Should We Abandon Vancomycin for Treatment of Methicillin-Resistant Staphylococcus aureus Pneumonia? Still Questions to Answer

To the Editor—We read with interest the article by Wunderink et al. [1] that showed that linezolid was superior to vancomycin in the treatment of pneumonia due to methicillin-resistant Staphylococcus aureus (MRSA). Several factors may affect the efficacy of vancomycin during the treatment of MRSA infection, including the minimal inhibitory concentration of the pathogen for the drug, the serum vancomycin concentration, or the poor penetration into solid organs such as the lungs. In addition, high vancomycin doses may be
nephrotoxic [2]. The development of other antimicrobial agents active against MRSA, such as linezolid, has raised the question whether vancomycin could still be recommended as first-line therapy when MRSA is suspected [3]. Wunderink et al’s study [1] suggests a greater clinical efficacy of linezolid when compared with vancomycin; however, as in previous studies, a suboptimal vancomycin regimen may have limited effectiveness against MRSA.

A recent study showed that >70% of patients failed to reach the recommended trough concentrations (of at least 15–20 mg/L) in a large cohort of MRSA pneumonia when standard regimens (15 mg/kg every 12 hours) were administered [4]. In particular, patients with creatinine clearance (CrCL) >60 mL/minute had the lowest probability of achieving target drug levels. Similarly, we found that the most important determinant of early insufficient vancomycin concentrations, when given as a continuous infusion, was a high CrCL [5]. Vancomycin is highly excreted through the kidneys, and vancomycin clearance could be significantly increased with high CrCL [6]. This could explain why, in the present study [1], linezolid had significantly more clinical success than did vancomycin (61% vs 48%) only in patients with CrCL >50 mL/min, whereas effects were quite similar in those with impaired renal function. This so-called augmented renal clearance (ARC) has been shown to be an important predictor of subtherapeutic concentrations for other hydrophilic antimicrobials [7]; because it remains difficult to identify ARC in a general cohort of patients, one may argue that excessive vancomycin elimination may have resulted in insufficient drug concentrations in a proportion of patients in this study and have contributed to reduce drug efficacy.

Indeed, 35 (20%) and 72 (41%) patients had vancomycin concentrations <8 mg/L and <12 mg/L at day 3, respectively. Although some studies did not report significant differences in treatment success rates between patients with different vancomycin trough concentrations, a recent single-center retrospective analysis of 320 patients with documented MRSA bacteremia showed that initial vancomycin trough concentration <15 mg/L was an independent predictor of therapy failure, suggesting that optimizing vancomycin by targeting higher early trough values of 15–20 mg/L in patients with severe infection should be considered [8]. In this context, measuring vancomycin levels at day 3 may be misleading; although this would reflect drug levels at the steady state, early and appropriate antibiotic therapy is mandatory to treat severe infection. We showed that some patients with insufficient drug levels on the first day of treatment could achieve target concentrations without changes in the daily dose during the therapy course. This could be explained by changes in drug pharmacokinetics and/or in renal function [6]. Thus, vancomycin levels obtained on day 3 cannot predict drug concentrations on the first day of treatment and could have likely underestimated antibiotic doses in the early phase of therapy.

The importance of a high loading dose to achieve therapeutic drug concentrations in the early phase of therapy has been highlighted in previous studies; in a cohort of patients with serious MRSA infection, a loading dose of 25 mg/kg of vancomycin was found to be safe and to rapidly achieve therapeutic drug concentrations [9]. Using Monte Carlo simulation, we found that higher-than-recommended loading (35 mg/kg) doses of vancomycin would be necessary to achieve therapeutic serum concentrations in the early phase of sepsis [10]. Recent guidelines also recommended a 25–30 mg/kg loading dose to rapidly optimize serum vancomycin concentrations in severe MRSA infection [11]. In this study [1], the use of a loading dose of 15 mg/kg could have contributed to delay in the achievement of therapeutical drug concentrations.

Note

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

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