interval, 0.65–3.2). The corresponding probability that daptomycin reduced mortality based on that trial data is 19% overall and only 7.5% for a risk ratio of 0.8 or lower. Although risk ratio and hazard ratio are not fully interchangeable, it is concerning that the results of this observational analysis are substantially different from the probability of that effect size based on the randomized trial.

Second, there is an important risk of immortal time bias. although the authors are careful to exclude patients who die within the first 3 days, there remains asymmetry between the daptomycin and vancomycin groups in terms of time at risk. Specifically, the authors categorize patients as undergoing a daptomycin switch "if they received 3 or more doses of daptomycin treatment within 3–5 consecutive days." Consequently, whereas vancomycin patients could die on any day after day 3, patients who were switched to daptomycin days 2 and 3 must live to days 5 and 6, respectively, or as long as up to day 8 if renally adjusted. It is unclear whether patients who received daptomycin before day 3 but died before their third dose were counted in the vancomycin group or excluded. We suggest this provides a varying degree of immortal time to the daptomycin group. Since many deaths due to *Staphylococcus aureus* bacteremia occur early, this seemingly small difference in immortal time could contribute to substantial differences in hazard ratio. In fact, the unadjusted χ^2 has a Fragility Index of only 3 [3].

Could the authors perform additional sensitivity analyses to control for this immortal time bias such as: (1) restricting the analysis to patients who have survived at least 6–7 days or (2) modelling daptomycin switch within the first 3 days as a time-varying covariate while removing the requirement for 3 or more days of use or (3) using a prevalent new-user cohort design [4]?

Overall, daptomycin may have some advantages in terms of ease of dosing and nephrotoxicity. Some of the vancomycin nephrotoxicity will be mitigated with area under the curve–based dosing strategies [5]. With generic formulations available, the price difference may be less relevant than it was a decade ago; however, daptomycin stewardship might also help preserve susceptibility within the hospital biome. Overall, vancomycin remains the agent with the most experience, and an accurate real-world comparison of the 2, as envisioned by the authors, remains an important piece of work.

Note

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References

1. Schweizer ML, Richardson K, Vaughan Sarrazin MS, et al. Comparative effectiveness of switching to daptomycin versus remaining on vancomycin among patients with methicillin-resistant Staphylococcus aureus (MRSA) bloodstream infections. Clin Infect Dis **2021**; 72:68–73.
2. Rehm SJ, Boucher H, Levine D, et al. Daptomycin versus vancomycin plus gentamicin for treatment of bacteraemia and endocarditis due to Staphylococcus aureus: subset analysis of patients infected with methicillin-resistant isolates. J Antimicrob Chemother **2008**; 62:1413–21.
3. Walsh M, Srinathan SK, McAuley DF, et al. The statistical significance of randomized controlled trial results is frequently fragile: a case for a Fragility Index. J Clin Epidemiol **2014**; 67:622–8.
4. Suissa S, Moodie EE, Dell'Aniello S. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. Pharmacoepidemiol Drug Saf **2017**; 26:459–68.
5. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm **2020**; 77:835–64.

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Early Switch From Vancomycin to Daptomycin in Methicillin-Resistant *Staphylococcus aureus* Bacteremia: Still More Questions Than Answers

To the Editor—Schweizer et al [1] report lower mortality (8.3% vs 17.4%; hazard ratio, 0.48) among patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia who switch to daptomycin from vancomycin within 3 days vs remaining on vancomycin. This study follows other retrospective reports that suggest a benefit of switching to daptomycin for MRSA infections [2–4]. We thank the authors for presenting new data on an important topic and also suggest caution in drawing conclusions from these retrospective studies. A randomized, controlled trial (RCT) compared antistaphylococcal penicillin or vancomycin plus gentamicin to daptomycin in *Staphylococcus aureus* bacteremia and endocarditis. In that study, it was found that daptomycin vs standard of care yielded a 12.6% difference in treatment success (95% confidence interval, –7.4% to 32.6%), favoring daptomycin for MRSA; however, this was confounded by addition of gentamicin to the standard care group. Further, there was not a better rate of mortality (10.8% vs 11.3%; $P = 1$) or clinical failure (3.3% vs 3.5%; $P = 1$) and nonsignificantly higher microbiologic failure (15.8% vs 9.6%; $P = .22$) [5]. We wish to highlight 3 points in Schweizer et al's work that may have predisposed to finding significantly different treatment effects.

First, defining the primary outcome as mortality within 30 days of receiving vancomycin introduced immortal time bias [6], as the median time to switch to daptomycin was 6 days. Excluding patients who died within ≥6 days of receiving vancomycin, rather than just 3 days, could have better addressed this bias, as would a matched cohort design that match patients based on survival

to the time of daptomycin switch in the daptomycin group.

Second, the 2 groups comprised patient populations that substantially differed, likely influencing the outcome independent of exposure. For example, the patients in the daptomycin group were younger, more likely to get an infectious diseases consultation, more likely to receive multiple anti-MRSA drugs, and more likely to receive care at high-complexity facilities. The authors provide results of Cox regression analyses but do not describe the final models in detail. A propensity score-matched cohort design might have better accounted for between-group differences, and analyses stratified by potential confounders could have identified treatment effects in subpopulations with an a priori expectation of benefit.

Finally, the adequacy of vancomycin therapeutic dose monitoring (TDM) was not reported. It is unclear if patients in the vancomycin group promptly achieved and maintained goal vancomycin concentrations. Another concern deals with the pharmacodynamic exposure targeted (ie, troughs vs area under the curve [AUC]). The 2020 vancomycin dosing guidelines recommend AUC rather than trough monitoring for serious MRSA infections, with a goal AUC/minimum inhibitory concentration$_{\text{broth dilution}}$ ratio of ≥400 [7]. Given that the study used data from 2007 through 2014, it is likely that all vancomycin was monitored via trough goals and may not reflect vancomycin outcomes with optimal TDM.

Given the points discussed, we are hesitant to conclude that early switch to daptomycin offers benefit for the treatment of MRSA bloodstream infections until future prospective/randomized studies can be performed. We do believe studies such as this should compel the funding of future RCTs to address real-world questions commonly encountered in infectious diseases.

Notes

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References

1. Schweizer ML, Richardson K, Vaughan Sarrazin MS, et al. Comparative effectiveness of switching to daptomycin versus remaining on vancomycin among patients with *methicillin-resistant Staphylococcus aureus* (MRSA) bloodstream infections. Clin Infect Dis **2021**; 72:68–73.
2. Claeys KC, Zasowski EJ, Casapao AM, et al. Daptomycin improves outcomes regardless of vancomycin mic in a propensity-matched analysis of *methicillin-resistant Staphylococcus aureus* bloodstream infections. Antimicrob Agents Chemother **2016**; 60:5841–8.
3. Murray KP, Zhao JJ, Davis SL, et al. Early use of daptomycin versus vancomycin for methicillin-resistant *Staphylococcus aureus* bacteremia with vancomycin minimum inhibitory concentration >1 mg/L: a matched cohort study. Clin Infect Dis **2013**; 56:1562–9.
4. Shime N, Saito N, Bokui M, et al. Clinical outcomes after initial treatment of methicillin-resistant *Staphylococcus aureus* infections. Infect Drug Resist **2018**; 11:1073–81.
5. Fowler VG Jr, Boucher HW, Corey GR, et al; S. aureus Endocarditis and Bacteremia Study Group. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. N Engl J Med **2006**; 355:653–65.
6. Yadav K, Lewis RJ. Immortal time bias in observational studies. JAMA **2021**; 325:686–7.
7. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm **2009**; 66: 82–98.

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Reply to Authors

To the Editor—We appreciate the opportunity to further discuss our study. In our publication, we found that switching from vancomycin to daptomycin within 3 days was significantly associated with lower 30-day mortality compared with patients who remained on vancomycin (hazard ratio [HR] = 0.48; 95% confidence interval [CI]: .25, .92) after statistically adjusting for infectious disease consultation within 3 days, intensive care unit (ICU) admission, facility complexity, endovascular infection, other anti-methicillin-resistant *Staphylococcus aureus* (MRSA) antibiotics, vancomycin minimum inhibitory concentration (MIC), acute kidney injury, and creatine kinase [1]. The latter 4 variables were treated as time-varying covariates. The other potential confounders listed in the methods section of the publication were introduced into the Cox model but were not retained after using forward stepwise regression.

When performing real-world comparative effectiveness studies, there is always tension between wanting the patients to receive a therapeutic level of the treatment of interest, addressing confounding by severity, and avoiding immortal time bias. Initially, we attempted to use the prevalent new-user design with time-conditional propensity scores (eg, matched cohort design); however, due to limited sample size, it was difficult to find a time-conditional propensity score matched comparator for each daptomycin patient. MRSA bloodstream infections are rare, and even multicenter studies have sample size limitations.