Reply to Taccone et al, Wolff and Mouvillier, Masuta and Iwata, and Lahey

To THE EDITOR—We thank the editor for the chance to respond to several comments regarding our recent manuscript [1].

Three of the letters [2–4] raise important issues regarding the relationship between vancomycin levels achieved by day 3 and clinical response rates in patients randomized to receive vancomycin treatment. Both Taccone et al [2] and Wolff and Mouvillier [3] suggest that accelerated renal clearance, possibly resulting in inadequate level achievement, may explain our findings that patients with greater creatinine clearance did worse with vancomycin. We agree with Taccone et al [2] that levels at day 3 may not necessarily reflect the adequacy of early vancomycin dosing, and it is very logical that a loading dose is more likely to result in earlier achievement of adequate serum levels.

The appropriate dosing regimen for vancomycin remains in a state of flux. The original US Food and Drug Administration (FDA) registration trials mandated a vancomycin dose of 1 g or, at most, 15 mg/kg every 12 hours [5, 6]. This dose is recognized as inadequate, particularly in critically ill patients [7]. Subsequent guidelines recommended adjusted-dose vancomycin to achieve a trough level of 15–20 mg/L if used for treatment of methicillin-resistant Staphylococcus aureus (MRSA) pneumonia [8], although at that time and since, no study has demonstrated a benefit in any clinical outcome. This vancomycin dosing strategy was, in fact, the one tested in this study. The inability to consistently achieve target vancomycin trough levels likely reflects current clinical practice throughout most of North America and Europe and adds to the clinical relevance of this trial.

Although the dose recommendations of Taccone et al [2] may improve clinical response to vancomycin in patients with MRSA pneumonia, this remains theoretical, because no clinical trial demonstrates this benefit. These recommendations were based on Monte Carlo simulation rather than an actual clinical trial [9]. The simulation was also based on continuous-infusion vancomycin, which has not been demonstrated to be superior to intermittent dosing in a randomized controlled trial [10], even when targeting higher trough levels. In addition, patients with normal creatinine clearance were the most likely to have increased risk of acute kidney injury (AKI) associated with vancomycin in our study [1]. Therefore, the theoretical benefit of this more aggressive dosing regimen in patients with normal renal function at baseline may be offset by a greater risk of AKI. The theoretical benefit of higher doses is also predicated on the relationship between serum vancomycin levels, principally the area under the inhibitory curve, and the vancomycin minimum inhibitory concentration (MIC). Almost all of the patients in this study had low MICs, making underdosing of vancomycin a less likely explanation for the difference in outcome. Because a large loading dose, higher weight-based daily dosing, and/or continuous-infusion vancomycin are all off-label use, FDA regulations would not allow a phase 4 comparative clinical trial, such as the one that we report, to dose vancomycin in this way, as suggested by Wolff and Mouvillier [3]. This will likely be true for phase 3 FDA registration trials of new agents as well. We therefore feel that vancomycin is unlikely to be the comparator for future studies of MRSA pneumonia and should not be, unless off-label dosing is allowed.

Masuta and Iwata [4] recommend longer duration of vancomycin therapy, based on expert opinion, to demonstrate therapeutic equivalence to linezolid. However, a randomized controlled trial of duration of therapy with significant numbers of quantitative culture–proven MRSA ventilator–associated pneumonia (VAP) treated with glycopeptides did not demonstrate any benefit of duration >8 days [11]. Increasing duration of therapy has also been associated with increased risk of AKI with vancomycin [12].

Masuta and Iwata [4] and Lahey [13] comment on the lack of mortality difference between the treatment groups. However, the study was neither designed nor powered to detect a mortality difference. In fact, no clinical trial of antibiotic treatment of pneumonia has ever demonstrated a mortality difference in the overall study. Subgroup analysis of patients with MRSA infection from phase 3 trials that include linezolid as either experimental [14] or control drug [15] are the only ones to even suggest a mortality difference, always in favor of linezolid. We discussed potential explanations for mortality differences from the original phase 3 subgroup analysis extensively in the manuscript [1]. In addition, a recent publication has suggested that VAP may not in fact have any attributable mortality [16]. If true, to expect an antibiotic treatment–based difference in mortality is unreasonable.

Dr Lahey appears to be unfamiliar with the routine finding of differences in some baseline characteristics in almost all clinical trials and with what constitutes a study population versus a subgroup analysis [13]. He also uses misleading statistics to suggest that baseline
differences between the 2 groups resulted in the outcome differences. For example, he states that there was “fully 52% less bacteremia” in the linezolid, group when the actual data were 9 of 172 patients (5.2%) for linezolid and 20 of 176 patients (10.8%) for vancomycin, all of whom achieved microbiologic cures with respect to bacteremia in both groups. Ironically, Lahey decries subgroup analysis of previous gram-positive pneumonia studies [14] in the same paragraph in which he uses subgroup analysis to question the results of the current study [13].

We fail to see why the inadequacies of vancomycin for treatment of pneumonia, particularly VAP, remain so controversial. Vancomycin does not have a specific indication for treatment of MRSA pneumonia and was essentially grandfathered into being the standard treatment because, at the time of development, no comparator existed. In most clinical trials, vancomycin has been inferior to the comparator when looking specifically at MRSA pneumonia, not just in comparison with linezolid [1, 14, 17], but also with telavancin [18]. The comparators to which vancomycin was equivalent were quinupristin-dalfopristin [19] and tigecycline [20], neither of which has an indication for nosocomial pneumonia. The loading dose and higher dosing regimens have not been proven to be better than linezolid and are clearly not the standard of care outside a few academic medical centers. The only aspect commending vancomycin over linezolid is cost. However, the cost of monitoring of levels and the risk of AKI associated with high-dose vancomycin [12], as well as the impending linezolid patent expiration, may obviate even that advantage.

Note

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