the lowest simulated dosing regimen of 6 mg/kg/day or at the fixed dose of 500 mg/day (Table 1). Furthermore, the administration of higher fixed doses (ie, 750 mg/day) seems to be associated with an increased risk of toxicity, as witnessed by the high probability of minimum plasma concentrations >24.3 mg/L (Table 1). These findings are not surprising, because only 12 of 58 patients received doses equal to 700 mg/day, whereas the dose range was between 175 and 612 mg/day in the remaining 46 patients [3].

In conclusion, the presence of sepsis may cause a reduction in PTA and CFR values during the first days of drug administration, which could require the careful revision of dosing strategies, as pointed out by Falcone et al [1]. On the contrary, the need for higher fixed doses after the first 72–96 hours of therapy could be questioned in patients with resolving sepsis, as daptomycin disposition is less severely altered and the risk for toxicity with higher fixed doses may increase. In this view, available protocols of therapeutic drug monitoring may further improve the safe and effective use of daptomycin for the treatment of severe infections sustained by gram-positive bacteria [5].

Note

Potential conflicts of interest. All authors: No reported conflicts.

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Reply to Di Paolo et al

To the Editor—We thank Di Paolo and colleagues for their comments about our recent publication [1, 2]. We agree that individualized daptomycin therapy through therapeutic drug monitoring would be optimal, as daptomycin clearance (CL) may change over time. Our daptomycin measurements were made during the first 96 hours of therapy, and so our suggestion of higher empiric fixed doses pertain to this time period [2]. The basis for this suggestion is that daptomycin CL is not related to body weight and we observed a subpopulation of patients with augmented daptomycin CL. This subpopulation with augmented daptomycin CL is not easily identified a priori by common clinical and laboratory measures [2]. In our opinion, septic patients have the potential for augmented CL, and an initial higher dose ensures optimal exposure. The alternative is to risk underexposure and treatment failure with standard doses. The risk of toxicity will be increased with higher daptomycin doses and could be mitigated by lowering the dose after the initial 72–96 hour period as suggested by Di Paolo et al [1]. The key point, nevertheless, is that this daptomycin dose is not better predicted by a weight-based compared with a fixed-dose approach.

Similar to our study, Di Paolo et al found no relationship between weight and daptomycin CL or volume of distribution [3]. This relationship is necessary to support weight-based dosing [4]. They observed a relationship between daptomycin CL and estimated creatinine CL, whereas our study did not. Specifically, their model estimated daptomycin CL with an estimated creatinine CL of 40 mL/minute, 80 mL/minute (referent), and 160 mL/minute is 0.6966 L/hour, 0.8016 L/hour (referent), and 0.9225 L/hour, respectively [3]. This 15% difference in daptomycin CL, relative to the referent value, is unlikely to be clinically meaningful. Of significance, they observed daptomycin CL values in their patients that are similar to our “normal” daptomycin CL population. As a consequence, their simulations match the trends observed in our simulations of patients without sepsis. As shown in Table 1 of their correspondence, 500 mg/day leads to probability of target attainment that is >95% but a much lower probability for toxicity compared with 8–10 mg/kg/day doses [1]. The harmonizing point of both our studies is that fixed doses of daptomycin may be sufficient in patients with severe gram-positive bacterial infections. The point of contention is whether that initial fixed dose should be 500 mg/day, 750 mg/day, or some other prospectively validated fixed dose. Alternatively, an empiric daptomycin regimen of 750 mg/day for 72–96 hours, followed by a reduction to 500 mg/day, may be supported by our studies [2, 3]. Identification of the “right” daptomycin regimen can be addressed through additional prospective studies that directly compare a fixed dosing regimen with the current standard of
weight-based dosing. Alternatively, clinicians with access to daptomycin therapeutic drug monitoring could independently compare these dosing paradigms. We have recently published a set of simplified equations that can be used to compute daptomycin areas under the curve based on peak and trough measurements to support such an investigation [5]. Optimal daptomycin dose selection will improve the safe and effective use of this antimicrobial.

Note

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