Rifampin for staphylococcal prosthetic joint infection: do we still need a randomized controlled trial?

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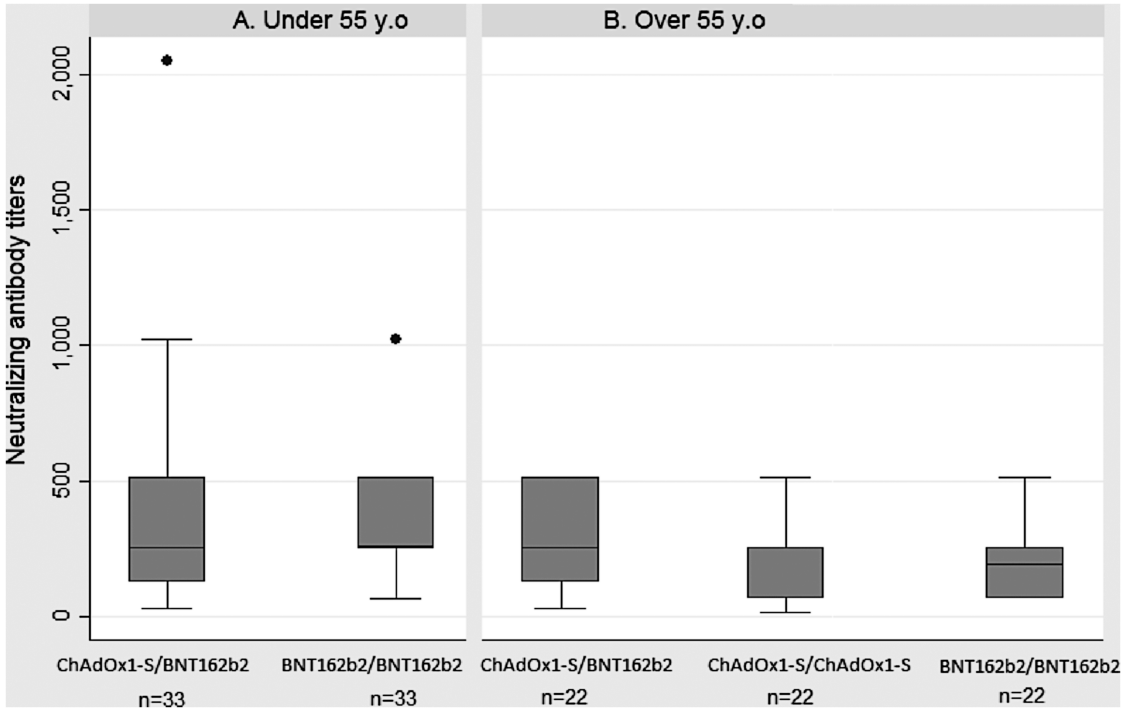

Figure 1. Distribution of neutralizing antibody titers according to vaccination schedule: homologous schedules (ChAdOx1-S/ChAdOx1-S; median delay between injections: 84 days; IQR: 79–84 days; or BNT162b2/BNT162b2; median delay: 28 days; IQR: 27–28 days) and heterologous schedule (ChAdOx1-S/BNT162b2; median delay: 83 days; IQR: 77–84 days). *A*: Among the HWCs under 55 years old; *B*, among the HCWs over 55 years old. Abbreviations: HWC, healthcare worker; IQR, interquartile range; y.o, years old. *outliers of the distribution.

Notes

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Rifampin for Staphylococcal Prosthetic Joint Infection: Do We Still Need a Randomized Controlled Trial?

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To the Editor—With great interest we read the observational study by Beldman et al [1] in which the additional value of rifampin for patients with staphylococcal prosthetic joint infection (PJI) was evaluated. Their data show a favorable effect of rifampin after adjustments. However, the data presented evoke the thought that the results remain flawed by confounding by indication and immortal time bias.

In general, 4 centers using rifampin were compared, with only 1 center not using rifampin. Centers can be outliers with regard to PJI treatment results. Over the years, success rates after

debridement, antibiotics, and retention of the implant (DAIR) showed large variety in different cohorts, ranging between 30% and 90% (Figure 1) [2]. Taking a single center as a reference may hence distort the outcome in a way that cannot be corrected for. Furthermore, as surgical strategies certainly improved over the past 20 years, the distribution of the data over time should be taken into account.

After excluding all patients who failed before switching to oral therapy, only the failure rate in the non-rifampin group dropped, from 54.2% to 45.4%. This indicates that baseline characteristics must have been substantially different (rifampin cannot explain this as it had not yet been started in both groups). It also shows the presence of immortal time bias. Hence, it would be interesting to know the outcome of a multivariate time-to-event Cox regression analysis, starting on the moment of antibiotic switch.

Confounding by indication was meant to be reduced by excluding patients in "rifampin centers" who were not treated with rifampin. However, confounding is more likely to be induced here as there is always a reason why patients in rifampin centers are not treated with rifampin (eg, because of early failure, because of continuing intravenous antibiotics, etc). In the non-rifampin center, these patients are included and may be responsible for a worse outcome.

Of note, the proportion of knee PJI in the rifampin group was lower than in the non-rifampin group (40% vs 46%; P = .13), which may also affect outcome.

Last, early start of rifampin (within 5 days after DAIR) was associated with an increased failure rate, which led to the conclusion that an early start should be discouraged. However, the presented data show that these early starters also had many more *Staphylococcus aureus* infections (74% vs 51%), less exchange of mobile parts, and later onset of DAIR after PJI diagnosis, all of which are known to be associated with failure. A multivariate Cox regression analysis of early versus later start of rifampin would be insightful. The difference in failure rate may disappear after correction for the above-mentioned risk factors. In that case, early start of rifampin is more an epiphenomenon rather than a risk factor for failure.

Although the association between using rifampin and success is statistically demonstrated in these pooled cohorts, confounding and immortal time bias are likely to be present. Even with multivariate analysis, proving causality is difficult, which is why a randomized controlled trial is the only way forward to solve this difficult but highly relevant clinical question.

Note

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure

Figure 1. Success rates over the years for staphylococcal PJI treated with DAIR and related to use of rifampicin (review of 64 studies) [2]. Abbreviations: DAIR, debridement, antibiotics, and retention of the implant; PJI, prosthetic joint infection.

of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Reply to Scheper and De Boer

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To the Editor—We thank Scheper and De Boer [1] for their constructive feedback to further reduce the possibility of confounding by indication and immortal time bias in our analysis. We acknowledge the fact that although maximum attempts can be made to minimize confounding and bias in observational studies, a well-designed, randomized, controlled trial remains the cornerstone to draw definite conclusions in the ongoing debate on the exact role of rifampin in establishing treatment success in implant-associated infections. Here, we respond to the following points addressed by the authors.

Center and time bias: Scheper and De Boer indicated that a single center cannot serve as a reference center, as the literature indicates a large variety in debridement, antibiotics, and implant retention success between different cohorts. We point out that we did not use 1 center as a reference center in our overall analysis. In addition, it must be noted that all centers included in our study had many years of experience treating periprosthetic joint infection (PJI). Moreover, when additionally including the type of center in the multivariate analysis, the use of rifampin remained an independent predictor for treatment success (odds ratio, 0.43; 95% confidence interval [CI]: .27–.68). Thus, we consider the fact that 1 center did not routinely add rifampin to the antibiotic regimen as a strength of the study and not a weakness.

Immortal time bias: Scheper and De Boer observed that when patients who failed prior to switching to oral therapy were excluded, only the failure rate in the nonrifampin group dropped and the failure rate in the rifampin group remained stable. They concluded that this must be explained by major differences in baseline characteristics between both cohorts and cannot be explained by rifampin since it had not yet been started. We want to clarify that the switch to oral therapy refers to the backbone of therapy and not to rifampin (which could have been started during the intravenous period). Nonetheless, we have additionally performed a multivariate time-to-event Cox regression analysis on the authors' request, including only those patients who were switched to an oral regimen. Also, in this analysis, rifampin remained an independent predictor of treatment success (hazard ratio [HR], 0.7; 95% CI: .52–.99; $P = .046$).

Confounding by indication: Scheper and De Boer indicated that confounding by indication is likely to be increased instead of decreased by excluding the patients not treated with rifampin in the rifampin centers in our subanalysis. In view of the observation that this subanalysis resulted in an additional increase in success rate in the rifampin group (instead of lowering it), we recognize that this indeed might be the case.

Early start of rifampin: We agree with Scheper and De Boer that our observation that early start of rifampin is associated with failure may be an epiphenomenon. For this reason, we carefully concluded in our article that this observation requires further investigation, particularly because resistance data in cases of failure were not collected. However, apart from the multivariate logistic regression analysis in which early start remained an independent predictor for treatment failure, we additionally performed a multivariate Cox regression analysis, as requested. Also, in this analysis, early start of rifampin (<5 days after debridement) remained an independent predictor of treatment failure (HR, 1.58; 95% CI: 1.03–2.42; $P = .04$).

In conclusion, our additional analyses consistently support the added value of rifampin in the treatment of acute staphylococcal PJI treated with surgical debridement. Although we recognize that there is space for a large, randomized trial, we recommend its use while waiting for new evidence.

Note

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Reference

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