

Prospective Evaluation of Persistently Positive Methicillin-resistant *Staphylococcus aureus* Blood Culture for the Presence of Subpopulations with Reduced Susceptibility to Vancomycin

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ABSTRACT

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) is a virulent pathogen commonly associated with nosocomial and community-acquired infections. Vancomycin had remained the treatment of choice of MRSA infections for over 40 years without evidence of developing resistance. However, several retrospective studies have shown an increased prevalence of heteroresistant vancomycin-intermediate *Staphylococcus aureus* (hVISA) isolates in patients with persistent MRSA bacteremia with frequency rates ranging from 14-20%. We postulate that due to limitations implicit in the standard microbiologic techniques used to detect the presence of hVISA, previous studies have likely underestimated the true prevalence of these intermediately resistant isolates.

Objective: The primary objective of this study is to determine if methicillin-resistant *Staphylococcus aureus* with reduced susceptibility to vancomycin is associated with persistently positive blood cultures using direct culture in vancomycin containing growth media.

Key scientific questions: This pilot project will address the following key scientific questions:

1. Is there an impact on vancomycin MICs determined for MRSA isolated from patients with prolonged MRSA bacteremia with continued organism vancomycin exposure during susceptibility testing?
2. Does the duration of the number of days of vancomycin therapy until blood cultures are persistently negative for MRSA correlate with MRSA growth on vancomycin containing agar at 2 µg/mL, 4 µg/mL, or 6 µg/mL?

We hypothesize that using a direct culture technique in which samples from MRSA positive blood cultures taken from patients actively receiving vancomycin are plated directly on vancomycin containing media will prevent the loss of acquired vancomycin resistance and increase the detection of hVISA.

Data collection and analysis: Patients with confirmed persistent MRSA bacteremia while on vancomycin therapy at a tertiary care academic medical center will be prospectively enrolled in this study during a 7-month period. MRSA blood isolates will be evaluated per standard microbiology procedures and evaluated using a procedure that continues organism vancomycin exposure during growth and susceptibility testing. Blood from the blood culture bottle containing vancomycin will be spun in a serum separating tube to concentrate the organism. The organism will be directly plated on to BHI agar with vancomycin concentrations of 2, 4, and 6 µg/mL. After 24 hours, the number of colony forming units on each plate will be counted. Isolate identification will be verified using a previously validated MRSA PCR methodology. Patient demographic, laboratory, and antimicrobial data will be collected and evaluated based on microbiology results.

Anticipated results and implications: To our knowledge, there have been no previous trials using this direct technique to prospectively evaluate persistent MRSA bacteremia for the presence of hVISA. If successful, the data from this pilot study could form the basis for a larger trial to prospectively evaluate

the relationship between hVISA and treatment outcomes. The data derived from this study could also have the potential to improve hVISA screening procedures, potentially aiding clinicians in the selection of appropriate antimicrobial therapy.