

Clinical Trials Increase Off-Study Drug Use: A Segmented Time-Series Analysis

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Background. The effect of participation in a clinical trial on concomitant off-study investigational drug use has not been described. We sought to determine if participation in the Daptomycin as Adjunctive Therapy for *Staphylococcus aureus* bacteremia (DASH) trial increased overall daptomycin prescribing at study sites.

Methods. We retrospectively analyzed daptomycin use for 8 years preceding the trial, off-study daptomycin use during the trial itself (31 months), and daptomycin use for 6 fiscal months after trial completion. We used a segmented linear regression analysis of an interrupted time series to analyze changes in each drug's defined daily doses (DDD) per 1000 patient-days. As a control, we analyzed use of linezolid over these periods and also accounted for rates of methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) infections.

Results. For 1.5 years before the DASH trial, daptomycin use was decreasing by -0.30 DDD per 1000 patient-days per fiscal period (95% CI, -0.52 to -0.07). Following the initiation of the study, there was a statistically significant increase in daptomycin use of 0.28 DDD per 1000 patient-days per fiscal period (95% CI, 0.03 to 0.52), despite low, stable rates of MRSA and VRE infections. Following trial completion, daptomycin use decreased back toward prestudy rates. Use of linezolid remained stable throughout.

Conclusions. Despite the DASH trial being a negative study, it impacted the prescribing habits of local clinicians during recruitment. Trialists should be aware of potential off-target study effects, and prescribers should be wary of early uptake of interventions before definitive study results.

Keywords. daptomycin; off-label prescribing; randomized controlled trial; *Staphylococcus aureus*.

Well-conducted randomized clinical trials are essential to advancing the science of medicine. Participating centers benefit from clinical trials in numerous ways: through potentially improved patient care, the advancement of knowledge, job creation, and generating recognition for research and innovation. However, an overlooked side effect of trial participation is the potential impact on off-study drug prescribing.

On an administrative level, hospitals participating in drug trials are more likely to expedite the addition of the study drug to their hospital formulary [1]. At the level of the individual prescriber, physicians who partake in industry-funded trials are more likely to go on to prescribe the study drug [2, 3]. These

off-target effects of drug trials are increasingly recognized. There are even examples of “seeding trials,” whereby a clinical trial is seemingly undertaken as a marketing tool for the study drug [4]. However, the effect of performing a trial free of industry sponsorship on physician prescribing practices has never been studied.

Greater recognition and investigation into the influence that clinical trial participation may have on institutional and individual prescribing habits is needed, particularly with respect to clinical appropriateness and the effect on nontrial participants. We sought to measure the influence of participating in a non-industry-funded clinical trial on study drug utilization at our health care center.

METHODS

Trial Procedures

The study protocol of the Daptomycin as Adjunctive Therapy for *Staphylococcus aureus* bacteremia (DASH) trial has been previously published [5, 6]. Briefly, between November 1, 2016, and June 30, 2019, 104 consenting patients with methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteremia who were receiving standard-of-care antibiotics (cefazolin or cloxacillin)

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were randomized to receive either adjunctive daptomycin or an intravenous saline placebo for 5 days. Only 5 of the 81 eligible patients who did not undergo randomization (6.2%) were excluded due to their treating physician wanting to prescribe daptomycin. The primary outcome was duration of bacteremia, with mortality as a secondary outcome. The study was performed at the McGill University Health Center (2 hospital sites totaling 770 tertiary care beds in Montréal, Canada) with approval from our institutional research ethics board.

At the study sites, an infectious diseases consultation is automatically performed for all patients with an *S. aureus* bloodstream infection. However, aside from 1 investigator (T.C.L.), no other faculty physicians were involved in any aspect of the trial design or in participant recruitment. During the study, participants were enrolled by infectious diseases and medical microbiology trainees (G.B.L., M.P.C., A.L., and S.D.L.) who were not on clinical service and were participating on a volunteer basis. The DASH research team was made aware of possible cases by an automated notification directly from the microbiology laboratory, independent of both the ID consulting service and the admitting team. Other than informal discussions on Twitter before the publication of results, the study was not specifically advertised or presented to clinicians in any form during the trial period and was free of all industry influence.

Study Procedures

For this analysis, we used our pharmacy database to determine the number of daptomycin daily defined doses (DDDs) administered for 8 fiscal years preceding the trial, during the DASH study period itself (31 months), and for 6 fiscal months following the completion of the trial. All daptomycin prescribed as part of the trial was excluded. We used linezolid as a control because of its similar spectrum of activity and indications. Defined daily doses were standardized per 1000 patient-days using data from the admission/discharge/transfer system. Both daptomycin and linezolid are restricted to the infectious disease service, with some exceptions, notably emergency departments and intensive care units. Ceftobiprole and tigecycline, the 2 other agents available on our formulary for the treatment of serious MRSA/VRE infections, are rarely used at our center.

To determine if any change in daptomycin use was driven by a concordant change in hospital epidemiology, we accessed the infection prevention and control department database and obtained methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) infection rates. At our center, MRSA and VRE infections are systematically recorded by trained infection control practitioners and are defined as the isolation of either organism in a clinical specimen in the context of clinical signs of infection. This reporting includes hospital-onset infections, as well as those occurring after discharge, using the National Healthcare Safety Network criteria [7]. Infection surveillance has been prospectively performed

since 2013 and is validated by a hospital epidemiologist, as mandated by provincial authorities.

Statistical Analysis

Data were analyzed using interrupted time series, allowing for both immediate-level and time-trend changes [8]. Of note, 1 of our 2 hospitals moved to a new building with all single patient rooms on April 26, 2015, leading to dramatic reductions in MRSA and VRE [9]. Therefore, our model included segments representing this move, the start of the DASH trial, and the 6 fiscal periods following trial completion. We compared linear, negative binomial, and overdispersed Poisson models and used the Akaike Information Criterion to find the best fit for the data [10]. While all models showed the same trends, the linear model performed best and is presented herein.

Funding

Both the DASH trial and this study were internally funded. Study drug and placebo were supplied, at cost, by our research pharmacy. This secondary study received a waiver of ethics from the McGill University Health Centre Research Ethics Board.

Patient Consent Statement

This study was approved by the Research Ethics Boards of McGill University Health Centre with a waiver of consent.

RESULTS

Since 2011, 4 statistically significant trends in daptomycin use were observed across the institution (Figure 1A, Table 1). First, preceding the hospital move, daptomycin use was increasing by 0.11 DDDs per 1000 patient-days per fiscal period (95% CI, 0.06 to 0.17). At the time, there was also a corresponding increase in VRE infection rates (Figure 2B). Second, following the hospital move in 2015, and corresponding with a temporal decline in VRE infection rates, daptomycin use decreased by -0.30 DDDs per 1000 patient-days per fiscal period (95% CI, -0.52 to -0.07). Following the initiation of the DASH trial, daptomycin use increased once again by 0.32 DDDs per 1000 patient-days per fiscal period (95% CI, 0.07 to 0.57). During this period, there was no corresponding statistically significant increase in VRE or MRSA infections. Finally, following the conclusion of the study, daptomycin use decreased by 2.88 DDDs per 1000 patient-days per fiscal period (95% CI, -4.33 to -1.43) and was approaching prestudy levels. In contrast to daptomycin, linezolid prescription rates remained stable throughout the entire period of investigation (Figure 1B, Table 1).

DISCUSSION

We found a temporal relationship between off-study daptomycin use in our hospital center and our clinical trial of daptomycin as an adjunctive agent in the treatment of MSSA

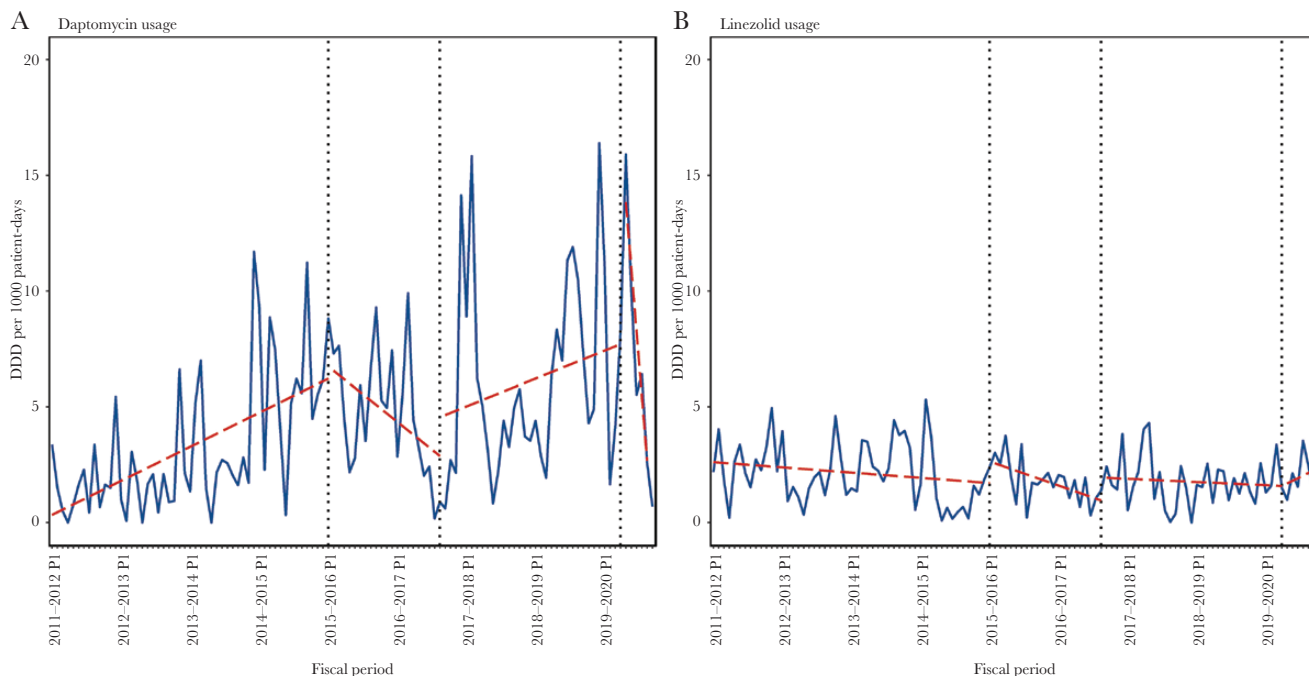


Figure 1. Defined daily doses per study period (DDD per 1000 patient-days). The left vertical line represents the hospital move. The middle vertical line corresponds to Daptomycin as Adjunctive Therapy for *Staphylococcus aureus* bacteremia (DASH) trial start. The right vertical line represents the end of patient enrollment into the DASH trial. A, Daptomycin usage shows a statistically significant gradual fall after the move, a statistically significant rise after DASH trial start, and a statistically significant return to pretrial levels following the end of DASH trial. B, Linezolid remains stable throughout.

bloodstream infection. There was no observed increase in linezolid over the same time frame, despite the primary indications being similar to daptomycin. It is unlikely that a

change in hospital epidemiology was responsible (or even contributory) to the observed increase in use, as both MRSA and VRE infection rates had reduced dramatically over the period

Table 1. Interrupted Time-Series Analysis Results for Daptomycin and Linezolid Usage (DDD per 1000 Patient-Days) per Study Period

Remove							
Daptomycin		Linezolid		MRSA		VRE	
Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope
0.22 (−1.46 to 1.90)	0.11 (0.06 to 0.17)*	2.63 (1.99 to 3.28)	−0.02 (−0.04 to −0.003)	2.22 (0.40 to 4.02)	−0.01 (−0.06 to 0.03)	−0.44 (−2.17 to 1.28)	0.05 (0.01 to 0.09)
Move							
Daptomycin		Linezolid		MRSA		VRE	
Immediate change	Trend change	Immediate change	Trend change	Immediate change	Trend change	Immediate change	Trend change
0.33 (−8.11 to 8.76)	−0.30 (−0.52 to −0.07)*	0.85 (−2.37 to 4.06)	−0.06 (−0.15 to 0.02)	−0.95 (−3.49 to 1.62)	0.06 (−0.02 to 0.14)	−1.41 (−3.85 to 0.97)	−0.09 (−0.16 to −0.02)*
DASH							
Daptomycin		Linezolid		MRSA		VRE	
Immediate change	Trend change	Immediate change	Trend change	Immediate change	Trend change	Immediate change	Trend change
1.77 (−6.66 to 10.3)	0.28 (0.03 to 0.52)*	0.98 (−2.23 to 4.17)	0.07 (−0.02 to 0.16)	−0.10 (−2.56 to 2.37)	−0.06 (−0.13 to 0.01)	0.49 (−1.92 to 2.92)	0.03 (−0.03 to 0.10)
Post-DASH							
Daptomycin		Linezolid		MRSA		VRE	
Immediate change	Trend change	Immediate change	Trend change	Immediate change	Trend change	Immediate change	Trend change
6.15 (−2.24 to 14.6)	−2.88 (−4.33 to −1.43)*	0.10 (−3.10 to 3.28)	0.12 (−0.42 to 0.67)	0.86 (−1.67 to 3.37)	0.12 (−0.31 to 0.55)	−0.41 (−2.82 to 2.02)	0.10 (−0.31 to 0.51)

Values for slopes and trend changes are given per financial periods.

Abbreviations: DASH, Daptomycin as Adjunctive Therapy for *Staphylococcus aureus* bacteremia study; DDD, defined daily dose; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

*Statistically significant changes from previous time period.

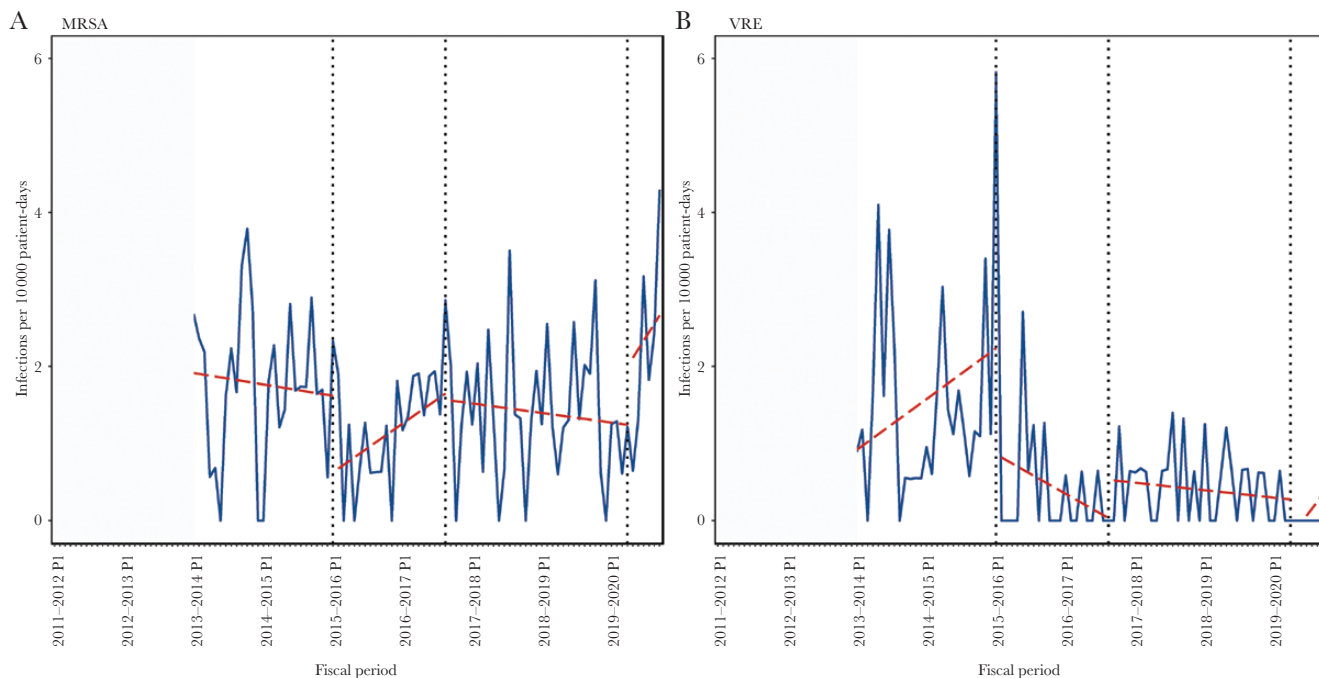


Figure 2. Infection rates per study period per 10 000 patient-days. The left vertical line represents the hospital move. The middle vertical line corresponds to the Daptomycin as Adjunctive Therapy for *Staphylococcus aureus* bacteremia (DASH) trial start. The right vertical line represents the end of patient enrollment into the DASH trial. Infection rates remained stable after the move. The gray areas indicate that data were not available for this time period. A, methicillin-resistant *S. aureus*. B, vancomycin-resistant *Enterococcus*.

leading up to the study and remained low throughout the trial. Moreover, while only 1 of our 2 hospitals moved to exclusively individual-patient rooms, leading to a reduction in VRE and MRSA infection rates [9], the overall infection rates for both sites dramatically decreased and thereafter remained at a stable level. This is due to changes in the distribution of patient demographics associated with the move to the new hospital and a concurrent increase in the proportion of renovated single-patient rooms at the older hospital site that remained open. Consequently, VRE and MRSA infections were unlikely to have contributed to increased daptomycin use at either site. This is further supported by declining institutional daptomycin use for a year and a half before the start of the clinical trial.

Previous studies have shown that doctors participating in a clinical trial are more likely to prescribe the study drug in their independent practice, especially when the physician is funded by the pharmaceutical industry [2, 3]. In our case, we only had access to pooled drug use from the pharmacy, and we could not discern which physicians were prescribing daptomycin or the indication. However, the trial was not industry funded, and only 1 out of 20 infectious diseases faculty members was directly involved in the study design and implementation. The study was primarily led by a team of residents and infectious disease fellows working on a volunteer basis. While the participating faculty member and the trainees responsible for recruitment may have felt more at ease prescribing

daptomycin than their peers, because of their limited clinical schedules, this is unlikely to account for the observed increase.

Without proving causality, participation in the DASH trial was the only hospital-wide intervention involving the use of daptomycin, and both the trial onset and conclusion were temporally associated with changes in daptomycin usage. Apart from the effect of the trial, the mechanism for the change in prescribing rates is not otherwise explained. We hypothesize that it is likely related to an increased familiarity with the drug and its safety profile, coupled with a word of mouth effect. Before the study, daptomycin was not particularly endorsed in our institution. During the trial, even without specific publicity, exposure to patients enrolled in the trial may have sparked discussion within the infectious diseases division and on the services caring for these patients. Naturally, teaching about the potential uses of daptomycin and the side effects of the study drug took place in those contexts. In a sense, the trial may have instilled both familiarity with and confidence in the drug. A gradual and cumulative change in prescribing, which propagated while the trial was ongoing, is supported by the interrupted time-series analysis. While we do not believe that this led to any patient harm, our data suggest that before DASH physicians may have chosen alternative therapeutic strategies.

The reduction in daptomycin use after trial completion is also interesting to consider. The trial results were not formally discussed or presented before publication, and the database for

the trial was not closed until August 2019. While there may have been some early informal discussion of results between colleagues, we believe it unlikely that the word of mouth effect could explain such a steep decrease in daptomycin use starting as early as July. Instead, we hypothesize that as trial completion coincided with the new academic year and the arrival of new residents (the last DASH patient was enrolled in the last week of June 2019), daptomycin use decreased back to previous levels due to falling “out of sight and out of mind.” That said, it is worth noting that the Combination Antibiotic Therapy for Methicillin-Resistant *Staphylococcus aureus* Bacteria (CAMERA2) trial was a high-profile international trial, and its results were first presented at the ECCMID conference in April 2019. This study demonstrated worse renal outcomes from the addition of a beta-lactam to vancomycin or daptomycin in MRSA bacteremia [11]. While unlikely to explain the increase in daptomycin use, the results may have contributed to the sharp decline in daptomycin prescribing seen in the last segment of this study.

Our study is limited by a lack of patient-level data; we cannot say for certain that increased daptomycin use was not clinically indicated. However, this seems unlikely given that there was no increase in VRE or MRSA infections and linezolid use remained stable during the entire period of investigation. There were no new clinical guidelines (local or national) published during this time period that advocated for more liberal use of daptomycin. While a higher daptomycin dosing strategy is now included in the Clinical and Laboratory Standards Institute laboratory guidelines for *Enterococci* [12], supporting evidence for the higher dosing strategy preceded the start of the DASH trial [13] and was already common practice for severe VRE infections at our center. We believe it is therefore likely that, in most instances, the choice of daptomycin over another agent with similar antimicrobial activity was influenced by the ongoing study. While only 5 patients were excluded from DASH because they were already receiving daptomycin at the time of enrollment, it is possible that some patients not meeting study inclusion criteria or with nonbacteremic *S. aureus* infections received the drug adjunctively off-label.

Accounting for limitations, we believe our study highlights some important findings. First, we provide further evidence for the potential impact of seeding trials. Even in a trial performed independent of industry, there was a clear change observed in prescribing practices. It may be relevant for future trials to collect off-study drug usage rates to assess for undue influence on prescribing patterns, with particular attention to any impact on patient outcomes. Second, clinicians should be wary of early adoption of an intervention before the publication of the definitive study results. While the DASH trial was ultimately a negative study, rapid uptake of the study drug may have been

related to a belief that adjunctive daptomycin would be beneficial to patients, and some prescribers may have developed an early conviction that the drug could decrease the duration of bacteremia and, by proxy, harder outcomes. Our study highlights the need to establish mechanisms to formally disseminate early, transparent, and reliable preliminary results to avoid unnecessary patient harm.

In conclusion, we found that prescriber exposure to a drug trial can be associated with an increased use of the study drug outside the confines of the trial. This suggests that investigators should consider collecting the necessary data to detect off-target effects in order to study, and even mitigate, the potential impact of the intervention on nontrial participants.

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References

- Denig P, Haaijer-Ruskamp FM, Wesseling H, Versluis A. Impact of clinical trials on the adoption of new drugs within a university hospital. *Eur J Clin Pharmacol* **1991**; 41:325–8.
- Andersen M, Kragstrup J, Søndergaard J. How conducting a clinical trial affects physicians' guideline adherence and drug preferences. *JAMA* **2006**; 295:2759–64.
- Chren MM, Landefeld CS. Physicians' behavior and their interactions with drug companies. A controlled study of physicians who requested additions to a hospital drug formulary. *JAMA* **1994**; 271:684–9.
- Hill KP, Ross JS, Egilman DS, Krumholz HM. The ADVANTAGE seeding trial: a review of internal documents. *Ann Intern Med* **2008**; 149:251–8.
- Cheng MP, Lawandi A, Butler-Laporte G, et al. Daptomycin versus placebo as an adjunct to beta-lactam therapy in the treatment of *Staphylococcus aureus* bacteremia: study protocol for a randomized controlled trial. *Trials* **2018**; 19:1–9.
- Cheng MP, Lawandi A, Butler-Laporte G, et al. Adjunctive daptomycin in the treatment of methicillin-susceptible *Staphylococcus aureus* bacteremia: a randomized controlled trial. *Clin Infect Dis*. **In press**.
- Center for Disease Control and Prevention, National Healthcare Safety Network. Tracking infections in acute care hospitals/facilities. **2018**. Available at: <https://www.cdc.gov/nhsn/acute-care-hospital/index.html>. Accessed June 2020.
- Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* **2002**; 27:299–309.
- McDonald EG, Dendukuri N, Frenette C, Lee TC. Time-series analysis of health care-associated infections in a new hospital with all private rooms. *JAMA Intern Med* **2019**; 179:1501–6.
- Bozdogan H. Model selection and Akaike's Information Criterion (AIC): the general theory and its analytical extensions. *Psychometrika* **1987**; 52:345–70.
- Tong SYC, Lye DC, Yahav D, et al; Australasian Society for Infectious Diseases Clinical Research Network. Effect of vancomycin or daptomycin with vs without an antistaphylococcal β -lactam on mortality, bacteremia, relapse, or treatment failure in patients with MRSA bacteremia: a randomized clinical trial. *JAMA* **2020**; 323:527–37.
- Phua J, Ngerng W, See K, et al. Characteristics and outcomes of culture-negative versus culture-positive severe sepsis. *Crit Care* **2013**; 17:1–12.
- Casapao AM, Kullar R, Davis SL, et al. Multicenter study of high-dose daptomycin for treatment of enterococcal infections. *Antimicrob Agents Chemother* **2013**; 57:4190–6.