Relationships between vancomycin (V) pharmacodynamics and the emergence of V intermediate *Staphylococcus aureus* (VISA) from heteroresistant VISA (hVISA)

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Background: Increasing reports of hVISA have raised concerns over V utility in treating these infections. Previous studies have demonstrated that hVISA is the first step toward VISA. It is unknown what V exposures are necessary to prevent hVISA from converting to VISA. The objective of this investigation is to evaluate the V area under the curve to minimum inhibitory concentration ratio (AUC/MIC) necessary to prevent the emergence of the GISA phenotype.

Methods: Two SA strains displaying hVISA by both population analysis and Etest, Mu3 and 1629, were evaluated. V exposures ranging from 750 – 5000 mg every 12 h (*f*AUC/MIC 105-799) were evaluated against high inoculum (8-9 $\log_{10}$ CFU/mL) simulations in an *in vitro* pharmacodynamic model (IVPM) over 72 h in duplicate. Bactericidal activity was defined by ≥ 3 log kill. The emergence of VISA was detected using 3 and 6 x MIC screening plates for each isolate tested. Increases in MIC values were evaluated by Etest methodology.

Results: Pre exposure V MIC values for each isolate were 2 mg/L. Bactericidal activity was displayed in all regimens tested by 24 h, however attenuation of kill occurred beyond this time. Increases in MICs up to 8 mg/L were noted in both strains at doses of 750 mg q12h (*f*AUC/MIC 105). Doses as high as 2 g q12h (*f*AUC/MIC 256) could not prevent the emergence of VISA in Mu3 (MIC 6), while doses up to 1500 mg q12h (*f*AUC/MIC 248) resulted in MICs of 3 mg/L in MRSA 1629. Supratherapeutic doses of V 5 g q12h (*f*AUC/MIC 799) against Mu 3 and 4 g q12h (*f*AUC/MIC 644) against 1629 prevented the emergence of MICs $>$ 2.

Conclusions: Current recommended doses of V (1g q12) tested against hVISA were insufficient in preventing the emergence of VISA. No additional V activity was displayed beyond 24 h, perhaps displaying a tolerance effect to the drug. Supratherapetic V doses resulted in no change in MIC. Further study is needed to understand the V dosing regimens necessary to optimize therapy in hVISA infections.