Reply to Soman et al

To the Editor—We thank Soman et al for their comments on our article and would like to clarify several points in reply [1, 2]. Continuous or extended infusion of β-lactam antibiotics is not currently standard practice. In fact, the frequency of use of extended/continuous infusion of β-lactam antibiotics differs widely between geographic regions [3, 4], and there is currently insufficient published evidence to inform the choice of extended/continuous infusions over intermittent dosing of β-lactam antibiotics [5, 6].
As highlighted by Soman et al, the application of pharmacokinetic/pharmacodynamic principles to inform clinical practice for specific patient groups requires a stepwise process of hypothesis testing and validation. Although both in vitro and ex vivo studies describe relationships for maximal antimicrobial efficacy, it is ultimately the results from in vivo testing in large-scale randomized controlled trials using patient-centered clinical outcomes that will have the greatest impact on evidence-based practice [7, 8].

We agree with Soman et al on the merit of a loading dose prior to the commencement of a β-lactam continuous infusion to prevent delay in achieving target antimicrobial concentrations. For this reason, an initial bolus dose was included as part of the protocol in the Beta-Lactam Infusion Group (BLING) trial [2], as well as in the subsequent BLING II trial (Australian New Zealand Clinical Trials Registry Number 12612000138886). Soman et al propose particular patient groups that may have the greatest benefit from extended or continuous β-lactam infusion, and we agree that patients with gram-negative infections, augmented renal clearance, and a compromised immune status warrant particular consideration.

The response to dosing strategy in different types of infection may well vary. However, a challenge for validation will always be the conduction of adequately powered studies in particular subgroups of interest. For "pharmacologically protected" sites of infection, such as bone and joint infections, it is already common practice for patients to be treated with continuous infusions of β-lactam antibiotics in a "hospital in the home" setting, owing to convenience of delivery. While the clinical benefit of continuous infusion in various settings warrants further study, we believe a large-scale trial in patients with severe sepsis is an immediate priority with the greatest likelihood of clinical advantage from continuous infusion of β-lactam antibiotics.

With regard to antibiotic resistance, while the mutant selection window has been demonstrated in vitro [9], robust data to describe its clinical relevance remain elusive and the effect of continuous infusion of β-lactam antibiotics in this context is yet to be defined. We believe that treatment that results in higher rates of definitive cure, combined with principles of good antimicrobial stewardship, are of most importance to clinicians and patients.

Note
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