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Dare to DAIR: Is Rifampin Always Necessary?

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The treatment of early post-operative staphylococcal prosthetic joint infection (PJI) with debridement, antibiotics, and retention of the implant (DAIR) is becoming increasingly common. This approach has many advantages, primarily more rapid mobilization and return to normal activities compared to a one- or two-stage revision [1]. A recent prospective multicenter observational study conducted at 27 hospitals in Australia and New Zealand found that DAIR was as successful as one or two-stage revisions, especially in patients with acute infections [2].

However, there is still considerable confusion as to the best antibiotics and duration of therapy. Some guidelines have adopted rifampin combination therapy as the cornerstone antibiotic treatment for staphylococcal PJI treated with DAIR, based on experimental animal models, one randomized trial, and several cohort studies [3,4]. However, rifampin combination therapy is associated with significant side effects and drug–drug interactions. A common justification for adding rifampin is a prospective randomized trial of early MSSA PJI conducted by Zimmerli and published in 1998 [5]. This was a prospective, randomized, double-blind trial that showed 100% success with combination therapy compared to 58% in the non-rifampin arm. Only 33 patients were included in this trial and only 24 completed the study. Of the 18 patients in the rifampin arm, there were 5 hip replacements, 3 knee replacements and 10 internal fixation devices. In the placebo arm, there were 3 hip replacements, 4 knee replacements and 8 internal fixation devices. This study was certainly a remarkable accomplishment; however, arguably, it should not be considered the definitive word on how to treat PJI with DAIR and drive clinical practice for decades. Unfortunately, it seems that this has been the case given the recommendations of current guidelines. (IDSA PJI guideline, MRSA guideline).

Some other studies also support the use of rifampin. In a recent systematic review and meta-analysis, success rates were stratified for the type of joint and type of micro-organism. Sixty-four studies were included. The pooled risk ratio for rifampin effectiveness was 1.10 (95% confidence interval, 1.00–1.22). The pooled success rate was 69% for *Staphylococcus aureus* hip PJI, 54% for *S. aureus* knee PJI, 83% for coagulase-negative staphylococci (CNS) hip PJI, and 73% for CNS knee PJI. The success rates for MRSA PJI (58%) were similar to MSSA PJI (60%). The meta-analysis suggested that rifampin may only prevent a small fraction of all treatment failures [6].

In a retrospective cohort study of 4,624 patients with *S. aureus* PJI managed with DAIR between 2003 and 2019, only 842 (18.2%) received at least one dose of rifampin. A total of 1785 (38.6%) patients experienced a recurrence of infection within two years. Rifampin treatment was associated with a significantly lower hazard ratio (HR) for recurrence during the first 90 days of treatment (HR 0.60; 95%CI 0.45–0.79) and between days 91 and 180 (HR 0.16; 17 95%CI 0.04–0.66), but no statistically significant protective effect was observed with longer than 180 days of treatment (HR 18 0.57; 95%CI 0.18–1.81). The benefit of rifampin was observed for subgroups including knee PJI, MSSA or MRSA infection, and early or late PJI. Interestingly, the use of rifampin did not seem to benefit patients with staphylococcal THA PJI [7].

In another retrospective cohort study of patients 18 years and older diagnosed with hip and knee PJI who underwent DAIR between 1 January 2008 and 31 December 2018 at Mayo Clinic, there were 247 cases of PJI with a median follow-up of 4.4 years after DAIR. There was no association between the duration of IV antibiotics and treatment failure. A shorter duration of oral antibiotic therapy was associated with a higher risk of failure. For staphylococcal knee PJI, both the use and longer duration of a rifampin-based regimen were associated with a lower risk of failure (both P = 0.025) [8].

However, other studies have failed to show the benefit of the routine addition of rifampin. In a prospective, multicenter randomized controlled trial, 99 patients with PJI after hip and knee arthroplasties were enrolled. They were randomly assigned to receive rifampin or not in addition to standard antimicrobial treatment with cloxacillin or vancomycin in case of methicillin resistance. The primary endpoint was no sign of infection after 2 years of follow-up. Forty-eight patients were included in the final analyses. There were no differences in patient characteristics or comorbidities between the two groups. There was no significant difference in the remission rate between the rifampin combination group (17 of 23 (74%)) and the monotherapy group (18 of 25 (72%) [9]. An analysis by Davis et al. determined that most of the risk factors for success and failure were not modifiable and that almost any antibiotic treatment worked as long as the infecting organism was susceptible. Of those treated with DAIR, rifampin was used in 176 episodes (51%). The treatment success was no different in those treated with rifampin versus those who were not [2].

Finally, rifampin may adversely affect outcomes when paired with certain antibiotics. In a report by Tornero et al., all patients with a PJI (hip or knee arthroplasties) between January 1999 and January 2013 were prospectively registered in a database and prospectively followed up. Patients with a PJI diagnosed during the first 90 days after joint arthroplasty were selected and retrospectively reviewed. One-hundred-and-forty-three patients met the inclusion criteria. The failure rate was 11.8%. In Gram-positive infections, rifampin administered in combination with linezolid, co-trimoxazole or clindamycin was associated with a higher failure rate (27.8%) than that in patients receiving a combination of rifampicin with levofloxacin, ciprofloxacin or amoxicillin (8.3%) or monotherapy with linezolid or co-trimoxazole (0%) [10].

Where does this leave us? Obviously, prospective, adequately powered studies are sorely needed to help answer this question. However, such studies will be difficult to complete and unlikely to become available any time soon. These studies should try to control for the experience of the surgeon and the adequacy of surgical debridement. Knee and hip prostheses should be examined separately as the current findings suggest that hip PJIs have a better chance of cure than knee PJI. It is unclear whether this is related to the modular nature of many hip arthroplasty systems allowing more thorough source control, whether it is related to the fact that hips are not always cemented as opposed to knees, or due to some other yet-unidentified variable.

In my opinion, the current data suggest that either adding or not adding rifampin can be justified. Guidelines should neither recommend nor not recommend the addition of rifampin for staphylococcal PJI. Decisions on antibiotic treatment after DAIR should be discussed with the patient, and the patient should participate in the decision. Factors such as age, potential for liver toxicity and drug interactions should be taken into account.

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