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Postoperative Treatment Regimens in Patients With Native Valve Endocarditis due to *Staphylococcus aureus* Who Undergo Valve Replacement or Repair

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Background. There remains a lack of consensus regarding the postoperative treatment regimen in patients with native valve *Staphylococcus aureus* infective endocarditis who undergo surgical valve replacement or repair.

Methods. We conducted a multicenter retrospective review of patients with *S aureus* native valve endocarditis who underwent surgical valve replacement or repair at Mayo Clinic Enterprise (Minnesota, Florida, Arizona, and Mayo Clinic Health Systems) between 1 January 2012 and 31 December 2022. Postoperative treatment regimens were classified as either monotherapy with a methicillin-sensitive or methicillin-resistant *S aureus* active agent or combination therapy that included rifampin and/or gentamicin with either active agent.

Results. Of the 339 patients diagnosed with *S aureus* native valve endocarditis, 61 underwent surgical valve replacement or repair within the initial 6 weeks of antimicrobial therapy. A total of 12 (20.2%) patients died during the 1-year follow-up period. Between patients postoperatively treated with monotherapy (n = 33) and combination therapy (n = 28), a propensity score–weighted analysis revealed that combination therapy was associated with increased risk of 1-year mortality ($P = .039$), 6-month relapse ($P = .016$), and treatment-related adverse events ($P < .001$).

Conclusions. Among patients treated for native valve infective endocarditis caused by *S aureus* after valvular surgical intervention, all study outcomes—adverse events and drug-drug interactions, 6-month infective endocarditis relapse, and 1-year mortality—were higher in the combination therapy group than the monotherapy group.

Keywords. endocarditis; gentamicin; prosthetic valve; rifampin; *Staphylococcus aureus*.

The 2015 American Heart Association scientific statement on infective endocarditis (IE) recommends a 6-week course of therapy for *Staphylococcus aureus* IE [1]. Monotherapy is recommended in native valve endocarditis (NVE) with a methicillin-susceptible *S aureus* (MSSA) active agent or a methicillin-resistant *S aureus* (MRSA) active agent. However, in prosthetic valve endocarditis (PVE), the addition of oral rifampin and intravenous gentamicin is recommended [1].

A common clinical dilemma occurs when a patient with *S aureus* NVE (SANVE) undergoes surgical valve replacement or repair during the first 6 weeks of intravenous antimicrobial therapy: should the postoperative treatment regimen change from NVE to PVE from monotherapy to combination therapy? The 2015 American Heart Association scientific statement lacked a consensus regarding this clinical question as limited evidence evaluating outcomes exists: "For patients with NVE who undergo valve resection with prosthetic valve replacement or repair with an annuloplasty ring, there is a lack of consensus as to whether the postoperative treatment regimen should be one that is recommended for PVE treatment rather than one that is recommended for native valve treatment" [1]. The 2023 European Society of Cardiology guidelines for the management of endocarditis recommend that the postoperative antibiotic regimen be that for NVE and not PVE, in cases of NVE requiring prosthesis during antibiotic therapy [2]. Moreover, the efficacy and safety of combination therapy as compared with monotherapy have garnered more attention recently [3, 4]. Synergistic regimens with aminoglycosides and rifampin remain widely used in clinical practice, despite a dearth of

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definitive evidence showing benefit in human trials [4]. Furthermore, the employment of these adjunctive agents is fraught with adverse events (AEs), drug-drug interactions (DDIs), and antimicrobial resistance [5–8].

We therefore conducted a multicenter retrospective review of patients with SANVE who underwent surgical valve replacement or repair surgery within 6 weeks of IE diagnosis treated across the Mayo Clinic Enterprise, and we conducted a comparative treatment analysis on clinical outcomes. We sought to ascertain if there were variations in outcomes for patients who had surgical intervention with valve replacement or repair for SANVE, depending on the type of postoperative antibiotic treatment administered.

METHODS

Study Design and Population

We conducted a retrospective multicenter cohort study of patients admitted with SANVE at Mayo Clinic Enterprise facilities in Minnesota, Florida, Arizona, and Mayo Clinic Health Systems from 1 January 2012 through 31 December 2022. The study was deemed exempt by the institutional review board (23-008894). To identify eligible participants, an institutional IE database was used. We verified if cases were confirmed, using the 2023 Duke–International Society for Cardiovascular Infectious Diseases criteria for definitive endocarditis [9]. Additionally, we reviewed the pathology records of patients who underwent valve surgery after being diagnosed with SANVE. Patients aged ≥18 years who underwent valve replacement or repair within 6 weeks of antibiotic initiation for SANVE were included. Patients had to receive at least 1 day of antibiotic treatment postoperatively after valve surgery to be included in the analysis. Patients who had polymicrobial infection, those who underwent surgical intervention beyond 6 weeks of antibiotic exposure for IE, and Minnesota patients without research authorization were excluded.

Definitions and Outcomes

Time zero was considered the date that the patient first received antibiotic therapy after surgical intervention, and treatment was classified as monotherapy vs combination therapy, according to the type of regimen that was initiated. The monotherapy group comprised patients receiving only backbone therapy with an MSSA or MRSA active agent. The combination group included those receiving backbone therapy with an MSSA or MRSA active agent with adjunctive rifampin and/or gentamicin. MSSA active agents consisted of antistaphylococcal penicillin (eg, oxacillin, cefazolin, nafcillin) and oral cefadroxil. MRSA active agents included vancomycin, daptomycin, doxycycline, and linezolid. In cases with a contraindication to antistaphylococcal penicillin, vancomycin and daptomycin were considered MSSA active agents.

In the combination group, start date (time zero) was considered the day when all the drugs were started, and the duration spanned the period that the patient was receiving all the components of the regimen. Antibiotic-related AEs were not prespecified. They were abstracted from chart review per clinician assessment of documentation. All the patients in our health care system undergo pharmacy review and counseling when they are prescribed rifampin/gentamicin and are linked to the outpatient parenteral antibiotic therapy (OPAT) program at dismissal. The OPAT team, which comprises a physician/advanced practitioner, a nurse, and an infectious diseases pharmacist, monitors the patient closely until completion of the antimicrobial course, with clear documentation of the therapy, including AEs, DDIs, and any changes. Patient charts were extensively reviewed to look for possible confounders, the indication for discontinuation of the antibiotic, and reversal of the AE with discontinuation of the offending antibiotic where applicable. Regarding DDIs, a similarly detailed chart review was conducted and cross-verified with OPAT records. The primary outcomes of interest were 1-year mortality and 6-month relapse. Patients were followed up for all-cause mortality through the Mayo Clinic's electronic medical record system. For 1-year mortality analyses, follow-up time was censored at last patient contact or at 1 year from treatment start, whichever occurred first. IE relapse was defined as IE due to the same bacterial species within 6 months of surgery. We explored whether certain types of combination therapy could be driving outcomes within the combination therapy group. For the purposes of comparison, the 2 subgroups receiving an MSSA/MRSA active agent plus gentamicin with or without rifampin were collapsed into a single subgroup and contrasted with the subgroup receiving an MSSA/MRSA active agent plus rifampin without gentamicin.

Statistical Analysis

Descriptive statistics on baseline data were calculated as median (IQR) for continuous variables and percentages for categorical variables. For follow-up outcomes (ie, 1-year mortality, 6-month relapse), time-to-event analysis based on Kaplan-Meier and Cox proportional hazards regression methods was used to describe cumulative event rates as a function of follow-up time and treatment group.

For the purposes of these analyses, patients were assigned to the treatment group (combination therapy or monotherapy) defined by the initial regimen given, regardless of subsequent crossovers, and their follow-up for outcomes was started with the initiation of treatment as time zero. In addition to unadjusted outcome analyses, the treatment comparisons were subjected to propensity score (PS) adjustment to control for potential confounders that may have influenced selection of therapy. The PS for treatment is the model-estimated probability that a patient will receive a specific therapy given one's baseline

characteristics. To this end, the propensity to receive combination therapy (vs monotherapy) was modeled in a multivariable logistic regression model with 7 covariates chosen a priori as potentially relevant to the selection of therapy: age, sex, injection drug use (IDU), prior hospitalization, Charlson Comorbidity Index, chronic hemodialysis (HD), and glomerular filtration rate. To adjust for these potential confounding effects in the outcome modeling, the estimated PSs were used as sampling weights based on inverse probability weighting. This weighting approach uses the full study population and weights patients by the inverse of their PSs to create balanced pseudo-populations.

The weighted logistic or Cox regression models were applied to the study outcomes with a robust sandwich variance estimator to account for uncertainty in the derivation of the weights. Covariate balance was examined before and after PS weighting by standardized mean difference measures, which computed the difference in mean rankings or proportions between groups in units of the pooled standard deviation. An absolute value <0.10 was considered well balanced for that specific covariate, while an absolute value <0.20 was considered acceptable. All analyses were done in R version 4.2.2.

RESULTS

Of the 339 patients who were diagnosed with SANVE, we identified 61 who underwent surgical intervention for these analyses (Table 1). The causative pathogens were identified as MSSA in 52 (85.2%) and MRSA in 9 (14.8%). Overall there were 26 (42.6%) women, the median age was 54 years (IQR, 42–64), and the majority (89.1%) of the patients were White. Sixteen (26.2%) patients had a history of active IDU and 19 (31.1%) had ongoing HD requirements. Patients typically had few comorbidities as indicated by low Charlson Comorbidity Index scores (IQR, 0–2). Left-sided valvular IE was noted in 56 patients (91.8%), with surgical intervention involving the mitral valve in 36 (64.3%) and aortic valve in 34 (60.7%). Among patients with infected valves, 49 (80.3%) underwent replacement, and the remainder had repair with implantation of prosthetic ring or clip. Multivalvular surgery was performed in 20 (31.3%) patients. The median duration between IE diagnosis and surgical intervention was 9 days (IQR, 6–14). Patients were categorized into 2 groups based on postoperative antibiotic regimen. The monotherapy group comprised 33 patients, while the combination group had 28 patients. In the combination group, 18 patients received adjunctive rifampin, 2 received adjunctive gentamicin, and 8 received rifampin and gentamicin therapy with an MSSA/MRSA active agent. Antibiotic-related AEs were noted in 20 (32.8%) patients in total: 2 (6.1%) in the monotherapy group and 18 (64.3%) in the combination therapy group. AE-related antibiotic discontinuation occurred in 14 patients. One of these 14 patients was in the monotherapy group with MRSA, in whom exposure to vancomycin resulted in a severe cutaneous allergic drug reaction and required a switch to daptomycin. The remaining 13 patients belonged to the combination therapy group, in whom nafcillin was discontinued and switched to cefazolin in 2 patients due to heart failure, rifampin was discontinued due to severe drug rash (3 patients) and hepatotoxicity (5 patients), and gentamicin was discontinued due to auditory/vestibular toxicity (2 patients) and nephrotoxicity (4 patients). In these 13 patients, rash was seen concurrently with nephrotoxicity in 2 patients and hepatotoxicity in 1 patient, and all 3 had improvement in rash upon discontinuation of rifampin. Antibiotic-related DDIs were observed in 20 patients, of whom 19 in the combination therapy group developed rifampin-related DDIs to warfarin (10 patients), clopidogrel (3 patients), hormonal contraceptives (2 patients), and phenytoin (2 patients), as well as direct oral anticoagulant, dolutegravir, and phenytoin (1 patient each). One patient had a DDI related to daptomycin with statin in the monotherapy group. Of these 19 patients (all in the combination therapy group), 4 required discontinuation of antibiotics due to significant DDIs with warfarin (3 patients who did not reach therapeutic coagulation goals) and phenytoin (1 patient with high risk of breakthrough seizures and intolerance to alternative anticonvulsants). Treatment-related data are shown in detail in Table 2.

A total of 12 patients died during the 1-year follow-up period (20.2% cumulative mortality at 1 year), and 11 deaths were attributable to the IE or its sequelae. Fourteen patients experienced IE relapse during the first 6 months of follow-up (23.8% cumulative incidence at 6 months). Of the 14 patients who developed IE relapse, 5 died within 3 days, and 3 others died within 1 year of their relapse. Kaplan-Meier curves showed a rapid rise in early mortality based on 2 deaths on day 6 in the combination therapy group (both patients had multiple septic emboli/infarcts and multiorgan failure) and 1 death in the monotherapy group (infected aortic aneurysm and hemorrhagic shock from an aortic cannulation bleed). All 3 of these patients with early deaths, within 7 days of surgery, were removed from the specific analysis. Similarly, there was 1 additional patient with early relapse (day 7) who was undergoing combination therapy and seemed to recover from this relapse. Of the remaining patients, 9 of 26 (34.6%) in the combination group had <30 days of treatment regimen, as compared with 4 of 32 patients (12.5%) in the monotherapy group. All 9 patients in the combination therapy group stopped rifampin/gentamicin before the end of 30 days (range, 1–24). Two of these patients had a relapse: 1 had a relapse on day 22 but stopped rifampin well before then, and 1 stopped rifampin a day before relapse.

In the unadjusted analysis, 1-year mortality was more likely (hazard ratio [HR], 6.3; 95% CI, 1.4–29.0; $P = .017$) to occur in the combination therapy group (10/28) than the monotherapy

Table 1. Baseline Characteristics of Patients in the Monotherapy and Combination Therapy Groups

Variable	No.[a]	Overall (n = 61)	Monotherapy (n = 33)	Combination Therapy (n = 28)
Age, y	61	54.4 (42.0–64.0)	50.1 (36.9–61.0)	55.9 (51.0–68.1)
Sex: male	61	57.4 (35)	66.7 (22)	46.4 (13)
Left-sided IE	61	91.8 (56)	84.8 (28)	100.0 (28)
Aortic valve	56	60.7 (34)	53.6 (15)	67.9 (19)
Mitral valve	56	64.3 (36)	67.9 (19)	60.7 (17)
Right-sided IE	61	21.3 (13)	21.2 (7)	21.4 (6)
Tricuspid valve	13	84.6 (11)	71.4 (5)	100.0 (6)
Solid organ transplant	61	4.9 (3)	3.0 (1)	7.1 (2)
Cardiac implantable electronic device	61	6.6 (4)	3.0 (1)	10.7 (3)
Congenital heart disease	61	13.1 (8)	15.2 (5)	10.7 (3)
Patent foramen ovale	61	33.3 (20)	30.3 (10)	37.0 (10)
Hospitalization prior to diagnosis	61	23.0 (14)	15.2 (5)	32.1 (9)
Type of valve surgery				
Valve replacement	61	80.3 (49)	72.7 (24)	89.3 (25)
Valve repair	61	19.7 (12)	27.3 (9)	10.7 (3)
Days between IE diagnosis and valve surgery	61	9.0 (6.0–14.0)	9.0 (6.0–14.0)	9.5 (5.8–14.8)
Pathologic criteria met[b]	57	87.7 (50)	82.8 (24)	92.9 (26)
FDG-PET/CT with findings equivalent to echocardiography	61	3.3 (2)	0.0 (0)	7.1 (2)
Intraoperative evidence of IE	61	95.1 (58)	90.9 (30)	100.0 (28)
Minor criteria for predisposition	61	63.9 (39)	63.6 (21)	64.3 (18)
Fever	61	75.4 (46)	69.7 (23)	82.1 (23)
Vascular phenomena	61	86.9 (53)	87.9 (29)	85.7 (24)
Immunologic phenomena	61	23.0 (14)	24.2 (8)	21.4 (6)
Staphylococcal species				
MSSA	61	85.2 (52)	90.9 (30)	78.6 (22)
MRSA	61	14.8 (9)	9.1 (3)	21.4 (6)
Charlson Comorbidity Index	61	0 (0–2)	0 (0–2)	1 (0–3)
Injection drug use	61	26.2 (16)	30.3 (10)	21.4 (6)
Hemodialysis	61	31.1 (19)	24.2 (8)	39.3 (11)
Glomerular filtration rate	61	55 (33–76)	59 (38–83)	52 (32–73)
Days between surgery and initiation of antibiotics	61	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.2)
0		4.9 (3)	6.1 (2)	3.6 (1)
1		83.6 (51)	93.9 (31)	71.4 (20)
2		4.9 (3)	0.0 (0)	10.7 (3)
3		3.3 (2)	0.0 (0)	7.1 (2)
4		3.3 (2)	0.0 (0)	7.1 (2)

Values represent the median (IQR) for continuous variables and percentage (frequency) for discrete variables.

Abbreviations: FDG-PET/CT, fluorodeoxyglucose–positron emission tomography/computed tomography; IE, infective endocarditis; MRSA, methicillin (oxacillin)–resistant *Staphylococcus aureus*; MSSA, methicillin (oxacillin)–susceptible *Staphylococcus aureus*.

[a]No. refers to the number of patients with available information.

[b]All patients met the 2023 Duke–International Society for Cardiovascular Infectious Diseases criteria for definitive endocarditis.

group (2/33). Similarly, 6-month relapse was more likely (HR, 5.6; 95% CI, 1.6–20.0; $P = .008$) to occur in the combination therapy (11/28) group than the monotherapy group (3/33; Supplementary Table 1, Supplementary Figure 1). Within the combination therapy group, patients who received gentamicin (n = 10) had high rates of antibiotic-related AEs (90.0%) and IE relapse (55.0% at 6 months; Supplementary Table 2).

Further analyses were performed to explore the possibility of treatment selection bias as an explanation for our unadjusted results. Namely, a PS-weighted analysis was used to correct for imbalances between treatment groups, based on 7 prespecified factors possibly relating to the selection of patients for combination therapy. Unweighted comparisons of the individual variables demonstrated statistical imbalances between the groups, as indicated by an absolute standardized difference ≥0.2 in all 7 factors (range, 0.20–0.51). However, all were reasonably well balanced after PS weighting (range, 0.03–0.11), including the PS itself, which dropped from an absolute standardized difference of 0.81 to 0.11 (Supplementary Table 3).

The improved comparability of the groups is further evidenced by the narrowing of the difference in the weighted empirical cumulative distributive function curves by treatment group (Supplementary Figure 2). Consistent with the prior unadjusted comparisons, the outcome analyses incorporating PS weighting showed significant differences in study outcomes

Table 2. Treatment-Related Data of Patients in the Monotherapy and Combination Therapy Groups

Characteristic	No.[a]	Overall (n = 61)	Monotherapy (n = 33)	Combination Therapy (n = 28)
Days of postoperative antibiotics	61	41.0 (38.0–42.0)	41.0 (34.0–42.0)	41.0 (38.8–42.2)
Duration of antibiotics <30 d	58	22.4 (13)	12.5 (4)	34.6 (9)
Antibiotics used for monotherapy	33			
MSSA active agent[b]		84.8 (28)	84.8 (28)	0
MRSA active agent[c]		6.1 (2)	6.1 (2)	0
Other[d]		9.1 (3)	9.1 (3)	0
Antibiotics used for combination therapy	28			
MSSA/MRSA active agent + rifampin		64.3 (18)	0	64.3 (18)
MSSA/MRSA active agent + gentamicin		7.1 (2)	0	7.1 (2)
MSSA/MRSA active agent + rifampin + gentamicin		28.6 (8)	0	28.6 (8)
Positive bacterial blood culture at IE diagnosis	61	65.6 (40)	60.6 (20)	71.4 (20)
Antibiotic-related DAE	61	32.8 (20)	6.1 (2)	64.3 (18)
Heart failure		4.9 (3)	0.0 (0)	10.7 (3)
Nephrotoxicity		9.8 (6)	0.0 (0)	21.4 (6)
Vestibular toxicity		1.6 (1)	0.0 (0)	3.6 (1)
Auditory toxicity		3.3 (2)	0.0 (0)	7.1 (2)
Hepatotoxicity		8.2 (5)	0.0 (0)	17.9 (5)
Rash		11.5 (7)	6.1 (2)	17.9 (5)
Gastrointestinal distress		6.6 (4)	3.0 (1)	10.7 (3)
Other[e]		1.6 (1)	0.0 (0)	3.6 (1)
Antibiotic discontinued due to DAE	20	70.0 (14)	50.0 (1)	72.2 (13)
Antibiotic-related DDI	61	32.8 (20)	3.0 (1)	67.9 (19)
Antibiotic discontinued due to DDI	20	20.0 (4)	0.0 (0)	21.1 (4)

Values represent the median (IQR) for continuous variables and percentage (frequency) for discrete variables.

Abbreviations: DAE, drug adverse event; DDI, drug-drug interaction; MRSA, methicillin (oxacillin)–resistant *Staphylococcus aureus*; MSSA, methicillin (oxacillin)–susceptible *Staphylococcus aureus*.

[a]No. refers to the number of patients with available information.

[b]MSSA active agent was an antistaphylococcal penicillin in all cases (nafcillin, oxacillin, cefazolin).

[c]MRSA active agent was vancomycin in both patients.

[d]Two patients with MSSA and injection drug use were discharged with 4 weeks of oral cefadroxil after completing 14 days of cefazolin in the hospital; 1 patient with MSSA developed severe hives in response to vancomycin and oxacillin and switched to daptomycin on day 4.

[e]One patient had oxacillin-related neutropenia.

by treatment regimen. Postoperative management of endocarditis cases with combination therapy vs monotherapy was associated with an increased risk of 12-month mortality (HR, 4.4; 95% CI, 1.1–18.2; $P = .039$), 6-month relapse (HR, 5.0; 95% CI, 1.4–18.6; $P = .016$), and on-treatment AEs ($P < .001$). A summary of the PS-weighted analyses of clinical outcomes is detailed in Figure 1 and Supplementary Table 4.

DISCUSSION

The results of our investigation highlight pertinent outcomes over the postoperative course of SANVE cases, including findings that combination vs monotherapy is associated with increased risks for 1-year mortality, 6-month IE relapse, and antibiotic-related AEs. Moreover, in the combination therapy group, gentamicin-containing regimens seemed to account for a higher rate of antibiotic-related AEs as compared with rifampin regimens. Our data suggest that patients with SANVE have better outcomes with monotherapy (MSSA/MRSA active agent) as compared with patients receiving combination treatment with adjunctive rifampin and/or gentamicin.

The lack of consensus in the 2015 American Heart Association scientific statement was primarily based on the fact that there were no clinical trial data to assist in securing consensus among writing group members. In a retrospective study of 53 patients with SANVE who underwent acute valve surgery, cure rates were similar regardless of the type of postoperative regimen used, whether monotherapy with an MSSA/MRSA active agent or combination therapy with gentamicin and/or rifampin. Of note, this investigation from our institution included a cohort that preceded that in the present study [10]. In addition, in a review of 74 cases with SANVE, Drinkovic et al observed that combination therapy is not superior to monotherapy in sterilizing infected valves [11].

The benefit-risk balance of an MSSA/MRSA active agent with an aminoglycoside regimen remains questionable, despite its synergy-driven rapid bactericidal activity for staphylococci. While this regimen may reduce the duration of bacteremia and more rapidly reduce elevated peripheral white blood cell counts, it is countered by a significant toxicity profile [12, 13] and no effect on mortality outcomes, as noted in prospective studies [14, 15]. A similar argument can be applied

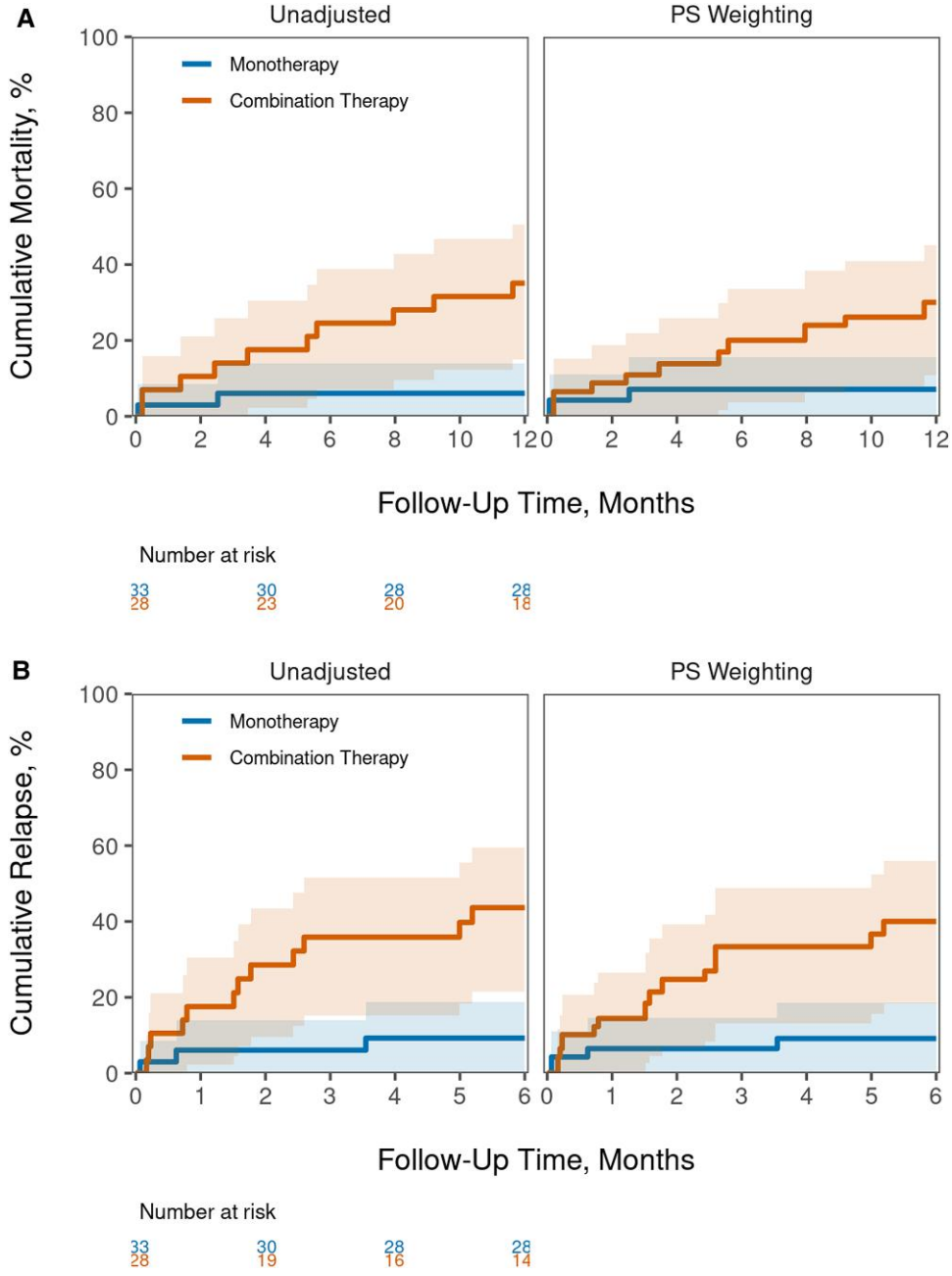

Figure 1. Comparison of unadjusted and PS-weighted analysis: *A*, 1-year mortality; *B*, 6-month infective endocarditis relapse. Shading indicates 95% CI. PS, propensity score.

to rifampin-containing regimens. Placebo-controlled trials showed no difference in the clinical outcomes of participants with *S aureus* bacteremia who were treated with adjunctive rifampin in addition to an MSSA/MRSA active agent, with more AEs and DDIs in the rifampin group as compared with the placebo group [6].

Despite guideline recommendations, combination therapy for PVE has come under debate in recent years. The justification for recommending rifampin for staphylococcal PVE (SPVE) stems from its observed inhibitory impact on planktonic/replicating bacteria, which has been shown in models of infection involving foreign bodies, orthopedic prostheses, and vascular implants [16–18]. The validity of this approach has been questioned, with recent data showing no difference in clinical outcomes in cases treated with or without adjunctive rifampin/gentamicin for SPVE [19, 20]. Rifampin's activity on biofilm may not be justifiable in the postoperative period after surgical intervention in SPVE, as supported by the notion that surgery targets a decrease or removal of biofilm burden [21].

Overall, there is a relative scarcity of data validating currently recommended combination regimens with adjunctive rifampin and gentamicin in SPVE [22].

Interestingly, our study showed higher observed rates of relapse and mortality in the combination therapy group than in the monotherapy group, although unadjusted analyses cannot rule out the possible confounding influences of factors such as age, IDU, and HD. Statistical imbalances between these groups revealed a tendency for patients receiving combination therapy to be older, have an increased prevalence of HD, and a slightly lower prevalence of IDU as compared with patients receiving monotherapy. However, even after correcting for imbalances by incorporating these risk factors into the PS and then weighting the data to make the groups comparable, the treatment differences in study outcomes remained consistent.

Contemporary data report a relapse rate of 2% to 8%, with an increased risk associated with IDU, surgical intervention, prolonged bacteremia, among other factors [23–26]. IE in patients undergoing chronic HD is a known complication, frequently associated with staphylococci, synthetic grafts and venous catheters, and high mortality. While these associations have been described in older publications, there are scant data on recurrent IE in the HD population that also underwent valve surgery [27–30].

The rapid rise of early mortality and relapse noted on Kaplan-Meier curves in the combination group could raise the possibility of immortal time bias and some degree of confounding due to unmeasured covariates, despite our attempts to control for this in the PS analysis. The monotherapy and combination therapy groups were different in regard to timing of postoperative antibiotic initiation. The relative delay in time zero noted in the combination group is likely attributable to the delay in initiation of rifampin, due to enteral access issues and providers wanting to start the rifampin after blood culture clearance for fear of promoting selection of resistance. When we saw the full distribution of duration between surgery and treatment start in days for each group, the differences were not striking.

The retrospective design of our study comes with inherent measurement bias for antibiotic-related AEs and DDIs. There is an implicit limitation with PS analysis that important but unmeasured covariates may exist that could negate our findings. Most of the existing data are from studies performed in cases of *S aureus* bacteremia, SANVE, or SPVE. The strength of our study is the focus on a niche study population: patients who underwent early surgical valvular intervention for SANVE. This focus resulted in a relatively small sample size, which makes therapeutic differences more difficult to detect. Despite the small sample, however, our study did find significantly worse outcomes after surgery in patients treated with combination therapy vs monotherapy. Another strength is the use of PS-weighted analyses to facilitate fair comparisons, which showed that worse outcomes with combination therapy persisted.

CONCLUSIONS

In conclusion, we found that patients treated with a postoperative regimen with combination therapy experienced worse outcomes as compared with monotherapy for SANVE after surgical valve replacement or repair. A review of existing, albeit limited, data does not justify the use of combined gentamicin and/or rifampin for SANVE after surgical intervention. Additionally, observational and prospective studies indicate that unnecessary usage of these adjunctive agents may be harmful, consistent with our findings. Given the lack of consensus from current guidelines, we propose the utilization of prospective studies with larger cohorts to further investigate this work's question.

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

Acknowledgments. S. K., L. M. B., S. C., and D. C. D. contributed to the conception and design of this study. S. K., J. A. Q.-M., M. C. B., and J. C. O. contributed to data extraction. Statistical design and analysis were performed by B. D. L. Figures were created by B. D. L. and S. K. All authors contributed significantly to the data analysis, writing, and review of the manuscript and approved its submission.

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Access to data. Data (supplementary tables and figures) cited in text are available in the supplementary material.

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References

1. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation **2015**; 132:1435–86.
2. Delgado V, Ajmone Marsan N, de Waha S, et al. 2023 ESC guidelines for the management of endocarditis. Eur Heart J **2023**; 44:3948–4042.
3. Lebeaux D, Fernández-Hidalgo N, Pilmis B, et al. Aminoglycosides for infective endocarditis: time to say goodbye? Clin Microbiol Infect **2020**; 26:723–8.
4. Pallotto C, Bolla C, Penpa S, et al. Adherence to 2015 ESC guidelines for the treatment of infective endocarditis: a retrospective multicentre study (LEIOT study). Antibiotics (Basel) **2023**; 12:705.
5. Falagas ME, Matthaiou DK, Bliziotis IA. The role of aminoglycosides in combination with a beta-lactam for the treatment of bacterial endocarditis: a meta-analysis of comparative trials. J Antimicrob Chemother **2006**; 57:639–47.

6. Thwaites GE, Scarborough M, Szubert A, et al. Adjunctive rifampicin to reduce early mortality from *Staphylococcus aureus* bacteraemia: the ARREST RCT. Health Technol Assess **2018**; 22:1–148.
7. Riedel DJ, Weekes E, Forrest GN. Addition of rifampin to standard therapy for treatment of native valve infective endocarditis caused by *Staphylococcus aureus*. Antimicrob Agents Chemother **2008**; 52:2463–7.
8. Cosgrove SE, Vigliani GA, Campion M. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. Clin Infect Dis **2009**; 48:713–21.
9. Fowler VG, Durack DT, Selton-Suty C, et al. The 2023 Duke–International Society for Cardiovascular Infectious Diseases criteria for infective endocarditis: updating the modified Duke criteria. Clin Infect Dis **2023**; 77:518–26.
10. Fadel HJ, Tleyjeh IM, Steckelberg JM, Wilson WR, Baddour LM. Evaluation of antibiotic therapy following valve replacement for native valve endocarditis. Eur J Clin Microbiol Infect Dis **2009**; 28:1395–8.
11. Drinkovic D, Morris AJ, Pottumarthy S, MacCulloch D, West T. Bacteriological outcome of combination versus single agent treatment for staphylococcal endocarditis. J Antimicrob Chemother **2003**; 52:820–5.
12. Watanakunakorn C, Glotzbecker C. Enhancement of the effects of anti-staphylococcal antibiotics by aminoglycosides. Antimicrob Agents Chemother **1974**; 6:802–6.
13. Sande MA, Johnson ML. Antimicrobial therapy of experimental endocarditis caused by *Staphylococcus aureus*. J Infect Dis **1975**; 131:367–75.
14. Korzeniowski O, Sande MA. Combination antimicrobial therapy for *Staphylococcus aureus* endocarditis in patients addicted to parenteral drugs and in nonaddicts: a prospective study. Ann Intern Med **1982**; 97:496–503.
15. Buchholtz K, Larsen CT, Hassager C, Bruun NE. Severity of gentamicin's nephrotoxic effect on patients with infective endocarditis: a prospective observational cohort study of 373 patients. Clin Infect Dis **2009**; 48:65–71.
16. Saeed K, Bal AM, Gould IM, et al. An update on *Staphylococcus aureus* infective endocarditis from the International Society of Antimicrobial Chemotherapy (ISAC). Int J Antimicrob Agents **2019**; 53:9–15.
17. Saeed K, Dryden M, Bassetti M, et al. Prosthetic joints: shining lights on challenging blind spots. Int J Antimicrob Agents **2017**; 49:153–61.
18. Zimmerli W, Widmer AF, Blatter M, Frei R, Ochsner PE; Foreign-Body Infection (FBI) Study Group. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. JAMA **1998**; 279: 1537–41.
19. Le Bot A, Lecomte R, Gazeau P, et al. Is rifampin use associated with better outcome in staphylococcal prosthetic valve endocarditis? A multicenter retrospective study. Clin Infect Dis **2021**; 72:e249–55.
20. Ramos-Martínez A, Muñoz Serrano A, de Alarcón González A, et al. Gentamicin may have no effect on mortality of staphylococcal prosthetic valve endocarditis. J Infect Chemother **2018**; 24:555–62.
21. Shrestha NK, Shah SY, Wang H, et al. Rifampin for surgically treated staphylococcal infective endocarditis: a propensity score–adjusted cohort study. Ann Thorac Surg **2016**; 101:2243–50.
22. Ryder JH, Tong SYC, Gallagher JC, et al. Deconstructing the dogma: systematic literature review and meta-analysis of adjunctive gentamicin and rifampin in staphylococcal prosthetic valve endocarditis. Open Forum Infect Dis **2022**; 9: ofac583.
23. Agrawal A, Ul Hassan Virk H, Riaz I, et al. Predictors of 30-day re-admissions in patients with infective endocarditis: a national population-based cohort study. Rev Cardiovasc Med **2020**; 21:123–7.
24. Calderón-Parra J, Kestler M, Ramos-Martínez A, et al. Clinical factors associated with reinfection versus relapse in infective endocarditis: prospective cohort study. J Clin Med **2021**; 10:748.
25. Scheggi V, Merilli I, Marcucci R, et al. Predictors of mortality and adverse events in patients with infective endocarditis: a retrospective real-world study in a surgical centre. BMC Cardiovasc Disord **2021**; 21:28.
26. Citro R, Chan K-L, Miglioranza MH, et al. Clinical profile and outcome of recurrent infective endocarditis. Heart **2022**; 108:1729–36.
27. McCarthy JT, Steckelberg JM. Infective endocarditis in patients receiving long-term hemodialysis. Mayo Clin Proc **2000**; 75:1008–14.
28. Doulton T, Sabharwal N, Cairns HS, et al. Infective endocarditis in dialysis patients: new challenges and old. Kidney Int **2003**; 64:720–7.
29. Schubert C, Moosa MR. Infective endocarditis in a hemodialysis patient: a dreaded complication. Hemodial Int **2007**; 11:379–84.
30. Chaudry MS, Carlson N, Gislason GH, et al. Risk of infective endocarditis in patients with end stage renal disease. Clin J Am Soc Nephrol **2017**; 12:1814–22.