ORIGINAL RESEARCH

Rifampin for Prosthetic Joint Infections: Lessons Learned Over 20 Years at a VA Medical Center

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Background: The Minneapolis Veterans Affairs Health Care System uses debridement and implant retention (DAIR) combined with oral rifampin and a second antibiotic to treat orthopedic implant infections. However, the success rate of this approach in a veteran population is unknown.

Methods: We performed a retrospective analysis of patients who underwent DAIR with a rifampin-containing regimen for an orthopedic implant infection over the past 20 years at the Minneapolis Veterans Affairs Health Care System. The primary outcome was treatment success among participants who were treated with curative intent, defined as planned device retention without ongoing antibiotic use. Secondary outcomes were treatment harms and therapy duration. Treatment success was defined as the absence of recurrent infection or further measures to suppress infection within 1 year of completing antimicrobial therapy.

Results: A total of 78 patients (88% male) were included (median age, 65.5 years), with 50 treated with curative intent (primary analysis group). Forty-one participants (82%) in the curative intent group experienced treatment success. The success rate was higher among participants whose implant was < 2 months old vs those whose implant was ≥ 2 months old (93% vs 65%, respectively; $P = .02$). The 28 participants treated without curative intent had more comorbidities, higher rates of chronic infection, and older implants than those treated with curative intent.

Conclusions: Veterans with orthopedic implant infections can be successfully treated with DAIR combined with a rifampin-containing antimicrobial regimen. Success is highest for patients with a recent implant. Debridement and implant retention using regimens that include rifampin is an evidence-based strategy for managing patients with infected prosthetic hardware. Here we report that this approach is feasible in a veteran population, especially with recently implanted prosthetic material.

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Orthopedic implants are frequently used to repair fractures and replace joints. The number of total joint replacements is high, with > 1 million total hip (THA) and total knee (TKA) arthroplasties performed in the United States each year.[1] While most joint arthroplasties are successful and significantly improve patient quality of life, a small proportion become infected.[2] Prosthetic joint infection (PJI) causes substantial morbidity and mortality, particularly among older patients, and is difficult and costly to treat.[3]

The historic gold standard treatment for PJI is a 2-stage replacement, wherein the prosthesis is removed in one procedure and a new prosthesis is implanted in a second procedure after an extended course of antibiotics. This approach requires the patient to undergo 2 major procedures and spend considerable time without a functioning prosthesis, contributing to immobility and deconditioning. This option is difficult for frail or older patients and is associated with high medical costs.[4]

In 1998, a novel method of treatment known as debridement, antibiotics, and implant retention (DAIR) was evaluated in a small, randomized controlled trial.[5] This study used a unique antimicrobial approach: the administration of ciprofloxacin plus either rifampin or placebo for 3 to 6 months, combined with a single surgical debridement. Eliminating a second surgical procedure and largely relying on oral antimicrobials reduces surgical risks and decreases costs.[4] Current guidelines endorse DAIR with rifampin and a second antibiotic for patients diagnosed with PJI within about 30 days of prosthesis implantation who have a well-fixed implant without evidence of a sinus tract.[6] Clinical trial data demonstrate that this approach is > 90% effective in patients with a well-fixed prosthesis and acute staphylococcal PJI.[3,7]

Thus far, clinical trials examining this approach have been small and did not include veterans who are typically older and have more comorbidities.[8] The Minneapolis Veterans Affairs Health Care System (MVAHCS) infectious disease section has implemented the rifampin-based DAIR approach for orthopedic device-related infections since this approach was first described in 1998 but has not systematically evaluated its effectiveness or whether there are areas for improvement.

TABLE Patient Demographic, Clinical, and Treatment Characteristics

Characteristics	Total (N = 78)	Intent to cure (n = 50)	Without intent to cure (n = 28)	*P* value
Age at PJI diagnosis, median (IQR), y	65 (27-88)	64 (27-88)	69 (32-84)	.24
Sex, No. (%)				.09
Male	69 (88)	40 (80)	27 (96)	
Female	9 (12)	10 (20)	1 (4)	
Implant age, median (IQR), mo	1.3 (0.6-30)	1 (0.6-22)	11 (1-50.5)	.22
Length of symptoms before surgery, mean (SD), d	7.6 (6.1)	7.1 (5.3)	8.4 (7.4)	.39
Implant, No. (%)				
Knee	38 (49)	22 (44)	16 (57)	.34
Hip	29 (37)	20 (40)	9 (32)	.63
Osteosynthesis	8 (10)	6 (12)	2 (7)	.74
Elbow or ankle	3 (4)	2 (4)	1 (4)	.99
Debridement, No. (%)				.65
Open	73 (94)	46 (92)	27 (96)	
Arthroscopic	5 (6)	4 (8)	1 (4)	
Charlson Comorbidity Index, mean (SD)	2.2 (1.4)	1.9 (1.4)	2.5 (1.3)	.09
Comorbidities, No. (%)				
Diabetes mellitus	29 (37)	16 (32)	13 (46)	.23
Rheumatoid arthritis	7 (9)	6 (12)	1 (4)	.41
Chronic infection, No. (%)	30 (38)	11 (22)	19 (68)	< .001
Pathogens identified, No. (%)[a]				
Staphylococcus aureus	42 (54)	30 (60)	12 (43)	.16
Coagulase-negative staphylococcus	31 (40)	18 (36)	13 (46)	.47
Gram-negative organisms	11 (14)	8 (16)	3 (11)	.73
Gram-positive anaerobic cocci	6 (8)	3 (6)	3 (11)	.66
Cutibacterium acnes	3 (4)	1 (2)	2 (7)	.29
Streptococcus agalactiae	3 (4)	2 (4)	1 (4)	.99
Diphtheroids	2 (3)	1 (2)	1 (4)	.99
No organisms detected	2 (3)	2 (4)	0 (0)	.52
Multiple organisms detected	20 (26)	13 (26)	7 (25)	.23
Candida albicans	1 (1)	0 (0)	1 (4)	.37
Antibiotic treatment, median (IQR)				.99
Duration of antibiotic therapy, mo	3 (1.4-3.0)	3 (1.4-3.0)	3 (1.4-6.0)	
Dosage of rifampin, mg	600 (600-900)	600 (600-900)	600 (600-900)	
Secondary antibiotic, No. (%)				
Fluoroquinolone	36 (46)	27 (54)	9 (32)	.10
Tetracycline	20 (26)	12 (24)	8 (29)	.79
Cephalosporin	6 (8)	3 (6)	3 (11)	.66
Penicillin	6 (8)	4 (8)	2 (7)	.99
Trimethoprim-sulfamethoxazole	4 (5)	1 (2)	3 (11)	.13
Azole antifungal	1 (1)	0 (0)	1 (4)	.37
Vancomycin	6 (8)	3 (6)	3 (11)	.66

Abbreviation: PJI, prosthetic joint infection

[a]Total percentage of pathogens isolated exceeds 100% due to multiple organisms isolated from some patients.

METHODS

We conducted a retrospective analysis of patients who underwent DAIR combined with a rifampin-containing regimen at the MVAHCS from January 1, 2001, through June 30, 2021. Inclusion required a diagnosis of orthopedic device-related infection and treatment with DAIR followed by antimicrobial therapy that included rifampin for 1 to 6 months. PJI was defined by meeting ≥ 1 of the following criteria: (1) isolation of the same microorganism from ≥ 2 cultures from joint aspirates or intraoperative tissue specimens; (2) purulence surrounding the

prosthesis at the time of surgery; (3) acute inflammation consistent with infection on histopathological examination or periprosthetic tissue; or (4) presence of a sinus tract communicating with the prosthesis.

All cases of orthopedic device infection managed with DAIR and rifampin were included, regardless of implant stability, age of the implant at the time of symptom onset, presence of a sinus tract, or infecting microorganism. Exclusion criteria included patients who started or finished PJI treatment at another facility, were lost to follow-up, discontinued rifampin, died within 1 year of completing antibiotic therapy due to reasons unrelated to treatment failure, received rifampin for < 50% of their antimicrobial treatment course, had complete hardware removal, or had < 1 year between the completion of antimicrobial therapy and the time of data collection.

Management of DAIR procedures at the MVAHCS involves evaluating the fixation of the prosthesis, tissue sampling for microbiological analysis, and thorough debridement of infected tissue. Following debridement, a course of IV antibiotics is administered before initiating oral antibiotic therapy. To protect against resistance, rifampin is combined with another antibiotic typically from the fluoroquinolone, tetracycline, or cephalosporin class. Current guidelines suggest 3 and 6 months of oral antibiotics for prosthetic hip and knee infections, respectively.[6]

Treatment Outcomes

The primary outcome was treatment success, defined as meeting all of the following: (1) lack of clinical signs and symptoms of infection; (2) absence of radiological signs of loosening or infection within 1 year after the conclusion of treatment; and (3) absence of additional PJI treatment interventions for the prosthesis of concern within 1 year after completing the original antibiotic treatment.

Treatment failure was defined as meeting any of the following: (1) recurrence of PJI (original strain or different microorganism) within 1 year after the completion of antibiotic therapy; (2) death attributed to PJI anytime after the initial debridement; (3) removal of the prosthetic joint within 1 year after the completion of antibiotic therapy; or (4) long-term antibiotic use to suppress the PJI after the completion of the initial antibiotic therapy.

Statistical Analysis

Descriptive statistics were used to define the baseline characteristics of patients receiving rifampin therapy for orthopedic implant infections at the MVAHCS. Variables analyzed were age, sex, race and ethnicity, type of implant, age of implant, duration of symptoms, comorbidities (diabetes and rheumatoid arthritis), and presence of chronic infection. Patients were classified as having a chronic infection if they received previous infection treatment (antibiotics or surgery) for the orthopedic device in question. We created this category because patients with persistent infection after a medical or surgical attempt at treatment are likely to have a higher probability of treatment failure compared with those with no prior therapy. Charlson Comorbidity Index was calculated using clinical information present at the onset of infection.[9] Fisher exact test was used to assess differences between categorical variables, and an independent *t* test was used to assess differences in continuous variables. $P < .05$ indicated statistical significance.

To assess the ability of a rifampin-based regimen to achieve a cure of PJI, we grouped participants into 2 categories: those with an intent to cure strategy and those without intent to cure based on documentation in the electronic health record (EHR). Participants who were prescribed rifampin with the documented goal of prosthesis retention with no further suppressive antibiotics were included in the intent-to-cure group, the primary focus of this study. Those excluded from the intent-to-cure group were given rifampin and another antibiotic, but there was a documented plan of either ongoing chronic suppression or eventual explantation; these participants were placed in the without-intent-to-cure group. Analysis of treatment success and failure was limited to the intent-to-cure group, whereas both groups were included for assessment of adverse effects (AEs) and treatment duration. This project was reviewed by the MVAHCS Institutional Review Board and determined to be a quality improvement initiative and

to not meet the definition of research, and as such did not require review; it was reviewed and approved by the MVAHCS Research and Development Committee.

RESULTS

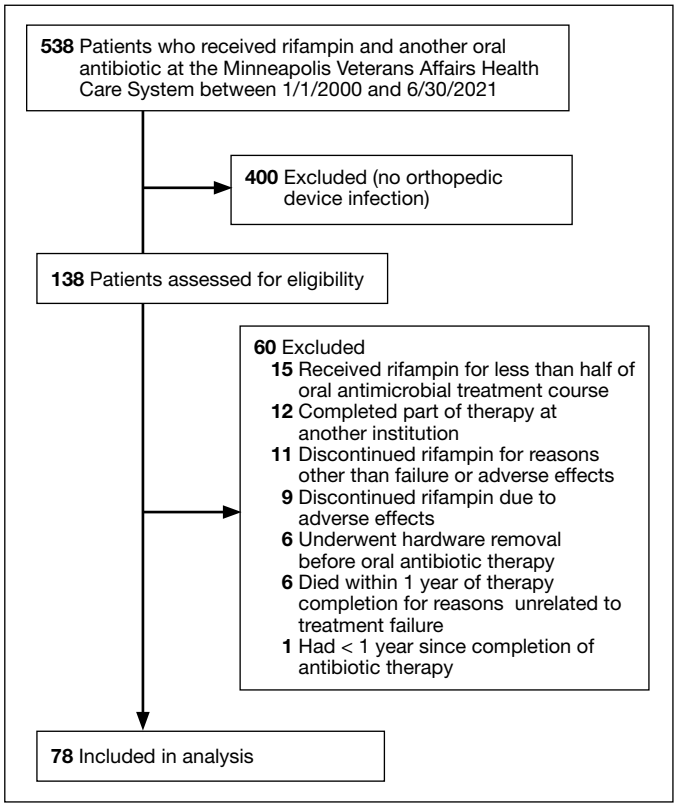
A total of 538 patients were identified who simultaneously received rifampin and another oral antibiotic between January 1, 2000, and June 30, 2021. No orthopedic device infection was present in 400 patients, leaving 138 potential participants. Of these, 60 were excluded, leaving 78 patients with a diagnosed orthopedic implant infection treated with DAIR and a rifampin-containing antimicrobial regimen who were included in the study (Figure). Most were male (n = 69; 88%) with a median age of 65 years (Table). The mean (SD) Charlson Comorbidity Index was 2.2 (1.4); diabetes was the most common comorbidity (n = 29; 37%). Thirty-eight participants (49%) had an infected knee prosthesis and 29 (37%) had an infected hip prosthesis, accounting for 86% of all infections, while 8 participants (10%) had infected bone fixation devices and the remaining 3 (4%) had infected elbow or ankle implants. The debridement procedure was open for 73 patients (94%) vs arthroscopic for 5 (6%) (all osteosynthesis infections). Rifampin was initiated after debridement in all cases. The median (IQR) implant age was 1.3 months (0.6-30 months). Thirty participants (38%) had a chronic infection. The mean (SD) duration of infection-related symptoms before surgery was 7.6 (6.1) days.

Forty-two participants (54%) had *Staphylococcus aureus* and 31 participants (40%) had coagulase-negative staphylococci infections, while 11 gram-negative organisms (14%) and 6 gram-positive anaerobic cocci (8%) infections were noted. *Cutibacterium acnes* and *Streptococcus agalactiae* were each found in 3 participants (4% of), and diphtheroids (not further identified) was found on 2 participants (3%). *Candida albicans* was identified in a single participant (1%), along with coagulase-negative staphylococci, and 2 participants (3%) had no identified organisms. There were multiple organisms isolated from 20 patients (26%).

Fifty participants had clear documentation in their EHR that cure of infection was the goal, meeting the criteria for the intent-to-cure group. The remaining 28 participants were placed in the without-intent-to-cure group. Success and failure rates were only measured in the intent-to-cure group, as by definition the without-intent-to-cure group patients would meet the criteria for failure (removal of prosthesis or long-term antibiotic use). The without-intent-to-cure group had a higher median age than the intent-to-cure group (69 years vs 64 years, $P = .24$) and a higher proportion of male participants (96% vs 80%, $P = .09$). The median (IQR) implant age of 11 months (1.0-50.5) in the without-intent-to-cure group was also higher than the median implant age of 1 month (0.6-22.0) in the primary group ($P = .22$). In the without-intent-to-cure group, 19 participants (68%) had a chronic infection, compared with 11 (22%) in the intent-to-cure group ($P < .001$).

The mean (SD) Charlson Comorbidity Index in the without-intent-to-cure group was 2.5 (1.3) compared with 1.9 (1.4) in the intent-to-cure group ($P = .09$). There was no significant difference in the type of implant or microbiology of the infecting

FIGURE Patient Flow and Exclusion



organism between the 2 groups, although it should be noted that in the intent-to-cure group, 48 patients (96%) had *Staphylococcus aureus* or coagulase-negative staphylococci isolated.

The median (IQR) dosage of rifampin was 600 mg (300-900). The secondary oral antibiotics used most often were 36 fluoroquinolones (46%) followed by 20 tetracyclines (26%), 6 cephalosporins (8%), and 6 penicillins (8%). Additionally, 6 participants (8%) received IV vancomycin, and 1 participant (1%) was given an oral antifungal in addition to a fluoroquinolone because cultures revealed bacterial and fungal growth. The median (IQR) duration of antimicrobial therapy was 3 months (1.4-3.0). The mean (SD) duration of antimicrobial therapy was 3.6 (2.4) months for TKA infections and 2.4 (0.9) months for THA infections.

Clinical Outcome

Forty-one intent-to-cure group participants (82%) experienced treatment success. We further subdivided the intent-to-cure group by implant age. Participants whose implant was < 2 months old had a success rate of 93%, whereas patients whose implant was older had a success rate of 65% ($P = .02$).

Secondary Outcomes

The median (IQR) duration of antimicrobial treatment was 3 months (1.4-3.0) for the 38 patients with TKA-related infections and 3 months (1.4-6.0) for the 29 patients with THA infections. AEs were recorded in 24 (31%) of all study participants. Of those with AEs, the average number reported per patient was 1.6. Diarrhea, gastric upset, and nausea were each reported 7 times, accounting for 87% of all recorded AEs. Five participants reported having a rash while on antibiotics, and 2 experienced dysgeusia. One participant reported developing a yeast infection and another experienced vaginitis.

DISCUSSION

Among patients with orthopedic implant infections treated with intent to cure using a rifampin-containing antibiotic regimen at the MVAHCS, 82% had clinical success. Although this is lower than the success rates reported in clinical trials, this is not entirely unexpected.[5,7] In most clinical trials studying DAIR and rifampin for PJI, patients are excluded if they do not have an acute staphylococcal infection in the setting of a well-fixed prosthesis without evidence of a sinus tract. Such exclusion criteria were not present in our retrospective study, which was designed to evaluate the real-world practice patterns at this facility. The population at the US Department of Veterans Affairs (VA) is older, more frail, and with more comorbid conditions than populations in prior studies. It is possible that patients with characteristics that would have caused them to be excluded from a clinical trial would be less likely to receive rifampin therapy with the intent to cure. This is suggested by the significantly higher prevalence of chronic infections (68%) in the without-intent-to-cure group compared with 22% in the intent-to-cure group. However, there were reasonably high proportions of participants included in the intent-to-cure group who did have conditions that would have led to their exclusion from prior trials, such as chronic infection (22%) and implant age ≥ 2 months (40%).

When evaluating participants by the age of their implant, treatment success rose to 93% for patients with implants < 2 months old compared with 65% for patients with older implants. This suggests that participants with a newer implant or more recent infection have a greater likelihood of successful treatment, which is consistent with the results of previous clinical trials.[5,10] Considering how difficult multiple surgeries can be for older adult patients with comorbidities, we suggest that DAIR with a rifampin-containing regimen be considered as the primary treatment option for early PJIs at the MVAHCS. We also note inconsistent adherence to IDSA treatment guidelines on rifampin therapy, in that patients without intent to cure were prescribed a regimen including rifampin. This may reflect appropriate variability in the care of individual patients but may also offer an opportunity to change processes to improve care.

Limitations

Our analysis has limitations. As with any retrospective study evaluating the efficacy

of a specific antibiotic, we were not able to attribute specific outcomes to the antibiotic of interest. Since the choice of antibiotics was left to the treating health care practitioner, therapy was not standardized, and because this was a retrospective study, causal relationships could not be inferred. Our analysis was also limited by the lack of intent to cure in 28 participants (36%), which could be an indication of practitioner bias in therapy selection or characteristic differences between the 2 groups. We looked for signs of infection failure 1 year after the completion of antimicrobial therapy, but longer follow-up could have led to higher rates of failure. Also, while participants' infections were considered cured if they never sought further medical care for the infection at the MVAHCS, it is possible that patients could have sought care at another facility. We note that 9 patients were excluded because they were unable to complete a treatment course due to rifampin AEs, meaning that the success rates reported here reflect the success that may be expected if a patient can tolerate and complete a rifampin-based regimen. This study was conducted in a single VA hospital and may not be generalizable to nonveterans or veterans seeking care at other facilities.

CONCLUSIONS

DAIR followed by a short course of IV antibiotics and an oral regimen including rifampin and another antimicrobial is a reasonable option for veterans with acute staphylococcal orthopedic device infections at the MVAHCS. Patients with a well-placed prosthesis and an acute infection seem especially well suited for this treatment, and treatment with intent to cure should be pursued in patients who meet the criteria for rifampin therapy.

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Ethics and consent

This project was reviewed by the Minneapolis VA Healthcare System (MVAHCS) Institutional Review Board and determined to be a quality improvement initiative and to not meet the definition of research, and as such did not require review from the Institutional Review Board. It was reviewed and approved by the MVAHCS Research and Development Committee.

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