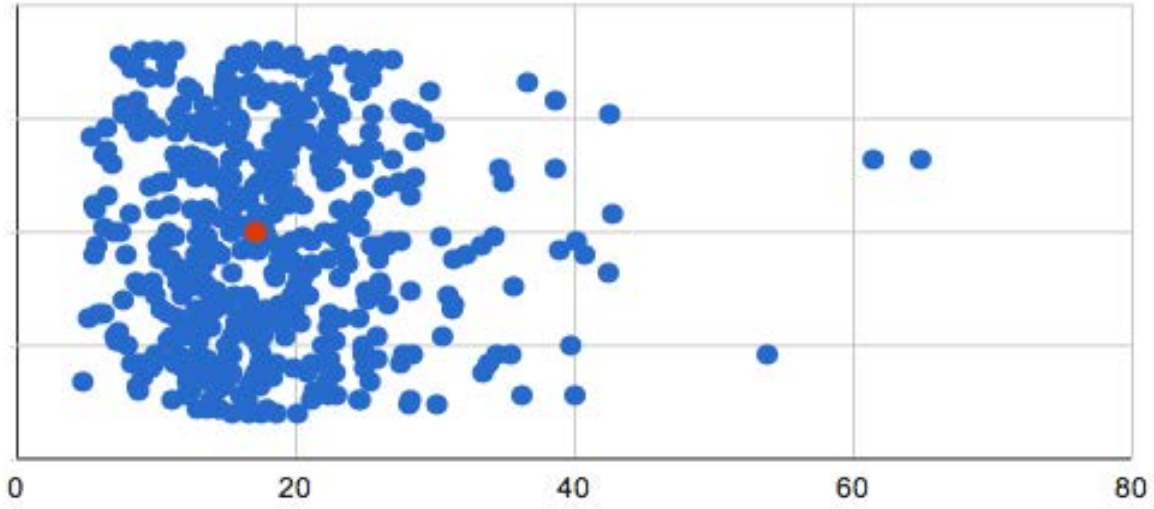
Lodise TP. *Antimicrob Agents Chemother.* 2008;52:1330-1336.

Initial Vancomycin Trough Concentration Detroit Medical Center

Total (N)	Missing	Unique	Min	Max	Mean	StDev	Percentile						
							.05	.10	.25	.50 Median	.75	.90	.95
472	0 (0%)	227	4.70	64.80	18.25	7.96	7.60	9.30	13.00	17.10	22.30	27.50	33.35

Lowest values: 4.7, 5.1, 5.3, 5.5, 5.5

Highest values: 42.5, 42.7, 53.8, 61.4, 64.8



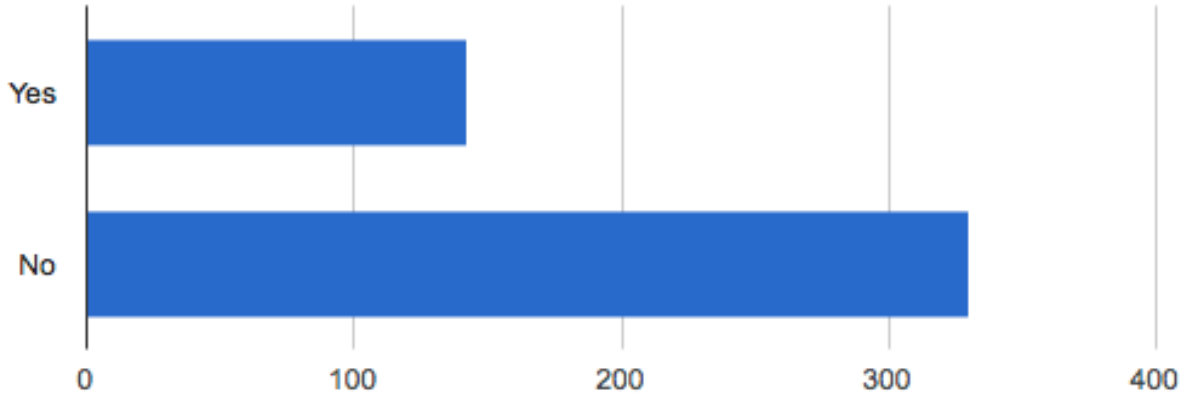
Data from the Detroit Medical Center 2014-15

Initial Vancomycin Trough Concentration 15-20 mg/l within 1st 72 hours Detroit Medical Center

15-20mg/L within 72 hours: Refresh Plot | View as Bar Chart

Total (N)	Missing	Unique
472	0 (0%)	2

Counts/frequency: Yes (142, 30.1%), No (330, 69.9%)



Data from the Detroit Medical Center 2014-15

Vancomycin Summary & Take Away

- Old and overused antibiotic
- Significant dose dependent nephrotoxicity
- High Association with failure
  - Suboptimal therapy
  - Elevated MICs
  - Tolerance
  - hVISA/VISA/VRSA
- Requires serum concentration monitoring
  - Target attainment highly variable
- Alternatives
  - Newer, safer & more potent

- Optimization of vancomycin may improve patient outcomes; however:
  - Difficult to achieve PK/PD target with MIC > 1 mg/L
  - Associated with higher rates of nephrotoxicity
  - Determination of the AUC may lower doses
  - AUC/MIC targets for individual infections are needed

Section End

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Clinical Meeting & Exhibition

Vancomycin is clinically alive and well

Manjunath (**Amit**) P. Pai, PharmD

Associate Professor of Pharmacy

University of Michigan

A 45 y/o male presents with **fever** and **extensive cellulitis** of the right foot, having **failed** outpatient therapy with oral **clindamycin**. He is **allergic to penicillin** (hives). H/o diabetes and hypertension. Preliminary results from a culture of the **wound drainage** is **Gram positive cocci in clusters**. Which of the following agents would you use empirically?

A Dalbavancin

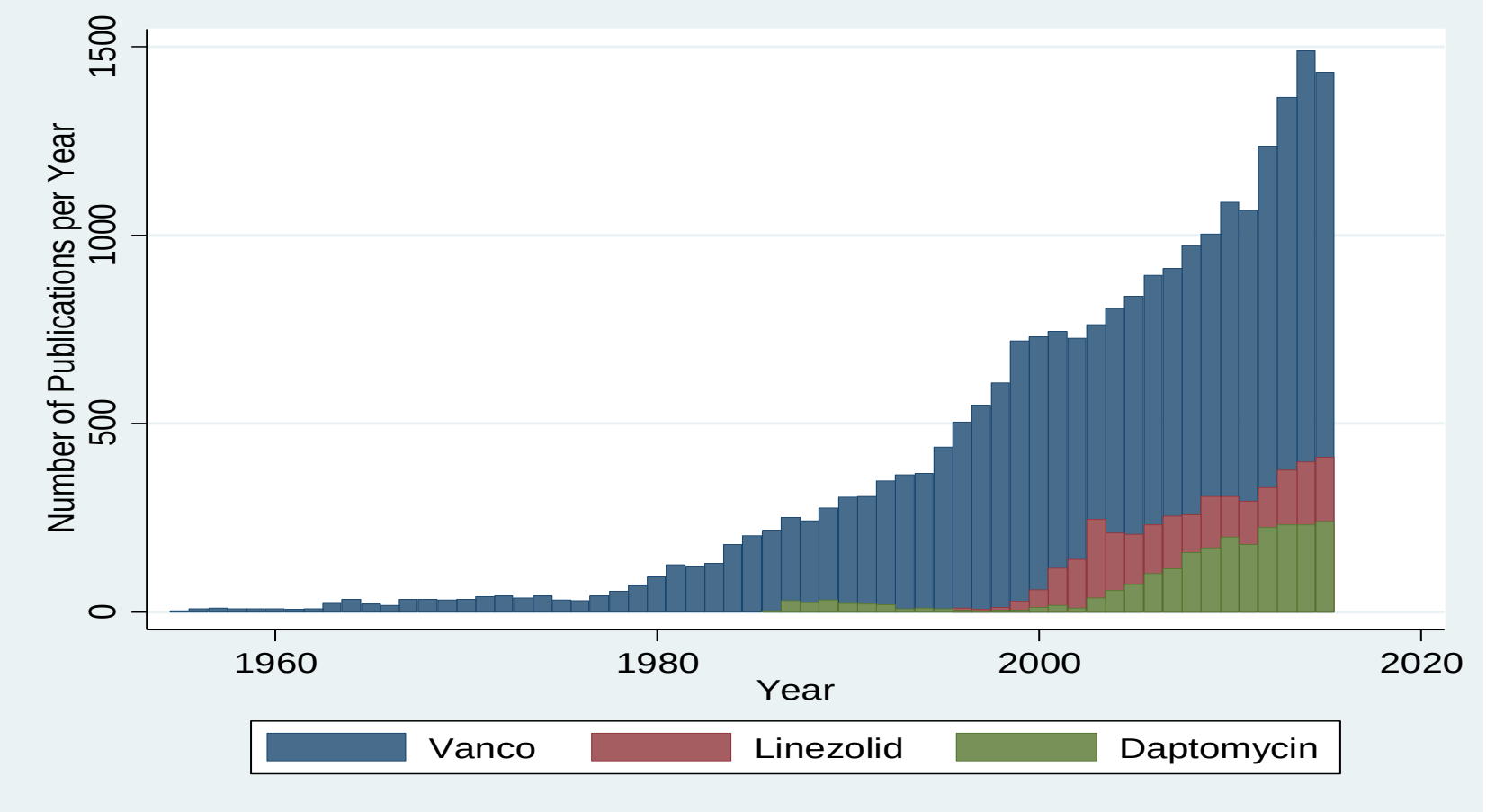
B Linezolid

C Daptomycin

D Vancomycin

The numbers favor….

Annual Number of Publications

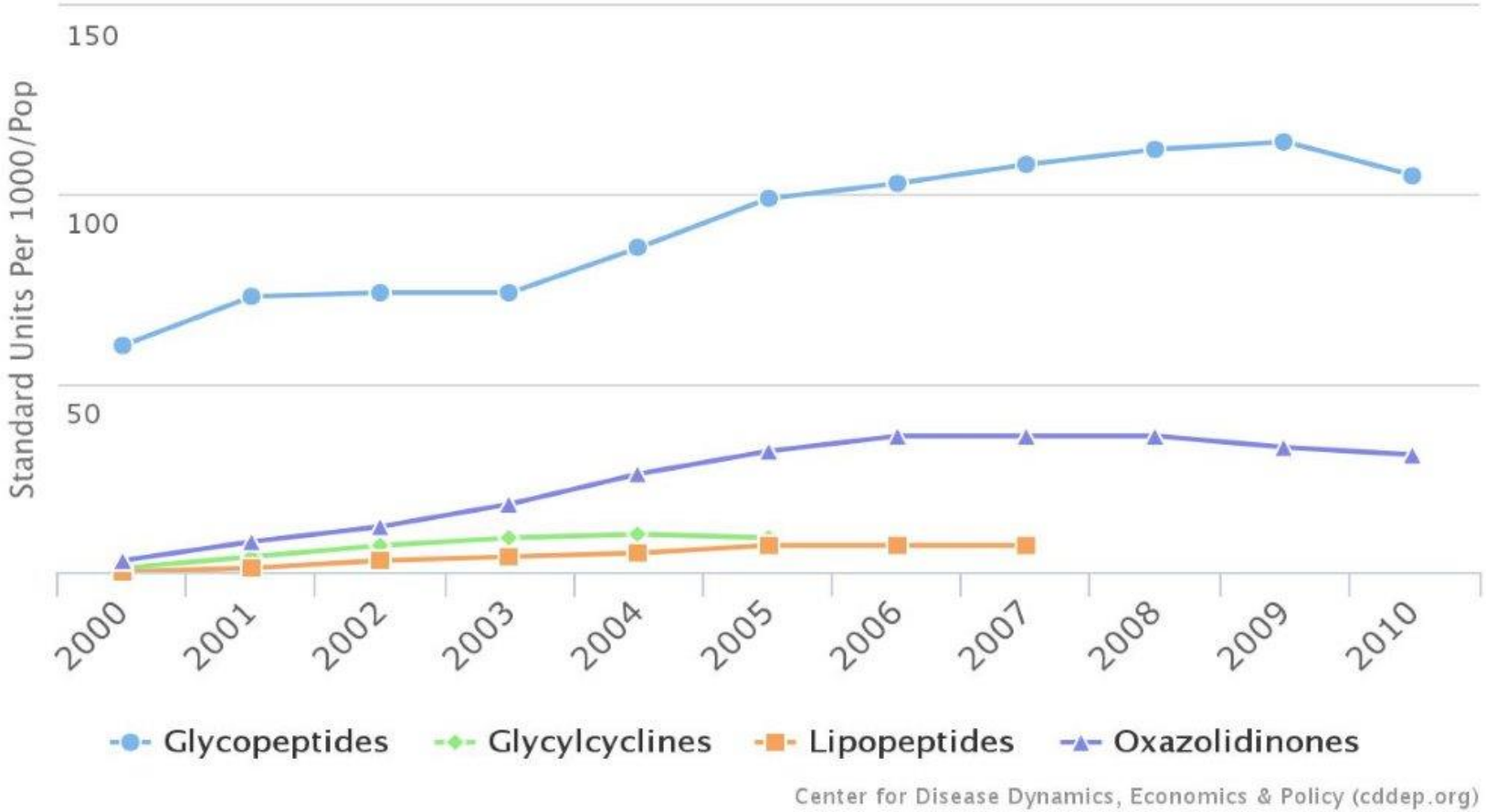


Google

Vancomycin	4,000,000
Linezolid	2,000,000
Daptomycin	500,000

Antibiotic Use in United States

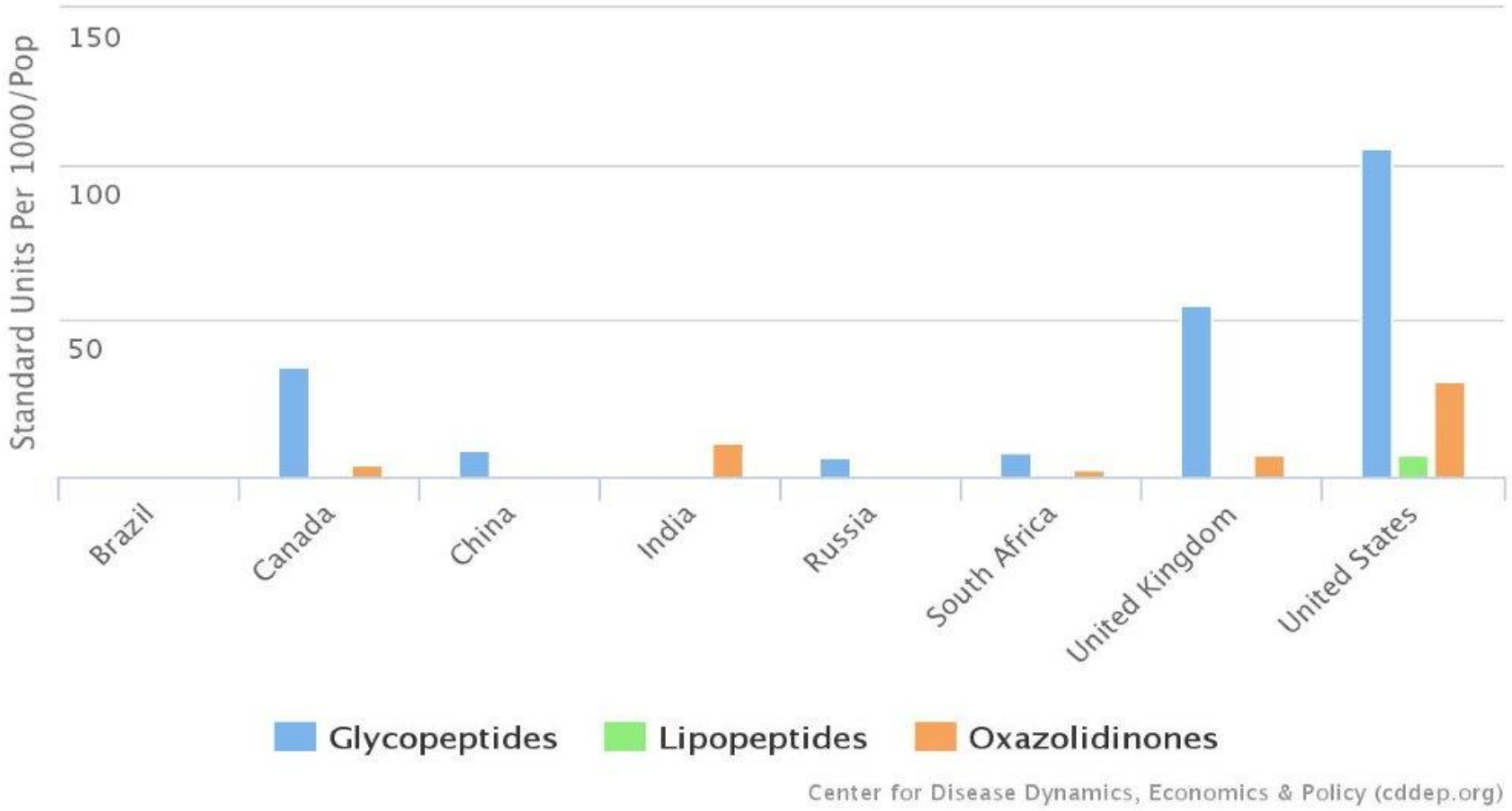
Source: IMS Health



Center for Disease Dynamics, Economics & Policy (cddep.org)

Antibiotic Use in 2010

Source: IMS Health



Center for Disease Dynamics, Economics & Policy (cddep.org)

2011	**Market Share**	**US ($)**
Vancomycin	82%	200 M
Linezolid	10%	600 M
Daptomycin	8%	700 M

Substitution of Vancomycin would have cost ~$8.7 Billion

How many manufacturers of vancomycin have been approved by the US FDA :

A 1 to 3

B 3 to 6

C 6 to 9

D >10

US FDA Approved Manufacturers

Drug	Manufacturers
Vancomycin*	Fresenis Kabi USA, Hospira, Mylan labs, Amneal Pharms, Akorn, Strides Pharma, Watson Labs, Sandoz, Lupin, Xelia Pharmas APS, Sagent Pharms. Teva Pharms, Emcure Pharms, CFT Pharmas, Aurobindo Pharma
Linezolid	Teva, Myland, Glenmark, Gate, Roxane, Sandoz, Hetero, Amneal , Fresenius, Alembic, Hospira, Alkem, Aurobindo, Novel
Daptomycin	Hospira, Teva, Crane
Telavancin	Theravance Biopharma
Ceftaroline	Forest Laboratories (Allergan)
Tedizolid	Cubist (Merck)
Oritavancin	The Medicines Company
Dalbavancin	Durata (Allergan)

*August 8, 2016

- Hospira had vancomycin **on shortage due to increased demand.**
- Fresenius Kabi has vancomycin injection on shortage due to increased demand.
- Mylan Institutional has vancomycin injection available.
- Baxter is allocating vancomycin.
- Sagent had vancomycin injection on allocation due to increased demand- See more at: http://www.ashp.org/menu/DrugShortages/CurrentShortages/Bulletin.aspx?id=132#sthash.lxVCxnGs.dpuf

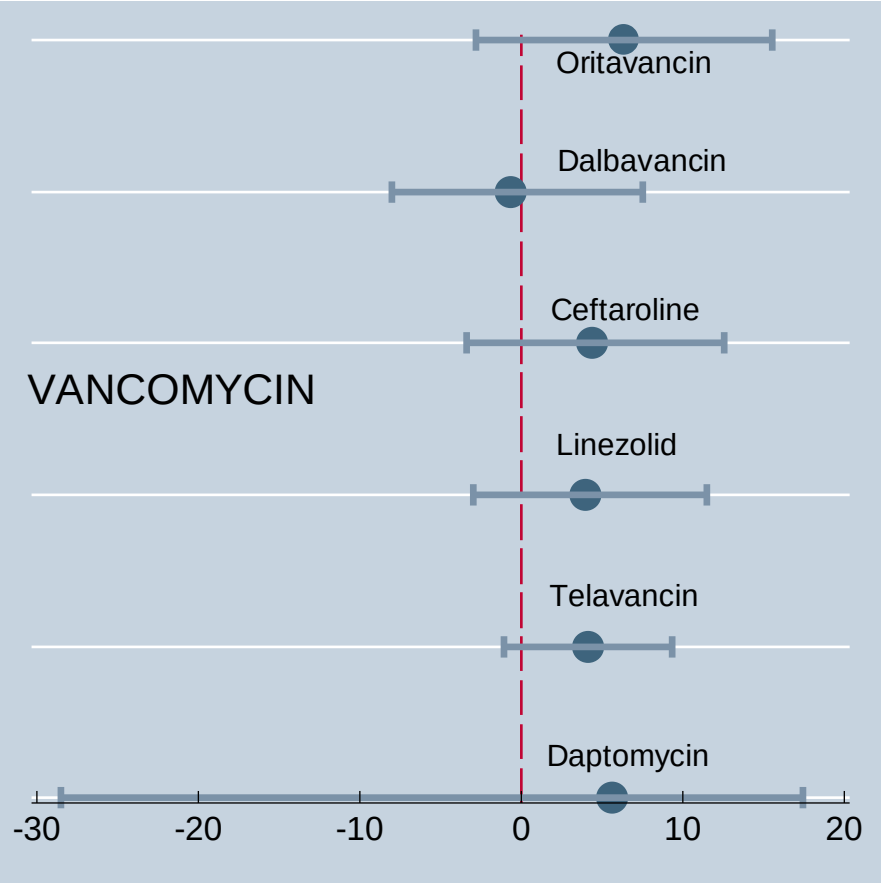
So many new alternatives. One of them has to be better, right?

Tried and Tested

Drug	FDA Approval Date	Indications
Vancomycin	1958	"Initial therapy when MRSA suspected", endocarditis (including prosthetic valve), "septicemia", bone infections, surgical measures, Penicillin allergies, etc
Linezolid	2000	C**SSTI**, CAP, Nosocomial pneumonia, VRE
Daptomycin	2003	C**SSTI**, Bacteremia (Right Sided endocarditis MSSA/MRSA)
Telavancin	2009	C**SSTI**
Ceftaroline	2010	AB**SSSI**, CAP
Tedizolid	2014	AB**SSSI**
Oritavancin	2014	AB**SSSI**
Dalbavancin	2014	AB**SSSI**

CSSTI, complicated skin and skin structure infections
ABSSSI, acute bacterial skin and skin structure infections
CAP, community acquired pneumonia

CSSTI/ABSSSI Studies



Randomized Control Trials

Corey GR, et al. *NEJM* 2014;370:2180-2190

Boucher HW, et al. *NEJM* 2014;370:2169-2179

Corey GR, et al. *Clin Infect Dis* 2010;51:641-650

Stryjewski ME, et al. *Clin Infect Dis* 2008;46:1683-1693

Arbeit RD, et al. *Clin Infect Dis* 2004;38:1673-1681

Itani KMF, et al. *Am J Surg* 2010;199:804-816

A 45 y/o male presents with **extensive cellulitis** of the right foot appears to be resolving but determined to also have **bone involvement**. His foot undergoes debridement but the patient requires **an additional 4-6 weeks** of therapy. What therapy would you select/continue:

A Oritavancin

B Linezolid

C Daptomycin

D Vancomycin

MRSA Guidelines

Clinical Infectious Diseases Advance Access published January 4, 2011

IDSA GUIDELINES

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus Aureus* Infections in Adults and Children

Catherine Liu,[1] Arnold Bayer,[3,5] Sara E. Cosgrove,[6] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9] Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E. Murray,[14] Michael J. Rybak,[12,13] David A. Talan,[4,5] and Henry F. Chambers[1,2]

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Evidence-based guidelines for the management of patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections were prepared by an Expert Panel of the Infectious Diseases Society of America (IDSA). The guidelines are intended for use by health care providers who care for adult and pediatric patients with MRSA infections. The guidelines discuss the management of a variety of clinical syndromes associated with MRSA disease, including skin and soft tissue infections (SSTI), bacteremia and endocarditis, pneumonia, bone and joint infections, and central nervous system (CNS) infections. Recommendations are provided regarding vancomycin dosing and monitoring, management of infections due to MRSA strains with reduced susceptibility to vancomycin, and vancomycin treatment failures.

EXECUTIVE SUMMARY

MRSA is a significant cause of both health care–associated and community-associated infections. This document constitutes the first guidelines of the IDSA on the treatment of MRSA infections. The primary objective of these guidelines is to provide recommendations on the management of some of the most common clinical syndromes encountered by adult and pediatric clinicians who care for patients with MRSA infections. The guidelines address issues related to the use of vancomycin therapy in the treatment of MRSA infections, including dosing and monitoring, current limitations of susceptibility testing, and the use of alternate therapies for those patients with vancomycin treatment failure and infection due to strains with reduced susceptibility to vancomycin. The guidelines do not discuss active surveillance testing or other MRSA infection–prevention strategies in health care settings, which are addressed in previously published guidelines [1, 2]. Each section of the guidelines begins

Received 28 October 2010; accepted 17 November 2010.

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

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Clinical Infectious Diseases 2011;1–38

1058-4838/2011/5203-0001$37.00
DOI: 10.1093/cid/ciq146

Antimicrobial Selection

- **Word use**
  - **Vancomycin : 292**
  - Linezolid: 118
  - Daptomycin: 105
  - Clindamycin: 77

Vancomycin ("first-line")
Prosthetic joint infection, MRSA
Prosthetic joint infection, penicillin-resistant *Enterococcus*
Meningitis, MRSA, SSTI

Acknowledged Role:
Daptomycin: Bacteremia

Linezolid: Pneumonia

The Top Contenders

Differentiation

- **Method of delivery (IV/PO):** Linezolid has the edge
- **Frequency of delivery:** Daptomycin has the edge
- **Direct Cost:** Linezolid has the edge

- **Safety:** Vancomycin (nephrotoxicity)
  Linezolid (Myelosuppression)
  Daptomycin (Evolved since approval)
- **Therapeutic Drug Monitoring**: Do you think you picked the right dosage regimen?

Post-Marketing Safety (MedWatch, Drugs@FDA.gov)

- **Daptomycin**
  - Multiple label changes related to safety
  - Hypersensitivity, DRESS
  - Eosinophilic pneumonia
  - *C. difficile* –associated diarrhea
  - Peripheral Neuropathy
  - Visual disturbances
  - Acute kidney injury

- **Linezolid**
  - Drug-Drug interactions, SSRIs, rifampin
  - Myelosuppression
  - Tooth and tongue discolorations

- **Vancomycin**
  - DRESS
  - Corn allergies

A 60 y/o male presents with **fever and chills**. Blood cultures are positive for **MRSA**. Vancomycin is initiated but then **switched to daptomycin** after 72 hours based on MIC results (vancomycin MIC is 2 mg/L). What dosage of daptomycin would you initiate empirically in this **80 kg** patient with normal kidney function?

A 320 mg (4 mg/kg/day)

B 480 mg (6 mg/kg/day)

C 640 mg (8 mg/kg/day)

D 800 mg (10 mg/kg/day)

Why are some experts suggesting the need for higher doses of daptomycin?

- If higher doses are “better” then does that not imply that there is an exposure-response relationship?
- What are the risks for underexposure?
- What are the risks for overexposure?
- How do we ensure that we are achieving the right exposure?

Evaluation of Daptomycin Exposure and Efficacy and Safety Endpoints To Support Risk-versus-Benefit Considerations

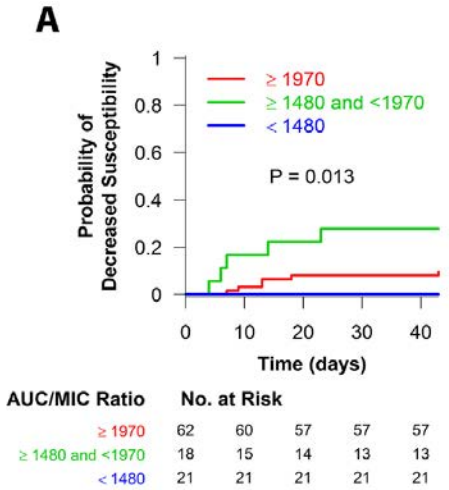
Sujata M. Bhavnani,[a] Paul G. Ambrose,[a] Jeffrey P. Hammel,[a] Christopher M. Rubino,[a] George L. Drusano[b]

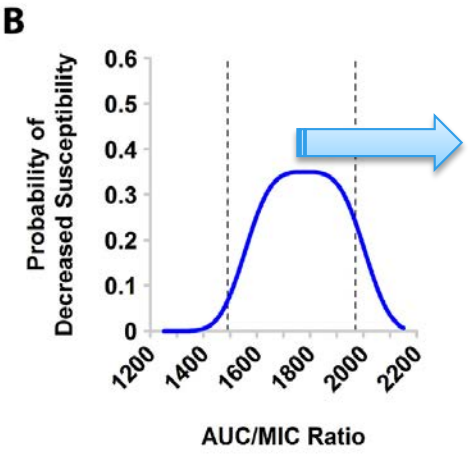
Institute for Clinical Pharmacodynamics, Latham, New York, USA[a]; Institute for Therapeutic Innovation, College of Medicine, University of Florida, Lake Nona, Florida, USA[b]

TABLE 2 Multivariable logistic regression model for clinical success

Variable and value	Parameter estimate (SE)	Odds ratio (95% CI[d])	Likelihood ratio *P* value
CL_{CR} (ml/min/1.73 m^2)			<0.001
≤51.2[a]		1	
>51.2 to ≤88.9	2.59 (1.18)	13.3 (1.32–135)	
>88.9	4.30 (1.35)	73.7 (5.21–1,042)	
AUC/MIC ratio			0.091
≤1,081[b]	NE	NE	
>1,081 to ≤2,334[a]		1	
>2,337	1.29 (0.94)	3.64 (0.57–23.2)	
Albumin concn (g/dl)			0.039
<2.9[a]		1	
≥2.9	1.55 (0.78)	4.70 (1.02–21.5)	
Diagnosis category[c]			0.086
1[a]		1	
2, 3, or 4	1.85 (1.28)	6.34 (0.52–77.2)	
5	3.03 (1.48)	20.8 (1.14–378)	

[a] Represents the reference group.
[b] With a 100% observed response (8/8) in the group with AUC/MIC ratios of ≤1,081, no estimates relative to this group could be obtained with maximum likelihood estimation. NE, not estimated.
[c] Diagnosis category definitions are as follows: 1, left-sided endocarditis; 2, 3, or 4, complicated right-sided endocarditis, uncomplicated right-sided endocarditis, or complicated bacteremia, respectively; 5, uncomplicated bacteremia.
[d] CI, confidence interval.





AUC/MIC of 1800 Equates to AUC of 450-900 h*mg/L, i.e. 4-8 mg/kg

Antimicrob Agents Chemother. 2015 Dec 28;60(3):1600-7.

Therapeutic Drug Monitoring

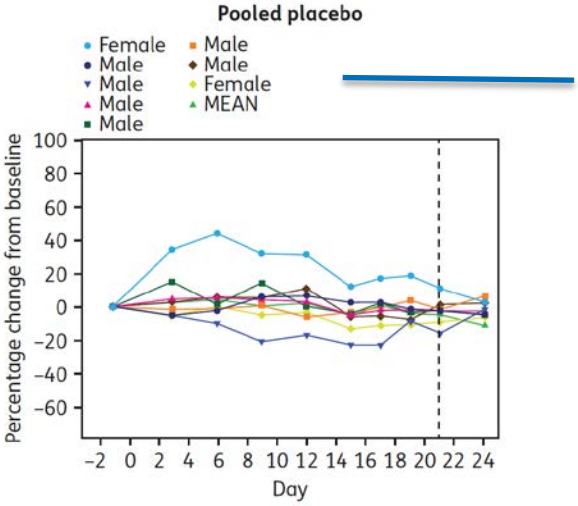
- **Vancomycin**
  - Target trough >10 mg/L to prevent emergence of resistance
  - Target trough of 15-20 mg/L for certain serious infections
  - Using twice the dosage as we did 20 years ago

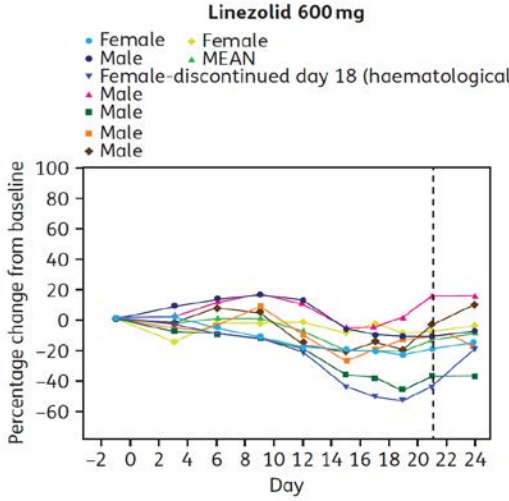
- **Daptomycin**
  - Not as predictable as you may think
  - Experts think we should use twice as much as we did 10 years ago
  - Why is there no need for therapeutic drug monitoring?

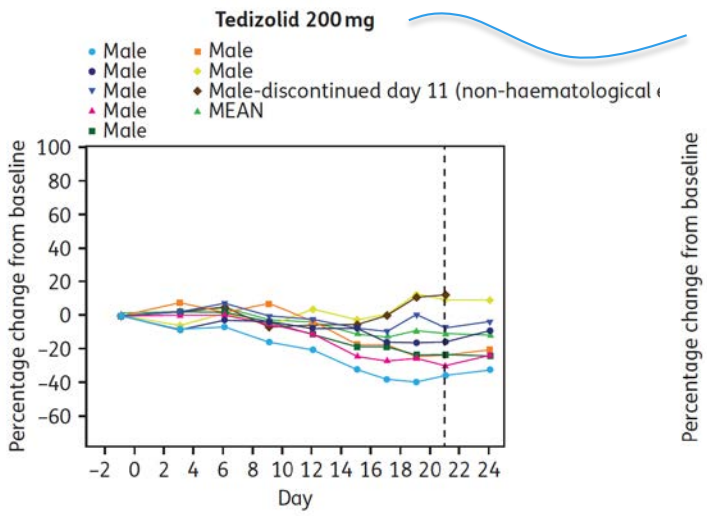
- **Linezolid**
  - High variability in PK profile
  - Emerging data to suggest that a trough 2-7 mg/L may be optimal
  - So why does one dose fit all?

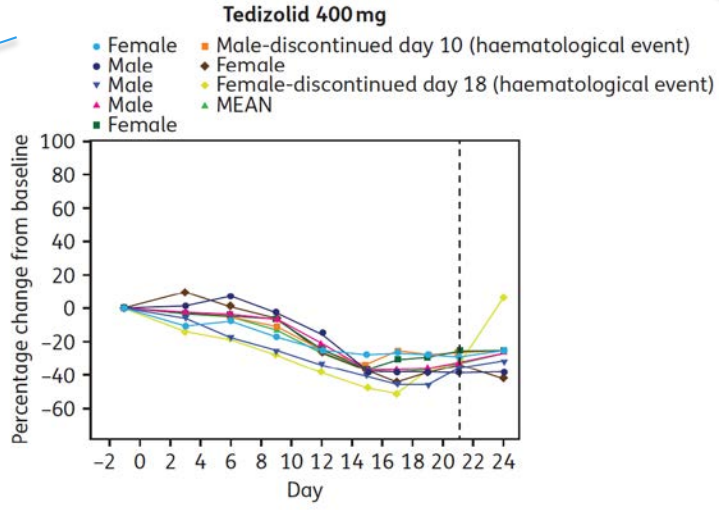
1. Am J Health Syst Pharm. 2009 Jan 1;66(1):82-98.
2. Drugs. 2016 Aug;76(12):1161-74.
3. Antimicrob Agents Chemother. 2016 Apr 22;60(5):3148-51.
4. Ther Drug Monit. 2015 Oct;37(5):634-40.
5. Expert Opin Drug Metab Toxicol. 2016 May;12(5):533-44.
6. J Antimicrob Chemother. 2015 Jan;70(1):198-206.

Oxazolidinones and Thrombocytopenia



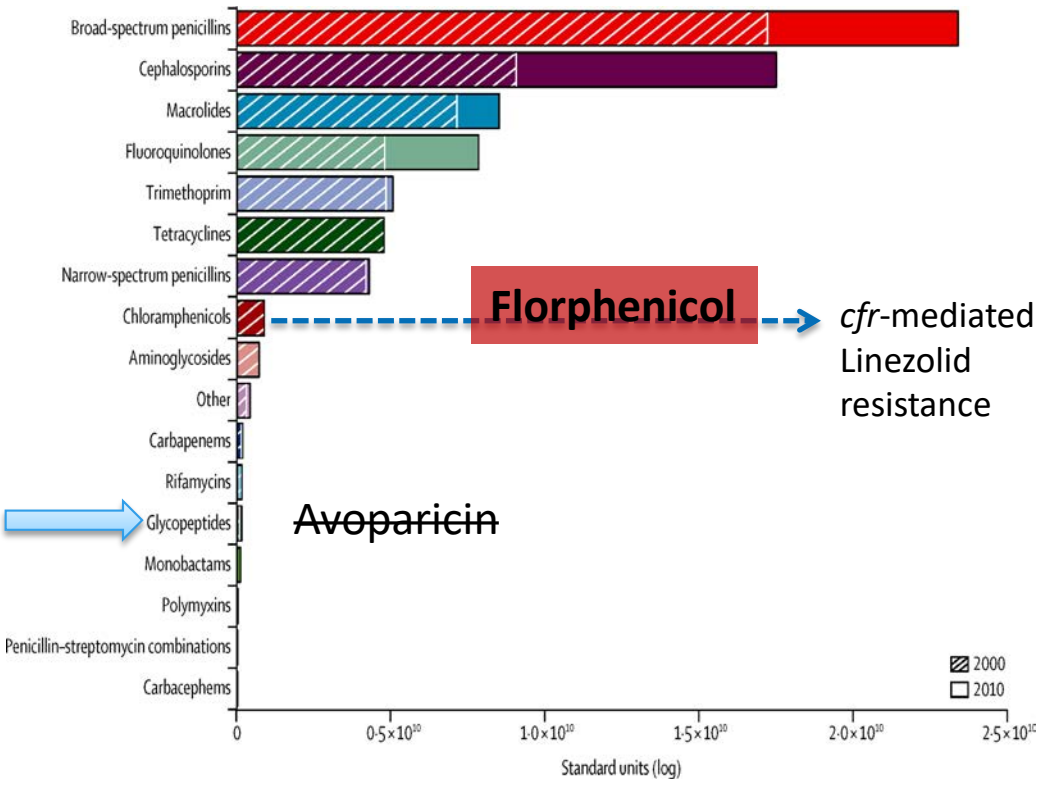






J Antimicrob Chemother. 2016 Sep;71(9):2553-8.

Global Antimicrobial Use



The Lancet Infectious Diseases 2014 14, 742-750DOI: (10.1016/S1473-3099(14)70780-7)

Antimicrobial Resistance

- 14 Cases of VRSA
  - **8** from Southeast Michigan
- **8 cases** of LRSA in 77 patients with cystic fibrosis,

  multiple such cases reported by several groups

Antimicrob Agents Chemother. 2011 Apr;55(4):1684-92.
Antimicrob Agents Chemother. 2013 Oct;57(10):51868
Antimicrob Agents Chemother. 2014 Nov;58(11):6592-8.

Key Takeaways

- **Vancomycin is alive**
  - Scientific interest and use of vancomycin remains robust because of our empiric need (may change with better diagnostics)
- **Vancomycin is well**
  - Randomized clinical trials maintain non-inferiority
- **Vancomycin is not without flaws but**
  - Other agents have safety concerns as well
  - Therapeutic drug monitoring may be needed for other agents
  - Over/misuse and resistance is a **concerning threat** for all agents

"Vancomycin's long reign as first-line therapy for serious MRSA infections may be in its twilight, but there is still no proven heir to the throne."

-Holland and Fowler (J Infect Dis. 2011; 204(3): 329-331)

Section End

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Rebutal

M. Rybak

Why Amit is Wrong?

- Regarding the argument that vancomycin is popular, has more publications or increasing in use:
  - Its use is high because MRSA is high
  - It is the cheapest MRSA drug $$$$
  - It is unrestricted and now used for prophylaxis
  - It has more clinical experience (papers) because it was made 60 years ago. It is a very very old drug!!!
  - It never went through randomized clinical trials for it's indications
    - It is likely that if assessed today, it may not be on the market

Why Amit is Wrong?

- The majority of clinical trials comparing vancomycin were non-inferiority studies
  - Powered to be equal and not superior!
- Skin and Soft Tissue Trials
  - Everything works
  - Includes surgical interventions
- Dapto vs. Vanco (vanco + aminoglycoside)
- Linezolid vs. Vanco
  - probably not the best comparator

Corey, GR. *NEJM* 2014;370:2180-90., Boucher HW. *NEJM* 2014; 370:2169-79., Corey, GR. *CID* 2008;51:641-50., Stryewski, ME. *CID*. 2004;38:1673-81., Itani, KMF. *Am J Surg.* 2010;199:804-16.

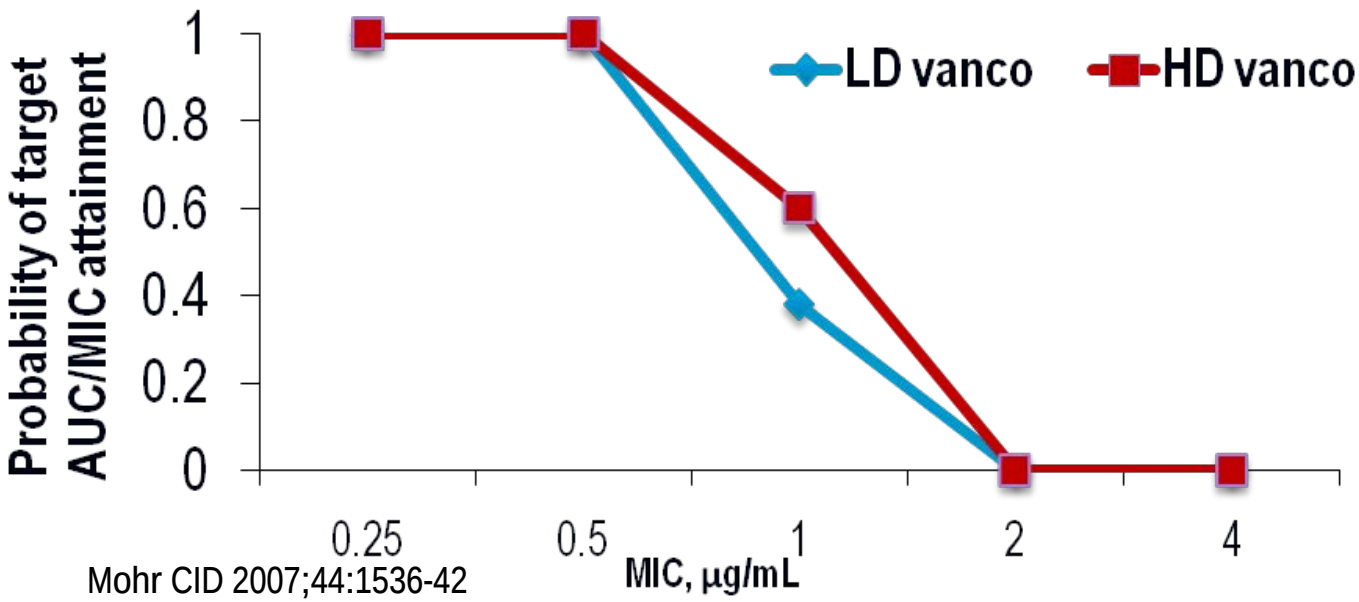
Dalbavancin bacteremia

- Open-label trial

Population	Outcome	Dalbavancin	Vancomycin	Risk Diff (95% CI)
mITT	Clinical success @TOC	87.0% (20/23)	50.0% (14/28)	37.0% (11.1-56.3%)
mITT	Micro success @TOC	95.7% (22/23)	78.6% (22/28)	17.1% (-2.9 - 35.5%)
CE	Clinical success @TOC	92.9% (13/14)	61.9% (13/21)	30.9% (1.1 - 52.7%)
CE	Micro success @TOC	100% (14/14)	80.0% (16/20)	20.0% (-4.6-41.6%)

Raad I, et al. *Clin Infect Dis* 2005;40:374-380.

Achieving the Vancomycin Targets



Mohr CID 2007;44:1536-42

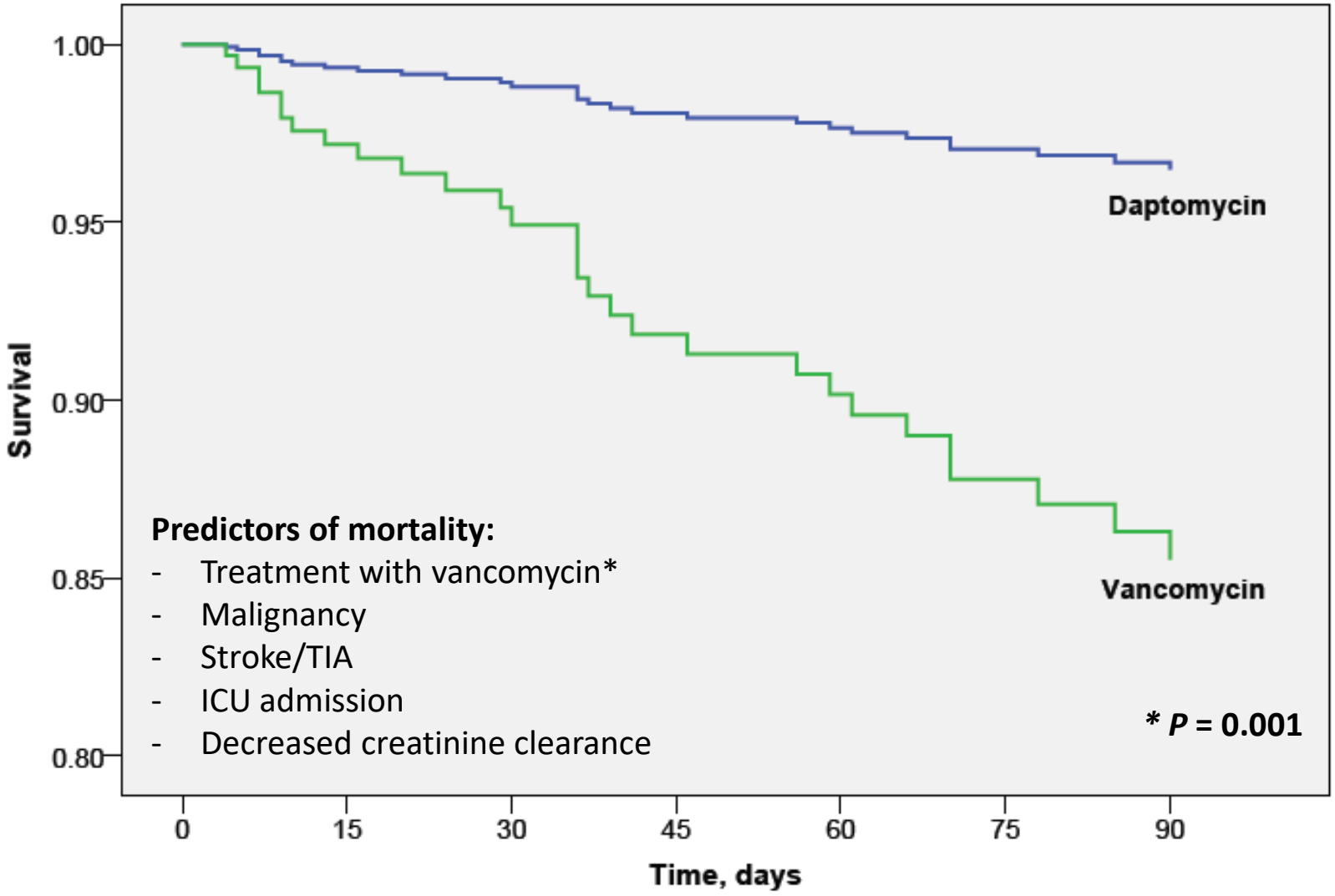
- Probability of achieving target AUC/ MIC is 0% if vancomycin MIC = 2 µg/mL with low or high-dose vancomycin
- Vanco MICs of 2 µg/mL associated with ↑ vanco Rx failures[1]
- "MIC creep" observed in some centers but not others[2]
  - Perhaps due to clonal dissemination or technical artifact

[1]Sakoulas *JCM* 2004;42:2398-402; Hidayat L *Arch Intern Med* 2006;166:2138-44; Lodise *AAC* 2008;52:3315-20; Maor *JID* 2009;199:619-24
[2]Alos *JAC* 2008;62:773-5; Holmes *AAC* 2008;52:757-60; Jones *CID* 2006;42:S13-24; Sader *AAC* 2009; 53:4127-32

Survival to 90 Days

Cox Proportional Hazards

n = 170



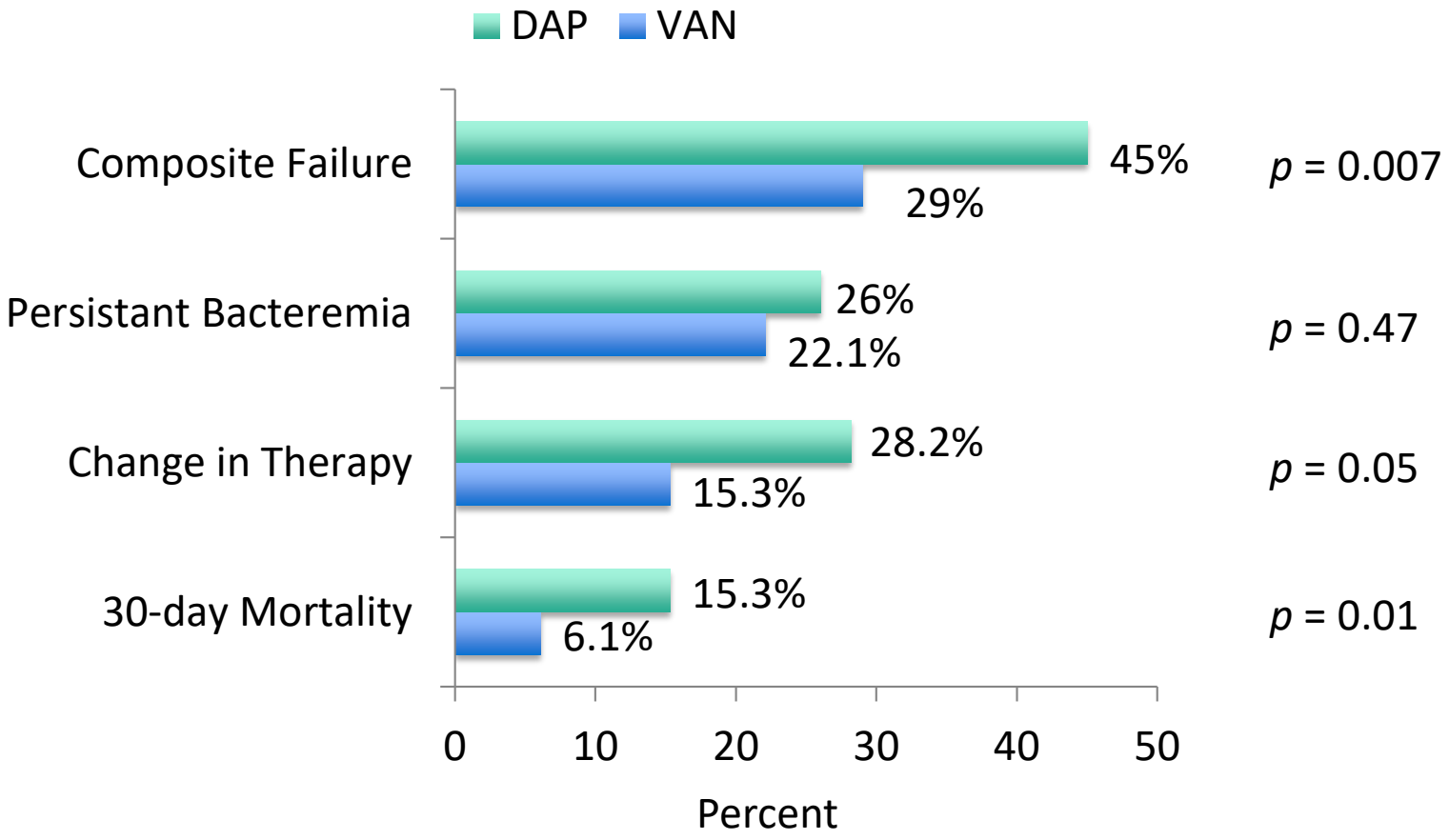
Predictors of mortality:

- Treatment with vancomycin*
- Malignancy
- Stroke/TIA
- ICU admission
- Decreased creatinine clearance

***P* = 0.001**

Murray, K. et al. *Clin Infect Dis*. 2013. 56; 96):1562-1569

Daptomycin Improves Outcomes Regardless of Vancomycin MIC in a Propensity-Matched Analysis of MRSA Bacteremia



Claeys, K.C. et al. *Antimicrob Agents Chemother*. 2016; 10 (60)

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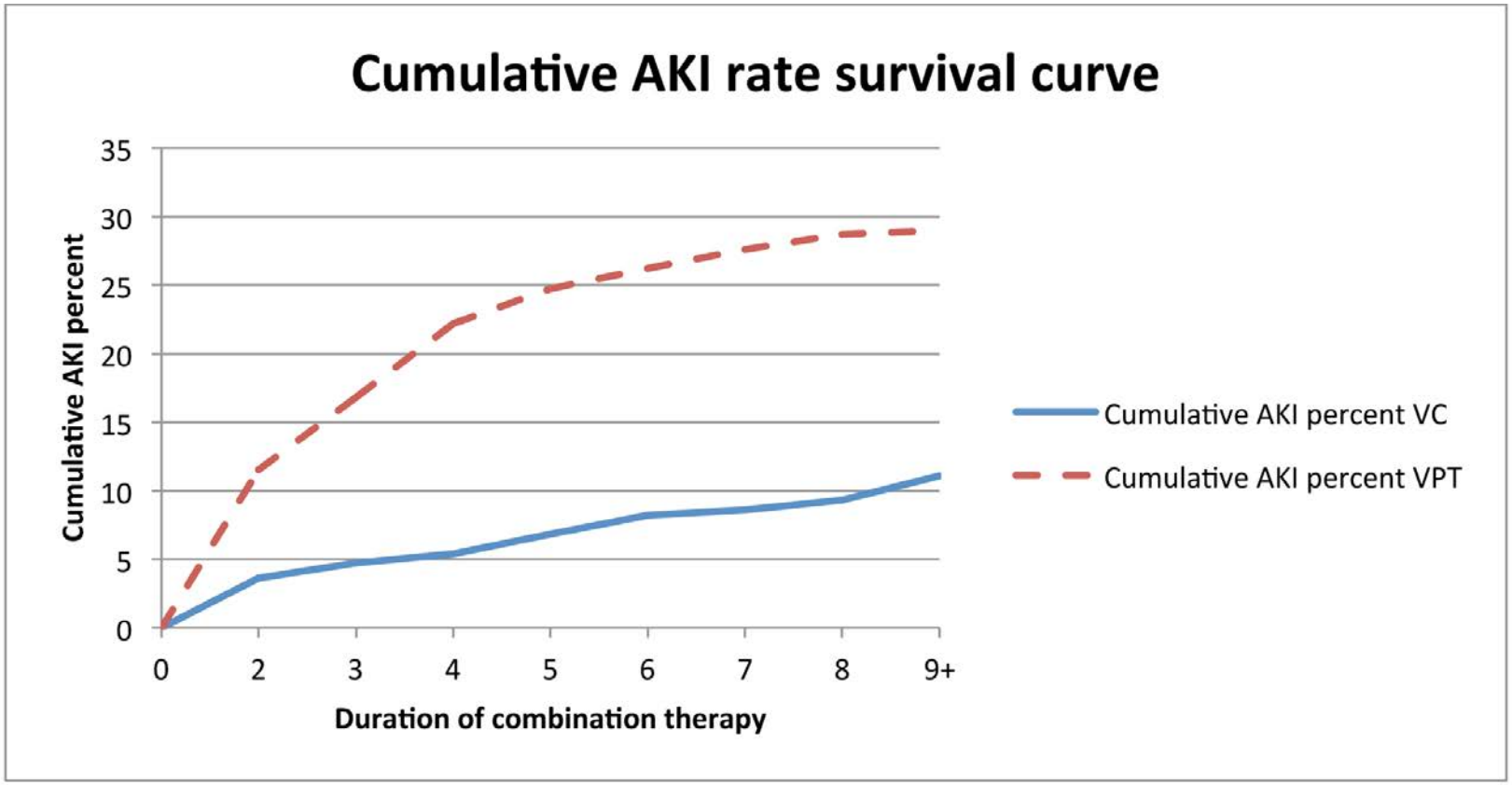
Vancomycin Combinaton Therapy



VC: Vancomycin-Cefepime; VPT: Vancomycin-Piperacillin-tazobactam; AKI: Acute Kidney Injury

Pogue J. et al. *CID* 2016 (accepted for publication)

Frustrations with Vancomycin

Re: Vancomycin Therapy – agree that vancomycin is a terrible drug. After staffing ASP full-time for the last 6 months (a new service for us), my threshold to recommend alternatives is low, especially when vancomycin doses push beyond my comfort zone for nephrotoxicity (generally > 4 g/day), troughs are below goal even on aggressive dosing, and/or we have recurrent positive blood cultures. Unfortunately, we already have a lot of scrutiny on our daptomycin spend so we try to be judicious, but I agree –for myself or a family member, I would want alternative therapy.