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Addition of Rifampin to Standard Therapy for Treatment of Native Valve Infective Endocarditis Caused by *Staphylococcus aureus*▽

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Staphylococcus aureus **is a common cause of native valve infective endocarditis (IE). Rifampin is often added to traditional therapy for the management of serious *S. aureus* infections. There are no large, prospective studies documenting the safety and efficacy of adjunctive therapy with rifampin for treatment of native valve *S. aureus* IE. We reviewed all cases of definite native valve *S. aureus* IE confirmed by modified Duke criteria in a large urban hospital between 1 January 2004 and 31 December 2005. A retrospective cohort analysis was used to assess the impact of the addition of rifampin to standard therapy. There were 42 cases of *S. aureus* IE treated with the addition of rifampin and 42 controls. Cases received a median of 20 days of rifampin (range, 14 to 48 days). Rifampin-resistant *S. aureus* isolates developed in nine cases who received rifampin before clearance of bacteremia (56%), while significant hepatic transaminase elevations also occurred in nine cases, all of whom had hepatitis C infection. Unrecognized significant drug-drug interactions with rifampin occurred frequently (52%). Cases were more likely to have a longer duration of bacteremia (5.2 versus 2.1 days; $P < 0.001$) and were less likely to survive (79% versus 95%; $P = 0.048$) than controls. Our results suggest that the potential for hepatotoxicity, drug-drug interactions, and the emergence of resistant *S. aureus* isolates warrants a careful risk-benefit assessment before adding rifampin to standard antibiotic treatment of native valve *S. aureus* IE until further clinical studies are performed.**

Staphylococcus aureus is now the most common cause of infective endocarditis (IE) in many parts of the world (8). While *S. aureus* IE has long been associated with significant morbidity and mortality (8, 23, 25), its management is now further complicated by the rising incidence of methicillin-resistant *S. aureus* (MRSA) strains causing disease (16), as well as the limited treatment options for MRSA (17, 22).

Rifampin has potent in vitro antistaphylococcal activity, though resistance to it invariably develops when it is used alone in *S. aureus* infections (15, 28). The addition of rifampin to traditional therapy for *S. aureus* IE has its basis in several areas: (i) current recommendations for treatment of staphylococcal infections of prosthetic valves (both *S. aureus* and coagulase-negative staphylococci) (1); (ii) animal studies of experimental foreign-body infections with *S. aureus* (2, 20); (iii) case reports of the benefit of adding rifampin to standard therapy for *S. aureus* IE (5, 21); and (iv) oral antibiotic regimens for uncomplicated right-sided *S. aureus* IE in injection drug users (4, 13). In the only prospective trial of rifampin as an adjunct to traditional therapy for *S. aureus* IE, rifampin combined with vancomycin for MRSA IE was not beneficial either for increasing survival or for decreasing the duration of bacteremia; however, their study sample was too small to endorse one regimen over the other (18). The routine addition of rifampin to standard therapy thus has not been recommended for the treatment of native valve *S. aureus* IE (1).

Despite the lack of endorsement of rifampin as an adjunct to therapy in the most recent guidelines for management of *S. aureus* IE (1), physicians may still add this agent when patients do not respond adequately to conventional antibiotic therapy (11). However, clinicians may neglect to identify the frequent and significant drug interactions associated with rifampin resulting from the drug's potent induction of the cytochrome P-450 system (6). In addition, possible adverse effects from rifampin alone or from increased toxicity from other interacting drugs may make the regular use of this agent potentially hazardous. Lastly, resistance to rifampin can develop rapidly in *S. aureus* (15, 28), and this process has been characterized at the genetic level after a single dose of rifampin for an MRSA isolate (24).

At our institution, we noted frequent utilization of rifampin in the management of native valve *S. aureus* IE, and we performed a retrospective review of all cases of *S. aureus* IE in which rifampin was added to traditional therapy in order to evaluate the safety and efficacy of this regimen.

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MATERIALS AND METHODS

Location. The University of Maryland Medical Center (UMMC) is a 600-bed tertiary care hospital in inner-city Baltimore, MD. It averages greater than 100 cases of proven IE annually, and *S. aureus* causes >75% of these cases. Cases

TABLE 1. Baseline demographic characteristics of cases and controls

Characteristic	Value for group		*P* value
	Cases	Controls	
Total no. of subjects	42	42	
Median age [yr (range)]	47 (26–89)	48 (22–80)	1.0
Male sex [no. (%)]	23 (55)	25 (60)	1.0
African-American race [no. (%)]	20 (48)	21 (50)	1.0
HIV infected [no. (%)]	5 (12)	10 (24)	0.3
Hepatitis C antibody positive [no. (%)]	20 (48)	20 (48)	1.0
Injection drug use [no. (%)]	21 (50)	27 (64)	0.19
Comorbid conditions [no. (%)]			
Diabetes	5 (12)	6 (14)	0.75
End-stage renal disease	9 (21)	11 (26)	0.6
Cirrhosis	0 (0)	2 (5)	0.16
Malignancy	5 (12)	3 (7)	0.50

usually include a large number secondary to injection drug use, as well as those referred to UMMC for further care from neighboring hospitals.

Patients and data collection. To determine the effect of rifampin on patients with native valve *S. aureus* IE, we performed a retrospective, matched-cohort study based on exposure to rifampin. Cases received at least one dose of rifampin. The control group was matched to cases by time of diagnosis. Matching was done in this way to limit confounders and differences between the two groups to the use of rifampin.

We identified all patients with *S. aureus* bacteremia admitted to UMMC between 1 January 2004 and 31 December 2005. Cases and controls were identified by searching the microbiology laboratory database for blood cultures growing *S. aureus*. All cases and controls had definite *S. aureus* IE based on the modified Duke criteria (19).

Both right- and left-sided IE were included in the analysis. We excluded all cases of prosthetic-valve IE (where use of rifampin is recommended in recent guidelines [1]). Other exclusion criteria were *S. aureus* bacteremia resulting from another clearly defined source, e.g., infected orthopedic hardware, arterial vascular grafts, or automatic implantable cardioverter defibrillators.

This protocol was approved by the Institutional Review Board of the University of Maryland.

Definitions. The primary outcome of interest was the microbiological and clinical response to the addition of rifampin to standard therapies in the treatment of native valve *S. aureus* IE. The factors examined included treatment outcome, duration of bacteremia (defined as the duration of bacteremia from the first day of bacteremia), emergence of rifampin resistance, drug interactions, and adverse drug effects. A successful treatment outcome was defined as survival at 30 days or hospital discharge (whichever occurred earlier) and clearance of bacteremia. Failure was defined (similar to other studies [7]) as recurrent bacteremia (any positive blood culture with the same organism within 6 weeks of completing therapy) or the development of rifampin resistance in any *S. aureus* isolate obtained, defined as an MIC of ≥ 2 μg/dl for rifampin.

The primary adverse drug event of interest was an elevation of hepatic transaminase levels (aspartate aminotransferase and alanine aminotransferase) to ≥ 5 times the baseline level. We also assessed whether prescribers recognized and adjusted other medications after the addition of rifampin, especially human immunodeficiency virus (HIV) protease inhibitors, warfarin, methadone, and phenytoin.

Statistical analysis. The statistical analysis involved assessing continuous variables (e.g., length of therapy and bacteremia clearance) with the Mann-Whitney U test, while categorical variables (e.g., mortality) were assessed with either chi-square analysis or Fisher's exact test, with a P value of <0.05 considered significant. All data and statistical analyses were performed using SPSS software, version 15 (SPSS; Chicago, IL).

RESULTS

In the review period, a total of 84 cases met the inclusion criteria for analysis. There were 42 cases of *S. aureus* IE treated with the addition of rifampin and 42 controls with *S. aureus* IE treated without the addition of rifampin. Demographic characteristics are shown in Table 1. Baseline demographic characteristics were similar between the two groups. Hepatic and renal function and the number of patients with either end-stage renal or liver disease were similar between the groups.

TABLE 2. Clinical characteristics of cases and controls[a]

Characteristic	Value for group		*P* value
	Cases	Controls	
Total no. of subjects	42	42	
Median WBC [cells/mm^3 (range)]	12.0 (0.5–39.2)	12.6 (1.3–10.7)	0.71
Median creatinine [mg/dl (range)]	1.6 (0.6–10.4)	1.1 (0.3–10.5)	0.12
Median AST [U/I (range)][b]	29 (14–137)	40 (7–156)	0.14
Median ALT [U/I (range)][b]	30 (12–189)	46 (15–165)	0.06
Median total bilirubin [mg/dl (range)]	0.6 (0.1–2.9)	0.8 (0.1–2.3)	0.55
Median APACHE II score (range)[c]	17 (7–31)	13 (6–28)	0.08
Type of IE [no. (%)]			
Right sided	25 (60)	30 (71)	0.3
Left sided only	14 (33)	3 (7)	0.003
Right and left sided	3 (7)	9 (21)	0.18
Any left sided	17 (40)	12 (29)	0.25
MSSA [no. (%)]	10 (24)	8 (19)	0.6
MRSA [no. (%)]	32 (76)	34 (81)	0.9
Metastatic complications [no. (%)]			
None	9 (21)	11 (26)	0.8
One site	21 (50)	22 (52)	0.8
Two sites	10 (24)	8 (19)	0.6
Three sites	2 (5)	1 (2)	0.6
Metastatic infection sites [no. (%)]			
Central nervous system	14 (33)	6 (14)	0.1
Pulmonary	17 (40)	20 (48)	0.4
Bone and joint[d]	11 (26)	12 (29)	0.9
Spleen	2 (5)	4 (10)	0.4
Primary antibiotic [no. (%)][e]			
Beta-lactam	7 (17)	5 (12)	0.6
Vancomycin	34 (81)	36 (86)	0.8
Rifampin treatment [days (range)][f]	20 (14–48)	0	NA
Gentamicin treatment [no. (%)][g]	34 (81)	7 (17)	<0.001

[a] WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; APACHE, acute physiology and chronic health evaluation; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable.

[b] AST and ALT levels are expressed in U/I.

[c] APACHE II scores were tabulated at the first day of bacteremia.

[d] Bone and joint infections included vertebral osteomyelitis and discitis and septic joints.

[e] One patient in the case and control groups received daptomycin; all beta-lactam antibiotics were nafcillin except with one control patient, who received cefazolin.

[f] Rifampin was added a median of 3 days (range, 0 to 19 days) after treatment initiation; 16 of 42 patients were still bacteremic at the time rifampin was added.

[g] Low-dose gentamicin (1 mg/kg of body weight or equivalent depending on renal function).

Clinical characteristics of cases and controls are shown in Table 2. The numbers of cases compared to controls with MRSA (32 versus 34; $P = 0.9$) and right-sided IE (25 versus 30; $P = 0.3$) were similar in both groups. The number of cases compared to controls with any left-sided IE involvement was similar (17 versus 12; $P = 0.25$) (Table 2). The number and sites of metastatic infections were also similar between the two groups (Table 2).

The primary antibiotic therapy was vancomycin in 81% of cases and for 86% of controls ($P = 0.8$), while nafcillin was used in 17% of cases and for 12% of controls ($P = 0.6$). One patient each in the control group received daptomycin and cefazolin, while one patient in the rifampin group received

TABLE 3. Adverse effects of rifampin for cases and controls

Characteristic or effect	Value for group		*P* value
	Cases	Controls	
Total no. of subjects	42	42	
Rifampin-resistant isolates [no. (%)][a]	9 (21)	0 (0)	<0.001
Median time to rifampin resistance[b] [days (range)]	16 (11–26)	NA[d]	NA
Elevated transaminases, ≥5 × baseline [no. (%)]	9 (21)	1 (2)	0.014
Drug interactions [no. (%)][c]	22 (52)	0 (0)	<0.001

[a] All nine isolates were from patients who were bacteremic at initiation of rifampin treatment.
[b] Nine isolates were analyzed.
[c] Drug interactions occurred with methadone (nine cases), warfarin (four cases), protease inhibitors (three cases), antifungal agents (e.g., fluconazole [three cases], voriconazole [one case]), and antiepileptic agents (e.g., phenytoin [two cases]).
[d] NA, not applicable.

TABLE 4. Clinical outcomes for cases and controls

Characteristic or outcome	Value for group		*P* value
	Cases	Controls	
Total no. of subjects	42	42	
Median length of bacteremia [days (range)]	5.2 (1–26)	2.1 (1–8)	<0.001
Requirement of hemodialysis [no. (%)]	8 (19)	7 (17)	0.8
Valve surgery [no. (%)]	9 (21)	2 (5)	0.03
Relapse [no. (%)]	9 (21)	4 (9)	0.22
Median length of stay [days (range)]	21.3 (2–66)	14.7 (4–62)	0.09
Survival [no. (%)]	33 (79)	40 (95)	0.048

daptomycin. More cases received gentamicin (81%) than did controls (17%) ($P < 0.001$). Cases received a median of 20 days of rifampin (range, 14 to 48 days), and rifampin was added a median of 3 days (range, 0 to 19 days) after treatment initiation; 16 of 42 patients (38%) were still bacteremic at the time rifampin was added.

The adverse effects of rifampin in cases compared to controls are in Table 3. Rifampin-resistant *S. aureus* isolates were detected in 9 of 42 cases (21%), and this occurred a median of 16 days after the addition of rifampin to the regimen (range, 11 to 26 days). All nine patients found to have rifampin-resistant *S. aureus* isolates were still bacteremic at the time rifampin was added.

Cases who received rifampin were more likely to have elevated hepatic transaminases ($n = 9$) than were controls ($n = 1$) ($P = 0.014$); this result occurred only in patients with hepatitis C virus (HCV) infection who had marginal elevations of hepatic transaminases at baseline. Unrecognized significant drug interactions with rifampin occurred in more than half of the cases, most commonly with methadone (nine cases), warfarin (four cases), and HIV protease inhibitors (three cases). Other interactions were with antifungal agents (e.g., fluconazole [three cases] or voriconazole [one case]) and antiepileptic agents (e.g., phenytoin [two cases]).

Cases were more likely to have a longer median total duration of bacteremia (5.2 days; range, 1 to 26 days) than controls (2.1 days; range, 1 to 8 days) ($P < 0.001$) (Table 4). On closer analysis of the cases, 16 of the 42 were prescribed rifampin before clearance of bacteremia had occurred. When comparing the median duration of bacteremia of these 16 cases to results for the control group (2.1 days), we found that the median duration of bacteremia in those 16 cases before addition of rifampin was 4.0 days (1 to 7 days; $P = 0.21$) and the median duration of bacteremia after the addition of rifampin was 4.0 days (1 to 19 days; $P = 0.004$), with the latter highly significant compared to findings for controls. No differences in outcomes were found after analysis by the primary antibiotic received by cases or controls (data not shown).

Cases were more likely to require surgery (nine versus zero; $P = 0.03$), and there was a trend toward higher rates of relapse (21% versus 9%; $P = 0.22$). Cases were less likely to have survived the episode of *S. aureus* IE than controls (79% versus 95%; $P = 0.048$).

DISCUSSION

Despite limited data regarding the utility of rifampin in the treatment of native valve *S. aureus* IE, our study indicates that it is still frequently used for this infection at our institution. A recent survey suggests that this practice appears to occur frequently (11). Despite using rifampin as an adjunctive treatment in combination with other therapy for native valve *S. aureus* IE, there was a high incidence of the development of *S. aureus* isolates resistant to rifampin, especially if patients were bacteremic at initiation (9 of 16 patients [56%]). HCV-infected patients who received rifampin often developed significant elevations of their hepatic transaminases. Additionally, unrecognized significant drug interactions were often overlooked (52%). Lastly, cases receiving rifampin with standard antibiotic therapy may have been more severely ill, since they had longer durations of bacteremia, were more likely to require surgery, and were less likely to survive than controls.

We found that rifampin is often added to standard antibiotic therapy for the treatment of native valve *S. aureus* IE at our institution. The most recent guidelines from the American Heart Association/Infectious Diseases Society of America for the treatment of native valve *S. aureus* IE currently do not recommend adding this agent to standard therapy, and in fact, they recommend against routine use of rifampin for this infection (1). However, the review by Hawkins et al. (12) and the survey by Hageman et al. (11) suggest that clinicians are still likely to add rifampin to patients who appear severely ill or have protracted bacteremia. Continued use of rifampin for this indication may reflect a perceived benefit for more-complicated *S. aureus* infections, such as left-sided, native valve IE with prolonged bacteremia.

The development of *S. aureus* isolates resistant to rifampin is a well-recognized disadvantage of its use for *S. aureus* infections (15, 28), and it has recently been shown at the genetic level to occur after only a single dose of rifampin in a patient with MRSA endocarditis (24). In our study, rifampin-resistant isolates developed in 56% of cases who were bacteremic at initiation of rifampin therapy, while there were no resistant isolates in cases who received rifampin after clearance of bacteremia. It is possible that more cases actually acquired rifampin-resistant isolates but were not detected, since follow-up

cultures were performed only as clinically indicated and not systematically. This problem has been noted in other studies in which rifampin was added to standard therapy for serious *S. aureus* infections (14, 31). The optimal timing for addition of rifampin (e.g., after clearance of bacteremia) to reduce the risk of developing resistance has not been shown prospectively, but some experts recommend waiting to add rifampin until after blood cultures have cleared (3), and our data support this approach.

Rifampin has numerous potential adverse effects, including anaphylaxis, gastrointestinal symptoms, hemolytic anemia, thrombocytopenia, acute renal failure, uveitis, and rash, in addition to hepatic toxicity (9, 30). In this study, patients with elevations in hepatic transaminases had underlying HCV infection and baseline elevations above the upper limit of normal, which may have predisposed them to this adverse effect; therefore, rifampin use should be initiated with caution in this patient population. Other studies that have added rifampin to standard therapy have also seen higher incidences of elevated transaminases or hepatitis in the rifampin groups (18, 26). Without clear documentation in most patient charts, it was not possible to determine whether rifampin led to other adverse effects.

Because rifampin is a potent inducer of the cytochrome P-450 system, potential drug-drug interactions are numerous (6). We found that unrecognized drug-drug interactions occurred in more than half (52%) of the patients in the rifampin group. Failure by clinicians to recognize rifampin's many drug-drug interactions could lead to higher rates of toxicity from rifampin itself or from the other drugs whose action is potentiated by decreased clearance and subsequently increased serum levels.

We cannot conclude whether the addition of rifampin to standard therapy for native valve *S. aureus* IE affects patient outcomes. Our data suggest that patients who received rifampin were less likely to have survived the episode of *S. aureus* IE than those who did not. One possible explanation for this finding is that patients who received rifampin had a more severe illness than those who did not; APACHE II scores were higher in rifampin-treated patients, though this difference was not statistically significant. When outcomes were analyzed by APACHE II scores, however, no difference between groups was found. In a retrospective study, it is difficult to isolate rifampin's effect on the outcome from other variables. The prospective randomized trial by Levine et al. (18) also showed that rifampin plus vancomycin was no better than vancomycin alone for treatment of MRSA IE, though that trial was likely underpowered to detect a true difference. One possibility for a lack of benefit from rifampin is that there is a negative interaction between the standard antibiotic therapy and rifampin such that serum levels of the former are reduced or its serum bactericidal activity for *S. aureus* is decreased. This possibility has been illustrated in vitro in previous studies with oxacillin (29, 32), nafcillin (10), vancomycin (10, 27), and teicoplanin (10).

We also found that patients who received rifampin had significantly longer total durations of bacteremia than did controls (median of 5.2 versus 2.1 days; $P < 0.001$). When these results were analyzed by whether bacteremia had cleared at the time of rifampin initiation, cases receiving rifampin before clearance of bacteremia still had statistically significantly longer durations of bacteremia than controls (median of 4.0 days versus 2.1 days; $P = 0.004$). Levine et al. (18) also found a longer median duration of bacteremia (9 versus 7 days) in the rifampin group in their prospective, randomized controlled trial, though this trend was not statistically significant. A recent retrospective, case-control study comparing outcomes of patients with persistent *S. aureus* bacteremia (>7 days) to those with nonpersistent *S. aureus* bacteremia (<3 days) also found that patients in the former group were more likely to receive either rifampin or gentamicin (odds ratio = 8.10), although they did not clarify the proportion receiving each drug (12). Thus, in our retrospective study, it is difficult to separate the effect of rifampin on the duration of bacteremia from the severity of illness; the fact that cases receiving rifampin before clearance of bacteremia still had significantly longer durations of bacteremia than controls may indicate that severity of illness played less of a role.

There are several potential limitations to this study. First, these results are based on patients from a single institution, and so the use of rifampin at our institution may not be generalizable to other institutions. The matched-cohort design of this study would have benefited from a larger control group to reduce confounding variables, especially confounding by indication, whereby patients with longer durations of bacteremia were the ones receiving rifampin; furthermore, a prospective trial would have made the findings more robust. Also, our study was not large enough to discern a difference between outcomes for patients with methicillin-sensitive *S. aureus* versus MRSA IE. More cases than controls received gentamicin, which also may have impacted the results—the fact that cases were more likely to have been prescribed gentamicin may be an indicator that they appeared sicker to clinicians; however, gentamicin is not generally noted to be hepatotoxic or to interfere with the cytochrome P-450 system, and so the toxicity and drug interaction findings of this study were unlikely to be affected by its use. Lastly, we could not determine the reasoning for why rifampin was added to standard therapy, because this information was rarely if ever documented by the treating clinicians in the patient's medical chart.

Our results suggest that adding rifampin to standard antibiotic therapy for the treatment of native valve *S. aureus* IE should be done with caution, especially if the patient has not cleared the bacteremia or is HCV infected. Potential problems of hepatotoxicity, drug-drug interactions, and the emergence of resistant *S. aureus* isolates should prompt a careful risk-benefit assessment before adding rifampin to standard antibiotic therapy for the treatment of native valve *S. aureus* IE until further clinical studies are performed.

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