Early Response Assessment to Guide Management of Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections With Vancomycin Therapy

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ABSTRACT

Background: A subset of vancomycin-treated patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection (BSI) developed persistent positive blood cultures. Treatment eventually failed.

Methods: A retrospective study was conducted to determine whether early response on day 3 after initiation of vancomycin therapy for MRSA BSI was associated with reduced rates of persistent bacteremia, end-of-treatment failure, and infection-related mortality. Patients' medical charts were reviewed. Susceptibility testing and molecular characterization of bacterial isolates were performed.

Results: In this elderly cohort (n = 111; median age 70 years, interquartile range: 57–80 years), early response was observed in 62% of patients and was significantly ($P < 0.0001$) associated with lower rates of end-of-treatment failure (19% vs 57%) and infection-related death (1% vs 29%), but not with persistent bacteremia (17% vs 29%, $P = 0.23$). Nearly half (46%; 46 of 100 patients) remained on vancomycin therapy for the entire treatment course; those who continued despite lack of early response had a trend toward a higher risk of death than those who were switched to alternative therapy (38% vs 10%, P = NS). Most (68%) isolates had vancomycin MIC of >1 μg/mL, whereas 10% showed heterogeneous glycopeptide-intermediate Staph aureus (hGISA) phenotype. Nearly half (47%) were typed with staphylococcal cassette chromosome *mec* IV or V. In a multivariate logistic regression model, lack of response at day 3 was the strongest predictor for end-of-treatment failure, after adjustment for confounders such as age, Acute Physiology And Chronic Health Evaluation II score, intensive care unit admission, vancomycin MIC >1 μg/mL, unbound trough concentration <4 to 5× MIC, and continued vancomycin therapy without change.

Conclusions: Early response assessment after initiation of vancomycin therapy appeared to be useful for considering further diagnostic workup or a switch to alternative therapy to affect a positive outcome in patients with MRSA BSI. (*Clin Ther*. 2013;35:995–1004)

Key words: MRSA, MRSA bloodstream infection, vancomycin.

INTRODUCTION

Invasive infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) have become a major public health problem in the United States, with bloodstream infections (BSIs) accounting for 75% of the invasive cases.[1] Vancomycin was the treatment of choice and was prescribed as empirical therapy in 75% of the patients in this surveillance study.[1] However, MRSA strains exhibiting different degrees of resistance to vancomycin have emerged, with resultant treatment failure.[2,3] Recently, a meta-analysis of 22 studies involving 3332 MRSA-infected

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patients (2383 patients had MRSA BSI) indicated that vancomycin MIC ≥1.5 μg/mL, irrespective of MIC testing methodologies or infection source, was predictive of treatment failure.[4]

Published guidelines currently recommend high-dose vancomycin therapy targeting trough concentrations of 15 to 20 μg/ml for selected MRSA infections (eg, pneumonia, bacteremia, meningitis, osteomyelitis).[5,6] However, high-dose therapy has been associated with increased risk of nephrotoxicity without necessarily improving outcomes for bacteremia caused by strains with elevated MIC.[7–9] Linezolid and daptomycin are more costly alternative treatment options compared with vancomycin, but in prospective comparative trials, neither has shown superior efficacy to vancomycin in treating MRSA BSI.[3] Data from a retrospective case–control study of MRSA BSI by Moore et al[10] suggested that patients infected with high vancomycin MIC strains (>1 μg/ml by Etest, bioMérieux, Inc, Durham, North Carolina) who were initiated on vancomycin but switched to daptomycin (n = 59) within 14 days after onset of infection had lower mortality rates than those who continued on vancomycin therapy (n = 119) (20% vs 9%, $P = 0.046$). However, this study did not achieve statistical significance on the primary endpoint of clinical failure between groups. Several factors might have hindered treatment success in the vancomycin group, such as potential inadequate dosing and less involvement of infectious disease consultation. Nonetheless, findings from the preceding studies supported recent guidelines that recommend a change to alternative therapy when the isolate has a high MIC in patients who are not improving.[5] However, the optimal time to change remains uncertain and appears to be highly variable in practice, dependent on prescriber preference, and the individual patient response as noted in the study by Moore et al.[10] The interquartile range for the time to switch was 3 to 9 days from initial therapy.

Because outcome determinants for MRSA BSI are likely multifactorial, interfacing organism susceptibility and virulence, drug exposure, and host immunity, we hypothesized that early response to vancomycin after therapy initiation might serve as a sensitive indicator of this interface and predict eventual outcome. We systematically applied a set of uniform criteria to assess patient response at day 3 (48–72 h) after initiation of vancomycin therapy for MRSA BSI in a cohort of adult patients to determine if early response predicted eventual outcome, and thus, might be used to guide treatment decisions.

METHODS

Study Design and Patient Population

A retrospective cohort study of adult patients with MRSA BSIs was conducted at Huntington Hospital, a 625-bed community teaching hospital in Pasadena, California. The study protocol was approved by the hospital's institutional review board. Informed consent was not required because confidentiality was guaranteed, and no interventions were performed. Microbiology computer records were used to identify all patients in whom MRSA was isolated from blood between July 2005 and January 2010. Inclusion criteria were (1) age >17 years, (2) blood culture positive for MRSA, (3) MRSA isolates saved and available for microbiologic analysis, and (4) receipt of at least 48 h of vancomycin therapy.

Bacterial Isolates

MRSA isolates collected from initial blood cultures of infected patients were stored in cryovials at −80°C for later testing. Isolates were identified as *S. aureus* by the tube coagulase method. Oxacillin resistance was confirmed using oxacillin agar screen test with 6 mg/L oxacillin on Mueller-Hinton agar containing 2% sodium chloride according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Vancomycin MIC and heterogeneous glycopeptide-intermediate Staph aureus (hGISA) phenotype were determined by Etest and the Glycopeptide Resistance Detection (GRD) test (bioMeriéux), respectively, according to the manufacturer's instructions. Strains with vancomycin MIC ≤ 2 g/mL were deemed susceptible as defined by CLSI interpretive criteria. A positive hGISA phenotype was defined as ≥8 μg/mL for either vancomycin or teicoplanin with the GRD test and MIC ≤4 μg/mL on the standard vancomycin Etest. ATCC 29213 was used as the quality control strain. The staphylococcal cassette chromosome (SCC) *mec* type and presence of *lukF/S* encoding panton-valentine leukocidin (PVL) toxin were determined on the index isolate from each patient by polymerase chain reaction assays using previously published methods.[11,12]