Right-Sided *Staphylococcus aureus* Endocarditis in Intravenous Drug Abusers: Two-Week Combination Therapy

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Study Objective: To determine the efficacy of short-course combination regimens for selected cases of *Staphylococcus aureus* endocarditis in intravenous drug abusers.

Design: Open study of nafcillin and tobramycin or vancomycin and tobramycin administered for 2 weeks with no further therapy.

Setting: County hospital.

Patients: Consecutive sample of 53 intravenous drug abusers with relatively uncomplicated right-sided *S. aureus* endocarditis, defined by clinical and echocardiographic criteria, and without renal insufficiency, extrapulmonary metastatic infectious complications requiring prolonged therapy or surgery for cure, meningitis, methicillin-resistant organism, aortic or mitral valve involvement, or pregnancy.

Interventions: Nafcillin, 1.5 g intravenously every 4 hours, plus tobramycin, 1 mg/kg body weight intravenously every 8 hours, administered for 2 weeks. Vancomycin, 30 mg/kg per day intravenously, in two or three divided doses, was used instead of nafcillin for patients allergic to penicillin.

Measurements and Main Results: Forty-seven of 50 patients (94%; 95% CI, 87 to 99+) treated with the nafcillin and tobramycin combination were cured. Only 1 of 3 patients treated with vancomycin plus tobramycin (33%, 95% CI, 2 to 86) was cured.

Conclusions: Selected patients with *S. aureus* endocarditis can be treated safely and effectively with a 2-week course of nafcillin plus tobramycin. Only one of three patients treated with vancomycin plus tobramycin was cured, but three patients are too few to define with confidence the efficacy of this regimen.

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The recommended therapy for *Staphylococcus aureus* endocarditis is 4 to 6 weeks of a semi-synthetic penicillin, a cephalosporin, or vancomycin (1-3). Combinations of these drugs with an aminoglycoside are more rapidly bactericidal in vitro and in animal models of endocarditis than are the single agents (4-6). However, such combinations given in a 4- to 6-week regimen have not proved superior to single-drug regimens for the treatment of *S. aureus* endocarditis in humans (7-9).

Antimicrobial combinations that rapidly eradicate *S. aureus* might be effective in courses of therapy shorter than the conventional 4 to 6 weeks. We therefore studied 2-week combination therapy consisting of either nafcillin or vancomycin plus tobramycin for right-sided *S. aureus* endocarditis in intravenous drug abusers. We studied these patients because staphylococcal endocarditis in intravenous drug abusers is well characterized and has a relatively good prognosis (10-12). The often disruptive behavior of intravenous drug abusers in the hospital, problems of compliance with prolonged treatment regimens, and the difficulty in maintaining prolonged intravenous access also make shorter courses of therapy an attractive option in these persons.

Materials and Methods

Patient Selection and Treatment

In this open study, to minimize selection bias, we evaluated for inclusion in the study every patient with suspected staphylococcal endocarditis admitted to San Francisco General Hospital Medical Center between August 1983 and September 1987. Patients who had two or more blood cultures reported as growing either gram-positive cocci in clusters or *S. aureus* were identified from the records kept by the clinical microbiology laboratory. The chart of each prospective patient was reviewed to confirm the presence of the entry criteria. Patients were eligible for the study if they were intravenous drug abusers, if the infection was community acquired (that is, suspected infection was the reason for hospitalization), and if two or more blood cultures were positive for *S. aureus*. All patients were enrolled unless they had a complication or contraindication specified in the exclusionary criteria.

Patients were excluded from enrollment if any one of several criteria was met: refusal to give informed consent; allergy to study drugs; serum creatinine level of 220 μmol/L or more; presence of other infectious complications (for example, osteomyelitis, pericarditis, spinal epidural abscess) requiring prolonged courses of therapy (that is, 4 to 6 weeks) or surgery for cure; meningitis with positive cerebrospinal fluid cultures; methicillin-resistant clinical isolate; evidence of mitral or aortic valve infection either by clinical examina-

tion (the presence of a characteristic aortic or mitral valve murmur, or systemic embolic events, including cutaneous stigmata because of their strong association with left-sided involvement [11]), or by echocardiographic examination (signs of mitral or aortic insufficiency or vegetations); or pregnancy. Patients were diagnosed with osteomyelitis if they had focal bone pain or tenderness and evidence of bone infection at the site by technecium-99 bone scan, gallium scan, or roentgenographic studies.

The patients lacking exclusionary criteria were enrolled in the study after informed consent was obtained. The protocol therapy was either nafcillin, 1.5 g intravenously every 4 hours, or vancomycin, 30 mg/kg body weight per day intravenously in two or three divided doses plus tobramycin 1 mg/kg intravenously every 8 hours.

Patients in the study were examined daily for development of the infectious complications listed above. Echocardiographic studies were done usually during the first week to assess mitral or aortic valve involvement. Patients found to have infectious or valvular complications satisfying exclusionary criteria were dropped from the study and treated with standard regimens. Patients who developed azotemia (a serum creatinine level of 220 μmol/L or greater) were also dropped from the study and treated with standard therapy. The remaining patients were treated with combination therapy for 14 days counting from the first dose of aminoglycoside.

The use of other antibiotics was permitted until blood cultures confirmed infection by a susceptible strain of *S. aureus*. Four patients received vancomycin instead of nafcillin for the first 24 to 96 hours because of initial uncertainty about the methicillin-susceptibility of the isolate. Five patients received gentamicin instead of tobramycin for 1 or 2 days and four patients received either ampicillin or penicillin for 1 day. Two patients received rifampin for 1 day. One patient received cefuroxime for 1 day; one, trimethoprim-sulfamethoxazole for 1 day; and one, erythromycin and cefamandole for 1 day.

Blood samples for peak tobramycin levels were obtained 30 minutes after tobramycin infusion. Blood samples for trough tobramycin levels were obtained 8 hours after infusion. Measurements were done in the clinical laboratories by radioimmunoassay.

Episodes of *S. aureus* bacteremia were classified as definite, probable, or possible right-sided endocarditis. Definite right-sided endocarditis was defined by the presence of tricuspid valvular vegetations (that is, an echogenic, mobile mass attached to the valve or perivalvular structures) on echocardiographic studies. Probable right-sided endocarditis was defined by a chest roentgenogram showing pulmonary infiltrates (with or without cavitation) or effusion, or by the presence of a murmur of tricuspid insufficiency (a systolic murmur located along the lower sternal border that increased in intensity with inspiration). Possible endocarditis was defined as the absence of criteria for definite or probable endocarditis and no identifiable extracardiac focus of infection as the source of the bacteremia.

Follow-up Evaluation for Cure

Patients completing the prescribed 2-week course of therapy were discharged on no antibiotics. Follow-up visits were scheduled at 2 weeks and 4 to 6 weeks after the end of therapy. At the 2-week visit, a complete physical examination was done, as well as a complete blood count and differential, electrolytes, serum blood urea nitrogen and serum creatinine levels, chest roentgenogram, and two blood cultures. At the 4-week visit, the physical examination was repeated and two more blood cultures were done. A bacteriologic cure was defined as the eradication of *S. aureus* from the blood 4 weeks after the end of therapy. For those patients for whom blood culture results were unavailable at 4 weeks or later after the end of therapy, clinical cure was defined as the absence of signs or symptoms of endocarditis for 2 months.

Data Analysis

Parametric data are expressed as mean ± SD. The 95% CIs for proportions were calculated using an approximation of the standard deviation for the binomial distribution (13). The Fisher exact test was used to calculate *P* values for nonparametric data.

Results

Clinical Features

Between August 1983 and September 1987, 127 intravenous drug abusers with 140 separate episodes of *S. aureus* bacteremia were identified. All suitable candidates were enrolled for a total of 70 episodes (50% of all episodes) in 68 patients, who consented to participate and met enrollment criteria (Table 1). In 17 episodes, exclusionary criteria developed during treatment, so that 53 episodes (76%) in 51 patients were treated with 2-week combination regimens. Fifty episodes were treated with nafcillin plus tobramycin and 3 episodes in patients allergic to penicillin were treated with vancomycin plus tobramycin.

The mean age of the patients was 35 ± 7 years. Twenty-seven (53%) were female. Forty-six of the study participants (88%) used heroin, 38 (74%) used cocaine, and 9 (18%) used amphetamines. The median duration of intravenous drug use was 7.5 years. Seventeen patients (32%) had a previous history of endocarditis. The median duration of symptoms before admission was 4 days.

Chest roentgenographic abnormalities suggestive of right-sided endocarditis (infiltrates in 36 patients; septic embolic, defined as peripheral nodular densities suggestive of embolization, in 23; pleural effusion in 17; cavitation in 4; and atelectasis in 2) were present in 74% of the episodes. Tricuspid valve insufficiency murmurs were present in 25 (47%). In 26 (52%) of 49 episodes (echocardiograms could not be obtained for 4 episodes), the echocardiogram showed some abnormality (for example, right-ventricular enlargement, nonspecific increased reflectance of the tricuspid, aortic, or mitral valve, or small pericardial effusion) and 8 (16%) echocardiograms showed unequivocal tricuspid valve vegetation.

According to the criteria outlined in the Methods section, 8 episodes (15%) were definite endocarditis, 35 (66%) were probable endocarditis, and 10 (19%) were possible endocarditis. Other manifestations of endocarditis are listed in Table 2.

Blood cultures, which were taken in standard blood culture medium just before a dose, were obtained during the first 48 hours of nafcillin-tobramycin therapy from 20 patients; 19 cultures were sterile. The mean number of days of temperature 38° C or greater was 3.5 ± 3.1. In seven patients fever persisted or recurred during week 2 of therapy. All patients had extensive pulmonary disease by chest roentgenogram: four had cavitation ($P = 0.002$ compared with the 46 patients who had resolution of fevers within the first week), seven had infiltrates ($P = 0.082$), and six had effusions ($P = 0.003$). All six episodes treated with naf-

cillintobramycin were cured. The one patient with persistent fever who was treated with vancomycin-tobramycin still had positive blood cultures on days 12 and 14 of therapy.

Results of Follow-up for Cure

Nafcillin plus Tobramycin

Of 50 episodes of endocarditis, 47 (94%; CI, 87 to 99+) were cured after 2 weeks of nafcillin plus tobramycin. Forty-three were classified as bacteriologic cures and 4 as clinical cures. Of the 4 clinical cures, one patient had sterile blood cultures and was clinically well at the 2-week follow-up visit, but failed to return for the 4-week visit. A telephone conversation with the patient's mother revealed that the patient had remained well until his death from a stab wound 4 months after the end of therapy. The second patient was jailed and never returned for follow-up, but was well at 6 months after treatment. The third patient was lost to follow-up for 17 months and had been well until a second episode of tricuspid valve staphylococcal endocarditis. The fourth patient missed both follow-up appointments for blood cultures, but was seen in elective surgery clinic for an unrelated problem 2 weeks and 4 weeks after the end of therapy. According to the patient's mother and sister, this patient remained well for 5 months after therapy had been discontinued.

Three episodes were not cured after 2 weeks of nafcillin and tobramycin. All three patients had relapses with positive blood cultures for *S. aureus* within 6 to 12 days after stopping therapy. The first relapse occurred in the only patient, who was originally categorized as having possible endocarditis, whose bacteremia persisted through day 4 of treatment. At the time of the relapse, the patient proved to have infection of the tricuspid valve, based on interval appearance of a tricuspid valve vegetation on echocardiogram. Treatment of the relapse with a standard 4-week regimen was successful.

The second relapse occurred in a patient who was originally categorized as having probable endocarditis. A break in therapy occurred on days 11 through 12 because the patient was mistakenly discharged from the hospital. On readmission, the patient was given only another 4 days of nafcillin plus tobramycin to complete a 14-day course. The patient returned 6 days later with *S. aureus* bacteremia. Based on the findings of a later echocardiogram, this patient also proved to have definite tricuspid valve involvement.

The third relapse occurred in a patient categorized as having definite endocarditis. On day 12 of therapy, a soft tissue mass, thought to be a subcutaneous abscess, was discovered in the right buttock. The patient refused needle aspiration or incision and drainage and was discharged after 14 days of therapy. This patient returned 12 days later with a large abscess involving the right buttock. Cultures of fluid from this abscess and from blood grew *S. aureus*. Retreatment with a standard 4-week regimen was successful.

Long-term follow-up was available after 41 episodes in 39 patients who were cured. Twenty-six patients who were followed for periods ranging from 2.5 to 35 months remained well and free of infections requiring hospitalization.

Thirteen patients were rehospitalized for a total of 20 episodes of serious infection related to intravenous drug use. Nine patients had 14 recurrent episodes of endocarditis. Six recurrences in 5 patients were caused by *S. aureus*. These recurrences occurred 3.5, 4, 8, 17, 21, and 37 months after the first episode. The recurrences at 3.5 and 8 months were in the same patient and involved the tricuspid and mitral valves. The strain isolated from the blood at 3.5 months was a different phage-type than the original strain. This patient died from the third episode of endocarditis.

The patient with the recurrence at 4 months had sterile blood cultures at the 4-week follow-up, at which time a subcutaneous abscess was incised and drained. The recurrence was treated at another hospital so the isolate was not available for phage-typing, but the patient had been well for 4 months after the first episode. The recurrence was an acute illness that followed a period of heavy intravenous drug use. Twenty-four months after the recurrence, the patient

Table 1. *Bacteremic Episodes Due to Staphylococcus aureus in Intravenous Drug Abusers Not Treated with 2-Week Combination Therapy*

	Not Enrolled ($n=70$)	Enrolled but Dropped from Study ($n=17$)
	n	
Left-sided endocarditis	26	1
Other infections	18*	10†
No consent	8	0
Methicillin-resistant strain	5	1
Penicillin allergy	4‡	0
Pregnancy	3	0
Renal insufficiency	3	2§
Transferred or signed out	2	2
Break in therapy	0	1‖

* Osteomyelitis, 10; meningitis, 2; epidural abscess, 6.

† Osteomyelitis, 5; polymicrobial endocarditis, 3; thoracotomy for empyema, 1; arthrotomy for a septic shoulder joint, 1.

‡ Penicillin allergy became an exclusion once the vancomycin arm of the study was terminated.

§ One patient had hypocomplementemic glomerulonephritis; the other had an abrupt rise in the serum creatinine level on day 3 of therapy, coincident with administration of indomethacin.

‖ Failure to renew medications.

Table 2. *Extrapulmonary Manifestations in 53 Episodes of Right-Sided Staphylococcus aureus Endocarditis Treated with 2-Week Combination Therapy*

Manifestation	Number
Abscess/cellulitis	3
Arthritis*	2
Aseptic meningitis†	2
Glomerulonephritis	4

* Cultures, which were obtained after initiation of antibiotics, were sterile.

† Defined as $> 5 \times 10^6$L leukocytes in cerebrospinal fluid and sterile culture.

returned with polymicrobial endocarditis.

Two patients had late recurrences: one, at 17 months after the first episode and the other, at 37 months. Both were retreated with the 2-week combination regimen. One has remained well for 9 months after the second episode and the other was well for 16 months until readmission for acute *S. aureus* epidural abscess.

The patient with recurrence at 21 months was infected with a new, methicillin-resistant strain of *S. aureus.*

Vancomycin plus Tobramycin

Of the three patients treated with vancomycin plus tobramycin, one, categorized as having possible endocarditis, was cured and has remained well for the 35 months of follow-up (33%; CI, 2 to 86). The second patient, also categorized as having possible endocarditis, had a relapse with right sternoclavicular osteomyelitis. This patient complained of neck pain at the 4-week follow-up visit. One of two blood cultures obtained from femoral vein sites grew *S. aureus.* Four subsequent blood cultures were negative, but over the next month a tender mass developed over the left sternoclavicular joint. A roentgenogram showed bony destruction. Cultures obtained by needle aspiration of the mass were sterile. The patient responded to vancomycin and has remained well for more than a year after treatment for presumed osteomyelitis.

The third patient, who had probable endocarditis, remained febrile and had positive blood cultures throughout the 14 days of vancomycin-tobramycin therapy. Results of echocardiograms were repeatedly normal and repeated examinations showed no extracardiac or extrapulmonary sources of infection. Vancomycin serum concentrations were in the therapeutic range. Rifampin was added and blood cultures became sterile. Because of persistent fever after 23 days of treatment, vancomycin was discontinued and nafcillin and tobramycin were administered in addition to rifampin. Within 3 days the fevers resolved. The patient was cured after a total of 22 days of the three-drug regimen. After this second relapse in three cases, the vancomycin arm of the study was terminated.

Tobramycin Concentrations and Toxicity

The mean peak tobramycin concentration achieved following a dose of 1 mg/kg was 3.3 ± 1.0 μg/mL (range, < 1 μg/mL to 5.7). The tobramycin concentration was less than 1 μg/mL at trough in 45 of 54 samples. The baseline and end-of-therapy mean serum creatinine levels were identical, 90 ± 40 μmol/L. No patient was dropped from the study because of tobramycin nephrotoxicity (Table 1).

Two patients developed a 50% increase in the serum creatinine level to above normal values (upper limit of normal, 130 μmol/L) on day 3. One patient had evidence of glomerulonephritis with microscopic hematuria. The other patient, whose serum creatinine level rose from 90 to 130 μmol/L, had a normal urinalysis. Dosage adjustments were made in these patients to achieve a peak tobramycin concentration of 3 to 4 μg/mL.

Discussion

Two weeks of nafcillin and tobramycin in combination cured 94% (CI, 87 to 99+) of 50 episodes of right-sided *S. aureus* endocarditis in intravenous drug abusers. Two of the three failures were associated with management errors (break in therapy and failure to drain an abscess); had these errors not occurred the results might have been even better.

Three studies (7-9) failed to show an advantage of combination therapy compared with single-drug therapy for *S. aureus* endocarditis when the total length of therapy was 4 to 6 weeks. We have shown that combination therapy can be used successfully in a short-course regimen of 2 weeks instead of 4 to 6 weeks. The 94% cure rate compares favorably with the 96% cure rate reported for 4-week therapy for right-sided *S. aureus* endocarditis in intravenous drug abusers (2). In the largest study of *S. aureus* endocarditis (9), in which the effect of adding gentamicin for 2 weeks to a 4- to 6-week regimen of nafcillin was studied, 78 patients were enrolled and 70 survived to complete therapy. Sixty-eight of these 70 patients were cured (97%; CI, 93 to 99+). Now that a 2-week combination regimen has been shown to be effective for selected cases of *S. aureus* endocarditis, future studies directly comparing 2-week combination regimens to 4-week regimens may be considered.

Single-agent therapy for endocarditis (14) or serious staphylococcal disease (15-17) for periods of less than 3 or 4 weeks is known to have an unacceptable failure rate; therefore, a single-drug regimen of nafcillin was not studied. Because the length of therapy was only 2 weeks, we selected combination regimens that were rapidly bactericidal against *S. aureus* in vitro and in animal models of endocarditis (4-6). Clinical experience with combination regimens for enterococcal and viridans streptococcal endocarditis also supported the choice of these regimens (18).

The selection criteria used in this study permitted identification of patients who had no primary or metastatic foci of infection that would lead to relapse (for example, osteomyelitis). The importance of this principle was emphasized by the patient whose relapse occurred because of an undrained abscess. Because left-sided endocarditis was excluded, the selection criteria also identified patients who were at low risk for serious complications such as congestive heart failure or strokes. This approach is analogous to selecting patients with uncomplicated viridans streptococcal endocarditis for 2-week penicillin-streptomycin therapy (19).

The presence of vegetations seen on echocardiogram has been suggested to affect adversely the outcome of right-sided endocarditis (20-22). Of the 8 patients enrolled in this study with vegetations detectable by echocardiography, 1 patient had a relapse. However, this relapse rate did not differ from 2 of 35 patients classified as having probable endocarditis or 2 of 10 patients classified as having possible endocarditis,

none of whom showed vegetations on echocardiogram. Although persistent fevers have been associated with vegetations seen on echocardiogram, only 1 of the 7 patients who had persistent fevers showed vegetations on echocardiogram, and this patient was cured. Nevertheless, the number of patients with vegetations seen on echocardiogram enrolled in our study was small, and because other reports suggest a higher complication rate for these patients, further studies to confirm the efficacy of 2-week combination therapy for this subgroup are needed.

The relatively low frequency of vegetations reported in our study may partly be due to the subjectivity inherent in interpretation of whether echoes represent vegetations. For this study, only echogenic masses, unequivocally present and attached to the valve, were interpreted as vegetations. In another 5 patients, increased reflectance of the tricuspid valve (which some echocardiographers might have interpreted as vegetations) was noted, but these were not classified as vegetations. Thus, of the 41 echocardiograms done on patients with definite or probable endocarditis, 13 (32%) could have been interpreted as having vegetations.

Another possible explanation for the relatively lower frequency of vegetations in this study is that criteria used to define endocarditis in other studies (20-22), which reported approximately a 70% frequency of vegetations detectable by echocardiogram, may have been biased toward selection of cases likely to have abnormal echocardiograms. For example, in two studies, patients were selected from those referred for echocardiogram, and endocarditis was defined as an echocardiogram showing vegetations (20, 21). In the prospective study reported by Bayer and colleagues (22), patients had to have signs and symptoms of pneumonia or septic pulmonary emboli before they were included in the study.

Because we tried to include all eligible patients who would be treated for endocarditis (in practical terms, all intravenous drug abusers with *S. aureus* bacteremia of unknown source), the patients enrolled in our study probably are representative of those a physician is likely to encounter in clinical practice. Eighty-five percent of the patients enrolled (43 patients with definite or probable endocarditis plus 2 patients with possible endocarditis, 1 of whom had a relapse with tricuspid infection and the other who had an enlarged right ventricle on echocardiogram) had an abnormal echocardiogram, a murmur of tricuspid insufficiency, or a compatible chest roentgenogram. Certainly, almost all, if not all, of the patients enrolled had right-sided endocarditis.

The role of 2-week combination therapy for staphylococcal bacteremia and suspected endocarditis in patients who do not use intravenous drugs has not been defined. The practice is to treat these patients as though they have endocarditis, if the infection cannot be ruled out. If patients are selected according to the criteria used in this study, then 2-week combination therapy might be effective.

The vancomycin-tobramycin combination seemed ineffective as a 2-week regimen. Only one of three patients was cured (33%; CI, 0+ to 86). Because culture results during the relapse of the first patient were inconclusive, we treated one more patient with the vancomycin-tobramycin combination. When blood cultures never became sterile in this patient, this arm of the study was terminated. A review of cases of *S. aureus* endocarditis in intravenous drug abusers who were treated primarily with vancomycin for at least 4 weeks revealed that 5 of 13 either relapsed or failed to respond. (Chambers HF. Unpublished data.) Although these data suggest that vancomycin may not be as effective as penicillinase-resistant penicillins for treatment of *S. aureus* endocarditis, the observations are retrospective and the numbers are too small to draw firm conclusions. Further studies comparing the efficacies of vancomycin and penicillinase-resistant penicillins are warranted.

Intravenous drug abusers are a difficult group of patients to treat with long courses of parenteral antibiotics. Establishing and maintaining intravenous access is a problem as is keeping the patient in the hospital. The patient's behavior can also be a problem. Outpatient therapy is not practical because compliance and follow-up are poor. A 2-week regimen minimizes problems associated with maintaining intravenous access and prolonged periods of hospitalization. Short-course combination regimens also can produce substantial benefits by reducing hospitalization costs. For example, assuming an average cost of $700 per hospital day, approximately one-half million dollars was saved over the course of this study. Two-week combination therapy with nafcillin and tobramycin is an effective alternative to longer courses of single-drug regimens in selected patients with methicillin-susceptible *S. aureus* right-sided endocarditis.

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