Sir,

We appreciate the informative response by Cleveland and Memon1 to our recent publication in JAC.2 Owing to space limitations, we were unable to provide as detailed a report as possible but would like to take the opportunity to respond to a few of their points.

With regard to the initial under-dosing of vancomycin (1 g intravenously every 24 h), a recent consensus paper recommended that a trough of 15–20 mg/L would be required to achieve an area under the curve to MIC (AUC/MIC) of ≥400, the pharmacodynamic parameter that best correlates with vancomycin efficacy.3 An estimation of our patient’s AUC/MIC on days 1–2,4 while assuming an MIC of 2 mg/L (Etest MIC was not available until day 7), gives a value of 974, suggesting that the initial vancomycin regimen was adequate. Regardless of the dose, in retrospect we feel the decision to change to daptomycin early on was sound. In a study by Patel et al.,5 using Monte Carlo simulation, a vancomycin regimen of 4 g/day only attained AUC/MIC ≥400 57% of the time, at a MIC of 2 mg/L. However, the probability of generating nephrotoxicity at such a dose was upwards of 35%.6 Infective endocarditis (IE) and vancomycin MIC >1 mg/L by Etest have been shown to be independent predictors of vancomycin failure.6 For these reasons and the necessary length of therapy, vancomycin would have been very difficult to maintain safely and effectively in a patient with pre-existing renal dysfunction, IE, and with an isolate with a vancomycin MIC of 2 mg/L by Etest.

The patient’s paraparesis gradually improved after paraspinal drainage, giving us a low threshold to repeat imaging. We do agree with the authors that if transoesophageal echocardiogram (TEE) had been performed sooner, surgery could have been expedited. At the time, the patient was already on antimicrobials, the initial transthoracic echocardiogram (TTE) found no vegetations, and subsequent auscultations by various clinicians did not suggest any cardiac abnormalities, prompting much debate (and possibly delay) on the need for repeat imaging. Indeed, if there is high clinical suspicion or if Staphylococcus aureus bacteremia with an unidentified source persists, then TEE is indicated.7

Cleveland and Memon are correct to point out that removal of the foci of infection played a significant role in achieving cure. Despite that, and early microbiological response with linezolid, telavancin monotherapy following daptomycin failure.8 However, the necessary length of therapy, vancomycin would have been very difficult to maintain safely and effectively in a patient with pre-existing renal dysfunction, IE, and with an isolate with a vancomycin MIC of 2 mg/L by Etest.

The patient’s paraparesis gradually improved after paraspinal drainage, giving us a low threshold to repeat imaging. We do agree with the authors that if transoesophageal echocardiogram (TEE) had been performed sooner, surgery could have been expedited. At the time, the patient was already on antimicrobials, the initial transthoracic echocardiogram (TTE) found no vegetations, and subsequent auscultations by various clinicians did not suggest any cardiac abnormalities, prompting much debate (and possibly delay) on the need for repeat imaging. Indeed, if there is high clinical suspicion or if Staphylococcus aureus bacteremia with an unidentified source persists, then TEE is indicated.7

Cleveland and Memon are correct to point out that removal of the foci of infection played a significant role in achieving cure. Despite that, and early microbiological response with linezolid, telavancin was well tolerated in completing the patient’s next 3 weeks of therapy and for maintaining negative blood cultures.

We would like to thank the authors for responding and hope our discussion provides valuable information to the medical community, especially in an era of increasing bacterial resistance and limited armamentarium.

References

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Comment on: Efficacy and safety of tigecycline: a systematic review and meta-analysis

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Keywords: antibiotics, dosing, mortality

Sir,

In a recent JAC article, Yahav et al.1 conducted a systematic review and meta-analysis of randomized controlled trials comparing the efficacy and safety of tigecycline with those of empirical antibiotic regimens for the treatment of any infection. The analysis was extensive and methodologically well performed; however, I disagree with their conclusions. The authors

Transparency declarations
None to declare.
concluded that ‘In the light of the increased mortality, probably explained by decreased clinical and microbiological efficacy, clinicians should avoid tigecycline monotherapy…’. However, in my view, the question remains, is tigecycline less effective than comparators or do other factors contribute to the increased mortality in tigecycline-treated patients?

In general, we can state that an antimicrobial agent is less effective than another if there was a poorer clinical outcome and it was properly dosed. Pathophysiological changes, such as an increased volume of distribution and/or increased clearance, may occur in critically ill patients, and may impact on antibiotic distribution and concentration, resulting in slow and possible incomplete penetration into infected tissues.\textsuperscript{2,3} A significant concern for clinicians is that the administration of standard antibiotic doses in such patients may result in a subtherapeutic concentration, leading to the suboptimal killing of bacteria.

In all evaluated studies, tigecycline was used at a fixed dose comprising an initial dose of 100 mg intravenously followed by 50 mg every 12 h, while the doses of the comparators in some studies were, correctly, adjusted on the basis of weight and creatinine clearance.\textsuperscript{4-7} The study of Freire et al.\textsuperscript{7} that compared the efficacy and safety of a tigecycline regimen with an imipenem/cilastatin regimen in hospital-acquired pneumonia patients is of particular interest to support my arguments. In this study, both clinical assessment and pharmacokinetic/pharmacodynamic (PK/PD) analysis were evaluated. Tigecycline was used at the usual fixed dosing regimen, while imipenem/cilastatin was administered at 500 mg to 1 g intravenously every 8 h on the basis of clinical judgement! A total of 123 patients in the modified intent-to-treat population died during the study; 66/467 (14.1%) in the tigecycline group and 57/467 (12.2%) in the imipenem/cilastatin group. A subanalysis revealed that in non-ventilator-associated pneumonia (VAP) patients, the mortality was the same in both regimens [41/336 (12.2%) in the tigecycline group and 43/345 (12.5%) in the imipenem/cilastatin group], but the mortality in VAP patients was 25/131 (19.1%) and 15/122 (12.3%) in the tigecycline and imipenem/cilastatin groups, respectively. This demonstrates increased mortality with tigecycline versus comparators in VAP patients. But why did this not happen in non-VAP patients?

The PK analysis of tigecycline revealed that the mean \(AUC_{0-12}\) was 2.726 and 3.198 mg.h/L (\(P \approx 0.041\)) in VAP and non-VAP patients, respectively. The clearance was also faster in VAP patients (23.3 L/h) compared with non-VAP patients (20.7 L/h). Moreover, the PK/PD analysis showed that the median \(AUC_{0-24}/MIC\) observed in VAP patients was 60% lower (\(P \approx 0.002\)) than the value observed in non-VAP patients (1.730 versus 4.389). The lower efficacy and the consequent higher mortality can potentially be explained by the lower drug exposure due to physiological changes that occur in patients with VAP.

Although the PK/PD behaviour of tigecycline in the other studies is not known, there is a high probability that the mortality was affected by the dosing, rather than by the ‘general’ decreased clinical and microbiological efficacy of the drug. In my opinion, the lesson that we learn from the tigecycline story is that in some patients the dose is not adequate. Future studies should explore higher doses of this drug in selected patients where pathophysiological changes may affect the PK of drugs. On the other hand, very few antimicrobial agents are now used at the doses approved after the Phase 3 studies. Clinical trials and clinical experience gained in the years following drug approval are often how we learn the correct dosing of antibiotics in different patients.

\textbf{Transparency declarations}

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\textbf{References}


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\textbf{Comment on: Efficacy and safety of tigecycline: a systematic review and meta-analysis}

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\textbf{Keywords}: randomized clinical trials, severe infections, test of heterogeneity