UWTASP
tele-antimicrobial stewardship program

Therapeutic Drug Concentration Monitoring (TDM) of Vancomycin

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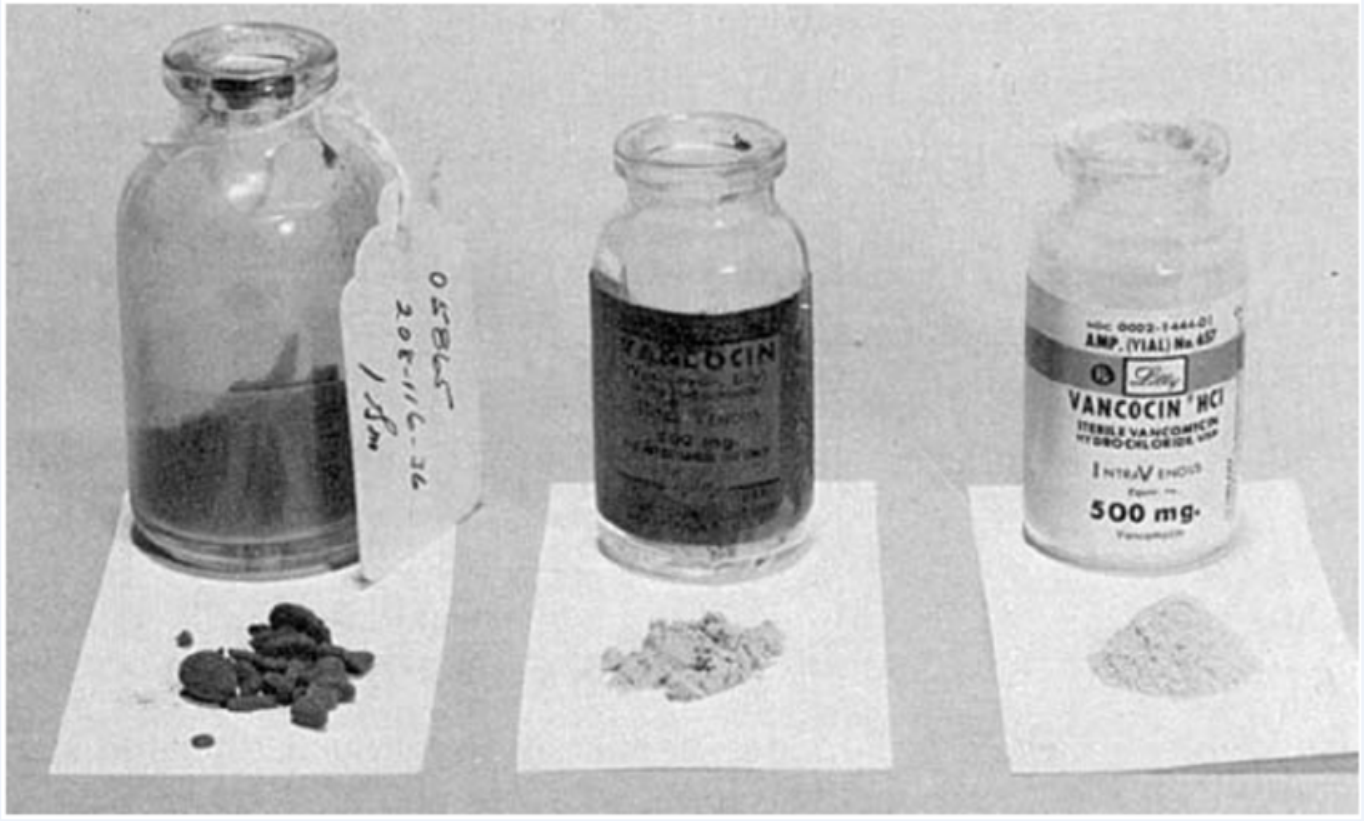
Agenda

1. Rationale and evidence for vancomycin serum concentration monitoring

2. Implication of targeting vancomycin serum trough concentration of 10-20 mcg/mL

3. Potential nephrotoxicity associated with vancomycin

Earlier Vancomycin Compound “Mississippi Mud”



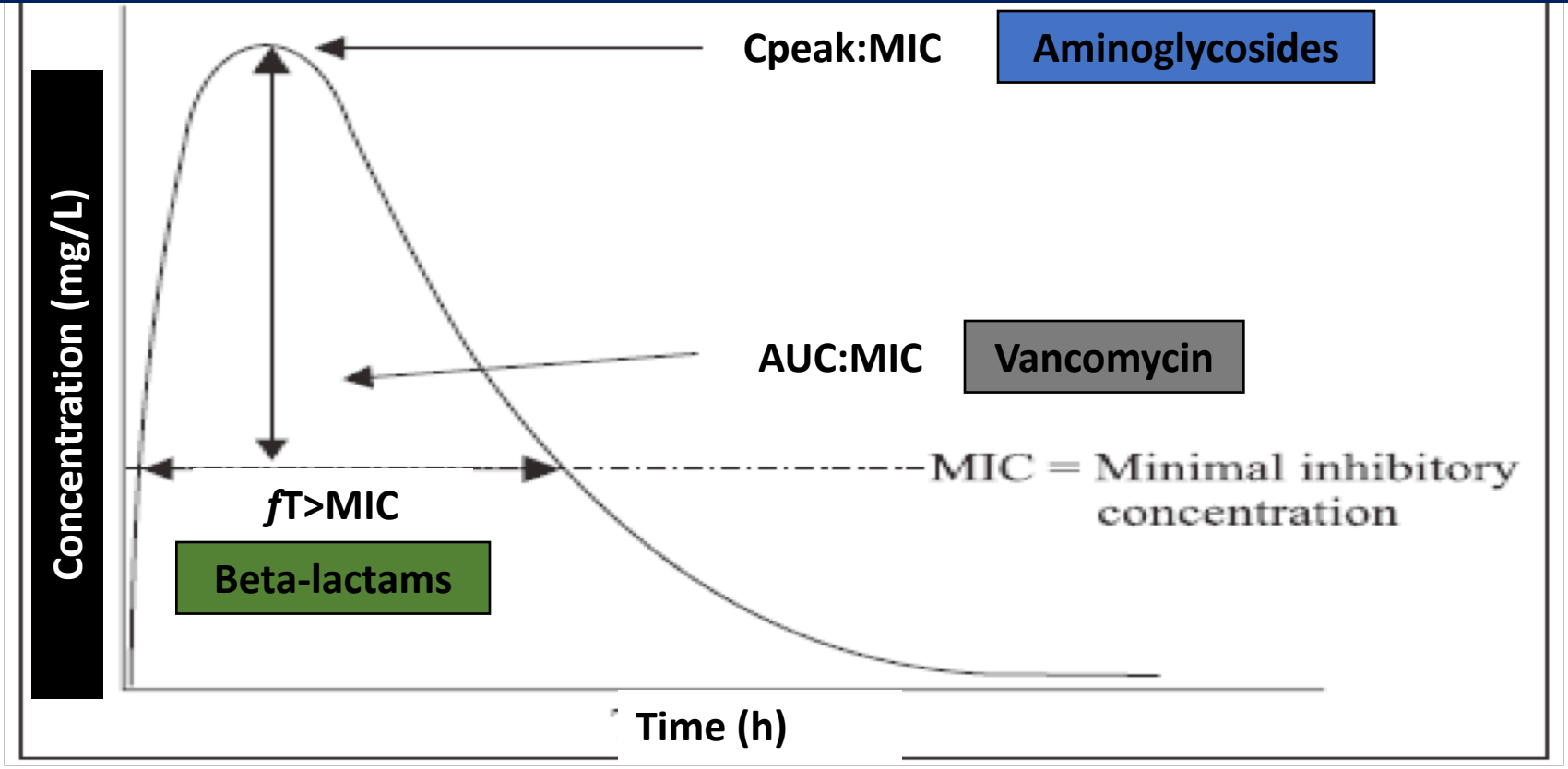
Historical Look at Vancomycin

- **Standard dose: 1gm IV Q12H**
- **Serum concentration monitoring secondary to impurity of the product**
- **Both peak and trough serum concentrations**
  - **Targeted peak level: 30-40 mcg/mL**
  - **Targeted trough level: 5-10 mcg/mL**

PK/PD Parameters

Pattern of killing activity	Drugs	Major PK-PD parameters
Concentration-dependent	Aminoglycosides Fluoroquinolones	Cmax/MIC
Time-dependent	β-lactams	Time above MIC, duration of *f*T>MIC
Time-dependent	Vancomycin	Time above MIC, 24h AUC/MIC

PK/PD Parameters



AUC = Area under the curve, MIC = Minimal inhibitory concentration

Santos Filho L et al. Braz J Microbiol. 2007 Apr/June;38(2):183-193.
Meagher AK et al. Antimicrob Agents Chemother. 2007 Jun;51(6):1939-45.
Craig WA. Infect Dis Clin North Am. 2003 Sep;17(3):479-501.

2009 ASHP/IDSA Guidelines

- AUC:MIC ratio ≥ 400 is most predictive of clinical effectiveness

- Target troughs most practical monitoring method as a surrogate marker
  - **≥ 10mcg/mL to minimize emergence of *S. aureus* resistance**
  - **15-20 mcg/mL for bacteremia, endocarditis, osteomyelitis, meningitis, and pneumonia caused by *S. aureus***

Clinical Implications

- Suboptimal vancomycin dosing has been suggested as alternative explanation for poorer outcomes
- Guidelines widely integrated into clinical practice
- More intensified vancomycin dosing to target trough level of 15-20 mcg/mL

Vancomycin Induced Nephrotoxicity

Larger Vancomycin Doses (at Least Four Grams per Day) Are Associated with an Increased Incidence of Nephrotoxicity▽

Thomas P. Lodise,[1,2]* Ben Lomaestro,[3] Jeffrey Graves,[1] and G. L. Drusano[2]

Albany College of Pharmacy, Albany, New York[1]; Ordway Research Institute, Albany, New York[2]; and Albany Medical Center Hospital, Albany, New York[3]

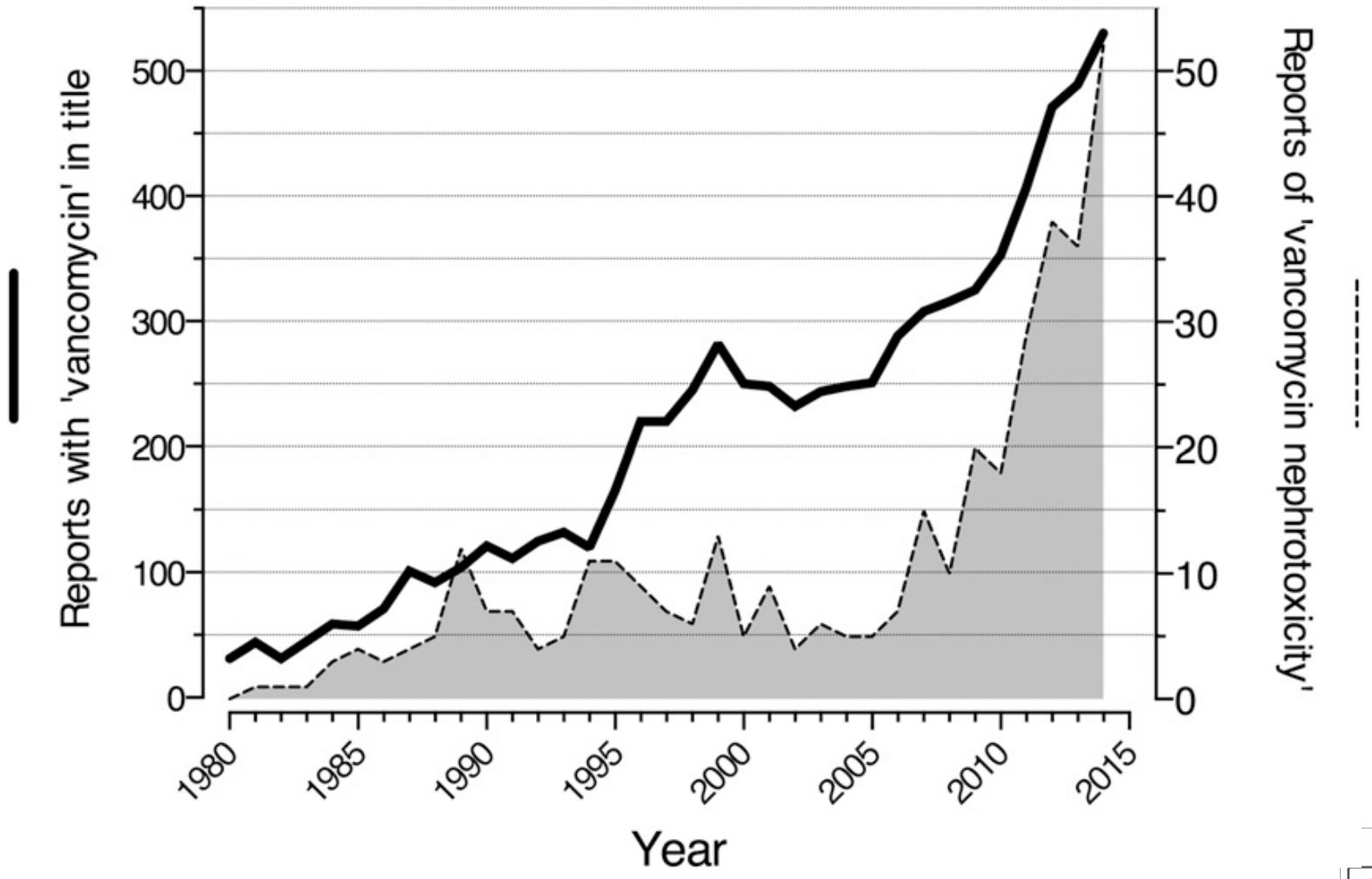
Relationship between Initial Vancomycin Concentration-Time Profile and Nephrotoxicity among Hospitalized Patients

Thomas P. Lodise,[1,2] Nimish Patel,[1] Ben M. Lomaestro,[3] Keith A. Rodvold,[4] and George L. Drusano[2]

A Retrospective Analysis of Possible Renal Toxicity Associated with Vancomycin in Patients with Health Care–Associated Methicillin-Resistant *Staphylococcus aure* Pneumonia

Meghan N. Jeffres, PharmD[1]; Warren Isakow, MD[2]; Joshua A. Doherty, BS[3]; Scott T. Micek, PharmD[1]; and Marin H. Kollef, MD[2]

Reports of Vancomycin Nephrotoxicity Increasing……



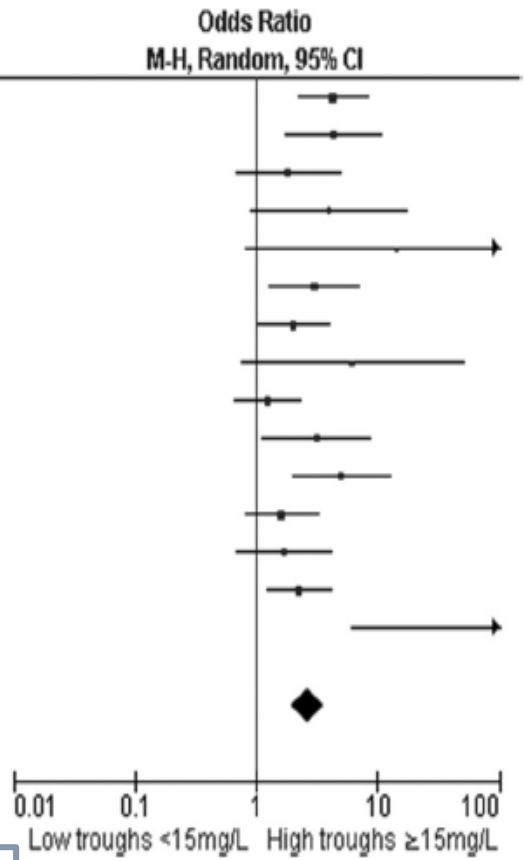
Nolin TD. Clin J Am Soc Nephrol 11: 2101–2103, 2016. doi: 10.2215/CJN.11011016

Meta-Analysis of Vancomycin-Induced Nephrotoxicity

Study or Subgroup	High troughs ≥15mg/L Events	Total	Low trough <15mg/L Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosso et al. (21)	42	142	13	146	9.8%	4.30 [2.19, 8.43]
Cano et al. (22)	22	89	7	99	7.2%	4.32 [1.74, 10.69]
Chung et al. (23)	12	25	16	48	6.5%	1.85 [0.69, 4.96]
Hermsen et al. (30)	5	16	4	39	3.6%	3.98 [0.91, 17.46]
Hidayat et al. (13)	11	63	0	32	1.1%	14.24 [0.81, 249.87]
Jeffres et al. (15)	27	49	13	45	7.7%	3.02 [1.28, 7.11]
Kralovicova et al. (31)	21	60	29	138	9.8%	2.02 [1.04, 3.96]
Kullar et al. (32)	8	116	1	84	2.0%	6.15 [0.75, 50.13]
Kullar et al. (8)	27	139	23	141	10.6%	1.24 [0.67, 2.28]
Lodise et al. (36)	7	27	14	139	6.2%	3.13 [1.12, 8.69]
McKamy et al. (38)	16	57	8	110	7.0%	4.98 [1.98, 12.52]
Minejima et al. (39)	17	72	25	155	9.6%	1.61 [0.80, 3.21]
Prabaker et al. (43)	7	54	24	294	7.3%	1.68 [0.68, 4.11]
Wunderink et al. (50)	26	118	24	215	10.7%	2.25 [1.22, 4.13]
Zimmermann et al. (51)	8	12	0	33	1.0%	126.56 [6.19, 2585.90]
Total (95% CI)		**1039**		**1718**	**100.0%**	**2.67 [1.95, 3.65]**
Total events	256		201			

Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 23.89$, df = 14 (P = 0.05); $I^2 = 41\%$

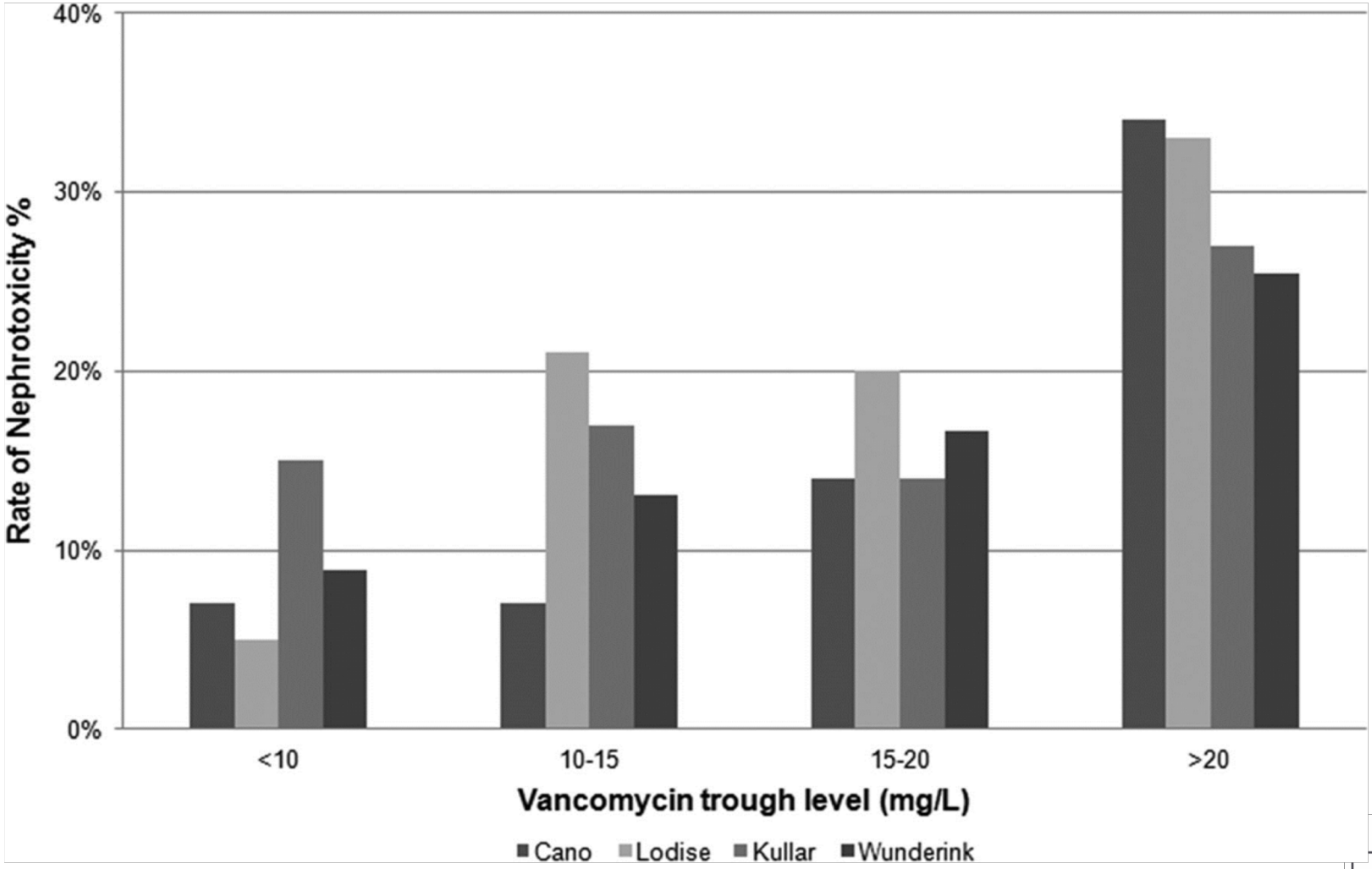
Test for overall effect: Z = 6.13 (P < 0.00001)



Odds Ratio = 2.67

S. J. van Hal et al. AAC 2013;57;734-744

Incidence of Vancomycin Nephrotoxicity with Rising Trough Levels



S. J. van Hal et al. Antimicrob. Agents Chemother. 2013; doi:10.1128/AAC.01568-12

Piperacillin/Tazobactam and Vancomycin

Clinical Infectious Diseases

VIEWPOINTS

Increasing Evidence of the Nephrotoxicity of Piperacillin/Tazobactam and Vancomycin Combination Therapy—What Is the Clinician to Do?

Richard R. Watkins[1,2] and Stan Deresinski[3]

Retrospective cohort study of hospitalized patients reported a two fold increased risk of nephrotoxicity in the setting of concomitant vanco and pip/tazo (16.3% vs. 8.1%) among patients treated with vanco alone

Burgess LD, et al. Pharmacotherapy 2014; 34:670-676

Fast Forward to 2015

AHA Scientific Statement

Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications

A Scientific Statement for Healthcare Professionals From the American Heart Association

Table 10. Therapy for NVE Caused by Staphylococci

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin or oxacillin	12 g/24 h IV in 4–6 equally divided doses	6	*Class I; Level of Evidence C*	For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, 2 wk (see text).
For penicillin-allergic (nonanaphylactoid type) patients				Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin.
Cefazolin*	6 g/24 h IV in 3 equally divided doses	6	*Class I; Level of Evidence B*	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases.
Oxacillin-resistant strains				
Vancomycin§	30 mg/kg per 24 h IV in 2 equally divided doses	6	*Class I; Level of Evidence C*	Adjust vancomycin dose to achieve trough concentration of 10–20 μg/mL (see text for vancomycin alternatives).
Daptomycin	≥8 mg/kg/dose	6	*Class IIb; Level of Evidence B*	Await additional study data to define optimal dosing.

IE indicates infective endocarditis; IV, intravenous; and NVE, native valve infective endocarditis.
*Doses recommended are for patients with normal renal function.
§For specific dosing adjustment and issues concerning vancomycin, se

Circulation. published online September 15, 2015;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Do pharmacists have collaborative drug therapy agreement for vancomycin at your institution?

Yes

No

Not sure

What vancomycin trough concentration does your institution target?

10-20 mcg/mL

15-20 mcg/mL

Not sure

2016 UW Medicine Guidelines

Organism	Targeted trough concentration	Comments
Staphylococcus aureus	10-20 mcg/ml	Trough range of 10-20 mcg/ml is sufficient for bacteremia, endocarditis, pneumonia, meningitis, or osteomyelitis.
Coagulase-negative Staphylococcus species or Enterococcus species	10-20 mcg/ml	Trough range of 10-20 mcg/ml is sufficient for bacteremia, endocarditis, pneumonia, meningitis, or osteomyelitis.
Empiric therapy when suspected organisms unknown (including neutropenic fever)	10-20 mcg/ml	Consider initial target trough range of 10- 20 mcg/ml for empiric therapy in patients with suspected infection.

Let’s examine the evidence….

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

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

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

Table 1.

Definitions of Levels and Grades for Recommendations[13]

Quality Indicator	Type of Evidence
Level of evidence	
I	Evidence from at least one properly randomized, controlled trial
II	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from more than one center); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
Grade of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation

Expert Panel Recommendations for Vancomycin Therapeutic Drug Monitoring

Variable	Recommendation	Level of Evidence	
Recommended TDM Parameters			
Optimal monitoring parameter	Trough serum vancomycin concentrations are the most accurate and practical method for monitoring efficacy.	IIB	Therapeutic vancomycin drug monitoring, Peak versus trough concentrations
Timing of monitoring			comycin drug eak versus trough s
Optimal trough concentration—complicated infections (bacteremia, endocarditis, osteomyelitis, meningit and hospital-acquired pneumonia caused by *Staphylococcus aureus*)	concentrations, and improve clinical outcomes.		comycin drug ptimal trough s
Dosing Regimen			
Dosing to achieve optimal			›mycin drug timal trough
Loading doses—complicated infections	(based on actual body weight) can be used to facilitate rapid attainment of target trough serum vancomycin concentration.		›mycin drug monitoring, Optimal trough concentrations
Continuous vs. intermittent dosing	Continuous infusion regimens are unlikely to substantially improve patient outcome when compared to intermittent dosing.	IIA	Impact of dosing strategies on pharmacokinetic and pharmacodynamic parameters
TDM for Vancomycin-Induced Nephrotoxicity			
Definition	A minimum of two or three consecutive documented increases in serum creatinine concentrations (defined as an increase of 0.5 mg/dL or a ≥50% increase from baseline, whichever is greater) after several days of vancomycin therapy.	IIB	Vancomycin toxicity; Incidence, mechanism, and definition of nephrotoxicity

Optimal trough concentrations

Trough concentrations of 15 – 20 mg/L are recommended to improve penetration, increase the probability of obtaining optimal target serum concentrations, and improve clinical outcomes.
Level of Evidence: IIIB

Dosing Regimens

Doses of 15 – 20 mg/kg given q 8-12 hr are recommended for most patients…to achieve the targeted AUC:MIC > 400
Level of Evidence: IIIB

Expert Panel Recommendations for Vancomycin Therapeutic Drug Monitoring

Variable	Recommendation	Level of Evidence	
Recommended TDM Parameters			
Optimal monitoring parameter	Trough serum vancomycin concentrations are the most accurate and practical method for monitoring efficacy.	IIB	Therapeutic vancomycin drug monitoring, Peak versus trough concentrations
Timing of monitoring			ycin drug versus trough
Optimal trough concentrations			ycin drug mal trough
infections)			
Optimal trough concentration—complicated infections (bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by *Staphylococcus aureus*)	are recommended to improve penetration, increase the probability of obtaining optimal target serum concentrations, and improve clinical outcomes.		ycin drug monitoring, Optimal trough concentrations
Dosing Regimen			
Dosing to achieve optimal trough concentrations	Doses of 15–20 mg/kg (as actual body weight) given every 8–12 hr are recommended for most patients with normal renal function to achieve the suggested serum concentrations when the MIC is ≤1 mg/L. In patients with normal renal function, the targeted AUC:MIC of >400 is not achievable with conventional dosing methods if the MIC is ≥2 mg/L in a patient with normal renal function.	IIIB	Therapeutic vancomycin drug monitoring, Optimal trough concentrations
Loading doses—complicated infections	In seriously ill patients, a loading dose of 25–30 mg/kg (based on actual body weight) can be used to facilitate rapid attainment of target trough serum vancomycin concentration.	IIIB	Therapeutic vancomycin drug monitoring, Optimal trough concentrations
Continuous vs. intermittent dosing	Continuous infusion regimens are unlikely to substantially improve patient outcome when compared to intermittent dosing.	IIA	Impact of dosing strategies on pharmacokinetic and pharmacodynamic parameters
TDM for Vancomycin-Induced Nephrotoxicity			
Definition	A minimum of two or three consecutive documented increases in serum creatinine concentrations (defined as an increase of 0.5 mg/dL or a ≥50% increase from baseline, whichever is greater) after several days of vancomycin therapy.	IIB	Vancomycin toxicity; Incidence, mechanism, and definition of nephrotoxicity

For a pathogen with an MIC of 1 mg/L, the minimum trough concentration would have to be at least 15 mg/L to generate the target AUC/MIC of 400.
Level of Evidence: IIIB

ASHP REPORT Vancomycin

Impact of Vancomycin Exposure on Outcomes in Patients with Methicillin-Resistant *Staphylococcus aureus* Bacteremia: Support for Consensus Guidelines Suggested Targets

Ravina Kull

Predictors of Mortality for Methicillin-Resistant *Staphylococcus aureus* Health-Care–Associated Pneumonia*

Specific Evaluation of Vancomycin Pharmacokinetic Indices

Meghan N. Jeffres, PharmD; Warren Isakow, MD; Joshua A. Doherty, BS; Peggy S. McKinnon, PharmD; David J. Ritchie, PharmD; Scott T. Micek, PharmD; and Marin H. Kollef, MD, FCCP

Journal of Intensive Care Medicine
26(6) 385-391

DOI: 10.1177/0885066610392893
http://jicm.sagepub.com
SAGE

Clinic Vanc *Staphylococcus aureus* Ventilator-Associated Pneumonia: Retrospective Analysis

Jeannie D. Chan, PharmD, MPH[1], Tam N. Pham, MD[2], Jenny Wong, PharmD[1], Michelle Hessel, PharmD[1], Joseph Cuschieri, MD[2], Margaret Neff, MD, MS[3], and Timothy H. Dellit, MD[4]

Staphylococcus aureus bacteremia

Evan C. Clemens[a], Jeannie D. Chan[a,*], John B. Lynch[b], Timothy H. Dellit[b]

[a]*Department of Pharmacy, Harborview Medical Center and School of Pharmacy, University of Washington, Seattle, WA 98104, USA*
[b]*Division of Allergy and Infectious Diseases, Department of Medicine, Harborview Medical Center and School of Medicine, University of Washington, Seattle, WA 98104, USA*

Received 29 April 2011; accepted 1 August 2011

Summary of clinical data

- Retrospective observational studies
- Multiple studies have NOT demonstrated a correlation between trough level ≥ 15 mcg/mL with clinical efficacy
- RCT of linezolid vs. vancomycin in MRSA pneumonia, trough level ≥ 15 mcg/mL was NOT associated with improved clinical response

Wunderink RG, et al. CID 2012;54:621-629

ORIGINAL INVESTIGATION

High-Dose Vancomycin Therapy for Methicillin-Resistant *Staphylococcus aureus* Infections

Efficacy and Toxicity

Levita K. Hidayat, PharmD; Donald I. Hsu, PharmD; Ryan Quist, PhD; Kimberly A. Shriner, MD; Annie Wong-Beringer, PharmD

- **Retrospective cohort of 95 patients with MRSA infections (77% with pneumonia and/or bacteremia)**
- **Primary Endpoint: clinical response, mortality, and nephrotoxicity**
- **Subgroup: high vs. low MIC (≥ 2 vs. <2 mcg/mL) and vancomycin level (≥ 15 vs. <15 mcg/mL)**

Hidayat LK, et al. Arch Intern Med 2006;166:2138-2144

High MIC is less responsive to vancomycin despite achieving trough of ≥ 15 µg/mL

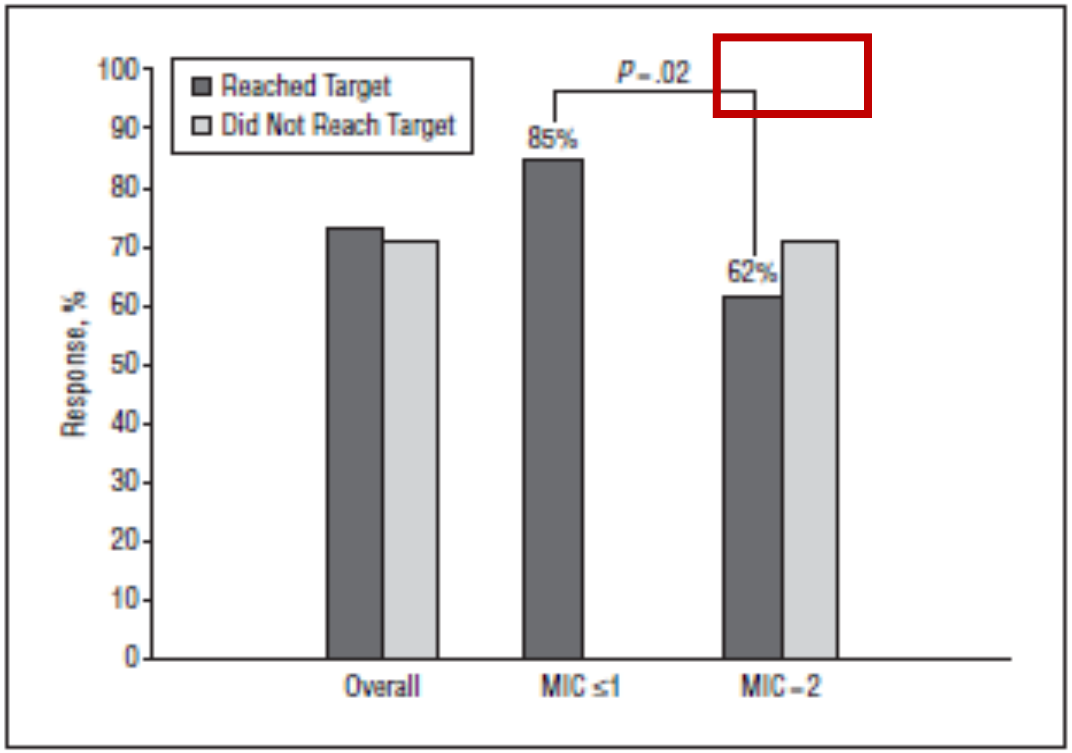


Figure 2. Final response based on target trough achievement. Evaluation was based on 86 patients (9 patients were excluded because of change in therapy from vancomycin hydrochloride). MIC indicates minimum inhibitory concentration.

Influence of Vancomycin Minimum Inhibitory Concentration on the Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Alex Soriano,[1] Francesc Marco,[2] José A. Martínez,[1] Elena Pisos,[1] Manel Almela,[2] Veselka P. Dimova,[2] Dolores Alamo,[2] Mar Ortega,[1] Josefina Lopez,[1] and Josep Mensa[1]

Departments of [1]Infectious Diseases and [2]Microbiology, Hospital Clinic of Barcelona, Barcelona, Spain

Clinical Infectious Diseases 2008; 46:193–200

- **Retrospective review of 414 episodes of MRSA bacteremia from 1991 to 2005 at an University hospital**
- **Primary Endpoint: predictors for mortality**

Table 5. Factors independently associated with mortality in a logistic regression model of patients with episodes of methicillin-resistant *Staphylococcus aureus* bacteremia.

Factor	OR (95% CI)	*P*
Age, per year	1.02 (1.00–1.04)	.013
Receipt of corticosteroids	1.85 (1.04–3.29)	.034
Prognosis of underlying disease		
Nonfatal	1	
Rapidly fatal	1.81 (1.06–3.10)	.029
Ultimately fatal	10.2 (2.85–36.8)	<.001
Source of bacteremia		
Low risk	1	
Intermediate risk	2.18 (1.17–4.04)	.014
High risk	3.60 (1.89–6.88)	<.001
Treatment group		
VMIC1	1	
VMIC1.5	2.86 (0.87–9.35)	.08
VMIC2	6.39 (1.68–24.3)	<.001
NA	3.62 (1.20–10.9)	<.001
Shock	7.38 (4.11–13.3)	<.001

MRSA isolates with elevated vancomycin MIC

- Increasing evidence that MRSA isolates with vancomycin MIC > 1 mcg/ml are associated with higher rate of treatment failure

- Ineffective vancomycin treatment vs. inherent microbiologic characteristics of the organism?

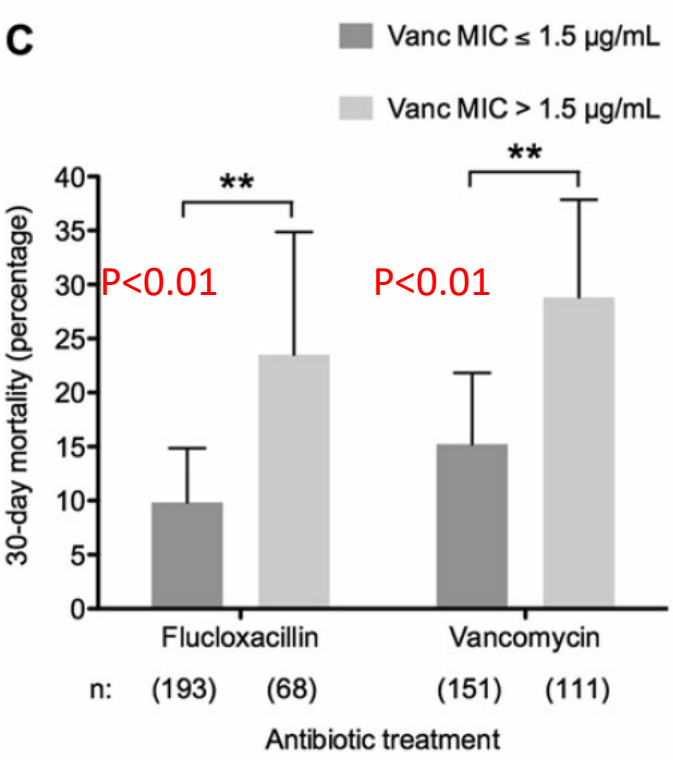
Antibiotic Choice May Not Explain Poorer Outcomes in Patients With *Staphylococcus aureus* Bacteremia and High Vancomycin Minimum Inhibitory Concentrations

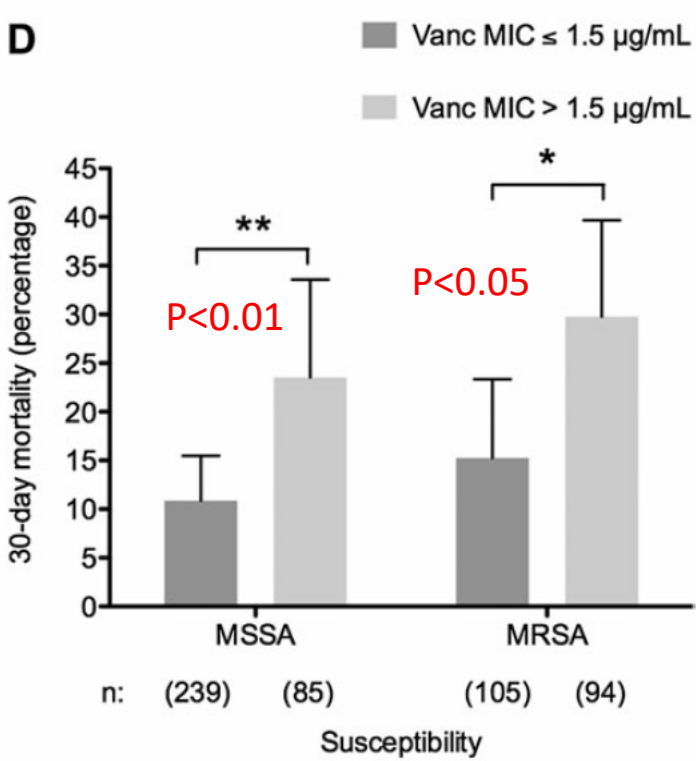
Natasha E. Holmes,[1] John D. Turnidge,[2,3] Wendy J. Munckhof,[4,5] James O. Robinson,[6] Tony M. Korman,[7,8] Matthew V. N. O'Sullivan,[9] Tara L. Anderson,[10,11] Sally A. Roberts,[2] Wei Gao,[12] Keryn J. Christiansen,[13,14] Geoffrey W. Coombs,[13] Paul D. R. Johnson,[1,15,16,a] and Benjamin P. Howden[1,12,15,17,a]

The Journal of Infectious Diseases 2011;204:340–47

- **Retrospective review of 532 patients with *S. aureus* bacteremia (both MRSA and MSSA) bacteremia from 8 hospitals**
- **Primary Endpoint: 30-day all cause mortality**

High MIC is associated with increased mortality regardless of methicillin resistance, even in patients with MSSA bacteremia treated with flucloxacillin





Conclusion

- Serum concentration vs. AUC monitoring
- Peak serum concentration are not necessary
- Maintain trough $\geq$ 10 mcg/mL to decrease emergence of resistance
- Consider target range of 10-20 mcg/mL

Conclusion

- Targeted trough level established *S. aureus*
  - **GPC other than MRSA**
  - **Site of infection**
- Trough of 15-20 mcg/mL is not absolute with increased risk of nephrotoxicity
- Concomitant medications that are potential nephrotoxins
- Avoid chasing numbers, consider drug accumulation over time