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Aggressive versus conservative initiation of antibiotics--authors' reply

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We appreciate the comments in response to our recent publication. However, before addressing the specific concerns, we wish to place the study in a clinical context.

We work in a 15-bed, surgical trauma intensive-care unit (ICU). As we write this letter, 13 of our patients meet at least two of the criteria for systemic inflammatory response syndrome and they all have at least one organ system dysfunction. Five are being treated for a documented infection, and the remaining eight could possibly be infected and are in various stages of assessment. The question is do we need to give antimicrobials to all these patients, who meet criteria for severe sepsis but not septic shock? We don't think so, yet the misinterpretation of previous retrospective studies implies this is the case. A more conservative approach, based on our data,[1] seems to be safe.

Our research showed improved mortality in haemodynamically stable, surgical ICU patients after waiting for objective evidence of infection before starting empirical antimicrobials. These findings might be related to our study of traumatised and postsurgical patients in whom persistent inflammation is common, decreasing the specificity of many signs of infection, including hyperthermia and leucocytosis. Additionally, our analysis excluded patients admitted to the ICU with sepsis, which was often the focus of past publications. Since infections in our study were all ICU-acquired, they were secondary events and, therefore, their characteristics might be different from those in which infection is the primary problem.

Delay in empirical antibiotic administration (12 h in the aggressive treatment group) might have confounded our study's results. How ever, these data are similar to the 17 h delay documented by Barie and colleagues[2] in a similar ICU. As a pragmatic, protocol implementation trial, these findings are probably typical in patients in whom diagnosis is not clear. Additionally, the timing data were based on time to definitive intervention, not antimicrobial admini stration. Thus, a patient who had blood cultures sent and antimicrobials started 1 h later, but 24 h later underwent drain placement, was considered as having their therapy started 24 h after blood culture, not 1 h.

In terms of empirical antibiotics, we used piperacillin/tazobactam and vancomycin according to institutional antibiotic stewardship guidelines. The most common pathogens that were treated inadequately were vancomycin-resistant enterococci (VRE) and yeast (predominantly *Candida albicans*). Whether substituting linezolid or daptomycin for vancomycin to empirically treat VRE would improve outcomes is unclear. Antifungal drugs were started empirically in patients with a high suspicion of a fungal infection (eg, upper

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gastrointestinal leak), but antifungal agents are unlikely to benefit all normotensive patients suspected of having a new infection. Finally, prophylactic perioperative antibiotics might have changed culture results. Most infections, however, occurred many days after an operation and this confounder might be of less importance.

Ideally, we would have done the study in two equivalent ICUs, where patients in one unit would have been treated under the aggressive protocol throughout the study to control for other changes in therapy, but we only have access to one surgical ICU. Also, we could have incorporated all patients admitted to the ICU into our data analysis, but ultimately chose to focus on those with infections. An expanded, multicentre study has been proposed to collect such variables. Finally, a randomised controlled study would have been an alternative trial design, but would not have answered questions of effectiveness (as opposed to efficacy) and would not have allowed a full understanding of the effect of the different approaches on unit-wide epidemiology. We hope to address these concerns in a multicentre study that will use cluster randomisation.

References

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