Aminoglycoside and Glycopeptide Dosing and Duration of Therapy

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PK/PD Indices: Aminoglycosides

- **Animal Models:** AUC/MIC and Peak/MIC are important indices for efficacy of aminoglycosides

  Efficacy Targets: 24-hr AUC/MIC ratio ≥ 100
  Peak/MIC ratio ≥ 8-10

  Humans: AUC/MIC and Peak/MIC are important indices for 90% efficacy in serious Gram-negative bacillary infections (bacteremia and pneumonia)

  Efficacy Targets: 24-hr AUC/MIC ratio > 110
  Peak/MIC ratio >8-10

Smith et al. Clin Ther 2001; 23:1231; Kashuba et al AAC 1999; 43:623; Moore et al. J Infect Dis 1987; 155:93

Systematic Review and Meta-Analysis of Aminoglycoside Monotherapy

- 27 trials in patients with urinary tract infections

  Equal efficacy with competitors (β-lactams and fluoroquinolones)

- 9 trials in patients with non-urinary tract infections

  Higher rate of failure with aminoglycosides

- More nephrotoxic effects with aminoglycosides

Vidal et al. J Amtimicrob Chemother 2007; 60:247

Expected Gentamicin Peak/MIC and AUC/MIC Values for Organisms with High MICs

PK/PD index	MIC	5 q 24h	7 q 24h	10 q 24h
Peak/MIC	1	14.7	20.5	29.3
AUC/MIC	1	55	77	110
EUCAST Breakpoint				
Peak/MIC	2	7.3	10.2	14.7
AUC/MIC	2	28	38	55
CLSI Breakpoint				
Peak/MIC	4	3.7	5.1	7.3
AUC/MIC	4	14	17	28

Meta-Analysis of β-Lactam + Aminoglycoside Combination Versus β-Lactam Monotherapy for *Pseudomonas aeruginosa* Infections

- Included 19 studies involving 1721 patients with *P. aeruginosa* infections
- No difference in mortality for patients receiving combination therapy compared to β-lactam monotherapy
- Slightly higher but non-significant clinical cure with combination therapy over monotherapy

Vardakas et al Int J Antimicrob Agents 2013; 41:Epub

Combination Therapy in Septic Shock

- Retrospective, propensity-matched, cohort study of septic shock from ICU patients at 28 academic and community hospitals in 3 countries between 1996-2007.
- Matched 1223 patients each receiving monotherapy or combination therapy

	ICU Mortality	Total Mortality	Ventilator Free Days
Monotherapy	37%	48%	10
Combination	29%	37%	17
p-value	0.0006	<0.0001	0.0008

Kumar et al Crit Care Med 2010; 38:1773

Delannoy et al Eur J Clin Microbiol Infect Dis 2012; 31:2293

Combination Therapy in Septic Shock

- **Mortality significantly increased with initial inappropriate antibiotic therapy than with appropriate antibiotic therapy (52% vs 36%)**
- **Initial inappropriate antibiotic therapy more common with monotherapy than combination therapy (36% versus 22%)**
- **Addition of aminoglycoside to a β-lactam decreases initial inappropriate antibiotic therapy mainly for ESBL or AmpC Enterobacteriaceae and *P. aeruginosa* (33% to 8%) and coverage is wider than with fluoroquinolones**
- **Combination therapy a significant independent factor for reducing mortality in septic shock in both neutropenic and non-neutropenic patients**

Micek et al Antimicrob Agents Chemother 2010; 54:1742
Martinez et al Antimicrob Agents Chemother 2010; 54:3590
Legrand et al Crit Care Med 2012; 40:43

Aminoglycoside Nephrotoxicity

- Megalin is a lipoprotein on the brush border of renal tubular cells that binds aminoglycosides and is important for uptake of these drugs by pinocytosis
- Animals deficient in megalin do not accumulate aminoglycosides in the kidney
- Binding to megalin by aminoglycosides is saturable
- Once-daily dosing results in less early uptake in human kidneys than thrice-daily or continuous infusion; nephrotoxicity occurs later with once-daily dosing – usually after 5-7 days

Nagai & Takano Drug Metab Pharmacokin 2004;19:159

Rougier F et al Antimicrob Agents Chemother 2003; 47:1010

Risk of Renal Toxicity with Short-Term (≤ 5 Days) Gentamicin Therapy

- All patients had community-acquired bacteremia

Short-Term Gentamicin	Rise in Serum Creatinine	Mortality
Yes	13/165 (7.9%)	7.9%
No	13/150 (8.7%)	7.3%

- Renal impairment in bacteremic patients is independent of short-term gentamicin therapy

Spanggard et al Scand J Infect Dis 2011; 43:953.

Optimizing Use of Aminoglycosides

- Once daily treatment of 5-10 mg/kg (gentamicin, tobramycin) or 15-30 mg/kg (amikacin) for short periods (5-7 days)

- For non-urinary tract infections: Target attainment inadequate for monotherapy against organisms with MICs > 0.5 mg/L (gentamicin, tobramycin) or 2.0 mg/L (amikacin)

- Addition of aminoglycoside to ß-lactam increases initial appropriate antibiotic therapy for resistant organisms, reduces early mortality in septic shock and increases ventilator/pressor-free days in ICU

PK/PD of Glycopeptides in Animals (Vancomycin, Teicoplanin, Telavancin)

24-Hour AUC/MIC is the major PK/PD index correlating best with in vivo antimicrobial efficacy of glycopeptides

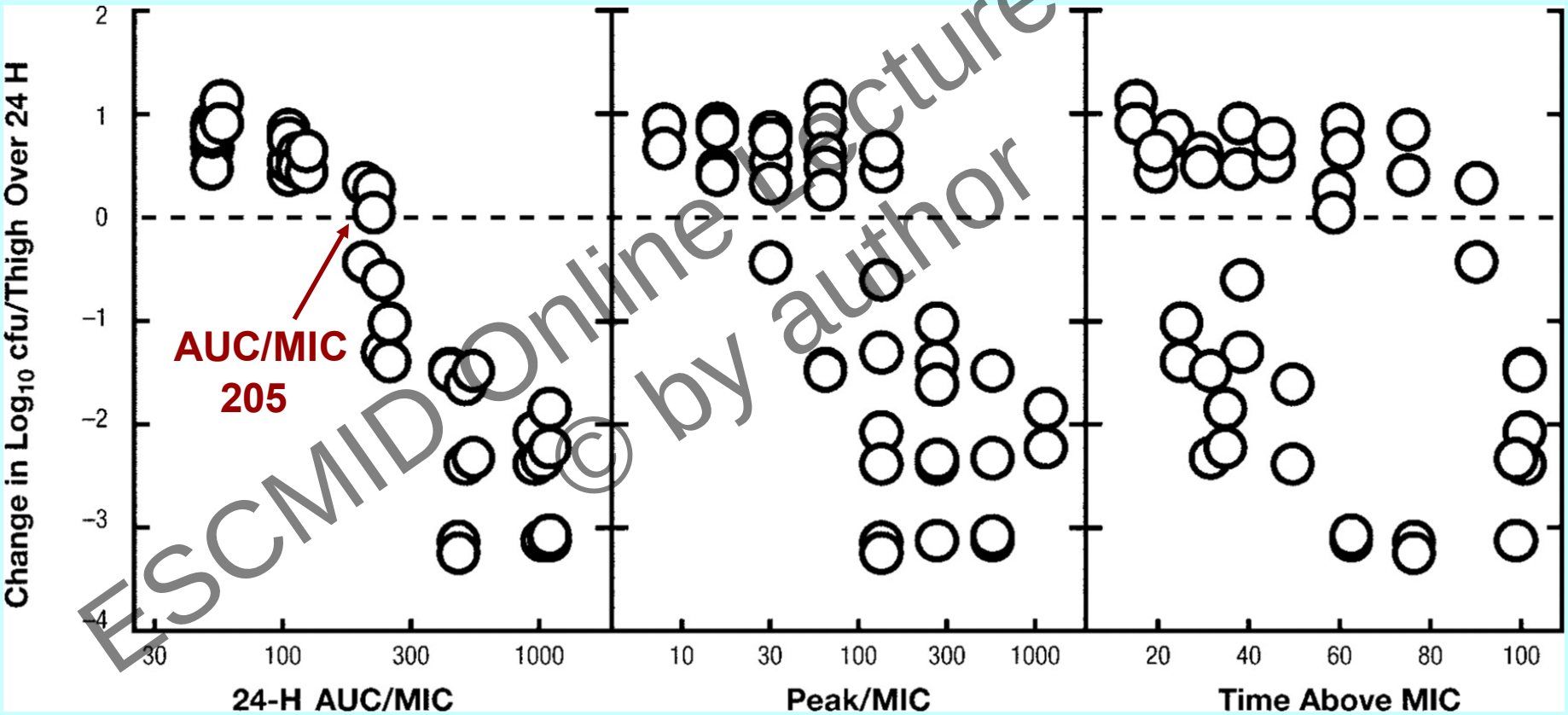
A few studies in non-neutropenic animals have also found good correlation with the Cmax/MIC index.

Ebert et al. 27th ICAAC, 1987

Knudsen et al Antimicrob Agents Chemother 2000; 44:1247

Hedge et al Antimicrob Agents Chemother 2004; 48:3034

Relationship between PK/PD indices for Vancomycin and Bacteriologic Efficacy against methicillin-susceptible *Staphylococcus aureus*



Ebert et al. 27th ICAAC, 1987
Rybak Clin Infect Dis 2006; 42:S35-S39

24-HR AUC/MIC for Stasis and 1 Log Kill with Vancomycin at Inocula of 10^5 and 10^7 against Strains of MRSA and *S. pneumoniae* in Opposite Thighs of Neutropenic Mice

Inocula	*S. aureus*		*S. pneumoniae*	
	Total SE (Free) 24-Hr AUC/MIC			
	Stasis	I Log Kill	Stasis	1 Log Kill
Low 10^5	33 5 (24.5)	85 14 (62.6)	17 4 (13)	38 8 (28)
High 10^7	212 31 (157)	399 60 (295)	23 4 (17)	39 7 (29)

Lee et al Antimicrobial Agents Chemother 2013; 57:1434

24-Hr AUC/MIC Values and Efficacy

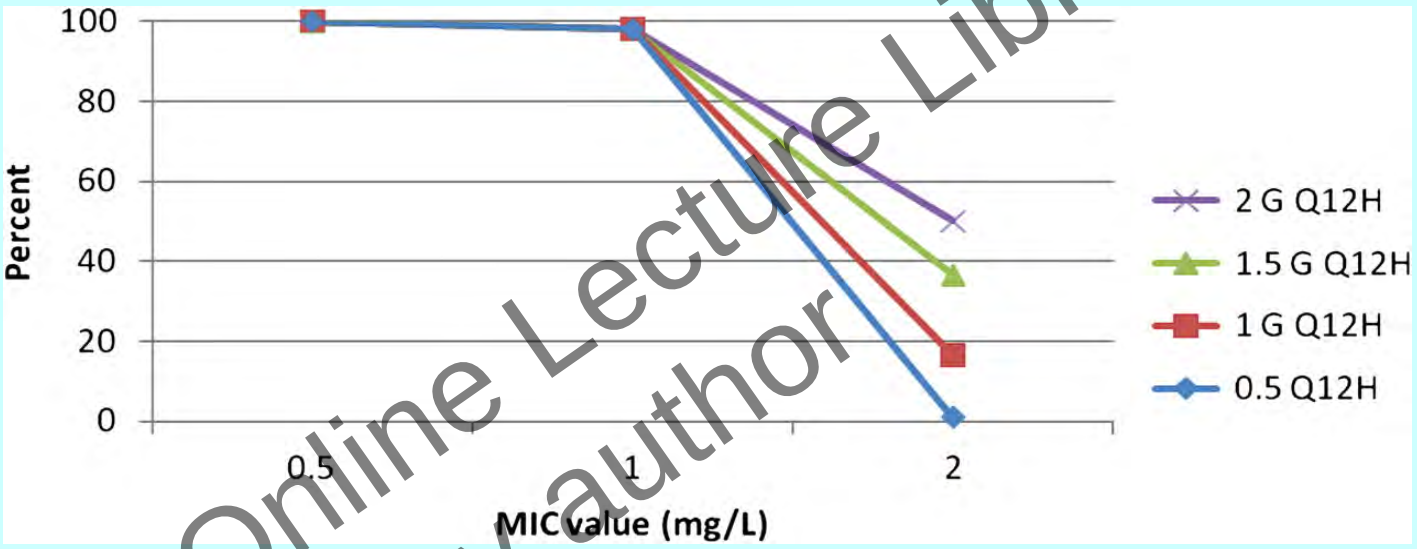
Pneumonia N=59	Bacteremia, Endocarditis N=320	Bacteremia, Endocarditis N=50	Septic Shock N=65	Bacteremia N=182
Single Center	Single Center	Single Center	Multiple Centers	Multiple Centers
≥350 Failure=37%	≥421 Failure=49%	≥211 Failure=19%	≥451 Failure=33%	>373 Failure=16%
<350 Failure=68%	<421 Failure=61%	<211 Failure=63%	<451 Failure=82%	≤373 Failure=28%
P-value 0.004	P-value 0.038	P-value 0.02	P-value 0.003	P-value 0.043

PK/PD Goal = 24-Hr AUC/MIC ≥ 400

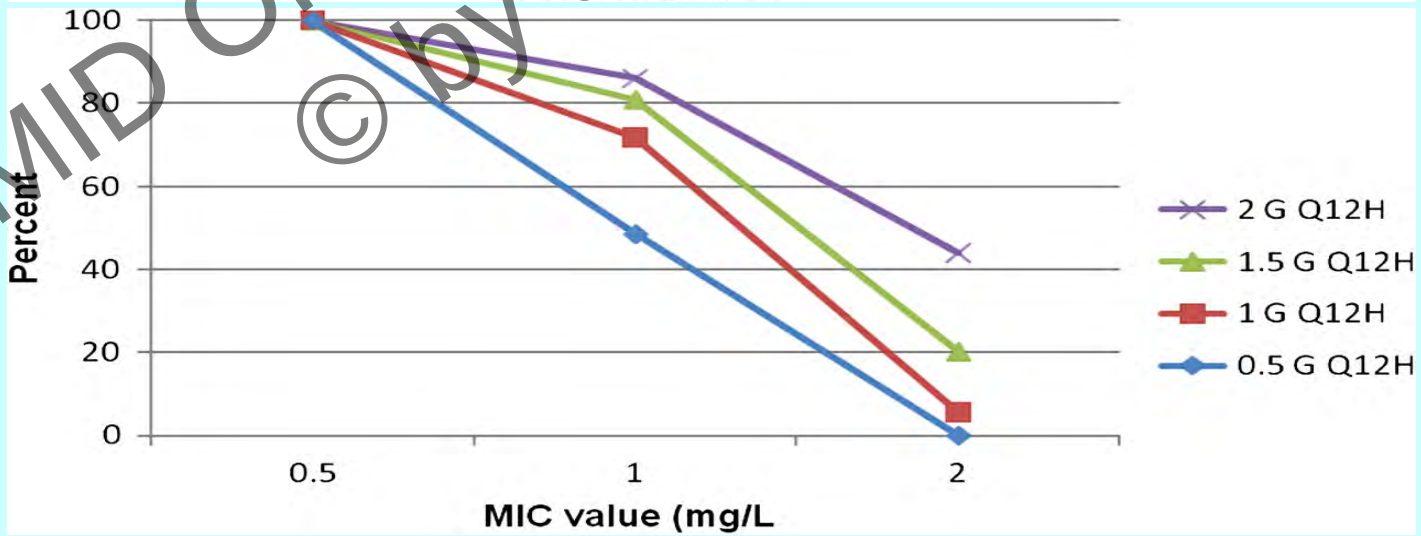
(1) Moise-Broder et al Clin Pharmacokinet 2004; 43:925; (2) Kuller et al Clin Infect Dis 2011; 52:975; (3) Brown et al Antimicrob Agents Chemother 2012; 56:634; (4) Zelensky et al Int J Antimicrob Agents 2013; 41:255; (5) Holmes et al Antimicrob Agents Chemother 2013; 57:1654

Probability of Achieving AUC/MIC Ratio ≥ 400

Trough 15-20 mg/L



Trough 10-15 mg/L



Patel et al Clin Infect Dis 2011; 52:969

Vancomycin Trough Concentration and Poor Outcomes

Trough (Cmin) Values	Vancomycin Failure (%)	P vs REF	Nephrotoxicity (%)	P vs REF
<10 mg/L	46/70 (66%)	0.001	10/65 (15%)	0.682
10-14.9 mg/L	52/90 (58%)	0.016	13/76 (17%)	0.476
15-20 mg/L	34/86 (39%)	REF	10/77 (13%)	REF
>20 mg/L	31/62 (50.0%)	0.206	17/62 (27%)	0.032

Nephrotoxicity was significantly higher in vancomycin failures (20% vs 11%); Nephrotoxicity higher with concomitant aminoglycosides (20% vs 11%)

Kuller et al Clin Infect Dis 2011; 52:975

Vancomycin and Nephrotoxicity

- Systemic review of 15 studies evaluating vancomycin troughs of 15-20 mg/L versus lower values
- Higher troughs associated with higher odds ratio (2.67; CI 1.95 to 3.65) for nephrotoxicity. Risk persisted after adjustment for other causes of nephrotoxicity
- Longer duration of therapy also increased rate of nephrotoxicity
- Most nephrotoxicity was reversible and few patients (3%) required dialysis

Van Hal et al Antimicrob Agents Chemother 2013; 57:734

Continuous Infusion of Vancomycin

- Vancomycin has concentration-independent bactericidal activity
- Continuous infusion could promote continual maximal bactericidal activity during therapy
- Most studies have target serum concentrations of 20-25 mg/L
- This would result in 24-hr AUCs of 480-600 mg-hr/L and would provide 24-hr AUC/MIC values above 400 for strains with MICs of 1 mg/L or less

Cataldo et al J Antimicrob Chemother 2012; 67:17

Continuous Versus Intermittent Infusion of Vancomycin

- Systemic reviews and meta-analysis of 1 prospective trial and 5-11 retrospective studies
- Overall mortality was not different between the two groups in either review
- Conflicting results in terms of safety between continuous and intermittent infusion
- One review showed a significantly lower risk of nephrotoxicity with continuous infusion, but 2 of 5 studies had a 12-14% lower exposure (total AUCs) with continuous infusion

Cataldo et al J Antimicrob Chemother 2012; 67:17
Dimondi & Rafferty Ann Pharmacother 2013; 47:219

PK/PD Targets for Teicoplanin

- A Cmin target of 13 mg/L and a 24-Hr AUC target of 750 mg-hr/L were associated with 90% eradication of MRSA
- In 70 patients with *S. aureus* bacteremia treated with teicoplanin, a mean Cmin ≥ 10 significantly increased the probability of a successful outcome
- A systematic review and meta-analysis of teicoplanin versus vancomycin showed no significant differences in clinical or microbiologic failure
- Teicoplanin was associated with significantly less nephrotoxicity and red man syndrome

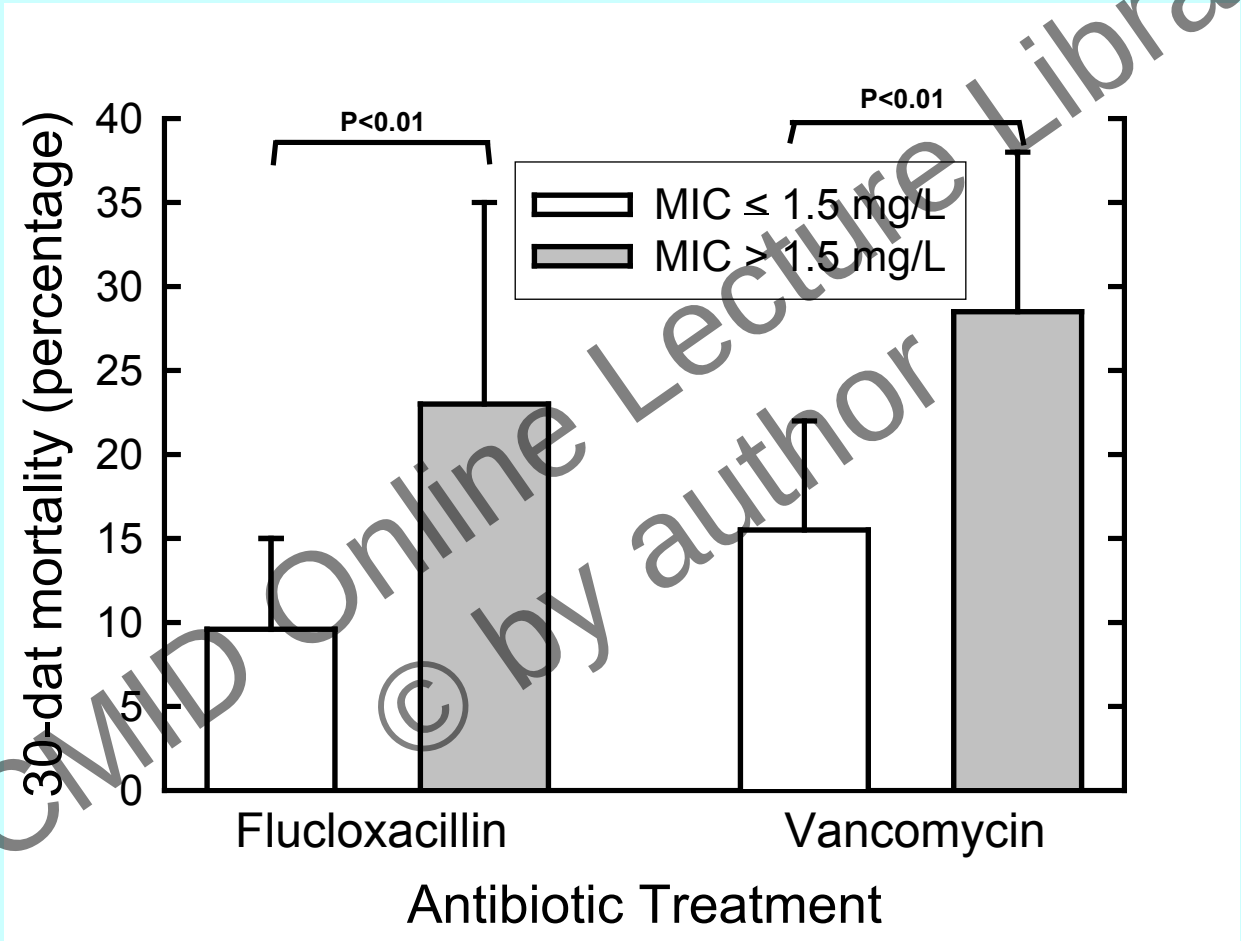
Kanazawa et al J Infect Chemother 2011; 17:297
Harding et al J Antimicrob Chemother 2000: 45:835
Svetitsky et al Antimicrob Agents Chemother 2009; 53:4069

PK/PD Targets for Telavancin

- AUC/MIC values for efficacy are lower for telavancin than vancomycin in various animal models
- A systematic review and meta-analysis of telavancin compared with vancomycin in 4 studies of complicated skin and soft tissue infections and in 2 studies of hospital-acquired pneumonia has shown comparable efficacy
- With MRSA infections telavancin has shown higher eradication rates and a trend to better clinical efficacy
- Higher rate of nephrotoxicity with telavancin

Hedge et al Antimicrob Agents Chemother 2004;48:3043;
Reyes et al Antimicrob Agents Chemother 2005; 49:4344;
Polyzos et al PLoS One 2012: 7:Epub

30-Day Mortality Versus Vancomycin MIC



High vancomycin MIC could reflect some unidentified host or organism factor that affect treatment outcomes

Holmes et al Clin Infect Dis 2011; 204:340

Mortality and Vancomycin MICs >1.0 mg/L by BMD or >1.5 mg/L by Etest

- 3 published systemic reviews and meta-analyses of high versus low vancomycin MICs
- Mortality significantly higher in patients infected with MRSA strains with a vancomycin MIC >1 mg/L by BMD and >1.5 mg/L by Etest
- Difference predominately driven by bloodstream infections
- 170 patients with MIC>1 matched 1:1 for daptomycin and vancomycin treatment had lower 30-day mortality (4% vs 13%) and persistent bacteremia (19% vs 42%) with daptomycin

van Hal et al Clin Infect Dis 2012; 54:755; Jacob & Diazgranados Int J Infect Dis 2013; 17:Epub; Marvos et al Int J Antimicrob Agents 2012; 40:496; Murray et al Clin Infect Dis 2013: Epub

Factors Affecting MRSA Eradication

Specific genotypic, phenotypic, and pharmacodynamic factors correlate with duration of MRSA bacteremia

		Median Time to Clearance	
Agr genotypes:	**agr III**	**3 days**	
	agr I	**10.5 days**	**p=0.001**
	agr II	**15 days**	
In vitro killing:			
	≥ 2.5 log killing	**6.5 days**	
	< 2.5 log killing	**>10.5 days**	**p=0.025**
24-hr AUC/MIC:	**≥ 400**	**10 days**	
	< 400	**>30 days**	**p=0.04**

Moise-Broder et al Clin Pharmacokinet 2004; 43:925;
Moise et al Antimicrob Agents Chemother 2007; 51:2582;
Moise et al J Infect Dis 2010; 201:233

Duration of Therapy with Glycopeptides

Infection	Duration of Therapy
Complicated bacteremia	4-6 weeks
• Relapse in complicated bacteremia much more frequent after 14 days of therapy than after 30 days of therapy	
Uncomplicated bacteremia	2 weeks
Endocarditis	6 weeks
Pneumonia	1-3 weeks
Complicated skin infections	1-2 weeks
Osteomyelitis	8 weeks
Septic arthritis	3-4 weeks

Liu et al Clin Infect Dis 2011; 52:285
Asgeirsson et al J Infect 2011; 62:339

Thank you for your attention