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Methodologic Considerations for Small Cohort Studies

TO THE EDITOR—Willekens et al [1] recently published a prospective cohort study in which they assessed the noninferiority of an early switch to oral linezolid compared to standard parenteral therapy (SPT) among *Staphylococcus aureus* bacteremia (SAB) patients. These findings are important due to the scarcity of studies that have assessed the alternatives to SPT for uncomplicated SAB. We offer some considerations regarding the study design that may influence the inferences that could be made related to this study.

The authors compared switching to linezolid between day 3 to 9 in 45 patients with a group of 90 propensity-score-matched patients who received SPT (without early switch to oral linezolid). The literature shows that bacteremia recurs in approximately 9% of patients despite appropriate antimicrobial therapy [2]. However, their study does not describe the smallest detectable difference to assess the noninferiority of the intervention, which determines the study's power and the adequacy of their sample size. Using the expected rate of the outcome in the literature, if the study aimed to detect a 5% noninferiority limit of reduction in the 90-day recurrence rate with 80% power and 5% type I error, at least 406 patients would be required in each treatment arm. Reducing the noninferiority

limit to 4% would increase the required sample size to 634/arm [3]. Although the authors acknowledged the low sample size of their study, acknowledging an adequate sample size specific to the research question would help readers to appreciate the relative power of the current study.

In addition, 26 patients who were switched to linezolid outside of the 3- to 9-day range from treatment start and 44 who died ≤ 7 days after index culture were excluded from analysis. The exclusion of patients who died prior to the follow-up period while patients could have been exposed to the treatment may also introduce survival bias. The patients who survived up to day 7 could have been exposed to either SPT or linezolid and developed the outcome. Taking into account the short follow-up period and small sample size, this bias could be reduced by conducting a nonparametric or semiparametric survival analysis and calculating the relative hazard of death.

Further, to reduce confounding by indication, the authors conducted propensity score matching, which resulted in the exclusion of 17 patients in the SPT group who did not have a match with the linezolid group. The proportion of many risk factors of death remained higher in the SPT group. When the number of patients in the control group is not large enough to allow for complete matching, weighted regression using the propensity score may be more appropriate to address confounding without introducing additional bias [4].

Finally, we believe the authors should have used Fisher exact test instead of χ^2 test to assess group differences for 90-day recurrence and 30-day and 90-day mortality due to having < 5 patients in ≥ 1 column.

In summary, Willekens et al's study spearheads future studies to find alternative oral treatments for uncomplicated SAB. This study could benefit from quantifying the limitations of the study power and from adopting alternative or additional statistical approaches to provide more valid inferences.

Note

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