ceived vancomycin versus oxacillin, leaving the possibility that these 58 subjects with methicillin-susceptible infection received an inferior regimen (i.e., vancomycin) [4, 5]. Including an inferior regimen for almost one-fourth of the control arm would almost certainly make non-inferiority an easier threshold to reach.

Finally, it is troubling that, in the 1 subset of patients with CRBSI for which linezolid was most likely to be used (i.e., those patients for which methicillin-resistant S. aureus was isolated), the lower limit of the 95% confidence interval was −26.2%. Using a drug that may be 26% less effective in this important patient population is not an appealing option. Taken together, these issues raise serious questions regarding the validity and applicability of these findings. Whether the use of linezolid is truly noninferior for treating patients with CRBSI is an unanswered question, one which needs further study, preferably with a trial that includes a robust comparator arm, and that is fully and transparently reported.

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References


Concerns about “Complicated Skin and Skin-Structure Infections and Catheter-Related Bloodstream Infections: Noninferiority of Linezolid in a Phase 3 Study”

To the Editor—We have several concerns regarding the recent article by Wilcox et al. [1]. The authors state that “the frequency and severity of adverse events were similar between groups” [1, p. 210]. This statement, however, is not consistent with their data. For 48 (13%) of 363 patients in the linezolid arm and for 25 (7%) of 363 patients in the control arm, treatment was discontinued secondary to adverse events. Although the authors do not present a statistical comparison, this difference is statistically significant (P = .006 by use of Fisher’s exact test). Thus, we cannot conclude that the frequency and severity of adverse events were similar between groups. In their table 5, the authors present data showing that the number of drug-related adverse events leading to discontinuation of the study was similar between the 2 arms (6 adverse events in the linezolid arm versus 4 adverse events in the control arm). However, it is unclear what is meant by drug-related versus non-drug-related adverse events leading to discontinuation of the study. It would have been helpful if the authors explained the difference; presumably 42 individuals in the linezolid arm and 21 individuals in the control arm discontinued treatment as a result of having nondrug-related adverse events.

With respect to the increased mortality seen in patients without gram-positive bacteremia, we disagree with the authors’ statement that “the post-hoc nature of these analyses and the size of these subsets of the primary analysis populations limit certainty” [1, p. 210]. The authors do not present a statistical analysis of the interaction between treatment group and the presence or absence of gram-positive bacteremia. On the basis of the frequencies presented in the article, we calculated that the presence of gram-positive bacteremia was a significant modifier of the association of the odds of mortality with the treatment arm (P = .058 by use of the Mantel-Haenszel test for homogeneity, with χ² = 3.6). Given that there is no reason to expect that linezolid therapy would be efficacious for patients without gram-positive bacteremia, we feel this interaction is compelling. The effect of linezolid therapy on mortality must be viewed in terms of the type of bacteremia present. When the patients without gram-positive bacteremia who received linezolid were evaluated (using the frequencies presented in Wilcox et al. [1]), we calculated an odds ratio of 2.3 (95% confidence interval, 1.3–4.4) for mortality during the follow-up period. Thus, patients who received linezolid without a gram-positive bacteremia had increased mortality during the course of the study.

In summary, on the basis of these data, we feel that linezolid should not be given as empirical therapy to patients with catheter-related bloodstream infections before the isolation and identification of a pathogenic organism. It would be better to start with vancomycin. Conversely, once a gram-positive organism has been isolated and identified, the data presented by Wilcox et al. [1] suggest that, depending on the clinical circumstances, linezolid could be used.

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Reply to Drekonja and to Lustberg et al.

To the Editor—Drekonja [1] and Lustberg et al. [2] raise several concerns about the study we published [3]. However, it is important to be meticulous about interpreting results from an inference that is based on a prespecified hypothesis with formal significance testing and on hypotheses that arise unexpectedly from post hoc inspection of the data. In our article, we were careful to explain the prespecified primary and secondary end points and to explain the mortality analysis that was performed post hoc. The same level of rigor is needed when relating findings from post hoc inspection of data to derive conclusions, particularly when the rhetoric of transparency is invoked.

As was clearly stated, the objective of our study was to compare the use of linezolid with either the use of vancomycin or vancomycin followed by β-lactams for the treatment of infections associated with intravenous catheters. These infections represent a spectrum of diseases ranging from purulence and cellulitis at the catheter site to infection on the surface or interior of the catheter (with or without confirmation by positive culture results from blood obtained through the catheter) and finally to associated systemic infection (with confirmation by positive peripheral blood culture results). In conjunction with experts in the field and regulatory authorities, and having been discussed in a public forum [4], the latter syndrome was designated as catheter-related bloodstream infection (CRBSI), whereas the other types of infection represented a subset of complicated skin and skin-structure infections (which were associated with the use of an intravenous catheter). We believe that these infections represent a spectrum of infectious complications that are associated with the use of an intravenous catheter. As such, it is logical to examine these infections both together and separately. Because the microbiologic success rates of linezolid therapy were similar for infections at the catheter site and infections associated with use of a contaminated catheter, the comment by Drekonja [1] about the trial being predisposed toward a favorable outcome is unwarranted.

Drekonja [1] is correct that some patients had methicillin-susceptible organisms recovered from samples, including Staphylococcus aureus. In the overall evaluable group (i.e., the first modified microbiologically evaluable group), 19 of 30 patients were switched to oxacillin-dicloxacillin. In the subgroup of patients with CRBSI (i.e., the second microbiologically evaluable group), 14 of 22 patients were switched to oxacillin-dicloxacillin. The microbiologic response rates are shown in table 1. Although the numbers of patients are too small to draw definitive conclusions, the efficacy of linezolid therapy was similar to the efficacy of β-lactam therapy, as was the case in properly powered clinical trials previously published [5].

Finally, regarding Drekonja’s concern about the wide confidence intervals in the CRBSI subset of patients with methicillin-resistant S. aureus (MRSA) infection, we would like to point out that the upper limit is also 27.4%, implying that linezolid could be that much better than the comparators. Given that the width of a confidence interval is a function of the number of subjects, these data must be associated with the proper amount of caution; hence, we did not provide a P value, nor did we perform a test of non-inferiority on this small subset of patients. Our study screened >20,000 patients for over 3 years at 100 medical centers to enroll 739 patients, 45 of whom had CRBSI due to MRSA. We considered that it would not be feasible to perform a study in which the primary objective was to prove statistically that linezolid therapy was noninferior for a subset of patients with CRBSI due to MRSA.

Lustberg et al. [2] have several concerns about the issue of the drug relatedness of adverse events; this is a standard analysis and is part of good clinical practice in clinical trials [6]. Drug relatedness allows the investigator at the bedside the opportunity to determine the likelihood of the event being related to the drug under study. In a study of patients, many of whom are in an intensive care unit, this is particularly important given multiple underlying comorbidities and competing causes of an adverse event that may or

Table 1. Microbiologic response rates to different drug treatments, by subgroup of patients with catheter-related bloodstream infection.

<table>
<thead>
<tr>
<th>Group</th>
<th>Linezolid</th>
<th>Vancomycin</th>
<th>Vancomycin switched to β-lactams</th>
</tr>
</thead>
<tbody>
<tr>
<td>MME-1</td>
<td>34/40 (85.0)</td>
<td>9/11 (81.8)</td>
<td>16/19 (84.2)</td>
</tr>
<tr>
<td>ME-2</td>
<td>26/31 (83.9)</td>
<td>6/6 (75.0)</td>
<td>12/14 (85.7)</td>
</tr>
</tbody>
</table>

NOTE. The microbiological response rate represents the percentage of patients who respond positively to treatment. ME-2, second microbiologically evaluable group; MME-1, first modified microbiologically evaluable group.