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BRIEF REPORT

Adjunctive Rifampin Following Debridement and Implant Retention for Staphylococcal Prosthetic Joint Infection: Is it Effective if not Combined With a Fluoroquinolone?

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Whether rifampin benefits retained staphylococcal prosthetic joint infection is unsettled. In a meta-analysis of 8 studies, we found greater clinical cure with fluoroquinolone-rifampin vs all other regimens (odds ratio [OR], 2.68; 95% CI, 1.43–5.02), but no greater cure with other rifampin combinations vs regimens without rifampin (OR, 1.22; 95% CI, 0.79–1.88).

Keywords. Prosthetic joint infection; staphylococcus; rifampin; fluoroquinolone

The Infectious Disease Society of America's 2012 guidelines for prosthetic joint infection (PJI) recommended 3–6 months of rifampin plus a companion antibiotic for staphylococcal PJI managed with debridement and implant retention (DAIR) [1]. This recommendation was based on a randomized controlled trial (RCT) of 33 patients with staphylococcal hardware infections (15 with PJI), whose intention-to-treat analysis found that combining rifampin with ciprofloxacin resulted in numerically higher disease-free survival (16/18 vs 9/15; $P = .1$) vs ciprofloxacin monotherapy, and whose per-protocol analysis had a fragility index of 1 [2].

Subsequent studies of adjunctive rifampin for staphylococcal PJI following DAIR have inconsistently indicated benefit, including a second RCT of 48 patients in which adding rifampin to glycopeptide or beta-lactam monotherapy did not improve cure [3]. A recent systematic review suggested that rifampin might marginally enhance cure in PJI following DAIR (relative risk [RR], 1.1; 95% CI, 1.00–1.22) [4]. However, the authors also found evidence of publication bias, which trim-and-fill analysis suggested may account for rifampin's perceived benefit (adjusted RR, 1.04; 95% CI, 0.94–1.14).

Observational studies suggest that receipt of combination fluoroquinolone-rifampin (FQ-rif) independently predicts treatment success in PJI following DAIR [5]. Before their RCT, Zimmerli et al. had shown that FQ-rif, but not teicoplanin plus rifampin, improved cure of experimental foreign body infections vs rifampin monotherapy and that the FQ-rif regimens yielded higher overall cure rates than glycopeptide–rifampin combinations [6]. We hypothesized that the inconsistency of rifampin's benefit in published observational studies of PJI may be partially explained by differences in rates of FQ-rif use if, rather than rifampin generally improving cure as an adjunctive agent, the specific FQ-rif combination produces superior outcomes to alternative regimens. We tested this hypothesis by performing a stratified analysis of the studies included in Scheper et al.'s meta-analysis [4] reporting outcomes in patients receiving FQ-rif vs other regimens.

METHODS

We utilized the systematic review performed by Scheper et al. [4] comparing the clinical cures reported in studies of staphylococcal PJI managed with DAIR with or without rifampin, subdividing the former group into patients who received either (a) FQ-rif or (b) nonfluoroquinolone rifampin combinations.

We performed random-effects analyses for all comparisons, evaluating both I^2 and P values for heterogeneity analyses. Using metaregression, we examined the influence of between-study differences in knee vs hip PJI, *S. aureus* vs coagulase-negative staphylococcal infection, and infection arising ≤90 days vs >90 days from the index arthroplasty on the antibiotic regimen's association with cure, as these variables were frequently reported and predict outcome in PJI managed with DAIR [5]. We evaluated publication bias with Egger's regression and estimated its effects with Duval and Tweedies' trim-and-fill analysis.

RESULTS

We collected clinical outcomes for specific antibiotic regimens directly from the text of 7 studies, and for 1 of the 3 remaining studies [7] the corresponding author provided stratified outcomes; thus, 8 studies were included in total (references in the Supplementary Data). Two studies did not include patients treated with FQ-rif and could only be included in analyses comparing nonfluoroquinolone rifampin combinations with regimens without rifampin.

We found that clinical cure was more likely in patients treated with FQ-rif vs all other regimens (odds ratio [OR], 2.68; 95%

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CI, 1.43–5.02; $P = .002$; $I^2 = 62\%$). Cure was also more likely when comparing patients given FQ-rif vs nonfluoroquinolone rifampin–containing regimens (OR, 2.99; 95% CI, 1.29–6.96; $P = .01$; $I^2 = 71\%$) and when comparing patients given FQ-rif vs regimens without rifampin (OR, 3.04; 95% CI, 1.99–3.04; $P < .001$; $I^2 = 6\%$). Among patients not given a fluoroquinolone, rifampin use was not associated with cure (OR, 1.22; 95% CI, 0.79–1.88). Forest plots for these comparisons are shown in Figure 1. When we compared nonfluoroquinolone rifampin combinations with all other regimens, we again found no suggestion of benefit with nonfluoroquinolone rifampin combinations (Supplementary Figure 1).

In metaregression, we did not find any significant associations between the relative benefit of FQ-rif vs other regimens and studies' proportions of knee vs nonknee PJI, *S. aureus* vs coagulase-negative staphylococcal infections, or early vs late PJI (Supplementary Table 1; Supplementary Figures 2–4). Egger's regression suggested publication bias for the comparison of FQ-rif vs all other regimens ($P = .01$), and trim-and-fill analysis to account for that attenuated the benefit of FQ-rif (OR, 1.66; 95% CI, 0.88–3.14). However, publication bias was not detected in the comparison of FQ-rif with regimens without rifampin (Egger's $P = .34$), and the apparent benefit of FQ-rif remained after adjustment for potential publication bias by trim and fill (OR, 2.61; 95% CI, 1.60–4.27).

DISCUSSION

It is tempting to believe that rifampin's biofilm-eradicating activity should benefit staphylococcal retained hardware infection regardless of the partner drug. However, we show that the published data for adjunctive rifampin in staphylococcal PJI managed with DAIR suggest greater treatment success with FQ-rif vs other regimens, including other rifampin combinations. In contrast, we found no evidence of benefit for adding rifampin to antibiotics other than fluoroquinolones.

Our findings are important because it remains common US practice to use intravenous beta-lactams or glycopeptides for definitive therapy of PJI due to staphylococci susceptible to oral antibiotics, and these data suggest that adding rifampin in such cases may be contributing toxicity (eg, hepatotoxicity, interactions with anticoagulation, antiplatelet agents, and opioid analgesia, and nausea) without benefit [8]. Our study adds to other work suggesting that the potential benefit of rifampin in staphylococcal PJI is restricted to specific clinical scenarios, such as knee vs hip PJI, and when rifampin is added later in the treatment course vs immediately after surgery [9, 10].

The primary limitation of this analysis is that most included studies are retrospective and confounded by indication. Patients deemed candidates for FQ-rif may be healthier (eg, without significant liver disease or comorbidities whose pharmacotherapy contraindicates rifampin) and predisposed to better outcomes. Such confounding is suggested in Li and colleagues' RCT of oral vs intravenous antibiotics for osteoarticular infections, whose Supplementary Figure 1 indicates that subjects planned to receive oral fluoroquinolones and randomized to oral vs IV therapy achieved similar rates of cure (189/209 [90.4%] vs 179/205 [87.3%]; $P = .31$) [11]. In any case, this confounding does not explain why nonfluoroquinolone rifampin combinations would show no benefit vs regimens without rifampin; in fact, confounding by indication might exaggerate the benefit of nonfluoroquinolone rifampin combinations just as it might exaggerate the benefit of FQ-rif. Moreover, our findings are concordant with the results of the 2 RCTs of adjunctive rifampin in staphylococcal PJI by Zimmerli and Karlsen, so while our results should be considered hypothesis-generating, we note that this hypothesis better fits the randomized data than the assumption that rifampin is beneficial regardless of partner drug. Other limitations of our study include potential publication bias, also identified in Scheper et al.'s original meta-analysis; however, publication bias was not evident in the comparison of FQ-rif with monotherapy, lending greater reliability to its benefit vs other rifampin combinations. Rifampin dosing was heterogenous between studies, which may have influenced both clinical cure and rifampin tolerability. Finally, the comparator group "rifampin combinations other than FQ-rif" was heterogenous, which isimportant because rifampin has the potential to induce the metabolism of a number of potential partner antibiotics to subtherapeutic levels. The clinical import of these interactions is unsettled; on the one hand, significant reduction of fusidic acid levels led to the early termination of at least 1 RCT in orthopedic infections, and yet clindamycin plus rifampin appeared highly effective for staphylococcal PJI in a large cohort by Beldman et al. despite rifampin's known potential to substantially reduce clindamycin serum levels [9, 12].

The FQ-rif regimen may be more poorly tolerated than alternatives. A modern retrospective cohort of staphylococcal PJI found a 35.6% unplanned drug discontinuation rate with fluoroquinolones vs 3% with other regimens, though notably another recent cohort study found a similarly high rate of unplanned change in antibiotics with standard intravenous antimicrobials [8, 13]. In addition, a recent Veterans Affairs cohort with 4624 patients who received DAIR for PJI suggested a small overall benefit to adjunctive rifampin, albeit with no stratification of outcomes by use of a quinolone [14]. Accordingly, we hesitate to conclude that FQ-rif should be universally preferred following DAIR for staphylococcal PJI. These data do indicate, however, that equipoise exists for a large RCT comparing FQ-rif with nonfluoroquinolone rifampin combinations with monotherapy without rifampin.

These findings should challenge practitioners who add rifampin for staphylococcal retained hardware infections regardless of partner drug to reconsider whether this practice is

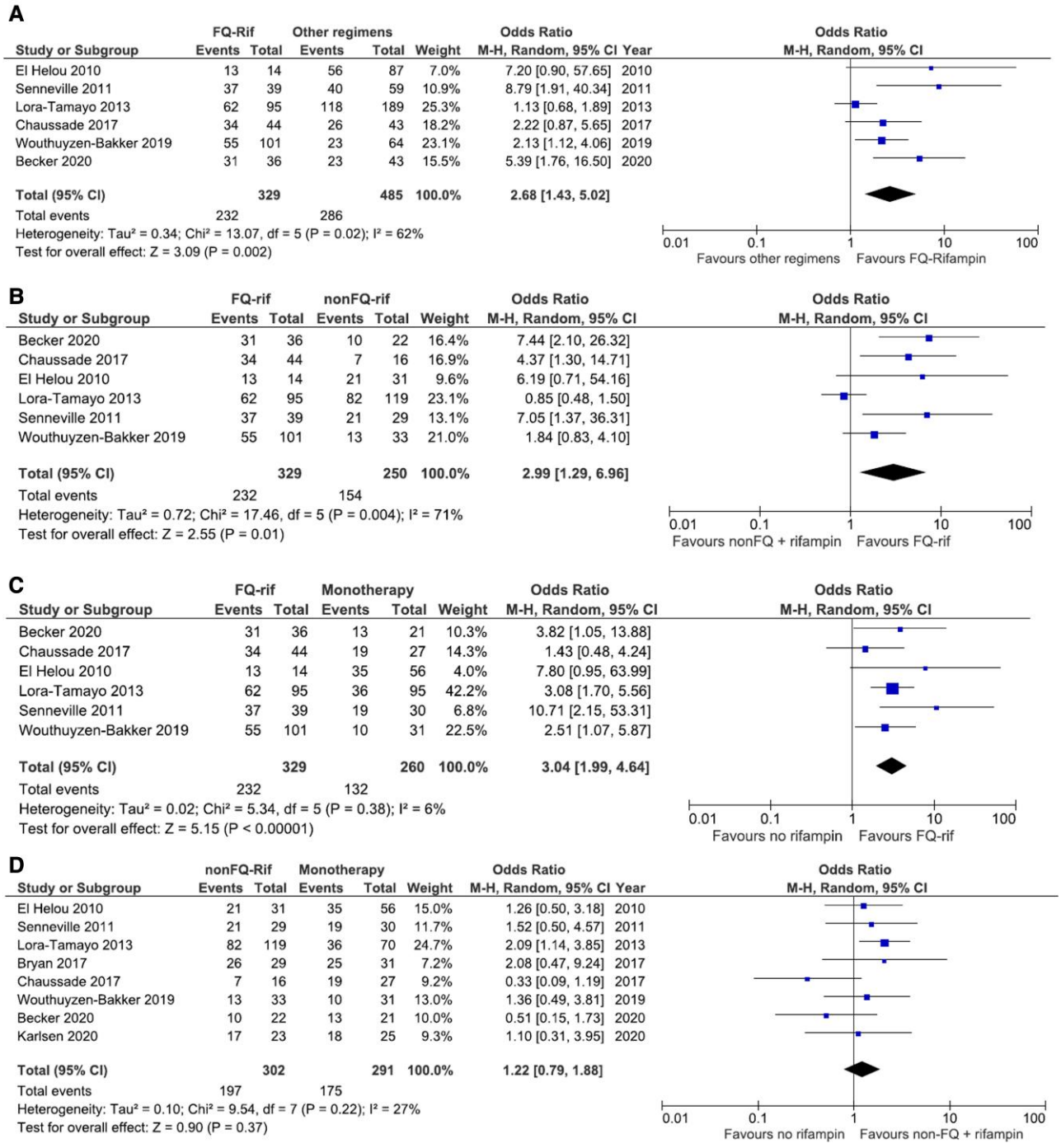

Figure 1. Fluoroquinolone-rifampin vs other regimens with or without rifampin: clinical cure in staphylococcal prosthetic joint infection managed with debridement and implant retention. *A,* Comparison of clinical cure rates achieved with fluoroquinolone-rifampin combinations vs all other regimens. *B,* Comparison of clinical cure rates achieved with fluoroquinolone-rifampin combinations vs nonfluoroquinolone rifampin combinations. *C,* Comparison of clinical cure rates achieved with fluoroquinolone-rifampin combinations vs regimens without rifampin. *D,* Comparison of clinical cure rates achieved with nonfluoroquinolone rifampin combinations vs regimens without rifampin. Event rates in several studies were not reported directly but could be back-calculated from the presented data.

evidence-based. Authors of future PJI guidelines should reevaluate whether the modern body of literature continues to support a strong general recommendation for adjunctive rifampin in staphylococcal PJI managed with DAIR, or whether the data for risks and benefits are uncertain and nuanced enough that an updated recommendation ought be conditional and narrower in scope. Either way, an adequately powered double-blind, double-placebo RCT is urgently needed to define

the optimal antimicrobial therapy for patients undergoing DAIR for PJI.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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