

Management of MRSA in South Africa

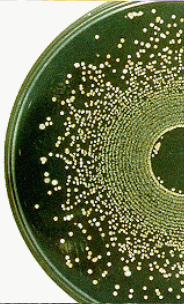
Adrian Brink

Clinical Microbiologist, Ampath National Laboratory Services,
Milpark Hospital, Johannesburg

Scope of the presentation



- Introduction
- Controversies with regards to dosing regimens for vancomycin in adult patients
- Vancomycin use in children and neonates
- Recommendations to achieve rapid therapeutic teicoplanin concentrations
- Is linezolid better than other antibiotics including vancomycin
- Conclusions



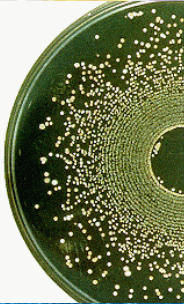


Introduction

Factors that may impact on anti-MRSA treatment options



- Cost
- Knowledge of local resistance
- Toxicity
- Availability of TDM
- MRSA infections in ICU pts and/or children/neonates





Controversies with regards to dosing regimens for vancomycin in adult patients

Effect of increasing vancomycin MIC's “ MIC “creep”



- Gradual increases in MIC's (minimum inhibitory concentrations) for vancomycin amongst MRSA isolates (so-called “MIC creep”) have been observed worldwide
- It is known that outcome is worse in patients treated with vancomycin if the MIC is elevated, despite being in the therapeutic range recommended by most authorities
- Treatment failures for MRSA infections have increasingly been reported in the literature, particularly for strains with MIC's of 1-2 $\mu\text{g/ml}$ including MRSA bacteraemia.....and higher vancomycin doses have been recommended

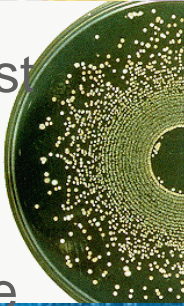
Deresinski S. *Clin Infect Dis* 2007; 44: 1543-1547

Moise-Broder, et al. *Clin Infect Dis* 2004;38:1700-5

British society for Antimicrobial Chemotherapy: Brown BSAC

Hidayat LK, Hsu DI, Quist R et al. *Arch Intern Med* 2006;166:2138-2144

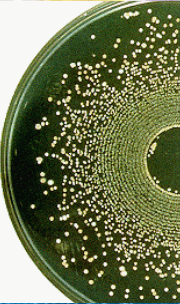
Soriano A et al. *Clin Infect Dis* 2007; 46:193-200.



Effect of increasing vancomycin MIC's “ MIC “creep”



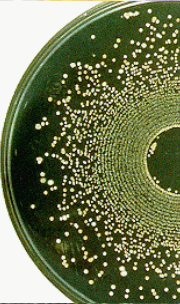
- However no good evidence is available that an increase in the trough concentration improves outcome.
- In fact two recent publications found no evidence that greater Cmin levels correlated with better hospital outcome.
- Jeffres *et al* retrospectively studied 102 patients with MRSA health-care associated pneumonia in which, although time to defervescence was shorter in those with an area-under the inhibitory curve -*AUIC of more than 400*,
.....the mean vancomycin trough concentrations and AUC values did not differ between survivors and non-survivors



Effect of increasing vancomycin MIC's “ MIC “creep”



- “Based on results aggressive dosing strategies for vancomycin (trough > 15 $\mu\text{g/ml}$) may not offer any advantage over traditional targets”



Effect of increasing vancomycin MIC's “ MIC “creep”



- In a prospective study, Hidayat *et al* divided patients with MRSA infections into subgroups based on attainment of a trough of 15 $\mu\text{g/ml}$ and high and low vancomycin MIC's (≥ 2 vs $< 2 \mu\text{g/ml}$)
- An initial response rate of 74% was achieved if the target troughs were attained irrespective of MIC
- However, despite achieving target troughs,
 - the high-MIC group had lower end-of-treatment responses [(62%, 24/39) vs (85%, 34/40) : $P=.021$]
 - and higher infection-related mortality [(24%, 11/51 vs 10%, 4/44: $P=.16$) compared with low-MIC group]



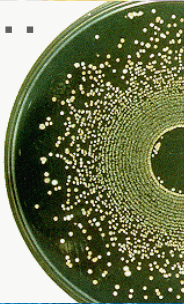
Effect of increasing vancomycin MIC's “ MIC “creep”



- This is in keeping with earlier data indicating that a higher MIC is associated with a worse clinical outcome.....



.....
but indicates that increasing the dose of vancomycin does not correct the problem.....



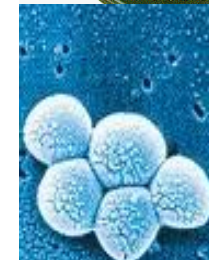
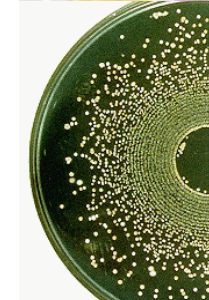
.....
and to complicate matters hetero-resistance to vancomycin has emerged



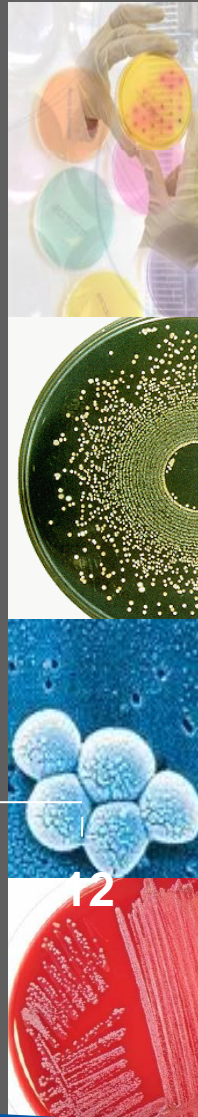
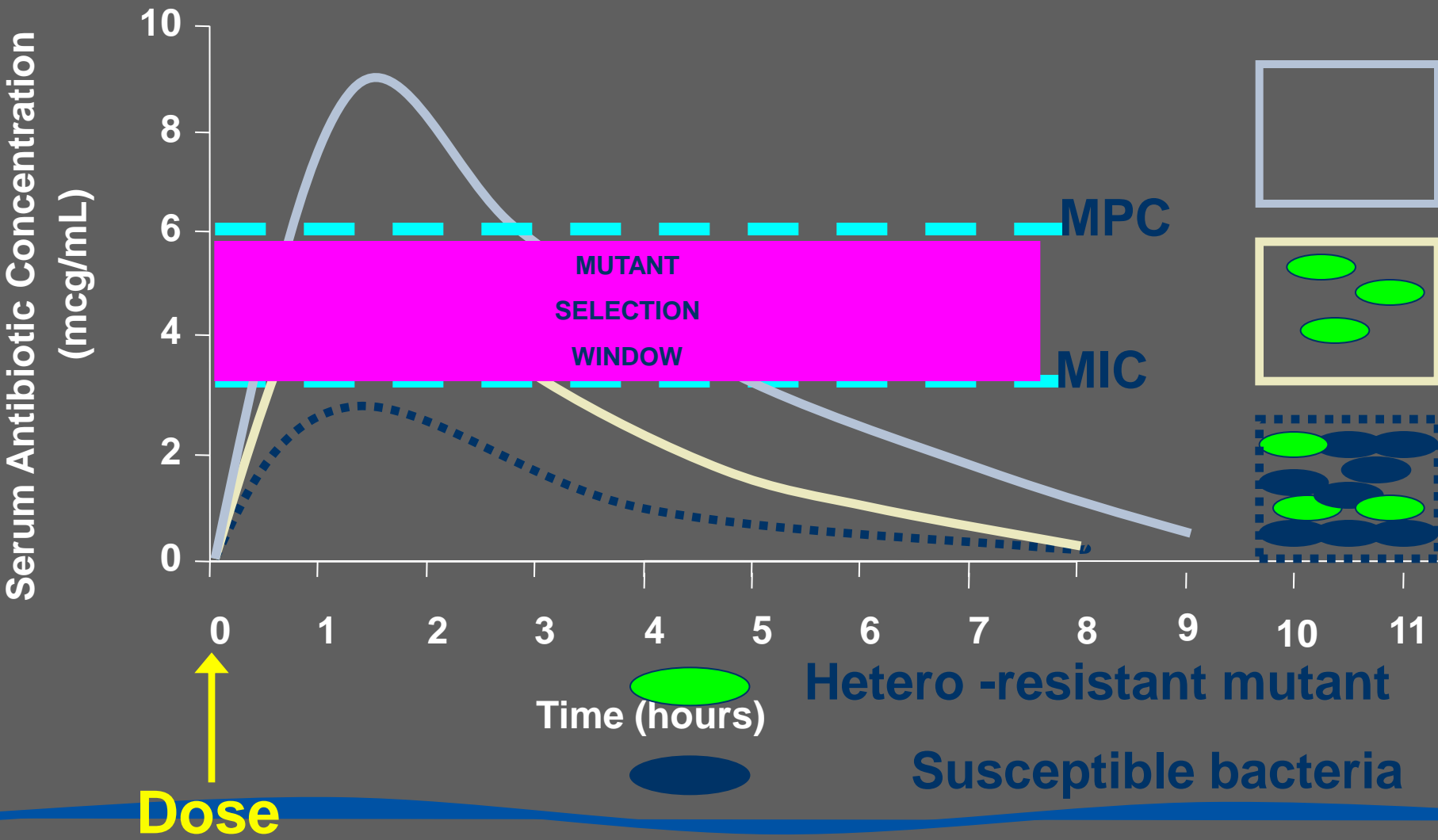
What is hetero Vanco Intermediate *S. aureus* (hVISA) ?



- hVISA isolates are a subpopulation of organisms that exhibit reduced killing with vancomycin
- hVISA are often associated with high bacterial load infections e.g. endocarditis, undrained abscesses and infected prosthetic material
- hVISA infections are associated with clinical failure of glycopeptide therapy including cases of bacteraemia¹
- MIC's of these phenotypic colonies, as detected in the routine clinical laboratory, are often within the susceptible range but most frequently on the higher side (1-2 mg/L) whilst the individual isolates have MIC's of >2 mg/L)
- Identifying hVISA in the laboratory therefore requires further testing which is not routinely available



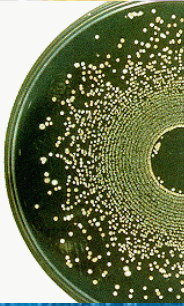
Mutant selection window



Clinical impact of hVISA on vancomycin use?



- Free AUC ratio of 500 is needed to optimize PD for hVISA
- Jeffres *et al*: mean trough of 9.4 = AUC 318
vs mean trough of 20.4 = AUC 418
- Monte Carlo simulation:
If MIC = 2, probability of achieving an AUC > 400 is 0% even with higher trough levels
If MIC = 0.5, probability is 100%



Craig W, Andes D. Abstract A-644. 46th ICAAC. San Francisco 2006

Jeffres MN, Isakow W, Doherty JA et al. *Chest* 2006; 130: 947-55

Increasing vancomycin MICs amongst MRSA in South Africa



RESULTS

Overall 50% (25/50) and 20% (10/50) of the strains screened positive for hGISA using the Etest Macromethod and the Etest GRD respectively.

Table 1. Susceptibility patterns of MRSA isolates, Gauteng, South Africa (n=50).

mg/L	Vancomycin	Teicoplanin	Linezolid
MIC ₅₀	1.5	2	1.5
MIC ₉₀	2	3	2
Range	0.5-2	0.74-4	1-2
Breakpoint	S≤2	S≤8	S≤4

Increasing toxicity with higher vancomycin doses



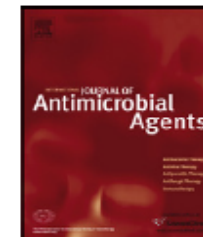
International Journal of Antimicrobial Agents 37 (2011) 95–101



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Review

Vancomycin-associated nephrotoxicity: a critical appraisal of risk with high-dose therapy

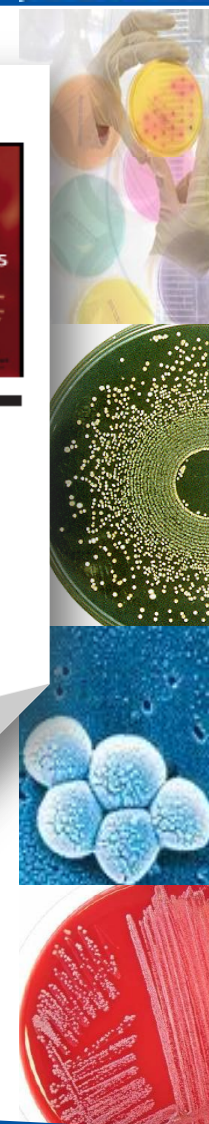
Annie Wong-Beringer^{a,b,*}, Julianne Joo^c, Edmund Tse^d, Paul Beringer^a

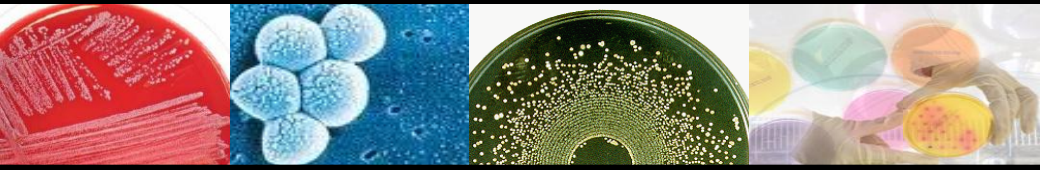
^a University of Southern California, School of Pharmacy, 1985 Zonal Avenue, Los Angeles, CA 90033, USA

^b Huntington Hospital, Department of Pharmacy Services, Pasadena, CA, USA

^c Olive View-UCLA Medical Center, Sylmar, CA, USA

^d Huntington Hospital, Department of Medicine-Nephrology, Pasadena, CA, USA



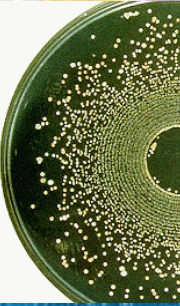


Vancomycin use in children and neonates

Pharmacokinetics of vancomycin in the septic neonate



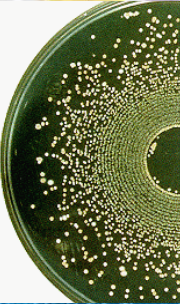
- Clearance predicted by size, post-natal age and renal function
- Traditionally, trough concentrations maintained between 5 and 10 mg/l
- PD: In adults, AUC/MIC of >400 recommended as target for clinical effectiveness
- Trough concentrations most practical method of monitoring effectiveness and avoiding resistance
- For serious infections, incl. bacteraemia, trough levels of 15-20 mg/l needed
- Recommendations are likely to apply to neonates, but further studies needed



Pharmacokinetics of vancomycin in the septic neonate



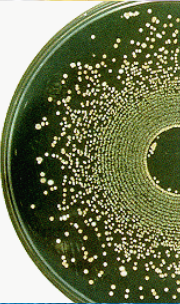
- Only one paediatric study looking at these new recommendations
- Children between 2-12 years
- Measurements & model to predict AUC/MIC for doses of 40 and 60 mg/kg/day
- If MRSA MIC was **1 mg/l**, then AUC/MIC of >400 only achieved with dose of 60 mg/kg/day
- If MIC was **2 mg/l** (breakpoint for susceptibility), then AUC/MIC consistently less than 400



Pharmacokinetics of vancomycin in the septic neonate



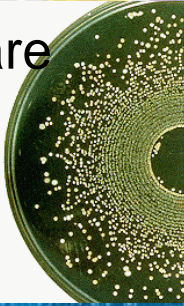
- A vancomycin dose of 40 mg/kg/d in children is unlikely to achieve the recommended pharmacodynamic target of $AUC_{24}/MIC >400$ for invasive MRSA infections even when MIC is 1.0 g/mL.
- A starting dose of 60 mg/kg/d should be used in settings where isolates with MIC of 1.0 are common.
- Alternatives to vancomycin should strongly be considered for patients with $MIC 2.0 \geq g/mL$.



What is the impact of MIC creep on MRSA bacteraemia in children?



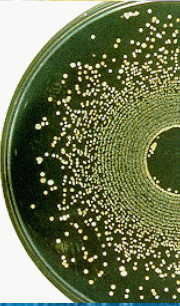
- Less is known about outcomes of MRSA bacteraemia treated with vancomycin in paediatric patients
- Outcomes and clinical characteristics studied in a retrospective cohort in patients treated with vancomycin > 5 days over a 20-month period in a large tertiary care center, n=22
- All patients the target trough was $\geq 15\text{mg/L}$
- Bivariate comparison of failures and successes
- Mean age 31.4 ± 58 months (1w-16yrs)
- Time to achieve vanco trough of $>15\text{ mg/l}$ was similar



What is the impact of MIC creep on MRSA bacteraemia in children?



- 50% (n=11) of cases regarded as vancomycin failure:
 - died (n=3 prems)
 - documented persistence of MRSA bacteraemia for > 7 days while receiving vancomycin (n=9), 1 confirmed hVISA
 - recurrence within 30 days (n=2)
- Premature infants were significantly more likely to fail vancomycin ($P = 0.02$)
- Microbiologically, PVL positive strains were significantly more likely to be associated with treatment failure than negative strains ($P = 0.008$)
- At a MIC of 1.5 mg/L, 81.8% (n=9) failed vs 72.7% (n=8). NS

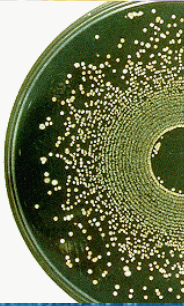


Conclusion & recommendations regarding vancomycin



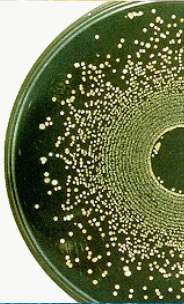
- It is becoming increasingly important to provide clinicians with MIC's of *S aureus* for vancomycin, as these organisms have been undergoing "MIC creep" a phenomenon which has been documented locally
 - Therefore, all MRSA isolates from clinically relevant specimens should be reported with MIC's for vancomycin.
 - If MIC \leq 1mg/L, continue with high dose vancomycin, otherwise switch to another agent
 - Screening for hVISA is recommended for MRSA infections with glycopeptide treatment failure as well as high bacterial load infections such as:
 - ~ undrained abscess collections
 - ~ infected prosthetic material
 - ~ endocarditis
- (NB: surgical debulking and removal of infected prosthetic material crucial)

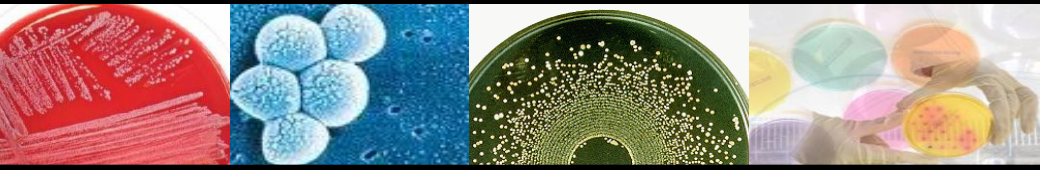
This implies is time to manage serious MRSA infections with routine MICs





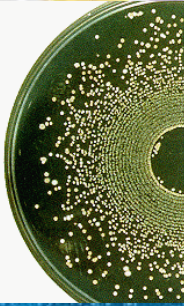
**Vancomycin and *Staphylococcus aureus*—An Antibiotic Enters
Obsolescence?**





Recommendations to achieve rapid therapeutic teicoplanin concentrations

Recommendations to achieve rapid therapeutic teicoplanin concentrations in critically ill patients



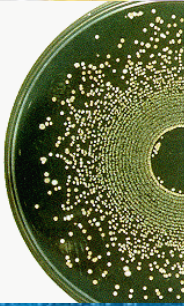
In critically ill patients with VAP the administration of high teicoplanin doses is required to reach sufficient trough antibiotic concentrations in lung tissues at steady state.

- ICU patients with VAP (n=13)
- SAPS II at inclusion 34 (17-67)
- Albumin level in serum at inclusion (g/l) 15.1 (4.2–28.4)
- 800mg BD (12mg/kg 12-hourly) for 48 hours followed by 800mg once-daily
- The median total and free concentrations of teicoplanin in serum at trough were 15.9 µg/ml (range 8.5–29.9) and 3.7 (2.0–5.4), respectively.
- The free concentration in ELF was 4.9 (2.0–11.8).

Latest recommendations to achieve rapid therapeutic teicoplanin concentrations in deep-seated MRSA infections



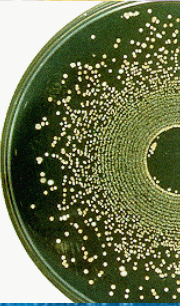
- To achieve rapid therapeutic trough concentrations (n=74):
Teicoplanin loading doses of 400mg BD (6mg/kg 12-hourly) for 48 hours followed by 400mg once-daily for infections other than deep-seated staphylococcal infections
Brink et al. Int J Antimicrob Chemother 2008;32:455-458
- Chronic osteo-myelitis/sternal sepsis/septic arthritis (n=10)
- 800mg BD (12mg/kg 12-hourly) for 48 hours followed on D3 by 800mg once-daily
- D3: Surgery with intra-operative bone specimens collected during debridement for analysis



Demographics



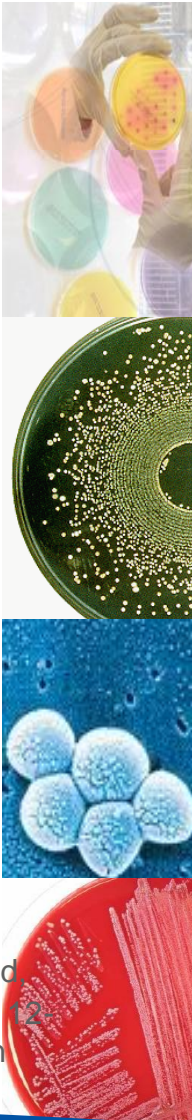
Parameter	Mean	Range
Sex	-	M 8 F2
Age	56	34-70
Duration of surgery (hours)	3.1	1-4.5
Bloodtransfusions (litre)		
Blood loss (litre)		
Post op highcare/ICU admission (hours)	86	24-192
Weight (kg)	84	65-115
Height (m)	1.73	1.53-1.86
eGFR (MDRD)		
D1	74.8	51->90
D2	76.8	56->90
D3 (n=9)	72.2	49->90
D4	77.1	57->90
Alb	20.2L	12-34
WBC	10.00H	5.8-13.2
CRP	67.6H	4-269
ESR (n=4)	16.05H	4-17
Iron	7.03L	2-16.4
Transferrin (n=9)	2.1L	1.3-3.3
% Saturation	13.66L	7-33



Steady-state pharmacokinetic parameters of teicoplanin determined using total and unbound concentration-time data. Data are reported as median (interquartile range)



	Total concentrations	Unbound concentrations
C _{max} (mg/L)	20.1 (15.7 – 22.2)	2.6 (2.3 – 3.1)
C _{min} (mg/L)	6.7 (4.0 – 10.2)	2.3 (1.3 – 2.5)
AUC ₀₋₁₂ (mg.h/L)	137.9 (83.1 – 168.2)	28.6 (21.4 – 33.2)
AUMC ₀₋₁₂ ()	608.1 (353.3 – 833.3)	167.9 (110.3 – 192.4)
CL (L/hr)	7.0 (6.8 – 9.8) →	33.5 (38.0 – 34.7)
MRT	4.4 (4.3 – 5.0)	5.9 (5.2 – 5.8)
K _{el} (h ⁻¹)	0.04 (0.03 – 0.07)	0.02 (0.02 – 0.07)
V _z (L/kg)	174.1 (101.6 –) →	196.6 (195.7 – 200.8)

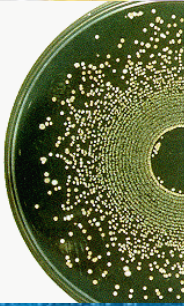
C_{max} – observed maximum concentration during sampling period; C_{min} – observed minimum concentration during sampling period; AUC₀₋₈ – area under the concentration-time curve during 12-hour dosing period; AUMC₀₋₈ – area under the moment curve during 12-hour dosing period; MRT – mean residence time; CL – total clearance; K_{el} – elimination rate constant; V_z – volume of distribution during terminal phase



PK results

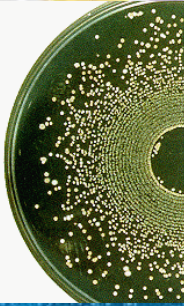



Day Through	Day 1		Day 2		Day 3	Day 4	
	T1	T2	T1	T2	T1	T1	
<u>Free</u>							
Mean	0.00	2.11	2.52			3.09	1.90
95% CI		0.21-5.62	0.0-6.87	0.0-5.76	0.00--6.40	0.0-4.79	
<u>Total</u>							
Mean	0.00	6.94	9.95			14.66	9.76
95% CI		2.87-11.52	1.77-22.37	4.07-17.07	8.93-19.66	4.84-14.43	
<u>% protein binding</u>							
Mean	-	69.60	74.68	77.58	78.93	80.54	
95% CI	-	51.21-92.69	69.29 -100	66.26-100	67.45 – 100	66.81-100	



Impact of hypo- albuminemia on teicoplanin

- GUTS II: Mean albumin 20.2L (range 12-34)
- Following identification of important covariates of unbound teicoplanin concentrations in univariate testing ($p < 0.2$), a multivariate logistic regression model (single step, forced entry) was constructed to determine the primary determinants of sub-therapeutic trough concentrations. Goodness of fit of the model was assessed by the Hosmer-Lemeshow statistic. All analyses employed IBM SPSS Statistics version 19 (Chicago, IL), and a p -value < 0.05 was considered as statistical significance.

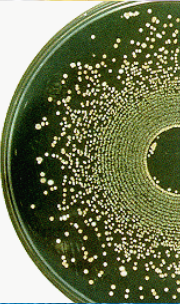


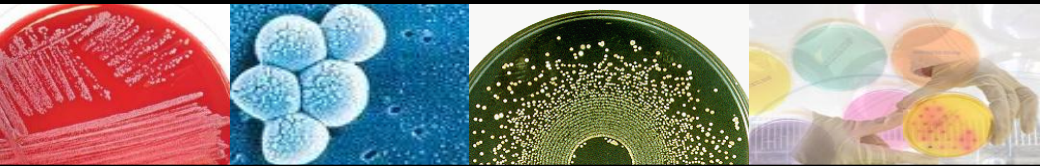
Logistic Regression Model – Unbound teicoplanin concentration		
Variable	Odds Ratio (95% CI)	p-value
Total concentration	0.180 (0.003-0.052)	0.174
Albumin	0.120 (0.078-0.180) 	< 0.001
Serum creatinine concentration	0.013 (0.001-0.025)	0.034

Impact of hypo- albuminemia on flucloxacillin in critically ill patients



- Flucloxacillin protein-binding is 95-97%
- Critically ill pts (n=10) with hypoalbuminaemia and normal renal Fx the total flucloxacillin VD was increased 2-fold compared with healthy volunteer data
- Unbound flucloxacillin concentrations after 2 g bolus fell below 1 mg/L 4-h after the end of the infusion, providing evidence that standard dosing would be insufficient for the treatment of methicillin-susceptible *Staphylococcus aureus* (MSSA) (MIC=2 mg/L)
- Administration of standard doses by intermittent bolus results in underdosing

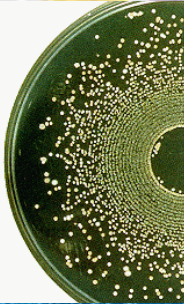




Is linezolid better than other antibiotics including vancomycin?

ZEPHYR (lineZolid in the trEatment of subjects with nosocomial Pneumonia proven to be due to methiCillin-Resistant Staphylococcus aureus (MRSA))

- Linezolid vs vancomycin in the treatment of nosocomial pneumonia proven due to MRSA
- This study is the largest trial of nosocomial pneumonia due to MRSA that has been conducted to date (n=1225, n=448 culture +MRSA, n=348 evaluable EOS):
 - Non-inferiority trial with a nested superiority hypothesis
 - Culture confirmed MRSA in nosocomial pneumonia & VAP
 - Mean APACHE II scores were 17.2 for LZD and 17.4 for VAN
 - 67% LZD and 74% of VAN subjects ventilated
 - Vancomycin dosing done to target trough >15mg/L (daily TDM)
(As a double-blind study, only the research pharmacist and unblinded monitor were aware of the levels)



Kunkel M, Chastre JE, Kollef M, Niederman M, Shorr AF, Wunderink RG, McGee W, Olvey S, Reisman A, Baruch. A. Abstract LB-49 Presented as late breaker oral symposium 23 October 2010, Vancouver, Canada

Main Endpoints



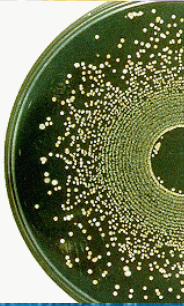
Only the primary endpoint was designed to prove superiority

- **Primary**

- Clinical response in evaluable MRSA subjects at the End of Study (EOS) visit in Per Protocol Group (PP)

- **Secondary**

- Clinical response at EOS in mITT group
- Clinical response at End of Therapy (EOT) – mITT and PP
- Microbiologic response at EOT and EOS – mITT and PP
- Survival status through 60 days post-treatment
- Safety analyses in the intent-to-treat population (MRSA and non-MRSA)



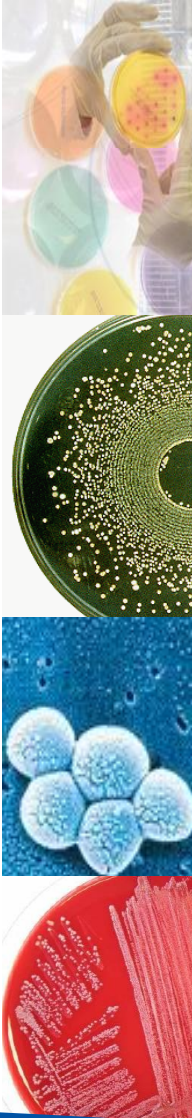
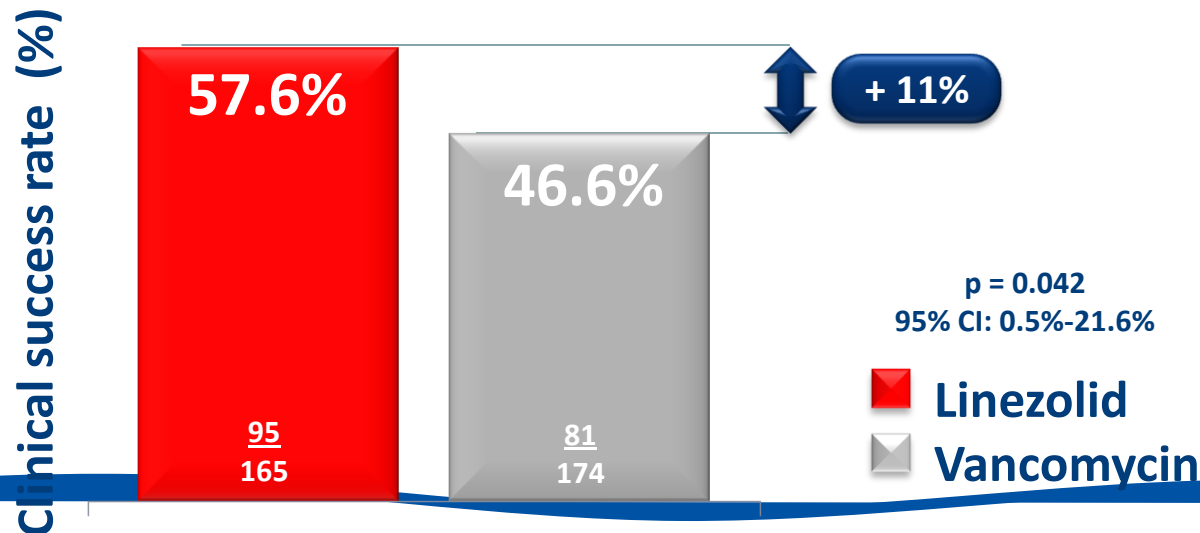
Primary Efficacy Endpoint: Per Protocol (PP) at End of Study (EOS)



	Linezolid n (%)	Vancomycin n (%)	P-Value	95% CI
Subjects	165 (100)	174 (100)		
Success/Cure	95 (57.6)	81 (46.6)	0.042	0.5-21.6%
Failure	70 (42.4)	93 (53.4)		
Unknown*	7	2		

*Excluded from analysis

**Superiority versus vancomycin for
primary end point**



Microbiological Response at EOT: PP

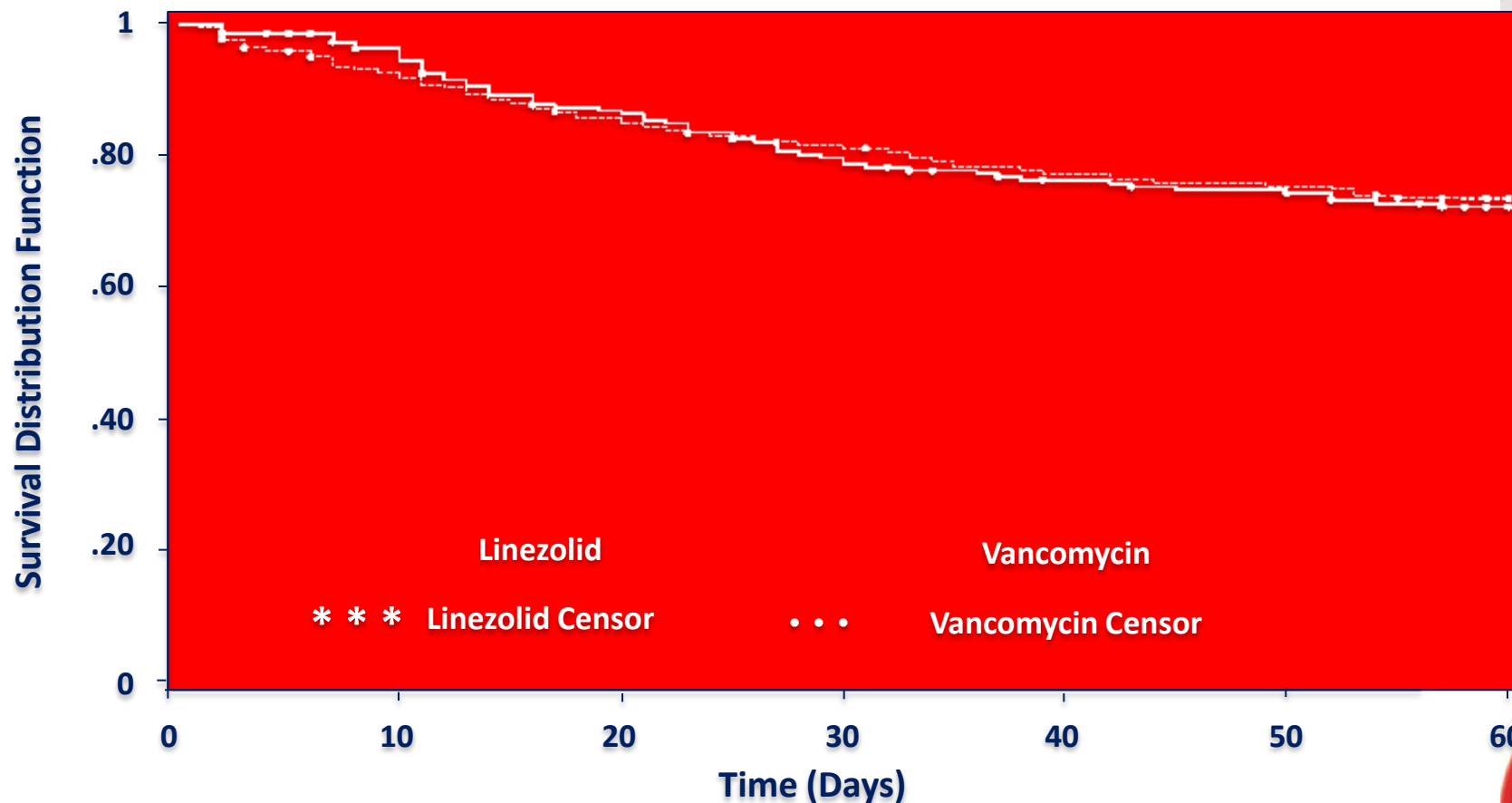
	Per Protocol	
	Linezolid n=182 n (%)	Vanco n=188 n (%)
Subjects in analysis	182 (100)	188 (100)
Success	149 (81.9)	114 (60.6)
Eradication	76	59
Presumed eradication	73	55
Failure	33 (18.1)	74 (39.4)
Persistence	16	50
Presumed persistence	17	24
Missing/indeterminate*	1	0



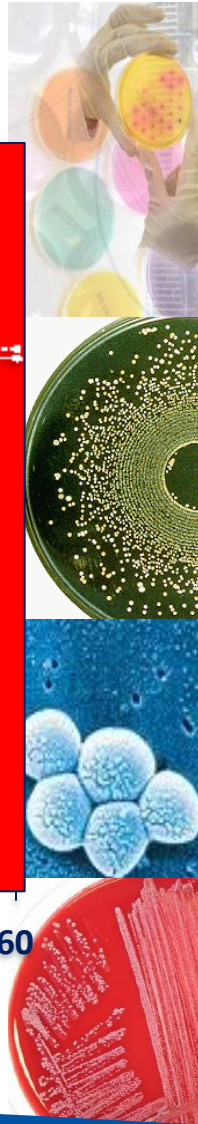
*Missing and indeterminate excluded from analysis

PP EOT Success: p-value = <0.001 95% CI (12.3%, 30.2%)

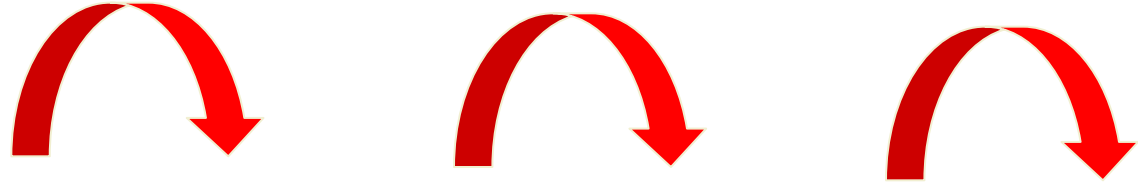
Mortality: Kaplan-Meier Plot – 60 Days: mITT



94 subject deaths (15.7%) in linezolid arm
100 subject deaths (17.0%) in vancomycin arm



Clinical Response by Maximum Vancomycin Trough Concentrations at Either Day 3, 6, or 9 (mITT at EOS)



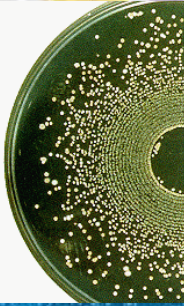
	0-11.35 ($\mu\text{g}/\text{mL}$) n=41 n (%)	>11.35-15 ($\mu\text{g}/\text{mL}$) n=42 n (%)	>15-22.2 ($\mu\text{g}/\text{mL}$) n=36 n (%)	>22.2 ($\mu\text{g}/\text{mL}$) n=38 n (%)
Success	20 (48.8)	20 (47.6)	17 (47.2)	17 (44.7)
Failure	21 (51.2)	22 (52.4)	19 (52.8)	21 (55.3)



As a double-blind study, only the research pharmacist and unblinded monitor were aware of the assignment

- Landmark trial demonstrates ZYVOXID statistical superiority over vancomycin for the treatment of nosocomial pneumonia due to MRSA

Does improved linezolid outcomes relate to PK/PD?

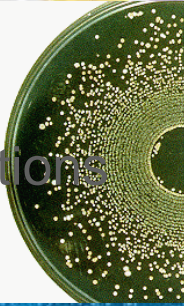


Kunkel M, Chastre JE, Kollef M, Niederman M, Shorr AF, Wunderink RG, McGee W, Olvey S, Reisman A, Baruch. A. Abstract LB-49 presented as late breaker oral symposium 23 October 2010, Vancouver, Canada

Vancomycin vs Linezolid PKs in the lung

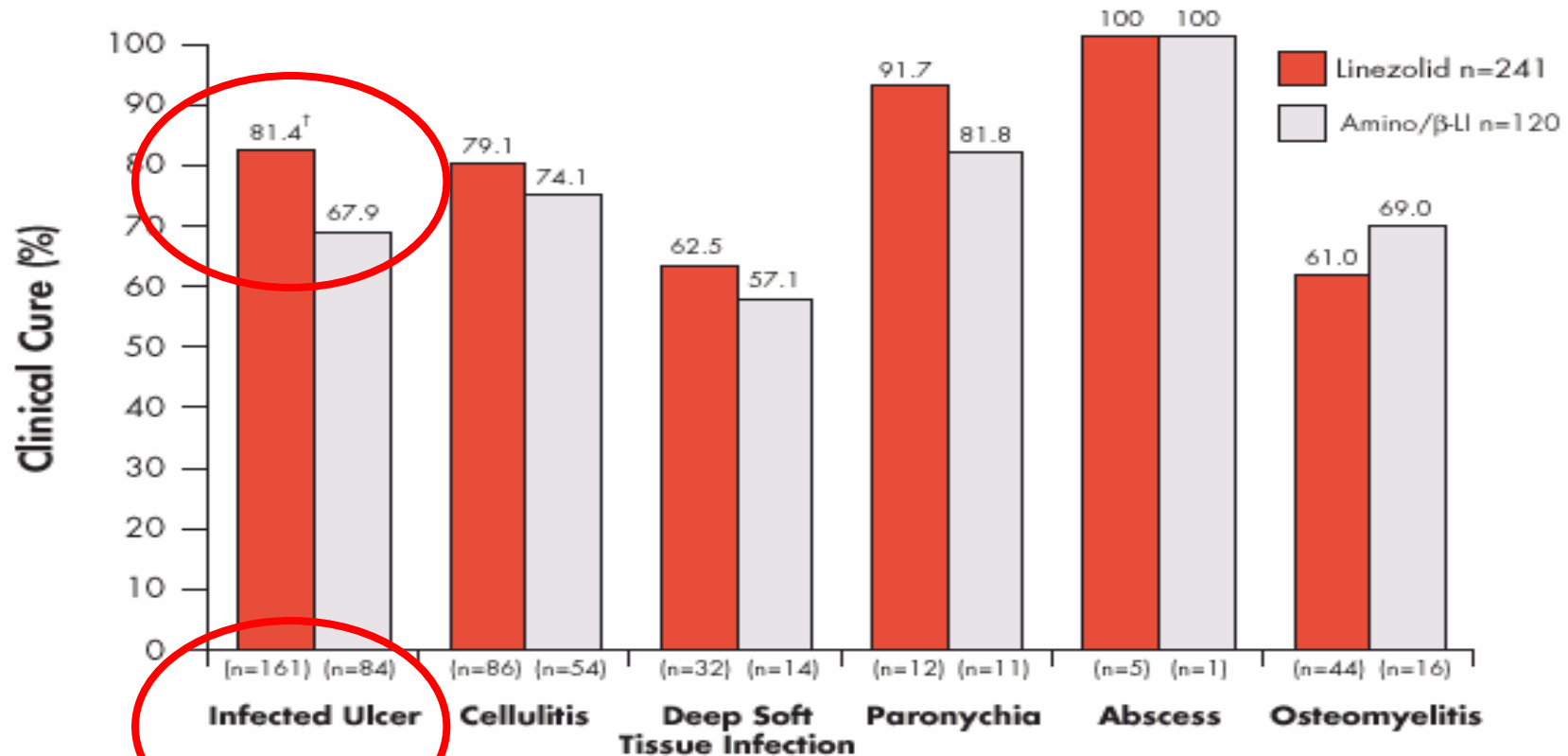


- In ventilated patients the vancomycin ELF is only ~ 14% of the serum level
- This equates to a vancomycin concentration of **2.86 mg/l** in the lung even with trough levels of 20 mg/l
- Critically ill ventilated pts (n=16). Mean linezolid peak and trough concentrations were: plasma **17.7± 4.0 mg/L** and **2.4 ±1.2 mg/L**
ELF **14.4 ± 5.6 mg/L** and **2.6 ±1.7 mg/L** respectively, showing a mean linezolid percentage penetration in ELF of approximately 100%
- Mean Linezolid AUC (area under concentration curve) was **154.6 mg·hr/L AUC₀₋₂₄**



Diabetic Foot Infections (DFIs): Linezolid Versus Ampicillin/Sulbactam and Amoxicillin/Clavulanate

FIGURE 2. Clinical outcome by primary infection-type diagnosis.*



Amino/β-LI = aminopenicillins/β-lactamase inhibitors.
*At least of cure in the intent-to-treat population.
†Significantly different.

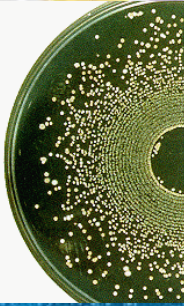
Diabetic Foot Infections (DFIs): Linezolid Versus Vancomycin



Predictors of clinical failure in patients with complicated skin and skin structure infections caused *Staphylococcus aureus* by diabetes mellitus status: results from three randomized controlled trials



Phase 3b/4 clinical trials to identify demographic or clinical predictors of clinical failure in treatment of cSSSI caused by MRSA in diabetic (N=287) and non-diabetic (N=558) patients treated with linezolid or vancomycin



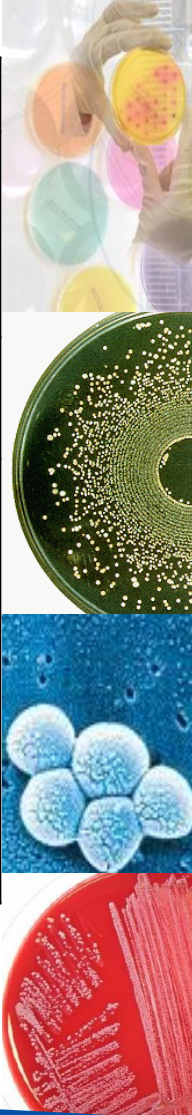
After selecting a number of clinical failure variables (interpatient demographics, treatment, wound diagnosis, and co morbidities) a **regression model found several statistically significant factors associated with a higher likelihood of clinical failure at EOS in treatment of cSSSI in diabetic and non-diabetic patients**



Diabetic Foot Infections (DFIs): Linezolid Versus Vancomycin



Population	Predictors of Clinical Failure *				
	Enrolled in Itani Study †	Presence of PVD	Polymicrobial Pathogens	Non-lower Extremity Involvement	Treatment with Vancomycin
Diabetic ‡ (n=287)	2.8 (1.52-5.15)	2.34 (1.30-4.18)	2.01 (1.15-3.53)	1.92 (1.07-3.44)	---
Non diabetic (n=558)	---	---	2.26 (1.35-3.68)	---	2.23 (1.35-3.68)

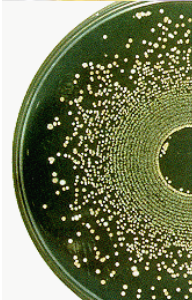


* Results listed as odds ratio (95% CI); odds ratios >1.0 indicate excess failure.
 † Itani study used weight-based vancomycin dosing and excluded patients with a primary baseline diagnosis of cellulitis.
 ‡ In diabetic population, decreased weight was associated with significance; heavier patients treated with linezolid had better outcomes.

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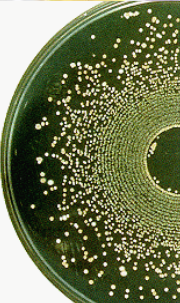


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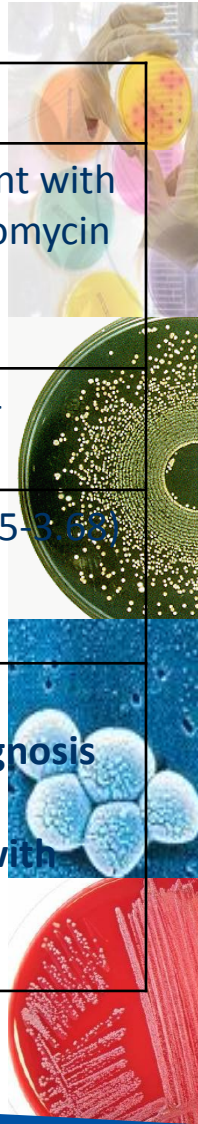
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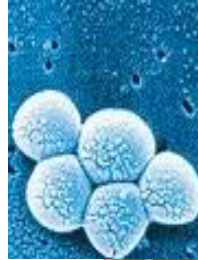
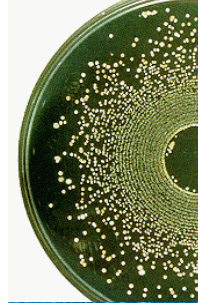
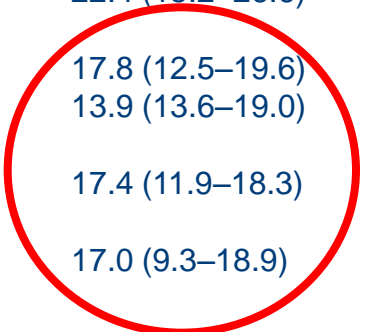
Does improved linezolid outcomes relate to PK/PD?



Linezolid concentrations in infected soft tissue and bone following repetitive doses in diabetic patients with bacterial foot infections

Main pharmacokinetic indices of linezolid in plasma and target tissues of diabetic foot infections following repetitive intravenous doses of 600 mg [median (range); n =3]

Tissue	C _{max} (mg/L)	T _{1/2} (h)	AUC ₀₋₂₄ (mg h/L) ^a	f AUC ₀₋₂₄ /MIC ^b
Plasma (total)	22.4 (15.2–26.6)	9.3 (7.2–11.1)	229.4 (198.6–331.7)	–
Plasma (free)	17.8 (12.5–19.6)	9.3 (7.2–11.1)	169.1 (162.7–263.2)	84.6 (81.4–131.6)
Subcutis (healthy)	13.9 (13.6–19.0)	8.8 (7.8–10.9)	245.3 (202.3–349.8)	122.6 (101.1–174.9)
Subcutis (inflamed)	17.4 (11.9–18.3)	9.3 (7.9–9.5)	210.9 (210.7–212.9)	105.4 (105.4–106.5)
Metatarsal bone	17.0 (9.3–18.9)	9.2 (8.1–12.2)	210.4 (165.6–266.0)	105.2 (82.8–133.0)



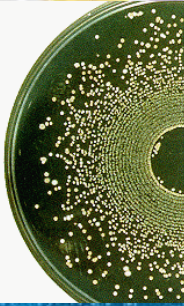
C_{max}, peak concentration; T_{1/2} __, half-life at __-phase; AUC_{0-x}, area under the concentration–time curve from 0–x h; f, free; MIC, minimum inhibitory concentration.

^a Calculated for twice daily administration (AUC₀₋₁₂ × 2).
^b Example for methicillin-resistant *Staphylococcus aureus* (MRSA) (MIC=2mg/L).



Conclusions

- Controversies with regards to dosing regimens for vancomycin in adult patients exists:
 - It appears that higher trough levels are not associated with improved outcome
 - In addition, that failure relates to increasing MICs and that MRSA with MICs $>$ or ≥ 1 mg/L (PD breakpoint) should probably be treated with another agent
 - Limited data to guide use in children and neonates
 - Furthermore, routine laboratory capabilities should include MIC testing and detection of hVISA
- Recommendations to achieve rapid therapeutic teicoplanin concentrations suggest:
 - 400mg BD for 48 hours followed by once-daily for infections other than deep-seated and/or ICU
 - For VAP, 800mg BD for 48 hours followed once-daily ensures appropriate free ELF levels
 - Hypo-albuminemia might impact on free teicoplanin levels in chronic bone sepsis pts



Conclusion



- Linezolid appears to be better than vancomycin and other antibiotics such as aminopenicillin/beta-lactamase inhibitors:
 - For confirmed MRSA NP or VAP
 - Ulcerated diabetic foot infections
 - Clinical and microbiological advantage may relate to PKs and tissue and bone penetration
- Not presented and also controversial until further data emanates:
 - The addition of rifampicin or aminoglycosides to improve serious MRSA infections
 - The added benefit of protein synthesis inhibition (PVL toxin inhibition), immuno-modulation and biofilm inhibition associated with such agents as opposed to the glycopeptides which lack these activities

