Reply to Nannini and Arias

To the Editor—We thank Nannini and Arias for their interest in our article [1]. They raise several important issues in assessing the impact of emergency department occult *Staphylococcus aureus* bacteremia on patient outcomes [2].

Although 30-day mortality is a commonly used study endpoint in most bacteremia outcome researches, we agree that a 30-day follow-up period might be inadequate for patients with *S. aureus* bacteremia. We therefore reanalyzed our data using 90-day survival as the study endpoint for occult *S. aureus* bacteremia patients (case group) and *S. aureus* bacteremia patients who were directly admitted at the time of their initial emergency department visit (control group). We found that there remained no survival difference between the case and control groups (Figure 1).

Attributable mortality has been used as the outcome variable in several *S. aureus* bacteremia studies. However, determining attributable mortality in connection with a particular bacteremia episode is subject to information bias, and is therefore appropriate only in a prospective study or randomized controlled trial in which the outcome is evaluated independent of knowledge of the predictor variables [3, 4]. Furthermore, it is well recognized that *S. aureus* bacteremia tends to be complicated by embolic events, mycotic aneurysms, and recurrent bacteremia. All of these...
complications contribute to delayed mortality in S. aureus bacteremia, and might not be detected by the operational definition of attributable mortality. Using attributable mortality as the outcome variable might, theoretically, underestimate the mortality associated with S. aureus bacteremia. Furthermore, a recent prospective study showed that all-cause mortality and attributable mortality are equally appropriate as outcome variables in validating the performance of different scoring systems in predicting S. aureus bacteremia outcomes [5]. We therefore believe that the use of all-cause mortality in our retrospective study was methodologically appropriate for the evaluation of the real impact of occult S. aureus bacteremia on patient outcomes.

We admit that it is difficult to control for residual confounding by indication in a nonrandomized study, and this remains a potential limitation of our report. However, the use of a strict matching strategy to restrict patients to a more homogenous population in our study provided the best estimate for the impact of occult S. aureus bacteremia on clinical outcomes [5]. Furthermore, our study provided important information on how emergency department physicians’ clinical assessment and disposition decisions affect patient outcomes in practice.

Finally, we agree that all S. aureus bacteremia patients should be hospitalized as soon as possible to allow comprehensive diagnostic evaluation and initiation of effective antimicrobial therapy. However, occult bacteremia remains a challenging clinical issue because blood culture results are not available at the time of emergency department evaluation, and a diagnostic tool for immediate recognition of bacteremia is absent. Therefore, for febrile patients without an immediate indication for hospital admission and without an apparent infection focus, the best action for first-line clinicians is prudent clinical evaluation; it is impractical to crowd these patients into the emergency department or the hospital while waiting for blood culture results.

Note
Potential conflicts of interest. All authors: No reported conflicts.
All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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DOI: 10.1093/cid/cit091

Figure 1. Kaplan-Meier survival curves for emergency department adult occult Staphylococcus aureus bacteremia patients (case group) and S. aureus bacteremia patients who were admitted at the time of their initial emergency department visit (control group).