Daptomycin for Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection and Elevated Vancomycin Minimum Inhibitory Concentrations: Has the Time Come?

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(See the article by Moore et al, on pages 51–8.)

In this issue, Moore et al [1] provide the first data investigating the results of using an alternative agent in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection (BSI) with elevated vancomycin minimum inhibitory concentrations (MICs). In this retrospective analysis, funded by an Investigator-Initiated Research Grant from Cubist Pharmaceuticals, investigators in Detroit, MI, attempt to tackle the daunting clinical issue of how to best manage these complex patients. Current Infectious Diseases Society of America (IDSA) guidelines 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” [2]. This formal guidance exists despite a paucity of clinical trial data. A growing body of literature suggests that a higher vancomycin MIC is associated with worse clinical outcomes. While not proven, difficulty in achieving optimal vancomycin exposure, measured via the area under the plasma concentration time curve (AUC)/MIC ratio, provides a plausible explanation [3]. However, data from several studies raise questions about this direct causal association. Holmes et al [4] found the association between higher vancomycin MICs and clinical failure persisted even in patients with methicillin-susceptible *S. aureus* treated with *ß*-lactam therapy. Recently, Walraven et al [5] published a study that showed that the site of MRSA infection, in their case pneumonia or endocarditis, was predictive of outcome rather than vancomycin MIC.

In this study, Moore et al [1] investigate the clinical outcomes of those patients who received daptomycin versus vancomycin in a cohort of patients with baseline vancomycin MICs of 1.5–2 mcg/mL and MRSA BSI. They report a lower incidence of the composite outcome of clinical failure, microbiologic failure, and mortality in daptomycin-treated patients. This result was primarily driven by an absolute 11% difference in mortality; differences in clinical failure and microbiologic failure were not statistically significant. We applaud Moore et al [1] for investigating clinical outcomes of patients who were switched to an alternative agent, as has been suggested by several studies and recent clinical guidelines [2].

Several factors may have influenced the results of the study, including the treatment strategy, actual observed vancomycin levels, use of infectious diseases consultation, potential inadequate vancomycin dosing, and patients’ severity of illness. The very design of this study raises questions about the overall conclusions. The protocol allowed for a switch to daptomycin from another therapy for MRSA; in most cases, vancomycin. In fact, 58/59 patients (98%) who received daptomycin were switched from vancomycin after an average of 5 days of therapy. This introduces selection and indication bias. Multiple reasons, known and unknown, may contribute to changes in therapy for a given patient. Indeed, the groups of patients who were and were not switched might have possessed different characteristics. For example, all of the switched patients had to survive long enough to make the switch. This is reflected in the Kaplan–Meier analysis, which shows survival in the daptomycin-treated patients starting at the time of change to daptomycin, not from the time of culture positivity. The authors attempt to minimize selection bias by classifying the reason for the switch, but some bias likely remains even beyond the 38% of patients for whom a reason for the switch
could not be determined. Further, it is possible that the reason(s) for the switch was not documented and hence could not be considered. On the other hand, a full 60% of the patients were switched because of documented vancomycin failure, a strategy aligned with current IDSA guidelines and deemed appropriate regardless of the vancomycin MIC. The investigators attempt to control for bias by indication by matching by age, Acute Physiology and Chronic Health Evaluation (APACHE)-II score, and risk level of source.

Interestingly, the high vancomycin MIC group included more patients with E-test results of 1.5 mcg/mL. The small number of patients with vancomycin MIC 2 mcg/mL (50/177, 28%), where the real trouble might begin [6], limits the power of that subgroup analysis as evidenced by a nonsignificant 26% difference in the composite outcome. In order to have an 80% power to detect a statistically significant 26% difference, at least 86 patients infected with MRSA with vancomycin MICs of 2 mcg/mL would have been needed, 36 more than were actually enrolled.

Daptomycin use required infectious diseases approval during the study. As expected, the data demonstrate a significant disparity in infectious diseases consultation; daptomycin-treated patients received twice as many consultations (38/118, 32% vs 38/59, 64%). As shown previously, there might be significant beneficial effects of infectious disease consultation that could have contributed to at least some of the better outcomes in daptomycin-treated patients. For instance, in the case of MRSA BSI, infectious diseases consultation often concentrates on the nondrug aspects of management, including removal of catheters and other foreign bodies, debridement of wounds, valve replacement for endocarditis, and appropriate search for metastatic foci of infection. All of these clearly impact success in treatment of S. aureus infection [7,8].

Ineffective or inadequate vancomycin therapy might also have impacted success. Reports of vancomycin treatment failure in MRSA infections, particularly BSI, endocarditis, osteomyelitis, and severe skin and skin structure infections, prompted several investigations that suggest that ineffective vancomycin therapy contributes to clinical failure [9]. Pharmacokinetic and pharmacodynamic studies, as well as clinical observations, suggest that weight-based vancomycin dosing with an initial loading dose leads to faster achievement of target trough concentrations [10]. A recent retrospective analysis demonstrated that low initial trough levels were associated with increased risk of failure, even more so than a vancomycin MIC > 1 mcg/mL [3]. Trough concentrations of 15–20 mcg/mL are currently recommended for therapy of serious MRSA infections [11]. However, in the current study, average initial vancomycin troughs were only 10 mcg/mL among vancomycin-treated patients, presumably increasing the risk of failure.

Finally, there was a trend, although statistically insignificant, toward a lower Charlson Comorbidity Index in the daptomycin-treated patients. Perhaps this group of patients was less severely ill, though treatment groups were well balanced in terms of APACHE-II and risk scores. With more patients in the study, might this difference may have become significant and also account for some disparity?

Concerns of toxicity and cost should also be addressed in order to fully place the results of Moore et al [1] into context. Vancomycin toxicity has been extensively described, though prospective randomized trials are lacking [12]. Interestingly, data from the current study suggest greater risk of death with higher initial vancomycin levels, raising the possibility of adverse effects related to these high initial drug concentrations, or perhaps due to unrecognized acute kidney injury as an independent risk factor for death with the increased vancomycin levels being a confounder. It is important to note, however, that the group with initial vancomycin troughs ≥15 mcg/mL represented only 20% of evaluable patients. Safety concerns with daptomycin therapy include myopathy, peripheral neuropathy, and eosinophilic pneumonia [2]. Concern with lower rates of success in daptomycin-treated patients with moderate renal impairment compared with vancomycin led to a November 2010 product insert change that cautions physicians when selecting daptomycin for these patients. An ongoing randomized controlled trial aims to further investigate this effect [13].

Increased daptomycin cost also merits consideration. The average wholesale price of daptomycin is $312.67/500 mg vial versus $16.25/1 g vial of vancomycin [13]. This does not account for the increased costs associated with more frequent dosing or therapeutic drug level monitoring with vancomycin. Nonetheless, if daptomycin was administered to all patients with infections caused by MRSA with elevated vancomycin MICs, pharmacy budgets could be impacted.

We commend Moore et al [1] for their work attempting to clarify a complicated question. In this study, patients with vancomycin MIC of 1.5–2 mcg/mL and evidence of clinical failure on vancomycin therapy who are switched to daptomycin showed improved survival. While the limitations noted above preclude our recommending daptomycin for all patients with elevated vancomycin MICs, we hope that future prospective studies will clarify the question of whether every patient with an elevated vancomycin MIC benefits from daptomycin therapy.

Notes

Acknowledgments. We are grateful to Drs Debra Poutsika and David Snydman for their thoughtful review of the manuscript.

Financial support. Dr Weston is supported by NIH (T-32AI055412-06).

Potential conflicts of interest. H. W. B. serves or has served as an adviser/consultant to Basilea, Cerexa, Durata, J&J, Merck (adjudication
committee), Rib-X, Wyeth/Pfizer (DSMB), and Targanta/TMC in the past 2 years. She previously served as a consultant for Cubist. A. W. reports no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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