Early High-Dose Daptomycin for Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections With Elevated Vancomycin Minimum Inhibitory Concentrations: Ready for Prime Time?

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(See the Major Article by Murray et al on pages 1562–9.)

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In this issue of *Clinical Infectious Diseases*, Murray and colleagues present results from a matched cohort study addressing the clinical conundrum of methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections caused by organisms with elevated vancomycin minimum inhibitory concentrations (MICs) [1]. The investigators conclude that high-dose daptomycin treatment led to better outcomes, and they advocate for an early switch from vancomycin to daptomycin based on finding a vancomycin MIC >1 μg/mL. Although the study provides new insight into this important clinical problem, several key questions remain.

A growing body of data shows that *S. aureus* isolates with higher vancomycin MICs are associated with a significant increase in the risk of worse clinical outcomes, including treatment failure and death [2, 3]. It is unknown whether these poor outcomes represent relative resistance to vancomycin, a marker for a more virulent organism, or some undefined third factor associated with worse outcomes. Holmes et al found that the association between higher vancomycin MICs and clinical failure persisted even in patients with methicillin-susceptible *S. aureus* treated with β-lactam therapy [4]. This makes the decision regarding treatment of patients with MRSA bloodstream infection with an elevated vancomycin MIC even less clear. Should they be switched to an alternative therapy early, based on MIC testing, or wait until they develop persistent bloodstream infection or other signs of clinical failure? Current guidelines from the Infectious Diseases Society of America recommend higher doses of vancomycin based largely on pharmacokinetic and pharmacodynamic data and suggest that “if the patient has not had a clinical or microbiologic response to vancomycin despite adequate debridement and removal of other foci of infection, an alternative to vancomycin is recommended regardless of MIC.” The experts acknowledge that a paucity of clinical trial data supports this recommendation [5]. Moore et al showed that patients switched to daptomycin after clinically failing vancomycin had improved mortality, but until now no one has investigated the early use of an alternative [6].

In this current study, Murray et al conducted a retrospective cohort study of patients with MRSA bloodstream infection who were switched to daptomycin early (after an average 1.7 days of therapy) on the basis of detection of a vancomycin MIC of >1 and ≤2 μg/L [1]. This limits the problem of bias-by-indication seen in prior studies, as no other factors played a role in the decision to switch. Their cohorts were well matched and represented a relatively ill population with an average Pitt bacteremia score of 2. Vancomycin levels were relatively high with a mean trough of 18.1 μg/mL, well within the recommended range, though few, about 10%, reached target exposures [1]. The investigators further attempted to avoid bias by defining bacteremia from the start of any MRSA therapy; they “counted” the duration of prior vancomycin therapy where applicable. We applaud these efforts to limit confounding that has been present in prior trials. In the primary analysis,
patients switched to daptomycin had a significantly decreased risk for treatment failure, primarily driven by a decrease in persistent bacteremia, defined as MRSA bacteremia lasting 7 or more days. Mortality at 30 days was also significantly lower in patients switched to daptomycin, though numbers were small [1].

Why did the daptomycin-treated patients have better outcomes? The daptomycin dose was higher than the approved dose and may well have contributed to the outcome. The median daily daptomycin dose was 8.4 mg/kg, well above the recommended Food and Drug Administration (FDA) dose of 6 mg/kg for *S. aureus* bloodstream infection and right-sided endocarditis. Given the observed improved outcomes here, it is possible that the FDA-recommended dose is too low, at least for some MRSA infections. The higher exposure achieved via administration of a higher dose may also decrease the development of resistance, evidenced by the low levels of resistance seen in this study [7]. Importantly, while some data shows the relative safety of high-dose daptomycin, this type of off-label usage has not been extensively studied and the true incidence of myopathy, peripheral neuropathy, and eosinophilic pneumonia is unknown in these patients [8, 9]. In pharmacokinetic models, doses of 8 mg/kg were predicted to have a probability of creatinine phosphokinase elevation with associated musculoskeletal adverse events of 3.57% compared to 2.31% with 6 mg/kg [10]. The practice of routine treatment of MRSA bloodstream infection with a vancomycin MIC of 2 mg/L with early high-dose daptomycin may be associated with more adverse events or toxicity.

Several issues limit the generalizability of this study. The study conduct spanned a 7-year period from 2005 through 2012. Importantly, the Detroit Medical Center clinical practice guideline dictating daptomycin therapy for infections caused by MRSA with higher vancomycin MICs was introduced in 2008, as was testing via the MicroScan. It is likely that other factors, known and unknown, were also introduced and may have affected treatment outcomes. Indeed, the patients treated earlier in the study may not be similar to those treated later; this limits our conclusions. The cohorts represent a select group of patients from these centers; including only about 10% (170/1652) of screened patients. Patients with MRSA bloodstream infection from an intravenous catheter, one of the most common reasons for a bloodstream infection, were excluded. Furthermore, patients with renal failure were excluded. These patients have a high burden of MRSA infection and a great need for treatment options. It is unfortunate that this study does not inform use of daptomycin in this important population, especially in light of warnings of possible decreased efficacy of daptomycin in patients with moderate to severe renal impairment [11, 12]. Antibiotic treatment was monitored only during the inpatient stay; the study did not account for the type, duration, or complications of outpatient treatment. This limits conclusions and generalizability to other similar studies that account for the entire duration of antistaphylococcal therapy [6, 13].

In addition, the duration of MRSA bacteremia was significantly shorter in both groups than the previously observed average of 8–9 days [13, 14]. Were these patients healthier than those treated in earlier studies or was this the result of the higher exposures to both vancomycin and daptomycin in this study?

The preponderance of data regarding poor outcomes with elevated vancomycin MICs uses Etest (bioMérieux) [2]. However, there are logistical and financial barriers to implementing this method of testing for every MRSA bloodstream infection. Furthermore, the Etest routinely provides an MIC 1 dilution higher compared to automated methods [15]. The majority of MICs in this study were determined via MicroScan (Siemens). It is less certain if this population of patients behaves similarly to patients with an MIC of 2 mg/L by Etest and it is unclear if the data that Murray et al provide can be extended to a much larger group of patients with MRSA bloodstream infection.

In addition to safety concerns associated with widespread, high-dose daptomycin usage, we must also take into account the financial implications of an automatic early switch policy. Murray et al describe an approximately $10,000 difference in drug costs per patient. The prevalence of MRSA isolates with an MIC ≥1.5 by Etest has been estimated to be as high as 40% [16]. At a larger institution, this may easily translate into elevated costs of $100,000 or more depending on the number of MRSA bloodstream infections seen.

Although we commend Murray et al for providing much-needed insight into the management of these complex patients, there does not appear to be enough data to recommend a broad policy switch to automatic early daptomycin at this time. We hope that future prospective studies will provide further guidance as to which patients will benefit most from early high-dose daptomycin.

### Notes

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