CONCISE COMMUNICATION

Institution-wide and Within-Patient Evolution of Daptomycin Susceptibility in Vancomycin-Resistant *Enterococcus faecium* Bloodstream Infections

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We report daptomycin minimum inhibitory concentrations (MICs) for vancomycin-resistant *Enterococcus faecium* isolated from bloodstream infections over a 4-year period. The daptomycin MIC increased over time hospital-wide for initial isolates and increased over time within patients, culminating in 40% of patients having daptomycin-nonsusceptible isolates in the final year of the study.

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Vancomycin-resistant *Enterococcus faecium* (VRE *faecium*) is a common cause of hospital-acquired bloodstream infections. In addition, VRE *faecium* are frequently resistant to all β-lactam antibiotics, aminoglycosides, and tetracycline derivatives, resulting in few reliable antibiotic options for the treatment of these infections. Daptomycin is a cyclic lipopeptide with in vitro bactericidal activity against VRE that is often used as first-line therapy for the treatment of invasive infections due to its favorable tolerability and minimal drug–drug interactions. Alarmingly, several institutions have reported the emergence of daptomycin nonsusceptibility among *Enterococcus* spp, defined as a minimum inhibitory concentration (MIC) > 4 μg/mL.[1–4] Although the Clinical and Laboratory Standards Institute has defined a MIC ≤ 4 μg/mL as susceptible, clinical breakpoints for "intermediate susceptibility" and "resistance" have not yet been established.[5] In this study, we describe the emergence of daptomycin nonsusceptible *Enterococcus faecium* (DNSE) among clinical isolates at a single institution; we focused on evaluating the relationship between the change in daptomycin MIC that occurs across the population over time and the change that occurs within individual patients.

METHODS

The University of Michigan Institutional Review Board approved this study. All patients admitted to a single tertiary-care hospital with at least 1 blood culture positive for VRE *faecium* from January 1, 2011, through December 31, 2014, were evaluated. Daptomycin MICs were determined using the E-test method throughout the study period, which was reported by our microbiology laboratory in units of 2-fold concentration. Per our protocol, the daptomycin MIC was determined for the initial bloodstream isolate and for subsequent positive blood cultures taken from a patient if susceptibility testing had not occurred in the previous 3 days. Daptomycin utilization was quantified as the number of patient days of therapy (DOT) per month across the hospital and was extracted from billing data.

Changes in daptomycin MICs over time within the patient (host) and hospital-wide were analyzed using linear regression of log-transformed MICs for both initial and subsequent isolates per patient. Descriptive statistics were utilized to evaluate hospital MIC trends according to year of initial isolate and initial isolate MIC.

RESULTS

A total of 211 patients were identified with VRE *faecium* bloodstream infections. Among these patients, 371 VRE *faecium* isolates were identified for which the daptomycin MIC was measured. The daptomycin MIC increased over time for both the initial isolate taken from a patient ($P < .0001$) and for subsequent isolates ($P = .0002$), with a doubling time of 4.1 years (Figure 1A). Additionally, the daptomycin MIC rose significantly within patients over time ($P = .008$), with an average doubling time of 91 days. Total daptomycin utilization across the hospital remained similar throughout the study period at 228 DOT per month in this ~ 1,000-bed hospital (Figure 1B).

The proportion of patients with a first isolate susceptible to daptomycin (MIC ≤ 4 μg/mL) decreased each year over the study period (Figure 2A, y-intercepts, 96%, 91%, 82%, and 77%, respectively; $P = .016$). The proportion of patients whose first isolate was susceptible but had at least 1 subsequent isolate that was daptomycin nonsusceptible (ie, MIC > 4 μg/mL) increased from 3.7% (2 of 53) in 2011 to 27.6% (8 of 37) in 2014 ($P = .029$) (Figure 2A).

The evolution of DNSE in patients with initially susceptible isolates occurred only in patients with an initial isolate MIC of 4 μg/mL (Figure 2B). Of the 64 patients with an initial isolate with MIC ≤ 2 μg/mL, none were later identified to have a nonsusceptible isolate (Figure 2C). However, increasing daptomycin MICs were observed within patients, irrespective of initial isolate MIC: MIC ≤ 2 μg/mL in 9 of 64 patients (14.1%) versus MIC = 4 μg/mL in 12 of 120 patients (10%) ($P = .60$).

DISCUSSION

The daptomycin MIC of the first isolate per patient and the propensity for DNSE to emerge within patients both increased over the 4-year study period. Over this study period, the daptomycin MIC of the first isolate identified per patient

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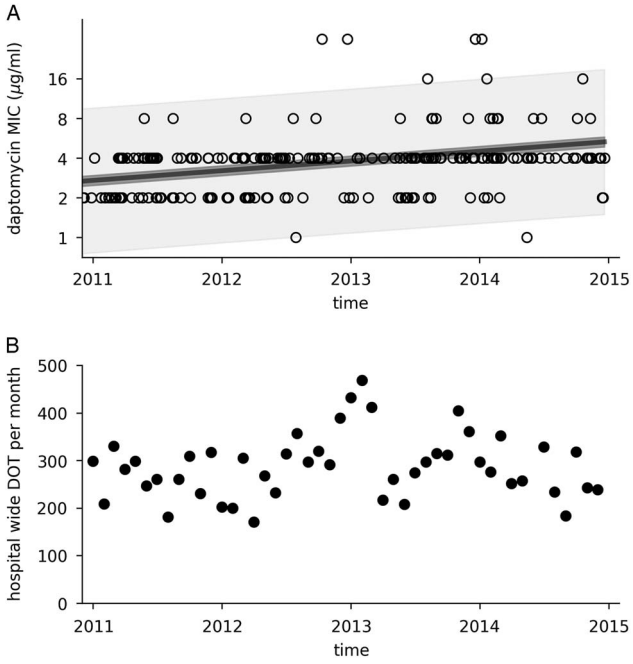

FIGURE 1. Daptomycin MIC of VRE *faecium* isolates over time as determined by E-test for the first bloodstream isolate from 211 patients with VRE *faecium* bloodstream infection between 2011 and 2014 (A). Simple linear regression was fit to the log-transformed MIC values of first isolate per patient (solid line, $P < .0001$, $r^2 = 0.08$), the 95% confidence interval for the regression is indicated in dark shade. The 95% prediction inteval (ie, range in which 95% of the values are expected to fall) is indicated by light shading, demonstrating a diversity of MIC measurement, despite a doubling of the average MIC. The number of days of therapy (DOT) of daptomycin per month (B).

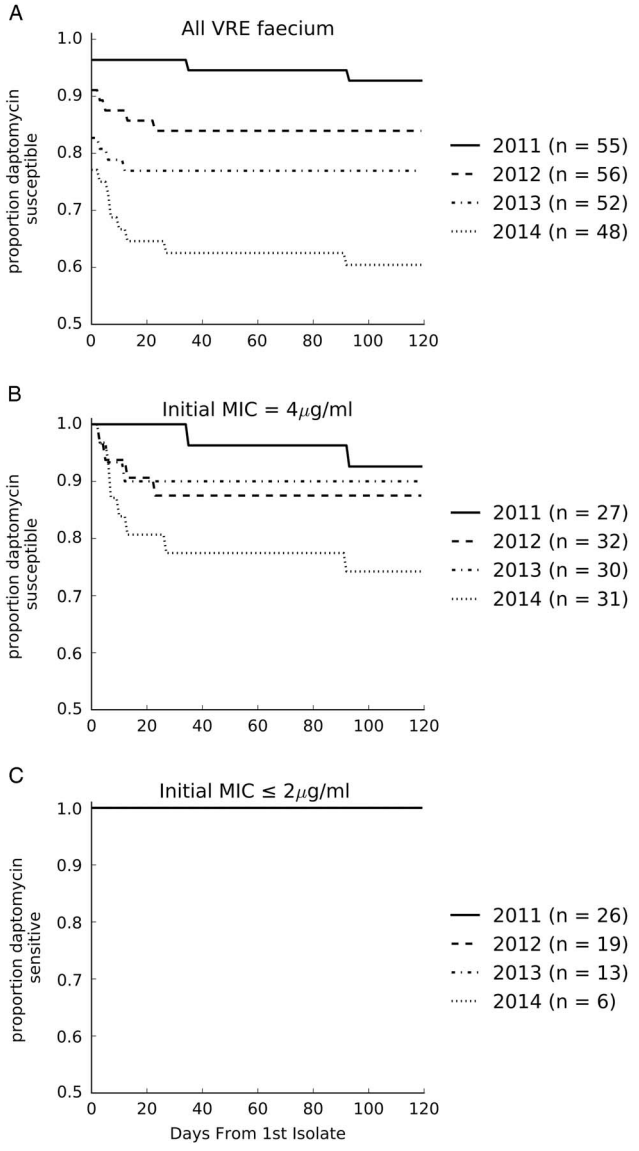

FIGURE 2. Evolution of daptomycin MICs. The proportion of patients that had no daptomycin-nonsusceptible VRE *faecium* isolated as a function of time since the first positive blood culture for all patient with VRE *faecium* bloodstream infections (A); only patients with an initial MIC of 4 μg/mL (B); and only patients with an initial MIC ≤ 2 μg/mL (C).

nearly doubled, a difference that can largely be explained by a loss of VRE *faecium* isolates with a daptomycin MIC ≤ 2 μg/mL and a relative increase in those with an MIC ≥ 4 μg/mL in this population (Figure 1A). This hospital-wide trend is concerning for transmission of strains with elevated daptomycin MICs. Daptomycin was the preferred antimicrobial agent for the treatment of invasive VRE infections at our institution during this period, resulting in significant exposures among patients (Figure 1B). Proper infection prevention practices and antimicrobial stewardship efforts may be critical in preventing widespread daptomycin resistance.

Also, DNSE commonly emerged within patients, and the propensity to become nonsusceptible over time increased during the study period. This trend is likely to be related to the increasing daptomycin MIC of first isolates. More patients were infected with strains just below the clinical breakpoint (MIC 4 μg/mL) later in the study, and only patients with an initial MIC of 4 μg/mL were at risk of developing DNSE (Figure 2B and C). Given this risk, caution should be used when treating VRE bloodstream infections with isolates with a daptomycin MIC of 4 μg/mL.

Combating antibiotic resistance requires identifying the dynamic process through which resistance evolves. This study raises the questions of where selection for daptomycin nonsusceptibility is occurring and whether this location is the same for resistance arising in clinical isolates from a single patient and from resistant strains potentially transmitted between patients.[6] While evolution was observed within individual patients over time, the bloodstream may not be the primary site of selection in transmitted strains. Indeed, the intestinal tract is the more obvious location of selection for transmitted resistance in this organism because *Enterococcus* spp can be a

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part of normal intestinal microbiota. Furthermore, the evolution of daptomycin nonsusceptibility among isolates of VRE causing intestinal colonization has been described.[7] Understanding the interaction between drivers of the hospital-wide resistance trend and the resistance evolution that occurs within hosts is important. Treatment strategies aimed to slow or prevent the emergence of resistance within patients, such as higher doses or combination therapy, could in principle be at odds with strategies used to slow or prevent the evolution of resistance in the gut, such as preventing intestinal domination of the gut by VRE[8] and reducing total exposure to daptomycin.[9]

Several groups have suggested lowering the daptomycin clinical breakpoint for *Enterococcus* from 4 to 2 μg/mL because patients who have an initial MIC of 3 or 4 μg/mL often have mutations associated with daptomycin nonsusceptibility and may have worse clinical outcomes.[5,10] In our study, only patients whose initial strains had an MIC of 4 μg/mL later developed daptomycin nonsusceptibility. However, those with an initial isolate MIC ≤ 2 μg/mL also experienced increases in MICs of twofold higher. Thus, lowering the clinical breakpoint would limit the use of daptomycin for the treatment of invasive VRE infections with daptomycin MIC > 2 μg/mL, but it would not be expected to prevent the emergence of DNSE within patients. If the cutoff for daptomycin susceptibility were changed such that 4 μg/mL were defined as intermediate and >4 μg/mL as resistant, only 5 of 48 blood infections in 2014 would have been fully susceptible throughout their infection, dramatically limiting the use of daptomycin in this hospital. Additional studies that evaluate the clinical impact of daptomycin MICs on treatment outcomes are necessary to determine the optimal clinical breakpoint.

In summary, we report a striking increase in daptomycin MICs among VRE isolated from patients with bloodstream infections over a 4-year study period. Our data add to the growing body of literature supporting the need for better infection prevention and antimicrobial stewardship practices to prevent the emergence and spread of DNSE.

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