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Prosthetic joint infections: new diagnostic and therapeutic strategies

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CHAPTER 4a

Rifampin for staphylococcal PJI, do we still need a randomized controlled trial?

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Chapter 4a - Rifampin for staphylococcal PJI, do we still need a randomized controlled trial?

With great interest we read the observational study by Beldman *et al.* in which the additional value of rifampin for patients with staphylococcal prosthetic joint infection was evaluated¹. 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, four centers using rifampin were compared with only one center not using rifampin. Centers can be outliers with regard to PJI treatment results. Over the years, success rates after 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.

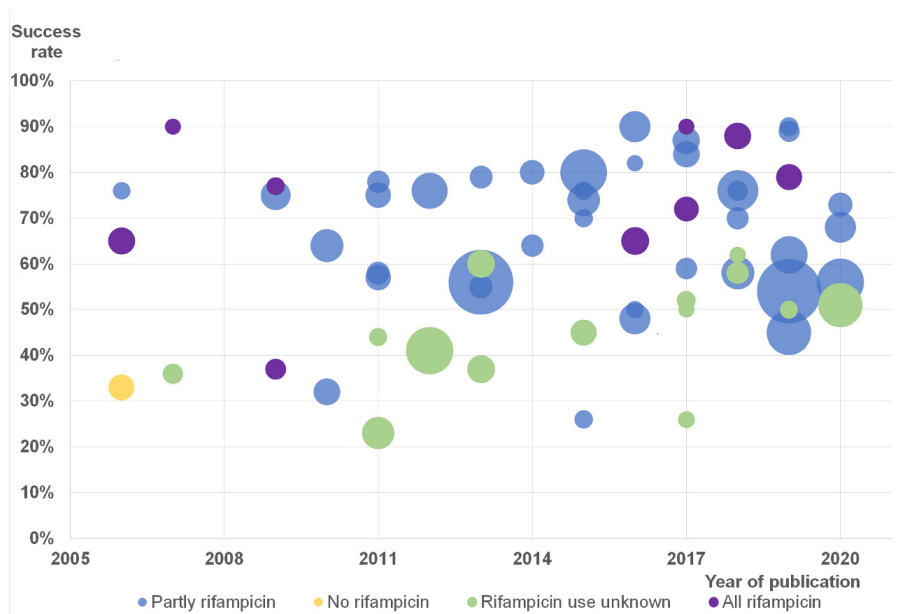


Figure 1. Success rates over the years for staphylococcal PJI treated with debridement, antibiotics, and retention of the implant (DAIR) and related to use of rifampicin (review of 64 studies) [2].

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 been started yet 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 (e.g., because of early failure, because of continuing intravenous antibiotics, et cetera). 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%, $p = 0.13$) which may also affect outcome.

Lastly, early start of rifampin (within 5 days after DAIR) was associated with an increased failure rate which led to the conclusion that early start should be discouraged. However, the presented data show that these early starters also had much more *S. aureus* infections (74% vs 51%), less exchange of mobile parts and later onset of DAIR after PJI diagnosis, all of which 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.

Potential conflicts of interest.

HS: No conflicts of interest. MdB: no conflicts of interest.

References

1. Beldman M, Lowik C, Soriano A, et al. If, when, and how to use rifampin in acute staphylococcal periprosthetic joint infections, a multicentre observational study. *Clin Infect Dis* 2021 doi: 10.1093/cid/ciab426 [published Online First: 2021/05/11]
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