Vancomycin-resistant Enterococcal Bloodstream Infections in Hematopoietic Stem Cell Transplant Recipients and Patients with Hematologic Malignancies: Impact of Daptomycin MICs of 3 to 4 mg/L

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ABSTRACT

Purpose: Case reports of treatment failure with standard-dose daptomycin (6 mg/kg) have recently surfaced in vancomycin-resistant *Enterococcus* (VRE) bloodstream infection (BSI) episodes with daptomycin MICs of 3 to 4 mg/L. The clinical implications of daptomycin MICs of 3 to 4 mg/L in VRE BSIs have not been elucidated.

Methods: We performed a single institutional retrospective analysis of adult stem cell transplant recipients and patients with hematologic malignancies diagnosed with VRE BSI from 2006 to 2014 and compared outcomes between those with daptomycin MICs of 3 to 4 mg/L those with 2 mg/L, as determined by Etest.

Findings: Forty-two daptomycin-treated VRE BSI episodes, all due to *Enterococcus faecium* were identified; 19 episodes with daptomycin MICs of 3 to 4 mg/L and 23 episodes with a daptomycin MIC of 2 mg/L. Patients in the higher daptomycin MIC group were more likely to be male, to be stem cell transplant recipients, and to have received high-dose daptomycin treatment (>6 mg/kg). In unadjusted analyses, microbiological failure in the daptomycin MICs 3 to 4 mg/L versus 2 mg/L groups (odds ratio = 1.79, 95% CI, 0.52–6.11; $P = 0.35$), the median duration of bacteremia (4 days in daptomycin MICs 3–4 mg/L vs 3 days in daptomycin MIC 2 mg/L; $P = 0.18$) and all-cause 30-day mortality (21% in daptomycin MICs 3–4 mg/L vs 35% in daptomycin MIC 2 mg/L group; $P = 0.49$) were not different. In adjusted analyses, the association between higher Pitt bacteremia scores and all-cause 30-day mortality was statistically significant ($P = 0.0006$), whereas the association between daptomycin MICs of 3 to 4 mg/L and all-cause 30-day mortality approached statistical significance ($P = 0.06$).

Implications: Duration of bacteremia and microbiological failure rates did not differ by daptomycin MICs in VRE BSI episodes in our patients, composed of adult stem cell transplant recipients and patients with hematologic malignancies. There was a nonsignificant trend in multivariable analysis suggesting that all-cause 30-day mortality was lower in patients whose VRE bloodstream isolates were with daptomycin MICs of 3 to 4 mg/L. (*Clin Ther.* 2016;38:2468–2476)

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INTRODUCTION

Vancomycin-resistant enterococcus (VRE) is the most common cause of bloodstream infection (BSI) in allogeneic stem cell transplant (HSCT) recipients at many institutions in the United States.[1,2] Its cumulative incidence during the first year post-transplantation is estimated to range from 3.6% to 22%, with 30-day mortality rates ranging between 38% and 88%.[1–5] Treatment of VRE BSIs can be challenging due to limited number of effective antimicrobial agents. Daptomycin is often used as first-line treatment for its bactericidal activity and is generally well tolerated. According to the Clinical and Laboratory Standards Institute (CLSI), *Enterococcus* isolates with daptomycin MICs of $\leq$4 mg/L, as determined by broth dilution or Etest, are considered daptomycin susceptible.[6]

Unfortunately, reports of treatment failure using standard-dose daptomycin (6 mg/kg) monotherapy in BSIs due to *Enterococcus faecium* with MICs of 3 to 4 mg/L have recently surfaced,[7] forcing clinicians to re-evaluate whether the current treatment approach is optimal. The clinical implications and whether a more aggressive treatment strategy should be used in VRE BSI with daptomycin MICs of 3 to 4 mg/L is currently unknown. In the absence of data from clinical trials to guide management, we performed a retrospective study at our institution to examine whether HSCT recipients and patients with hematologic malignancies in whom VRE BSI develops with daptomycin MICs of 3 to 4 mg/L have worse outcomes compared with those with an MIC of 2 mg/L.

MATERIALS AND METHODS

Study Population

All patients with $\geq$1 positive blood cultures for VRE between September 2006 and September 2014 were identified in our computerized microbiology database. This time period was chosen because routine daptomycin susceptibility testing of VRE bloodstream isolates commenced in September 2006 at our institution. A retrospective chart review of adult HSCT recipients and patients with hematologic malignancies (18 years of age and older) with VRE bacteremia treated with daptomycin monotherapy for at least 72 hours was performed. Patients who received VRE-active therapy other than daptomycin were excluded. The University of North Carolina Institutional Review Board approved this study.

Definitions

VRE BSI was defined as the isolation of vancomycin-resistant *Enterococcus* species from $\geq$1 blood cultures. Duration of bacteremia was defined as the number of days between the first positive and first negative blood cultures. VRE BSIs were considered recurrent if VRE was isolated from blood cultures after completion of appropriate antibiotic treatment course with $\geq$1 negative interim blood cultures and resolution of symptoms associated with the first BSI episode. A copathogen was defined as any pathogen other than VRE isolated from $\geq$1 blood cultures within the same BSI episode. Daptomycin susceptibility was defined as an MIC of $\leq$4 mg/L according to the CLSI criteria and determined using Etest for the entire study period. VRE isolates with a daptomycin MIC of 3 mg/L were rounded up to the next doubling dilution (4 mg/L) and were reported as such. Effective antibiotic therapy was defined as the antibiotic(s) with activity against VRE with which negative blood cultures was attained.

We used the Pitt bacteremia score to measure severity of illness in this study. The maximum score 48 hours before or on the day of the first positive blood culture was recorded and considered the Pitt bacteremia score for that VRE BSI episode. The severity of VRE BSI episodes was also assessed by the presence or absence of septic shock, defined as hypotension requiring any amount of vasopressor(s). The source of VRE BSI was categorized as central line–associated bloodstream infection, gastrointestinal or other sites such as the urinary tract, osteomyelitis, and cellulitis. BSIs occurring in the presence of a central venous catheter or within 48 hours of removal of a central venous catheter and that cannot be attributed to an infection unrelated to the catheter were considered to be central line–associated bloodstream infections, as defined by the National Healthcare Safety Network.[8] The presence of radiographic or endoscopic evidence of enterocolitis within 7 days of the first positive blood culture for VRE was considered gastrointestinal in origin.

Primary outcomes of interest include the duration of bacteremia for VRE BSIs, all-cause 30-day