Reply to Sachdev et al

To the Editor—We thank Sachdev et al for their interest in and evaluation of our article [1]. The respondents present data from a survey of providers in metropolitan areas with the highest human immunodeficiency virus incidence, and their results complement and support our findings. Unlike our article, which specifically surveyed infectious disease physicians, the respondents captured responses from primary care providers. Their results demonstrate that provider self-efficacy and normative beliefs about preexposure prophylaxis (PrEP) were associated with intention to prescribe PrEP. These data build on our findings that complex and multiple barriers exist to the provision of PrEP among both infectious disease specialists and primary care providers. In addition, their work supports our conclusion that multifaceted approaches will likely be necessary to the successful provision of real-world PrEP.

Notes

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Reference

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Different Recommendations for Daptomycin Dosing Over Time in Patients With Severe Infections

To the Editor—We read with interest the recent article by Falcone and colleagues regarding the higher incidence of severe sepsis, septic shock, higher Sequential Organ Failure Assessment score, or methicillin-resistant *Staphylococcus aureus* bacteremia among patients with altered clearance of daptomycin [1]. It is worth noting that the evaluation of probability of target attainment (PTA) and cumulative fraction of response (CFR) suggests the use of weight-based doses of at least 10 mg/kg or a fixed daily dose of 750 mg, whereas higher doses increase the risk of toxic effects associated with minimum plasma concentrations >24.3 mg/L [2]. However, no covariates were identified as having a significant effect on daptomycin disposition despite intensive drug monitoring during the first 96 hours of daptomycin administration. It is interesting to point out that previous results in 58 patients did identify creatinine clearance as a significant covariate affecting drug disposition, but not septicemia (7 patients) or severe sepsis (22 patients) [3]. In fact, drug clearance did not significantly differ in patients with or without sepsis (mean ± standard deviation, 0.85 ± 0.09 or 0.81 ± 0.16 L/h, respectively).

The different schedule of blood sampling between the 2 studies may explain these striking differences. Falcone and colleagues focused their investigation in previously untreated patients during the first 96 hours of therapy, when both infection severity and patients' performance status may have the greatest effects on drug disposition. In contrast, Di Paolo et al adopted a less intensive, prolonged therapeutic drug monitoring protocol starting after the fourth dose of daptomycin [3], and the results suggest that the impact of sepsis in altering drug disposition decreases over time. Indeed, a simulation on the basis of the published pharmacokinetic model [3] according to the described procedure [4] shows that CFR values are >95% even at

Table 1. Cumulative Fraction of Response and Probability of $C_{min,ss}$ Values >24.3 mg/L

	%CFR Based on AUC_{0-24}/MIC			
Daily Dose	≥579	≥666	≥753	Probability of $C_{min,ss}$ >24.3 mg/L
Weight-based dosing				
6 mg/kg/d	98.9	97.9	96.6	2.50
8 mg/kg/d	99.4	99.0	98.2	6.17
10 mg/kg/d	99.7	99.4	99.0	8.35
Fixed dosing				
500 mg/d	99.3	98.9	98.4	2.54
750 mg/d	100	99.9	99.7	17.74
1000 mg/d	100	100	100	40.09

The cumulative fraction of response (CFR) and the probability of $C_{min,ss}$ of daptomycin >24.3 mg/L for weight-based and fixed doses is shown. Results were obtained in 5000 simulated individuals with a median weight of 70.60 kg (95% confidence interval [CI], 46.84–98.71 kg) and creatinine clearance of 83.25 mL/minute (95% CI, 41.35–124.50 mL/minute).

Abbreviations: AUC_{0-24}, area under the time/concentration curve from time 0 up to 24 hours; $C_{min,ss}$, minimum plasma concentration at steady state; MIC, minimum inhibitory concentration.