Vancomycin (Van), Ceftriaxone (Cef), Daptomycin (Dap) and Linezolid (Lin) Pharmacodynamics against Methicillin-Resistant *Staphylococcus aureus* (MRSA) with Van MICs of 2 mg/L

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**ABSTRACT**

**BACKGROUND:** There is mounting evidence that Van therapy is inadequate for MRSA with MICs of 2 mg/L (MRSA2). Although alternatives are recommended, antimicrobial PD data for this subset of isolates is limited.

**METHODS:** Using 2007-2010 CANWARD surveillance data from Canadian hospitals, MRSA pathogens were identified and antimicrobial activity ( broth microdilution) was determined. Van (1 g iv q12h), Cef (500 mg q24h), Dap (4, 6, 10 (off-label) mg/kg q24h) and Lin (600 mg q12h) were evaluated using Monte Carlo simulations. Population pharmacokinetics with variances were applied to patient cohorts (n=1083). Using 2007-2010 CANWARD surveillance data from Canadian hospitals, MRSA pathogens were identified and antimicrobial activity ( broth microdilution) was determined. Van (1 g iv q12h), Cef (500 mg q24h), Dap (4, 6, 10 (off-label) mg/kg q24h) and Lin (600 mg q12h) were evaluated using Monte Carlo simulations. Population pharmacokinetics with variances were applied to patient cohorts (n=1083). **RESULTS:** Of 1103 MRSA, 2.4% had Van MICs (broth microdilution) of 2 mg/L. A majority of MRSA2 were isolated from respiratory (32%), blood (23%) and urinary (20%) swabs. Most (95%) were healthcare associated infections, primarily USA300. Cef of 28%, 2 g iv q12h and 3 g iv q8h, was significantly reduced to 20% (2 g iv q8h) and 20% (2 g iv q12h) in 100% and 54% of MRSA2 cases compared with 100%, 95% and 90% of MRSA2 cases. Dap 4 mg/kg showed similar reductions, whereas 10 mg/kg more effectively achieved targets in <40% of cases with minimal differences between MRSA2 and MRSA1 cases. **CONCLUSIONS:** This study showed that Dap target attainment, the Van, was significantly compromised for MRSA with Van MICs of 2 mg/L. Although the use of alternative therapies is being suggested, antimicrobial pharmacodynamic (PD) data for the subset of MRSA with Van MICs of 2 mg/L is limited.

**RESULTS:**

- 1 110 MRSA were identified, and 2.4% (27) were classified as MRSA2 based on broth microdilution MICs.
- MRSA2 infections were more likely to be healthcare-associated (P=0.002) and involve the respiratory tract (P=0.005).
- MRSA2 was identified in 56.6% (197) and 25.9% (727) of MRSA1 and MRSA2, respectively.
- Isolate characteristics are summarized in Table 1 and antimicrobial MIC distributions for MRSA2 compared with MRSA1 are shown in Figure 1.

**CONCLUSIONS:**

- Daptomycin pharmacodynamic target attainment at standard doses was significantly reduced for MRSA isolates with Van MICs at the CLSI susceptible breakpoint of 2 mg/L.
- Ceftriaxone and linezolid maintained pharmacodynamic activity against the subset of MRSA with Van MICs of 2 mg/L, as did daptomycin at the higher, 10 mg/kg q24h (off-label) dose.