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MAJOR ARTICLE

Effectiveness and Optimal Duration of Adjunctive Rifampin Treatment in the Management of *Staphylococcus aureus* Prosthetic Joint Infections After Debridement, Antibiotics, and Implant Retention

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Background. Rifampin is recommended as adjunctive therapy for patients with a *Staphylococcus aureus* prosthetic joint infection (PJI) managed with debridement, antibiotics, and implant retention (DAIR), with no solid consensus on the optimal duration of therapy. Our study assessed the effectiveness and optimal duration of rifampin for *S aureus* PJI using Veterans Health Administration (VHA) data.

Methods. We conducted a retrospective cohort study of patients with *S aureus* PJI managed with DAIR between 2003 and 2019 in VHA hospitals. Patients who died within 14 days after DAIR were excluded. The primary outcome was a time to microbiological recurrence from 15 days up to 2 years after DAIR. Rifampin use was analyzed as a time-varying exposure, and time-dependent hazard ratios (HRs) for recurrence were calculated according to the duration of rifampin treatment.

Results. Among 4624 patients, 842 (18.2%) received at least 1 dose of rifampin; 1785 (38.6%) experienced recurrence within 2 years. Rifampin treatment was associated with significantly lower HRs for recurrence during the first 90 days of treatment (HR, 0.60 [95% confidence interval {CI}, .45–.79]) and between days 91 and 180 (HR, 0.16 [95% CI, .04–.66]) but no statistically significant protective effect was observed with longer than 180 days (HR, 0.57 [95% CI, .18–1.81]). The benefit of rifampin was observed for subgroups including knee PJI, methicillin-susceptible or -resistant *S aureus* infection, and early or late PJI.

Conclusions. This study supports current guidelines that recommend adjunctive rifampin use for up to 6 months among patients with *S aureus* PJI treated with DAIR.

Keywords. antibiotics and implant retention; debridement; prosthetic joint infection; rifampin; *Staphylococcus aureus*; Veterans Health Administration.

Prosthetic joint infection (PJI) is a challenging complication after total joint arthroplasty [1]. Biofilm-forming pathogens, such as *Staphylococcus aureus*, are responsible for a large proportion of PJIs and are difficult to eradicate with standard antibiotic regimens [2, 3].

Rifampin has been used as an adjunctive antibiotic primarily in staphylococcal PJI treatment since the 1990s based on its favorable activity against staphylococcal biofilms [4] and after a randomized controlled trial (RCT) conducted by Zimmerli et al showed the effectiveness of adjunctive rifampin [5]. Supported by that RCT and other observational studies [6, 7], the Infectious Diseases Society of America (IDSA) treatment guidelines recommended rifampin as an adjunctive antibiotic for staphylococcal PJI, particularly among patients managed with debridement, antibiotics, and implant retention (DAIR) [8]. Despite the recommendation, the clinical role of adjunctive rifampin remains controversial [4, 9]. A recent systematic review and meta-analysis suggested that rifampin was associated with a 10% higher success rate for staphylococcal PJI [10]. However, those results need to be interpreted cautiously because most of the included studies were observational studies with <500 patients, and each study used different inclusion and exclusion criteria and outcome definitions. More recently, a multicenter observational study conducted mainly in European countries showed a 70% reduction in treatment failure in patients who received adjunctive rifampin among 669

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patients with acute staphylococcal PJI [11]. While those studies have supported the use of rifampin, there are still unanswered questions such as the optimal duration of rifampin treatment, and which patient groups benefit most from adjunctive rifampin treatment. To address those questions, we conducted a retrospective study using Veterans Health Administration (VHA) data to assess the effectiveness and optimal duration of rifampin therapy for patients with *S aureus* PJI managed with DAIR.

METHODS

Patient Consent Statement

The institutional review board of the University of Iowa and the Iowa City Veterans Affairs Health Care System Research and Development Committee approved this study and granted a waiver for informed consent (IRB ID#201112749).

Study Design and Patient Population

This retrospective cohort study included all patients admitted to acute care VHA hospitals for DAIR to manage *S aureus* PJI from 2003 to 2019. We defined *S aureus* PJI as the growth of *S aureus* from synovial tissue, synovial fluid, surgical wound, or blood culture 14 days before or after DAIR. We only included patients who survived for at least 15 days after DAIR, as it was unlikely that rifampin would have directly affected the outcome of patients who died early after DAIR. Among the 49 patients who died within 14 days from DAIR and therefore were excluded from this study, no patient received rifampin.

Data Source

Data on demographics, microbiology, pharmacy, laboratory, *International Classification of Diseases, Ninth Revision* (*ICD-9*) or *Tenth Revision* (*ICD-10*) procedure codes, and *Current Procedural Terminology* (*CPT*) codes were extracted from the Veterans Affairs (VA) Corporate Data Warehouse databases and accessed through the VA Informatics and Computing Infrastructure. Patients with hip or knee PJI managed with DAIR were identified using *ICD* procedure codes or *CPT* codes used in a previous study [12] (Supplementary Table 1). If a patient experienced 2 or more episodes of *S aureus* PJI managed with DAIR during the study period, only the first episode was included.

Definitions

The primary outcome of this study was microbiological recurrence in the time period between 15 days and 2 years after DAIR, accounting for mortality as a competing risk event. Recurrence was defined as the isolation of *S aureus* from synovial fluid, joint tissue, or wound at the site of surgery or blood during the follow-up period. As a secondary outcome, the composite outcome of recurrence and all-cause mortality was also examined during the follow-up period. Any inpatient or outpatient rifampin use starting after day 15 from DAIR was collected. Duration of rifampin treatment was counted continuously unless there was a gap longer than 30 days during treatment.

ICD-9/10 diagnostic codes were used to identify comorbidities (Supplementary Table 1). Using methodology from a previous study, the modified Acute Physiology and Chronic Health Evaluation (mAPACHE) III score was calculated from vital signs and laboratory values within 24 hours before or after DAIR [13]. Any missing laboratory values were assumed to be normal to calculate the mAPACHE III score. We assumed that any anti-staphylococcal oral antibiotic prescription within 90 days from DAIR was a continued treatment because we were unable to obtain reliable outpatient parenteral antimicrobial therapy (OPAT) data.

Statistical Analyses

Summary statistics were computed using frequencies and percentages for categorical variables and means with standard deviations for continuous variables. A cumulative incidence function plot was used to describe the probability of recurrence over time for the entire total cohort. Patients who did not experience recurrence 2 years after DAIR were censored. We analyzed rifampin use as a time-dependent exposure using days 15 after DAIR as time = 0. This avoided immortal time bias in associations and allowed us to explore associations between duration of rifampin exposure and recurrence. Using a step function, we separated active rifampin treatment as: $R_1(t) = 1$ if active rifampin treatment for $t \geq 1$ day but ≤ 90 days, $R_2(t) = 1$ if active rifampin treatment for $t > 90$ days but ≤ 180 days, and $R_3(t) = 1$ if active rifampin treatment for $t > 180$ days up to 2 years. Otherwise, $R_j(t) = 0$ including time prior to rifampin treatment [14]. Days 90 and 180 were selected based on the guideline-recommended treatment durations of rifampin and companion oral antibiotics for 3 months after hip surgery and 6 months after knee surgery [8]. We also used a time-dependent covariate approach to estimate the effects of rifampin exposure over varying follow-up intervals. This allowed us to examine whether rifampin exposure was associated with lower hazards of recurrence at later follow-up time points, after the rifampin was stopped, among patients without recurrence while receiving rifampin. We created 2 time-dependent coefficients for postrifampin (PR) treatment periods: $PR_1(t) = 1$ for a postrifampin period after rifampin treatment for $t \leq 90$ days and $PR_2(t) = 1$ for a postrifampin period after rifampin treatment for $t > 90$ days. We then fitted Fine-Gray subdistribution hazard regression models to estimate the hazard ratios (HRs) for various timings of rifampin treatment (first 90 days, 91–180 days, >180 days, posttreatment after ≤90 days of rifampin, or posttreatment after >90 days of rifampin) on recurrence while accounting for mortality as a competing event [15, 16]. The multivariate model also adjusted for patient demographic characteristics, body mass index, comorbidities, geographic area of VA medical center, methicillin susceptibility, and mAPACHE

III score at the time of DAIR. Variables were included in the risk-adjustment model if there were bivariate associations with the outcomes at $P < .1$. Variables were further selected for the final model with a backward elimination strategy. For the secondary analysis, we assessed the time to the composite outcome of recurrence or all-cause mortality during the follow-up period using multivariate Cox regression models using the same time-dependent variables for rifampin treatment and covariates used for the primary outcome.

We also conducted several subgroup analyses according to the location of PJI (knee or hip), drug susceptibility of *S aureus* (methicillin-susceptible *S aureus* [MSSA] or methicillin-resistant *S aureus* [MRSA]), and limiting to early PJI (ie, PJI within 90 days after initial total joint arthroplasty) or late PJI (ie, PJI after 90 days of DAIR).

All inferential analyses were 2-tailed, and a P value $< .05$ was considered statistically significant. All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

In total, 4624 patients from 101 VHA hospitals were included. Of these, 842 (18.2%) received at least 1 dose of rifampin for *S aureus* PJI (Table 1) during the study period. In contrast to only 14.5% of patients who received rifampin in 2003 or 2004, 21.6% of patients received rifampin in 2017–2019. The median duration of rifampin treatment was 36 days (interquartile range, 13–105 days). Among patients who received rifampin, 83.0% started within 14 days after DAIR. During the follow-up period, we identified 2084 patients with composite outcomes of recurrence or death (45.1%). Of these, 1785 patients had recurrence (85.7%), and 562 patients died (27.0%). Figure 1 shows the cumulative incidence function plot of recurrence during the follow-up period. More than half of all recurrences happened within the first 100 days (54.3%). The numbers of events and patient-days according to rifampin treatment status are described in Supplementary Table 2.

In the multivariate Fine-Gray subdistribution hazard regression model, rifampin treatment was associated with a significantly lower hazard of recurrence during the first 90 days (HR, 0.60 [95% confidence interval {CI}, .45–.79]) and days 91–180 (HR, 0.16 [95% CI, .04–.66]), but no statistically significant protective effect was observed for continued rifampin use after 180 days (HR, 0.57 [95% CI, .18–1.81]) (Table 2). HRs of postrifampin treatment were not significant ($PR_1(t) = 1$: HR, 1.12 [95% CI, .95–1.31] and $PR_2(t) = 1$: HR, 1.07 [95% CI, .75–1.51]) (Table 2), indicating that rifampin was associated with lower recurrence while it was used, but not with lower rates of additional recurrences after it was stopped. Of note, patients who received at least 1 dose of rifampin received longer antistaphylococcal treatment (Supplementary Table 3). In addition to rifampin treatment, being overweight and diagnosed in a more recent year were associated with lower hazards of recurrence. In contrast, higher mAPACHE III score, MRSA PJI, and having comorbidities were associated with higher HR for recurrence (Table 2).

In the subgroup analysis for knee PJI, there was a significant protective effect of rifampin on recurrence during the first 90 days of treatment (HR, 0.55 [95% CI, .40–.76]) and days 91–180 (HR, 0.19 [95% CI, .05–.75]) but not seen after 180 days of treatment or in the post–rifampin treatment periods (Table 3). In contrast, there was not a statistically significant effect of rifampin among patients with hip PJI (days 1–90: HR, 0.74 [95% CI, .40–1.38]). In the subgroup analysis by the susceptibilities of *S aureus*, rifampin treatment was associated with a lower hazard of recurrence among patients with MSSA PJI (HR, 0.62 [95% CI, .43–.89]) and among patients with MRSA PJI (HR, 0.58 [95% CI, .37–.90]) during the first 90 days of rifampin treatment but not afterward (Table 3). When we stratified the cohort by the timing of the PJI (early vs late), rifampin treatment was associated with a significantly lower hazard of recurrence compared to no rifampin during the first 90 days of rifampin treatment (HR, 0.47 [95% CI, .30–.74] for early PJI and HR, 0.33 [95% CI, .16–.67] for late PJI) (Table 3).

As a secondary analysis, we analyzed the effect of rifampin on the composite outcome of recurrence or mortality (Supplementary Table 4). Similar to the results of semi-competing risk analysis, there was a statistically significant protective effect of rifampin during the first 90 days of treatment (HR, 0.51 [95% CI, .39–.68]) and day 91–180 of treatment (HR, 0.14 [95% CI, .04–.58]) but not after 180 days and posttreatment.

DISCUSSION

Our study found that receipt of adjunctive rifampin was associated with a significantly lower hazard of recurrence for *S aureus* PJI compared with no rifampin. The protective effect was statistically significant during the first 180 days of treatment, supporting guideline recommendations for duration of rifampin use. The benefit of rifampin was seen in multiple subgroups including patients with knee PJI, MSSA infection, MRSA infection, and early or late PJI.

Findings from our study are consistent with a previous RCT among patients treated with DAIR for staphylococcal orthopedic implant–related infections [5]. Our findings are also in line with the recent multicenter observational study by Beldman et al [11]. Our study differed from their study in several important definitions. First, we limited our cohort to *S aureus* PJI, whereas Beldman et al included all *Staphylococcus* species. Second, we defined recurrence as a microbiological failure with the detection of *S aureus* in culture, whereas Beldman et al defined recurrence as the need for any further surgical procedure related to infection. We elected to use microbiological failure as our outcome because additional debridement is sometimes required for PJI treatment, even if a patient is on appropriate antibiotic

Table 1. Basic Characteristics of the Cohort, Stratified by the Composite Outcome of Recurrence or Death

Characteristic	Total (N = 4624)	Patients Who Had the Composite Outcome (n = 2084)	Patients Who Did Not Have the Composite Outcome (n = 2540)
Age, y, mean (SD)	64.3 (11.3)	65.4 (11.3)	63.3 (11.1)
Male sex	4466 (96.6)	2016 (96.7)	2450 (96.5)
Race			
White	3391 (73.3)	1531 (73.5)	1860 (73.2)
Black	830 (18.0)	355 (17.0)	475 (18.7)
Other	403 (8.7)	198 (9.5)	205 (8.1)
BMI, kg/m^2			
Underweight (BMI <20)	44 (1.1)	25 (1.3)	19 (0.9)
Normal (BMI ≥20 and <25)	541 (13.2)	291 (15.6)	250 (11.2)
Overweight (BMI ≥25 and <30)	1161 (28.4)	519 (27.8)	642 (28.8)
Obese (BMI = 30)	2346 (57.3)	1030 (55.2)	1316 (59.1)
Geographic area			
Northeast	605 (13.1)	248 (11.9)	357 (14.1)
South	1778 (38.5)	793 (38.1)	985 (38.8)
Central	1271 (27.5)	585 (28.1)	686 (27.0)
West	970 (21.0)	458 (22.0)	512 (20.2)
Year of PJI			
2003–2004	401 (8.7)	202 (9.7)	199 (7.8)
2005–2007	820 (17.7)	387 (18.6)	433 (17.1)
2008–2010	857 (18.5)	406 (19.5)	451 (17.8)
2011–2013	828 (17.9)	357 (17.1)	471 (18.5)
2014–2016	820 (17.7)	354 (17.0)	466 (18.4)
2017–2019	898 (19.4)	378 (18.1)	520 (20.5)
Joint			
Knee	3779 (81.7)	1706 (81.9)	2073 (81.6)
Hip	813 (17.6)	362 (17.4)	451 (17.8)
Timing of PJI from previous joint surgery			
Early (within 90 d)	1150 (24.9)	445 (21.4)	705 (27.7)
Late (after 90 d)	1056 (22.8)	458 (22.0)	598 (23.5)
Unknown	2418 (52.3)	1181 (56.7)	1237 (48.7)
Modified APACHE III score			
≤21	3276 (70.9)	1285 (61.7)	1991 (78.4)
22–32	902 (19.5)	511 (24.5)	391 (15.4)
33–45	341 (7.4)	209 (10.0)	132 (5.2)
>45	105 (2.3)	79 (3.8)	26 (1.0)
Staphylococcus aureus susceptibility			
MSSA	3405 (73.6)	1456 (69.9)	1949 (76.7)
MRSA	1219 (26.4)	628 (30.1)	591 (23.3)
Polymicrobial infection	1111 (24.3)	485 (23.9)	626 (24.7)
Comorbidities			
Myocardial infarction	367 (8.0)	198 (9.5)	169 (6.7)
Congestive heart failure	755 (16.4)	457 (22.0)	298 (11.8)
COPD	1433 (31.2)	699 (33.7)	734 (29.1)
Peripheral vascular disease	925 (20.1)	528 (25.4)	397 (15.8)
	665 (14.5)	341 (16.4)	324 (12.9)
Cerebrovascular disease			
Dementia	86 (1.9)	41 (2.0)	45 (1.8)
Hemiplegia	160 (3.5)	98 (4.7)	62 (2.5)
Autoimmune disease	294 (6.4)	153 (7.4)	141 (5.6)
Diabetes mellitus	1792 (39.0)	929 (44.8)	863 (34.3)
Peptic ulcer	253 (5.5)	137 (6.6)	116 (4.6)
Liver disease	670 (14.6)	362 (17.4)	308 (12.2)
Chronic kidney disease	648 (14.1)	376 (18.1)	272 (10.8)
Solid cancer	805 (17.5)	433 (20.9)	372 (14.8)
Hematologic malignancy	106 (2.3)	69 (3.3)	37 (1.5)
HIV/AIDS	51 (1.1)	27 (1.3)	24 (1.0)
Duration of rifampin treatment from day 15 after DAIR			
0 d	3782 (81.8)	1742 (83.6)	2040 (80.3)
1–90 d	610 (13.2)	290 (13.9)	320 (12.6)
91–180 d	143 (3.1)	33 (1.6)	110 (4.3)
181–731 d	89 (1.9)	19 (0.9)	70 (2.8)
Duration of antibiotic treatment from day 15 after DAIR			
≤90	3602 (77.9)	1802 (86.5)	1800 (70.9)
91–180 d	286 (6.2)	114 (5.5)	172 (6.8)
181–270 d	164 (3.6)	62 (3.0)	102 (4.0)
≥271 d	572 (12.4)	106 (5.1)	466 (18.4)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DAIR, debridement, antibiotics, and implant retention; HIV, human immunodeficiency virus; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PJI, prosthetic joint infection; SD, standard deviation.

treatment. Additionally, some patients might not have been healthy enough for additional surgical treatment. We acknowledge that our approach might have missed some recurrences without microbiological confirmation or included some patients with *S aureus* bacteremia from a source not related to PJI. More importantly, Beldman et al defined receipt of chronic antibiotic suppression (CAS) as a treatment failure. CAS is a noncurative strategy to prevent PJI recurrence [17, 18]. It is reported that more than one-third of patients aged >80 years with PJI were treated with CAS, and 60% of them were event-free at 24 months [19]. In practice, treatment with CAS does not necessarily mean the patient failed treatment.

The protective effect of rifampin was statistically significant throughout subgroups except for patients with hip PJI. This may be due to a clinical effect or small sample sizes in these subgroups. In the previous study by Beldman et al, the most prominent effect of rifampin was observed in patients with knee PJI compared to patients with hip PJI, although rifampin was

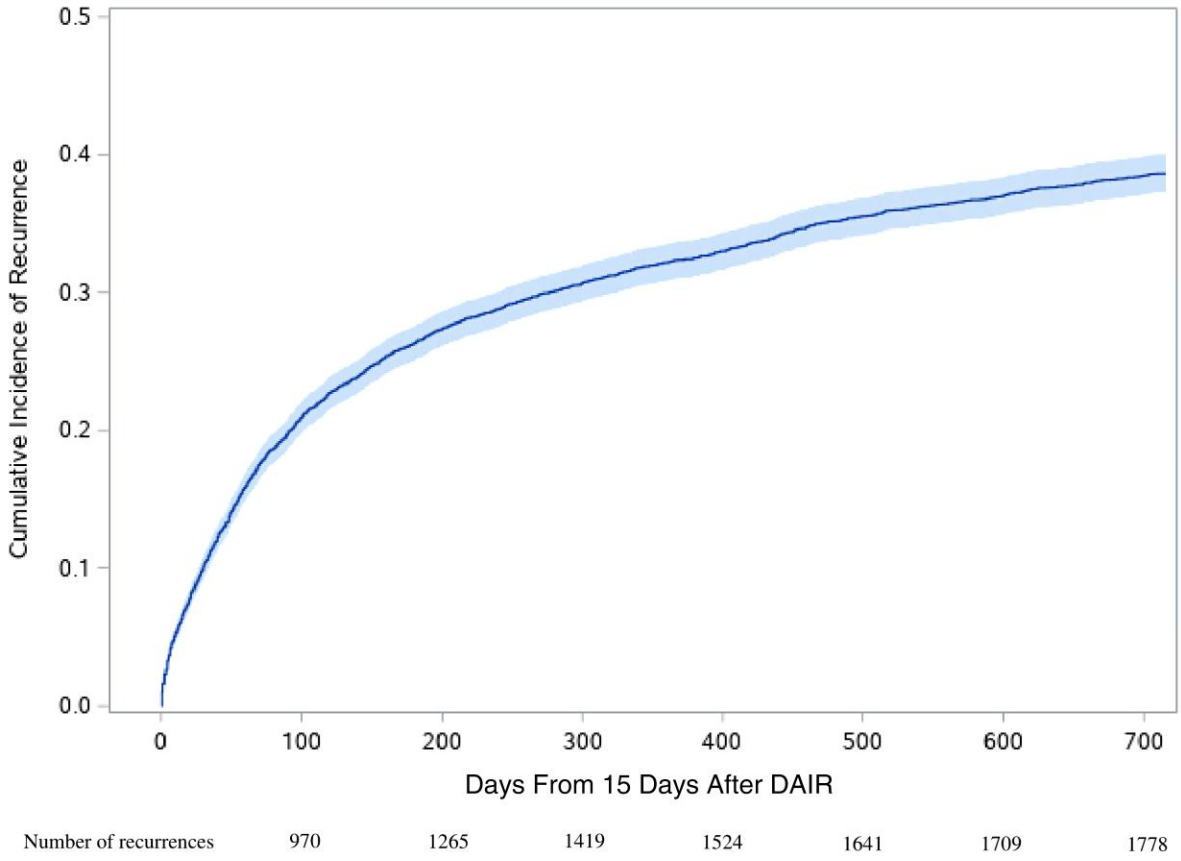

Figure 1. Crude cumulative incidence function plot for recurrence. Abbreviation: DAIR, debridement, antibiotics, and implant retention.

protective for patients with hip PJI [11]. The difference may be from the analytical method in that we used rifampin treatment as a time-dependent variable. Patients with hip PJI might have received a shorter duration of rifampin therapy compared to knee PJI according to IDSA guidelines, and a smaller number of patients with hip PJI were included in this study. Considering those factors, the power to detect the difference might have been smaller in patients with hip PJI.

Our study suggested that rifampin treatment was beneficial up to 180 days of treatment. Although the hazard ratio after 180 days of treatment was 0.57, which appeared protective, it was not statistically significant. A longer duration of rifampin therapy was associated with better clinical outcome in a previous small multicenter observational study [20], but that study was criticized because of the concern for immortal time bias [21]. We addressed immortal time bias by including rifampin use as a time-dependent exposure in our study. A small RCT by Lora-Tamayo et al that compared 8 weeks of levofloxacin plus rifampin versus traditional treatment found that short duration of combination therapy might be noninferior to traditional treatment [22]. That RCT was not able to exclude the benefit of long-term treatment for *S aureus* knee PJI. We believe our results support the recommendation of rifampin treatment for 6 months for knee PJI, while the effectiveness and optimal duration of rifampin treatment for hip PJI need to be investigated in future studies.

The IDSA guidelines recommending adjunctive rifampin therapy for patients with staphylococcal PJI treated with DAIR were published in 2013, which was midway through our cohort study [8]. Yet, we found that in the years 2017–2019, only 21.6% of our patients received rifampin. Thus, there may be a need for quality improvement projects and implementation science research studies to improve the use of rifampin in this patient population.

Our study has several limitations. First, there is a possibility for residual confounding related to unmeasured risk factors such as adequacy of debridement, choice and duration of additional antibiotics, use of topical antibiotic during DAIR, physician treatment preference, and treatment adherence. We elected not to analyze combination antibiotic treatment duration because we were unable to obtain the duration of OPAT, which would be the majority of initial antibiotic therapy for PJI in the United States, due to our inability to evaluate data on antibiotics used outside the VHA system. Since a recent RCT failed to show noninferiority of 6 weeks of antibiotic treatment over 12 weeks for PJI [23], the duration of antibiotic treatment could have affected the outcome. Second, we were unable

Table 2. Bivariate and Multivariate Cox Regression Model to Estimate Recurrence

Groups	Crude HR (95% CI)	Adjusted HR (95% CI)
Rifampin treatment		
No rifampin	Reference	Reference
Active rifampin treatment (days 1–90)	0.57 (.43–.75)	0.60 (.45–.79)
Active rifampin treatment (days 91–180)	0.15 (.04–.59)	0.16 (.04–.66)
Active rifampin treatment (days 181–731)	0.43 (.14–1.37)	0.57 (.18–1.81)
Postrifampin treatment (total ≤90 d)	1.09 (.93–1.27)	1.12 (.95–1.31)
Postrifampin treatment (total >90 d)	1.03 (.74–1.42)	1.07 (.75–1.51)
Age, y		
<45	Reference	Reference
45–54	1.51 (1.05–2.16)	1.33 (.93–1.90)
55–64	1.52 (1.07–2.14)	1.30 (.93–1.82)
65–74	1.49 (1.04–2.12)	1.20 (.85–1.69)
75–84	1.51 (1.05–2.18)	1.10 (.76–1.57)
≥85	1.85 (1.24–2.77)	1.06 (.70–1.63)
Sex		
Male	0.98 (.75–1.27)	NA[a]
Female	Reference	NA[a]
Race		
White	1.01 (.85–1.21)	1.16 (.95–1.42)
Black	0.91 (.74–1.12)	1.03 (.82–1.29)
Other	Reference	Reference
BMI, kg/m^2		
Normal (BMI ≥20 and <25)	Reference	Reference
Underweight (BMI <20)	0.96 (.64–1.44)	1.08 (.71–1.64)
Overweight (BMI ≥25 and <30)	0.79 (.69–.92)	0.83 (.70–.97)
Obese (BMI ≥30)	0.81 (.70–.92)	0.88 (.76–1.02)
Year of PJI		
2003–2004	Reference	Reference
2005–2007	0.85 (.70–1.03)	0.92 (.75–1.13)
2008–2010	0.82 (.68–1.00)	0.90 (.73–1.09)
2011–2013	0.73 (.61–.89)	0.73 (.60–.90)
2014–2016	0.70 (.57–.85)	0.69 (.56–.85)
2017–2019	0.68 (.56–.83)	0.66 (.54–.81)
Geographic area		
Northeast	0.86 (.73–1.03)	NA[a]
South	0.92 (.81–1.05)	NA[a]
Central	0.97 (.85–1.10)	NA[a]
West	Reference	NA[a]
Modified APACHE III score		
≤21	Reference	Reference
22–32	1.43 (1.27–1.62)	1.30 (1.15–1.48)
33–45	1.62 (1.37–1.91)	1.37 (1.15–1.64)
>45	2.27 (1.76–2.94)	1.86 (1.41–2.46)
Staphylococcus aureus susceptibility		
MSSA	Reference	Reference
MRSA	1.32 (1.18–1.47)	1.27 (1.13–1.42)
Polymicrobial infection	0.96 (.86–1.07)	NA[a]
Joint		
Knee	0.78 (.48–1.28)	NA[a]
Hip	0.77 (.47–1.28)	NA[a]
Timing of PJI from previous joint surgery		
Early (within 90 d)	0.85 (.74–.97)	NA[a]
Late (after 90 d)	0.93 (.83–1.06)	NA[a]
Unknown	Reference	NA[a]
Comorbidities		
Congestive heart failure	1.29 (1.14–1.47)	1.18 (1.04–1.35)
Peripheral vascular disease	1.20 (1.07–1.35)	1.22 (1.08–1.37)
Hemiplegia	1.40 (1.13–1.74)	1.37 (1.09–1.72)
Diabetes mellitus	1.15 (1.03–1.27)	1.19 (1.06–1.32)
Liver disease	1.18 (1.04–1.34)	1.15 (1.01–1.32)
Solid cancer	1.15 (1.02–1.31)	1.19 (1.05–1.34)
Peptic ulcer	1.15 (.96–1.37)	1.18 (.98–1.42)
Myocardial infarction	1.04 (.89–1.23)	NA[a]
COPD	0.97 (.88–1.08)	NA[a]
Cerebrovascular disease	0.93 (.82–1.06)	NA[a]
Autoimmune disease	0.95 (.80–1.14)	NA[a]
Hematologic malignancy	1.09 (.82–1.45)	NA[a]
Chronic kidney disease	1.06 (.94–1.21)	NA[a]

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; NA, not applicable; PJI, prosthetic joint infection.

[a]Variable was not selected in the final multivariate model.

to capture positive culture results outside the VHA system; therefore, there would be a possibility of missing recurrences that happened outside the VHA system. Third, we did not evaluate some aspects of rifampin treatment, such as the dose of rifampin treatment, or adverse reactions potentially related to antibiotic therapy. Fourth, we could not obtain the resistance pattern of *S aureus* to rifampin, which could be important for the effect of rifampin therapy. We were also unable to determine if recurrence was caused by the same strain of *S aureus* or infection by a different strain. Fifth, although this was a very large multicenter cohort study, we may have been underpowered to find statistically significant differences in our subgroup analyses. Furthermore, as only 88 patients received rifampin for >180 days, we may have very limited power to detect the benefit of longer rifampin treatment. Finally, since our study used a VHA database that includes mainly older male patients, there could be concern about its generalizability to different patient populations. Nevertheless, our study is an important addition to the PJI literature since it included 19 years of data from 101 VHA hospitals and analyzed validated clinical outcomes among multiple subgroups. We used rifampin treatment as a time-dependent variable, which allowed us to assess the duration of rifampin treatment.

In conclusion, adjunctive rifampin use was associated with a significantly lower hazard of microbiological recurrence in the 6 months following DAIR for *S aureus* PJI, compared with no rifampin. The protective effect was prominent within the first 180 days of rifampin treatment and was present throughout most subgroups. This study supports the current guidelines,

Table 3. Hazard Ratios of Various Timing of Rifampin Treatment and Postrifampin Treatment for Recurrence Across Subgroup Analyses

	Active Rifampin Treatment			Postrifampin Treatment	
Groups	Active Rifampin Treatment: Days 1–90 (n = 842)	Active Rifampin Treatment: Days 91–180 (n = 231)	Active Rifampin Treatment: Days 181–731 (n = 88)	Post–Rifampin Treatment: Total ≤90 d (n = 546)	Post Rifampin Treatment: Total >90 d (n = 226)
Total cohort (N = 4624)	0.60 (.45–.79)	0.16 (.04–.66)	0.57 (.18–1.81)	1.12 (.95–1.31)	1.07 (.75–1.51)
Knee (n = 3779)	0.55 (.40–.76)	0.19 (.05–.75)	0.61 (.19–1.92)	1.12 (.94–1.33)	1.17 (.82–1.67)
Hip (n = 813)	0.74 (.40–1.38)	(0–∞)[a]	(0–∞)[a]	1.16 (.79–1.72)	0.42 (.10–1.72)
MSSA (n = 3405)	0.62 (.43–.89)	0.26 (.07–1.04)	0.55 (.13–2.22)	1.18 (.97–1.45)	1.01 (.67–1.53)
MRSA (n = 1219)	0.58 (.37–.90)	(0–∞)[a]	0.65 (.09–4.99)	1.01 (.78–1.30)	1.21 (.65–2.26)
Early PJI (n = 1150)	0.47 (.30–.74)	(0–∞)[a]	1.14 (.28–4.70)	1.07 (.81–1.40)	0.68 (.38–1.21)
Late PJI (n = 1056)	0.33 (.16–.67)	0.23 (.03–1.66)	(0–∞)[a]	0.94 (.69–1.29)	1.45 (.83–2.53)

Data are presented as hazard ratio (95% confidence interval).

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PJI, prosthetic joint infection.

[a]Hazard ratio and confidence interval could not be reliably estimated in subgroups having few patients during a given time period and no recurrences.

which recommend the use of adjunctive rifampin for up to 6 months among patients with *S aureus* PJI treated with DAIR. Given the low rate of rifampin use in this cohort, wider use of adjunctive rifampin for *S aureus* PJI after DAIR should be encouraged to improve the outcome.

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.

Notes

Disclaimer. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

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