

Vancomycin & New Agents for MRSA Infections

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Objectives

- ① Using vancomycin MIC values define what is meant by vancomycin sensitive, h-VISA, intermediate (VISA/GISA), & resistant MRSA.
- ① Define how tolerance affects vancomycin performance.
- ① Identify how the vancomycin MIC affects the eradication of MRSA from blood, overall cure, and risk of mortality.
- ① Define vancomycin performance from a pharmacodynamic perspective (rapid vs slow bacterial killing, cidal vs static, appropriate PD outcome parameter and targeted value).
- ① Identify the value and risks of current clinical strategies to use higher trough serum concentrations.
- ① Identify appropriate antibiotic alternative to vancomycin and their potential limitations.

MRSA Treatment Options

① Currently Available Options

- ▶ Vancomycin
- ▶ Clindamycin
- ▶ TMP/SMX
- ▶ Doxycycline/Minocycline
- ▶ Quinupristin/Dalfopristin
- ▶ Linezolid
- ▶ Daptomycin
- ▶ Tigecycline
- ▶ Telavancin (Approvable Letter from FDA)
- ▶ Delbavancin (Approvable Letter from FDA)

Vancomycin Susceptibility *S. aureus* CLSI 2006

- ① Sensitive (VSSA)
 - ▶ Vancomycin MIC ≤ 2 mg/L
- ① Heteroresistant strain (h-VISA)
 - ▶ H-VISA likely when vancomycin MIC = 1 or 2 mg/L (Surrogate Marker)
 - ▶ Most labs will not do definitive testing
- ① Intermediate (VISA or GISA)
 - ▶ Vancomycin MIC = 4-8 mg/L
- ① Resistant (VRSA)
 - ▶ Vancomycin MIC ≥ 16 mg/L
 - Lab needs to backup primary testing with 6mg/L vancomycin overnight plate
- ① Tolerance (MBC / MIC $\geq 16-32$)

Vancomycin Treatment Guidelines

Guideline	Organ	Dose	Trough (mg/L)
HAP/VAP	ATS/IDSA	15 mg/Kg Q12H	15-20
Meningitis	IDSA	15 mg/Kg Q8 or 12H	15-20*
Endocarditis	BSAC	1Gm Q12H	10-15
Endocarditis	AHA	15 mg/Kg Q12H	10-15*

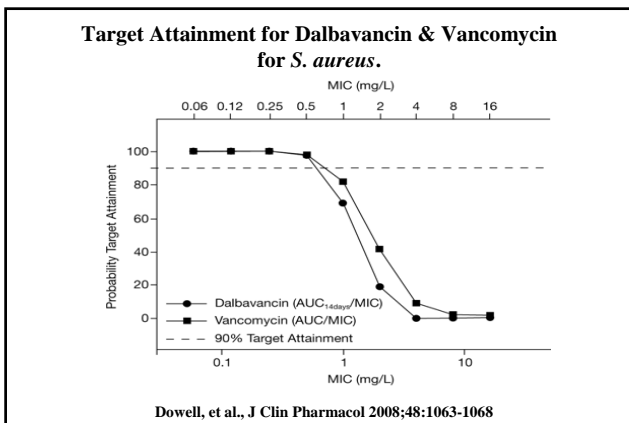
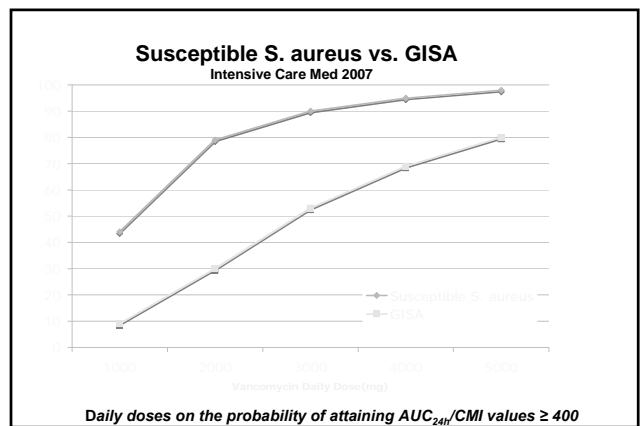
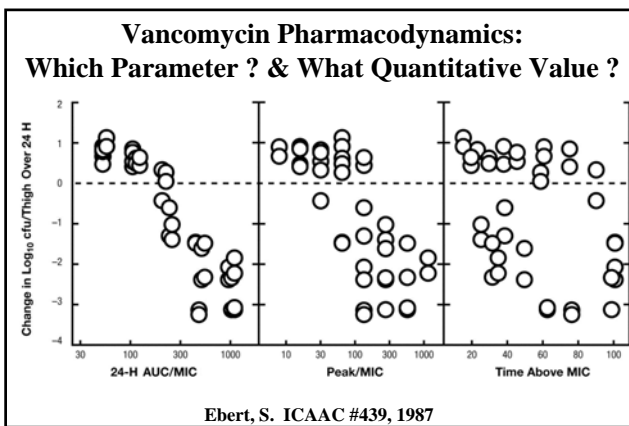
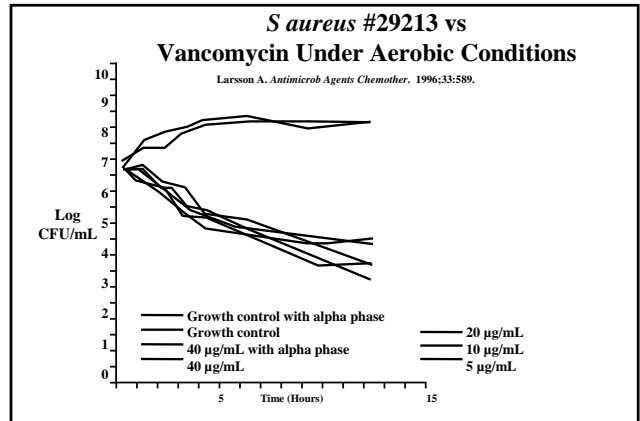
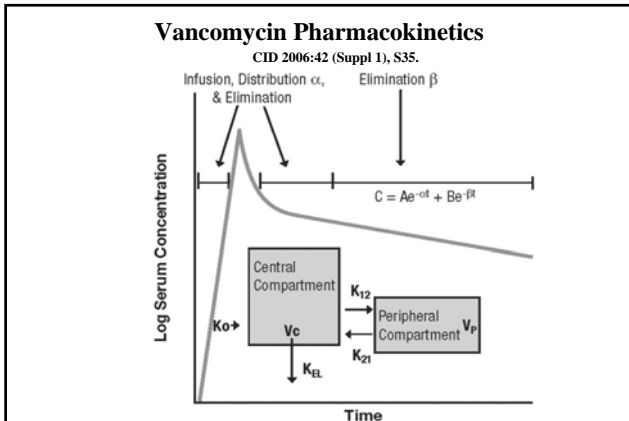
* Graded Recommendation

•No evidence offered that:

- Initial dose will produce desired troughs
- That higher troughs are more effective
- That higher troughs are safe

Factors Affecting Vancomycin Clinical Performance

- ① Poor tissue penetration
- ① Bactericidal but a slow killer of gram positive pathogens
- ① Level of glycoalyx production
- ① Limited to no affect on toxin production
- ① Lysis of cell wall could aid toxin release
- ① High bacterial inoculum
- ① Anaerobic conditions



Clinical Laboratory Support for Vancomycin Susceptibility Reporting

- ⊙ Many hospitals still report (S) – susceptible, (I) - intermediate, or (R) - resistant
- ⊙ Automated systems in the past would report an MIC ≤ 1 mg/L (Vitek II) or ≤ 2 mg/L (Microscan)
 - Vitek II Fall 2008 will change to ≤ 0.5 mg/L
 - 5.01 software update required
 - Microscan Dec 2007 changed to ≤ 0.25 mg/L
 - Need 3.0 software upgrade or 2.0 & Pos 29 or Pos 26 panel
- ⊙ Limited evidence of Vancomycin MIC creep over the years

Relationship of MIC & Bactericidal Activity to Efficacy of Vancomycin for the Treatment of MRSA Bacteremia

Sakoulas, G et al J Clin Micro 42:2398-2402, 2004

- ☉ If MRSA MIC \leq 0.5 mg/L
 - ▶ 55.6% successful outcome
- ☉ If MIC 1 or 2 mg/L
 - ▶ 9.5% successful outcome
- ☉ High vancomycin MIC's may increase risk of resistance to newer agents (i.e. Daptomycin)

Median Duration of Bacteremia & Fever in MRSA Endocarditis

Adapted: Levine Ann Intern Med 115:574, 1991

	N	Median Duration Bacteremia Days	Median Duration Fever Days (95% CI)
All	42	9 (6-11)	7 (4-9)
Vancomycin	22	7 (5-11)	7 (3-8)
Vanc/Rifampin	20	9 (6-13)	7 (3-10)
Left Sided	8	9 (3-10)	7 (N/A)
Right Sided	34	7 (5-11)	8 (3-10)

Vancomycin MIC versus eradication rates

Vancomycin (μ g/ml)	No. of Isolates	Median DTE ^a	Median Duration of Vancomycin Therapy (days)	Eradication Rate by EOT ^b	Median Reduction in log ₁₀ CFU/ml
0.5	13	6.0	13.0	10/13 (77)	3.06
1.0	7	9.5	17.0	5/7 (71)	3.09
2.0	14	> 15.0 ^c	18.5	3/14 (21)	2.75

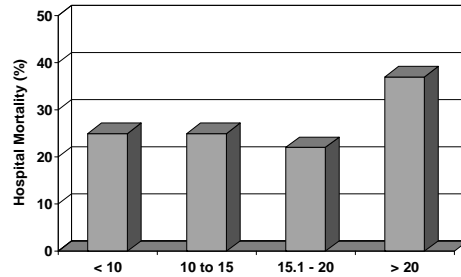
^aDTE, day to eradication.

^bEOT, end of treatment.

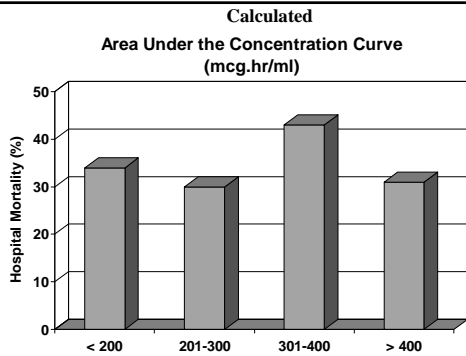
^cThe median time to eradication is >15 days, as only 21% of patients showed clearance of bacteremia.

Moise, PA et al AAC 51(7): 2582-2586, 2007

Vancomycin Trough Concentrations (mcg/ml) vs Hospital Mortality

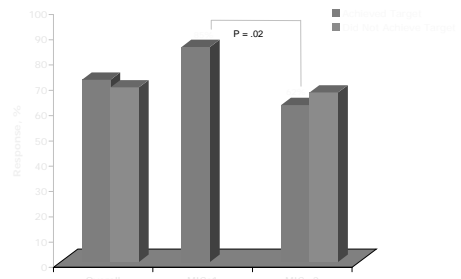


Jeffres, MN et al Chest 130:947-955, 2006



Jeffres, MN et al Chest 130:947-955, 2006

Clinical Response Based on Targeted Trough (Goal = Unbound Trough Concentration \geq 4 X MIC)



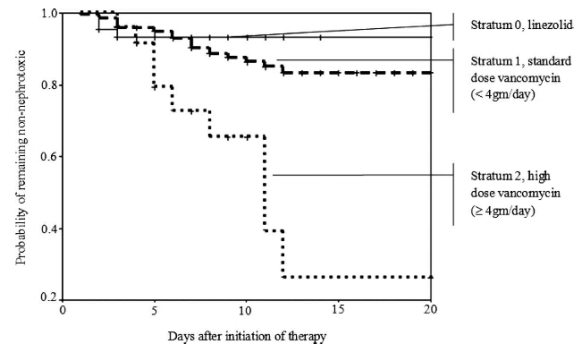
Hidayat, LK et al Arch Intern Med 166:2138-2144, 2006

Vancomycin Nephrotoxicity

	$C_{p_{min}} < 15 \text{ mg/L}$	$C_{p_{min}} \geq 15 \text{ mg/L}$
Jeffres K789 ICAAC 2006	30.2%	58.8%
Such L1298 ICAAC 2006	0.0%	15.0%
Hidayat Arch Intern Med 2006	0.0%	12.0%
Nguyen K1096 ICAAC 2007	6.2%	18.2%

Kaplan Meier Plot $\geq 4 \text{ Gm/day}$ Vancomycin & Nephrotoxicity

Lodise, TP et al AAC 52:1330-1336, 2008



Therapeutic monitoring of vancomycin in adult patients: A consensus review of the ASHP, IDSA, and SIDP

Am J Health Syst Pharm January 2009

- ☉ Troughs are the most accurate & practical method for monitoring efficacy
- ☉ Troughs should be maintained $> 10 \text{ mg/L}$
 - 15-20 mg/L for complicated infections ($\text{AUC/MIC} \geq 400$)
- ☉ Monitoring trough serum concentrations to reduce nephrotoxicity
 - Best suited for aggressive dosing (troughs 15-20 mg/L)
 - Recommended for patients with unstable renal function
- ☉ All patients receiving prolonged therapy should have at least one steady state trough concentration ($> 4^{\text{th}}$ dose)

Therapeutic monitoring of vancomycin in adult patients: A consensus review of the ASHP, IDSA, and SIDP

Am J Health Syst Pharm January 2009

- ☉ For rapid target attainment in seriously ill patients a 25-30 mg/Kg loading dose should be considered
 - 15-20 mg/Kg Q8-12H required if *S. aureus* $\text{MIC} \leq 1 \text{ mg/L}$
 - If *S. aureus* $\text{MIC} \geq 2 \text{ mg/L}$ dynamic target will not be achieved
- ☉ Frequent monitoring for short course therapy or for troughs $< 15 \text{ mg/L}$ not recommended
- ☉ Limited data to support safety of troughs 15-20 mg/L

Suggested First Line Agents for CA-MRSA S/STI IDSA Guidelines 41:1373-1830, 2005

- ☉ Clindamycin (D-test to screen for inducible resistance)
 - 300-450 mg 3 times per day oral
- ☉ TMP/SMX (Does not cover Group A Streptococcus)
 - DS tab (160mg/800mg) Q12H X 10-14 days oral
- ☉ Minocycline or Doxycycline (21% failure rates reported)
 - 100mg Q12H X 10-14 days oral
- ☉ + Adjunct Therapy
 - 4% Chlorhexidine gluconate wash Q24H X 5 days
 - 2% Calcium Mupirocin 1Gm single use tube Q12H X 10 days

2007 ATS/IDSA CAP Guidelines

Mandell, LA et al CID 44(suppl 2) 2007

☉ Community Acquired MRSA (CA-MRSA)

▸ Background

- Influenza common preceding CA-MRSA or concomitant
- Gram positive cocci in groups on gram stain
- X-ray has cavitary infiltrates \pm multiple lobes
- CA-MRSA prolific toxin producer & can kill quickly

▸ Treatment (No preference)

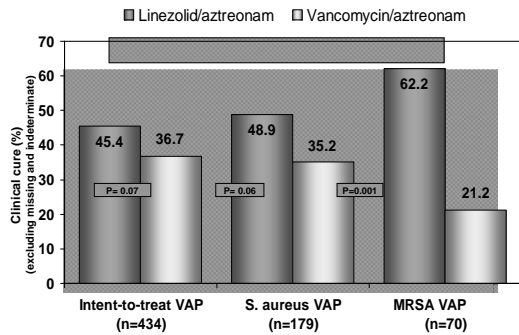
– Vancomycin

- Possible issues with lung penetration, slow kill rate, failure to shut down toxin production, & cell lysis upon death

– Linezolid

- Note:
 - Recommendations for pneumonia different than S/STI
 - Daptomycin cannot be used for pneumonia

Superior results for linezolid vs vancomycin in ventilator-associated pneumonia (VAP)



MRSA Treatment Options

- ⦿ Investigational agents when approved will likely have complicated skin infection as only FDA approved indication
 - Oritavancin (Targenta)
 - Ceftobiprole
 - Ceftaroline
 - Iclaprim (Arpida)

New Agents

- ⦿ Where should these new drugs be used
 - VRE
 - When MRSA Vancomycin MIC ≥ 1 mg/L
 - Automated testing may under estimate MIC value
 - Difficult to call if MIC $\leq 1-2$ mg/L or S,I, or R
 - Empiric therapy for HAP / VAP
 - Exception Daptomycin which binds to surfactant
- ⦿ Where not to use the drug
 - First line agent MSSA or VSE
 - First line therapy for CA-MRSA
 - Possible exception pneumonia

Conclusions

- ⦿ Tremendous diversity in what we call staphylococci today
- ⦿ Decision to use vancomycin is complicated & at minimum probably requires a MIC
- ⦿ Concerns about the future utility of vancomycin as a first line agent
- ⦿ Been difficult to establish new agents as superior to vancomycin
 - Pharmacoeconomic arguments favor new agents