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Comparative Effectiveness of Vancomycin Versus Daptomycin for MRSA Bacteremia With Vancomycin MIC >1 mg/L: A Multicenter Evaluation

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ABSTRACT

Purpose: Clinical studies comparing vancomycin with alternative therapy for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia are limited. The objective of this study was to compare outcomes of early daptomycin versus vancomycin treatment for MRSA bacteremia with high vancomycin MICs in a geographically diverse multicenter evaluation.

Methods: This nationwide, retrospective, multicenter (N = 11), matched, cohort study compared outcomes of early daptomycin with vancomycin for MRSA bloodstream infection (BSI) with vancomycin MICs 1.5 to 2 μg/mL. Matching variables, based on propensity regression analysis, included age, intensive care unit (ICU), and type of BSI. Outcomes were as follows: (1) composite failure (60-day all-cause mortality, 7-day clinical or microbiologic failure, 30-day BSI relapse, or end-of-treatment failure (EOT; discontinue/change daptomycin or vancomycin because of treatment failure or adverse event]); (2) nephrotoxicity; and (2) day 4 BSI clearance.

Findings: A total of 170 patients were included. The median (interquartile range) age was 60 years (50–74); the median (range) Acute Physiology and Chronic Health Evaluation II score was 15 (10–18); 31% were in an ICU; and 92% had an infectious disease consultation. BSI types included endocarditis/endovascular (39%), extravascular (55%), and central catheter (6%). The median daptomycin dose was 6 mg/kg, and the vancomycin trough level was

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17 mg/L. Overall composite failure was 35% (59 of 170): 15% due to 60-day all-cause mortality, 14% for lack of clinical or microbiologic response by 7 days, and 17% due to failure at end of therapy (discontinue/change because of treatment failure or adverse event). Predictors of composite failure according to multivariate analysis were age >60 years (odds ratio, 3.7; $P < 0.01$) and ICU stay (odds ratio, 2.64; $P = 0.03$). Notable differences between treatment groups were seen with: (1) end of therapy failure rates (11% vs 24% for daptomycin vs vancomycin; $P = 0.025$); (2) acute kidney injury rates (9% vs 23% for daptomycin vs vancomycin; $P = 0.043$); and (3) day 4 bacteremia clearance rates for immunocompromised patients (n = 26) (94% vs 56% for daptomycin vs vancomycin; $P = 0.035$).

Implications: Results from this multicenter study provide, for the first time, a geographically diverse evaluation of daptomycin versus vancomycin for patients with vancomycin-susceptible MRSA bacteremia with vancomycin MIC values >1 μg/mL. Although the overall composite failure rates did not differ between the vancomycin and daptomycin groups when intensively matched according to risks for failure, the rates of acute kidney injury were significantly lower in the daptomycin group. These findings suggest that daptomycin is a useful therapy for clinicians treating patients who have MRSA bacteremia. Prospective, randomized trials should be conducted to better assess the potential significance of elevated vancomycin MIC. (*Clin Ther.* 2015;▮:▮▮▮–▮▮▮)

Key words: daptomycin, high MIC, multicenter, MRSA bacteremia, vancomycin.

INTRODUCTION

Growing evidence suggests that the efficacy of vancomycin may decline in methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections (BSIs) with higher vancomycin MICs (ie, >1 μg/mL).[1–4] Based on these data, many clinicians consider alternative therapies for MRSA bacteremia when the vancomycin MIC is >1 μg/mL.[5,6] However, the clinical data to support alternative antimicrobial therapy for these patients are limited.[6–9] According to MRSA treatment guidelines from the Infectious Diseases Society of America, therapy should not be altered solely on the basis of elevated vancomycin MIC.[10] Observational studies have suggested that daptomycin-treated patients may have improved outcomes relative to vancomycin for MRSA BSIs when the vancomycin MIC is high (>1 μg/mL).[6,7] These trials were limited because they were retrospective, single-center studies from the same geographic region, however. In addition, none of the subjects in the *S. aureus* bacteremia Phase 3 registration study had a baseline MRSA isolate with a vancomycin MIC >1 μg/ml.[11,12]

To better understand the impact of daptomycin compared with vancomycin for MRSA BSIs with vancomycin MIC >1 μg/mL, we analyzed clinical and microbiologic outcomes of patients treated with early daptomycin (≤5 days before vancomycin) versus patients treated with vancomycin in a geographically diverse, multicenter, matched-cohort study.

PATIENTS AND METHODS

Study Design and Setting

This multicenter, retrospective matched cohort study was performed in 11 US hospitals from 8 states (California, Connecticut, Louisiana, Michigan, Ohio, Oklahoma, New Jersey, and Nevada); 8 were teaching hospitals, and 6 had >500 beds. All institutions used therapeutic drug monitoring, with target vancomycin trough levels ≥15 mg/L for bacteremia. Before study commencement, approval was granted by the institutional review boards at each participating institution. Electronic case report forms were used to collect clinical and microbiologic information by independent, trained study investigators at each site. Data monitoring was conducted by an independent third-party.

Patient Inclusion and Exclusion Criteria

Hospitalized subjects with MRSA bacteremia with a vancomycin MIC of 1.5 or 2 μg/mL were eligible for inclusion. Subjects were required to be ≥18 years of age; receiving initial anti-MRSA antibiotic therapy within 72 hours of the index blood culture; and receiving daptomycin or vancomycin for at least 3 days as treatment for MRSA bacteremia. The daptomycin dosing requirement was ≥6 mg/kg (based on actual body weight). A documented vancomycin trough level ≥10 mg/L was required for the vancomycin group.

Subjects were excluded if they had: a known episode of MRSA bacteremia in the previous 30 days; prosthetic valve endocarditis; an infected cardiac