Staphylococcus aureus Bacteremia

Recurrence and the Impact of Antibiotic Treatment in a Prospective Multicenter Study

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Abstract: *Staphylococcus aureus* bacteremia is associated with substantial morbidity. Recurrence is common, but incidence and risk factors for recurrence are uncertain. The emergence of methicillin resistance and the ease of administering vancomycin, especially in patients who have renal insufficiency, have led to reliance on this drug with the assumption that it is as effective as β-lactam antibiotics, an assumption that remains open to debate.

We initiated a multicenter, prospective observational study in 6 university hospitals and enrolled 505 consecutive patients with *S. aureus* bacteremia. All patients were monitored for 6 months and patients with endocarditis were followed for 3 years. Recurrence was defined as return of *S. aureus* bacteremia after documentation of negative blood cultures and/or clinical improvement after completing a course of antistaphylococcal antibiotic therapy. All blood isolates taken from patients with recurrent bacteremia underwent pulsed-field gel electrophoresis testing. Recurrence was subclassified as reinfection (different pulsed-field gel electrophoresis patterns) or relapse (same pulsed-field gel electrophoresis pattern).

Forty-two patients experienced 56 episodes of recurrence (79% were relapses and 21% were reinfection). Relapse occurred earlier than reinfection (median, 36 versus 99 d, $p < 0.06$). Risk factors for relapse of *S. aureus* bacteremia included valvular heart disease, cirrhosis of the liver, and deep-seated infection (including endocarditis). Nafcillin was superior to vancomycin in preventing bacteriologic failure (persistent bacteremia or relapse) for methicillin-susceptible *S. aureus* (MSSA) bacteremia. Failure to remove infected intravascular devices/catheters and vancomycin therapy were common factors in patients experiencing multiple (greater than 2) relapses. However, by multivariate analysis, only endocarditis and therapy with vancomycin (versus nafcillin) were significantly associated with relapse.

Recurrences occurred in 9.4% of *S. aureus* bacteremias following antistaphylococcal therapy, and most were relapses. Duration of antistaphylococcal therapy was not associated with relapse, but type of antibiotic therapy was. Nafcillin was superior to vancomycin in efficacy in patients with MSSA bacteremia.

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INTRODUCTION

Recurrence (defined as relapse or reinfection) appears to be common following bacteremia caused by *Staphylococcus aureus*, despite administration of antibiotics active in vitro. The reported rate of recurrence for *S. aureus* bacteremia after termination of antistaphylococcal therapy has ranged from 5% to 12%[1,6,15,17,18,21]. Factors linked to recurrence include the following: a) endocarditis[1,15,24], b) distal septic complications[1,6,18], and c) short duration (less than 10 days) of parenteral antibiotic treatment for catheter-related bacteremia[17,21]. Anecdotal cases of bacterial tolerance (that is, ratio of MBC/MIC > 32) predisposing to relapse[19,20,22] have also been described. Recurrence of bacteremia and the need for an additional course of therapy can lead to increased patient morbidity and mortality.

Studies of recurrent *S. aureus* bacteremia have been either retrospective in design or small in sample size. Recurrence of *S. aureus* bacteremia after completion of a course of antibiotic therapy active in vitro may be due to relapse with the original infecting strain or reinfection with a different strain of the same species. Differentiating relapse from reinfection has important implications for patient management. Molecular typing methods may now allow clinicians to differentiate between episodes of relapse versus reinfection with new strains[25].

We performed a large-scale prospective, multicenter, observational study of *S. aureus* bacteremia that included follow-up for 6 months after the completion of therapy in order to assess risk factors for recurrence. Objective criteria

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were used for clinical manifestations, severity of illness, diagnosis of endocarditis, and outcome endpoints. Pulsed-field gel electrophoresis of the chromosomal DNA of *S. aureus* was used to differentiate relapse from reinfection.

METHODS

Study Design

In 6 tertiary care hospitals from August 1994 to March 1996, every patient with *S. aureus* bacteremia was identified by a daily review of blood culture results in the microbiology laboratory; these patients were then evaluated prospectively by an investigator. Institutional Review Board review was performed at all hospitals as per local IRB requirements. During the study, 505 consecutive patients experienced 554 episodes of *S. aureus* bacteremia in 6 hospitals; the mean number of cases at each hospital was 82 (range, 64–174 cases). The study was observational in that all treatment decisions were made by the primary physicians. For example, subsequent blood cultures were obtained when the primary physicians felt it was clinically indicated (usually when the patients had persistent or recurrent fever on or after therapy). After discharge, all patients were prospectively monitored by review of clinic visits or follow-up by telephone for a total time of 6 months after the time of the first positive blood culture. Patients with endocarditis were monitored at 1, 2, and 3 years follow-up. Patients who failed to receive at least 4 days of antistaphylococcal therapy in the first week following bacteremia were excluded from analysis of antibiotic efficacy (that is, nafcillin versus vancomycin) but were included in the other analyses. Patients with polymicrobial bacteremia were excluded from the analyses.

In Vitro Susceptibility Testing

Susceptibility of nafcillin was tested by disk diffusion using a 1 μg oxacillin disk and standard criteria for zone size (NCCLS 90). In a representative sample of methicillin-resistant *S. aureus* (MRSA) strains, the minimum inhibitory concentration (MIC) was determined by commercial plates (Pos Combo Panel 4I, MicroScan R, West Sacramento, CA), in Mueller Hinton broth with oxacillin of 1 and 2 μg/mL, supplemented with 2% sodium chloride. The microdilution trays were inoculated with an inoculum of 10^5 cfu/mL and incubated at 35 °C for 24 hours. Following the National Committee for Clinical Laboratory Standards criteria, the organism was considered resistant to nafcillin (MRSA) if the MIC was greater than 2 μg/mL, and susceptible to nafcillin (MSSA) if the MIC was $\leq$2 μg/mL.

Definitions

Onset of bacteremia was defined as the date when the first positive blood culture was obtained. Persistent bacteremia was defined as blood cultures remaining positive despite receipt of antistaphylococcal antibiotic therapy. Persistent bacteremia was subclassified by receipt of therapy at greater than 3 days (persistent bacteremia >3 d) or greater than 7 days (persistent bacteremia >7 d). Recurrence was defined as the return of *S. aureus* bacteremia after documentation of negative blood cultures or clinical improvement after completing a course of antistaphylococcal therapy. Recurrence was further subclassified as reinfection or relapse: If the pulsed-field gel electrophoresis pattern of a recurrent isolate was different from the original infecting strain, the recurrence was considered a reinfection. Conversely, if the pulsed-field gel electrophoresis patterns of sequential isolates were indistinguishable, the recurrent episode was considered to be a relapse. Bacteriologic failure was defined as the presence of relapse or persistent bacteremia of greater than 7 days.

Antibiotic therapy was classified as optimal, acceptable, or suboptimal based on in vitro susceptibility testing of the blood isolates, specific antibiotic administered, duration of antistaphylococcal therapy, source of infection, and type of infection; these definitions are presented in Table 1. Concerning nafcillin versus vancomycin: Patients were considered to have received vancomycin or nafcillin if they received at least 10 days of the antibiotic within the first 14 days of therapy. Community versus nosocomial *S. aureus* bacteremia was classified according to Centers for Disease Control guidelines[9]. Bacteremia was considered community acquired if the blood specimen for the first positive culture was obtained on or within 72 hours of admission or if microbiologically documented *S. aureus* infection was present at another site at the time of admission. Bacteremia was considered to be nosocomial in origin if the first positive blood culture was obtained after 72 hours of admission and there was no other *S. aureus* infection documented at another site before or at the time of admission. Portal of entry was determined by the investigator based on clinical manifestations and by isolation of *S. aureus* from the sites other than blood. Endocarditis was defined according to the Duke criteria[5]. Severity of illness was assessed for each patient at the time of initial documentation of bacteremia using the APACHE III score[14] and the Pitt Bacteremia score[4]. The Pitt bacteremia score has been independently validated by Hill et al[12] in a study of 424 cases of *S. aureus* bacteremia.

Pulsed-Field Gel Electrophoresis

Pulsed-field gel electrophoresis was performed as previously described[10]. After restriction at buffer containing 20 units of SmaI (New England BioLabs, Beverly, MA), chromosomal restriction fragment patterns were analyzed with the CHEF-DR II electrophoresis cell (Bio-Rad, Melville, NY). The pulsed-field gel electrophoresis banding pattern was interpreted by criteria described previously[25].

TABLE 1. Relapse Rate in Different Categories of Infection*: Category 1 Infections Were More Likely to Relapse Regardless of Presumed Efficacy or Duration of Therapy

	Relapse Rate		
Therapy	**Category 1†**	**Category 2†**	**p Value**
Type of therapy‡			
Optimal	11.7% (15/128)	4.4% (8/182)	.026
In vitro active	0% (0/7)	4% (1/25)	NS
Suboptimal	11.1% (1/9)	25% (1/4)	NS
Total	11.1% (16/144)	4.7% (10/211)	.036
Duration of therapy§			
Optimal	14% (7/50)	6.5 (5/77)	NS
Acceptable	7.7% (1/13)	3.3 (3/86)	NS
Suboptimal	9.9% (8/81)	4.2% (2/48)	NS
Total	11.1% (16/144)	4.7% (10/211)	.036

Abbreviations: PFGE = pulsed-field gel electrophresis, NS = not significant.

*Excludes polymicrobial bacteremias (57 patients), deaths before day 14 (n = 71), patients with different PFGE patterns of *S. aureus* at recurrence (n = 7), patients with no isolates available for PFGE testing (n = 7), and patients with insufficient history for accurate categorization (n = 8) (total = 150).

†Category 1 infection was defined as bacteremia resulting from endocarditis, bacteremia with no apparent source, and bacteremia due to focus that could not be cured or removed. Category 2 infection was defined as bacteremia resulting from a source that was amenable to definitive cure (such as an intravascular device that could be removed, an infected bone that could be resected, or an abscess that could be incised and drained).

‡Type of therapy: Optimal therapy was defined as parenteral therapy with an antistaphylococcal antibiotic, that is, a penicillinase-resistant semisynthetic penicillin, a first-generation cephalosporin or vancomycin, to which the organism was susceptible in vitro. In vitro active therapy was defined as parenteral therapy with an in vitro active antibiotic not listed in optimal therapy, for example, clindamycin. Suboptimal therapy was defined as therapy with an antibiotic not active against *S. aureus* in vitro.

§Duration of therapy: For Category 1 infection, optimal therapy was defined as ≥28 days of parenteral therapy *after defervescence*. Acceptable therapy was defined as ≥28 days of parenteral therapy. Suboptimal therapy was defined as <28 days of parenteral therapy. For Category 2 infection, optimal therapy was defined as >14 days of parenteral therapy after defervescence. Acceptable therapy was defined as 10–14 days of parenteral therapy. Suboptimal therapy was defined as <10 days of parenteral therapy.

Data Management and Analyses

Clinical and laboratory data for analysis were entered into a computer database (Prophet version 6.0, AbTech, Charlottesville, VA). Categorical data were analyzed using a chi-square or Fisher exact test. Continuous variables were compared by using the t test or the Mann-Whitney test. A logistic regression model was used to examine the effects of multiple risk factors on recurrence. The factors used in the regression model included those found to be significant by univariate analysis and those hypothesized to affect recurrence.

In analysis of risk factors for relapse and reinfection, the following patients were excluded: patients who died before day 14 (since they would not have an opportunity to experience recurrence) and patients who experienced recurrence but whose blood isolates were not available, so pulsed-field gel electrophoresis could not be done. Patients classified as having relapse were excluded from the analysis of risk factors for reinfection and, likewise, patients classified as having reinfection were excluded from the analysis of risk factors for relapse.

RESULTS

Patient Demographics

A total of 505 patients with *S. aureus* bacteremia were enrolled; 298 were infected by methicillin-susceptible *S. aureus* (MSSA), 146 by MRSA, and 4 were of unknown susceptibility in vitro. Fifty-seven patients who had polymicrobial bacteremia were excluded, leaving 448 patients for evaluation for demographic information. Age ranged from 16 to 97 years (mean, 56.5 yr; median, 58 yr); 132 patients were female and 316 were male. The distribution of race was white, 66% (296/448); black, 30% (136/448); Hispanic, 3% (12/448); and Asian, 1% (4/448).

Twenty-five percent had been discharged from a hospital within 2 weeks of the current admission, and 10% were transferred from a nursing home. The underlying conditions were skin disease, 25%; coronary artery disease, 28%; valvular heart disease, 15% (12% native valve disease and 3% prosthetic valve); hypertensive heart disease, 38%; diabetes mellitus, 32%; cirrhosis of the liver, 6%; hemodialysis, 19%; human immunodeficiency virus infection, 7%; intravenous drug user (IVDU), 9%; malignancy, 26% (4% hematologic malignancy, 17% solid cancer, and 5% metastasis); neutropenia, 3%; chemotherapy, 6%; corticosteroids within the previous 1 month, 20%; surgery within last 2 weeks, 17%. Forty-three percent of patients were critically ill as defined by the Pitt bacteremia score. The mean APACHE III score was 51.1. Thirty-one percent of patients with MRSA infection had community-acquired infection (not including hemodialysis patients and admissions from nursing homes).

Recurrent *S. aureus* Bacteremia

Forty-two patients had 56 recurrent episodes of *S. aureus* bacteremia; 2 patients with polymicrobial bacteremia were excluded. Pulsed-field gel electrophoresis revealed the recurrent isolates to be identical to the initial bloodstream isolates in 26 patients, and these episodes were considered relapses. In 7 cases, the pulsed-field gel electrophoresis patterns were different between the initial bacteremia and the recurrent episode; these were considered reinfections. Isolates were not available for typing on 7 patients.

The incidence of native valve disease (p = .017) or endocarditis (p = 0.01) was significantly greater among

TABLE 2. Relapse and Reinfection in Patients with *S. aureus* Bacteremia*

Factor	Relapse (n = 26) (%)	Reinfection (n = 7) (%)	No Recurrence (n = 337) (%)	p Value†
Native valve disease	31	14	9	.017
Prosthetic valve	12	0	2	NS (.09)
Catheter removal	86	67	90	NS
Cirrhosis	15	0	4	NS (.06)
Hemodialysis	23	43	18	NS
Renal failure (creatinine >2 mg/dL)	46	57	28	NS (.06)
Endocarditis	35	14	10	.01

Abbreviations: See previous tables. NS = not significant, p > 0.20, unless otherwise indicated.
*Includes patients with endocarditis but excludes patients who died before 14 days (n = 71), those with polymicrobial bacteremias (n = 57), and those with isolates not available for PFGE testing (n = 7).
†P values are calculated by 3-way analyses with chi-square likelihood ratio.

patients with recurrence (relapse, reinfection) than without recurrence (Table 2). In this analysis, patients who died before 14 days were excluded since they could not be evaluated for recurrence. When patients with endocarditis were excluded, relapse of *S. aureus* bacteremia was significantly associated with presence of cirrhosis of the liver by univariate analysis (Table 3). When native valve disease, cirrhosis, age, and neutropenia were entered into a logistic regression model, native valvular disease (p = 0.02) and cirrhosis (p = 0.03) were significantly associated with relapse.

Eight patients experienced multiple recurrences of *S. aureus* bacteremia as confirmed by pulsed-field gel electrophoresis typing, which therefore were considered relapses by definition. Seventy-five percent (6/8) were infected by MSSA. Intravascular catheters were not removed in the 7 patients with such devices. All 8 received vancomycin. Seven patients experienced reinfection as defined by differing pulsed-field gel electrophoresis pattern between initial and subsequent blood isolates; 2 were nondiabetic hemodialysis patients, 2 were diabetic hemodialysis patients, 1 was an insulin-dependent diabetic, 1 was an intravenous drug user, and 1 had a nephrostomy tube.

The onset of recurrence of *S. aureus* bacteremia occurred earlier for episodes of relapse than for episodes of reinfection; 65% (17/26) of relapse episodes versus 43% (3/7) of reinfection episodes occurred within 2 months after completion of antibiotic therapy. The median number of days after completion of antibiotic therapy for relapse to occur was 36 days (mean, 70 d; range, 10-190 d) versus 99 days (mean, 105 d; range, 45-194 d) for reinfection (p = 0.06).

Relapse occurred significantly more often (p = 0.036, see Table 1) in Category 1 patients (those likely to have endocarditis) than in Category 2 patients (those with removable foci of *S. aureus* infection). Even after adjusting for severity of illness and duration of treatment, Category 1 patients were more likely to relapse than Category 2 patients (p = .0.01; odds ratio [OR] = 2.8; 95% confidence interval [CI] = 1.2-6.4). Surprisingly, there appeared to be no significant differences in relapse rate when assessing type of therapy (see definition in Table 1) or duration of therapy.

TABLE 3. Factors Associated with Relapse in Patients with *S. aureus* Bacteremia by Univariate and Multivariate Analyses*

			p Value	
Factor	Relapse (n = 17) (%)	No Relapse (n = 302) (%)	Univariate	Multivariate
Native valve disease	29	10	0.028	0.02
Prosthetic valve	6	1	NS	
Cirrhosis	24	4	.005	0.01
Transplant	18	7	NS (.13)	
Hematologic malignancy	12	4	NS (.12)	
Chemotherapy	12	7	NS	
Neutropenia	12	3	NS (.11)	
Skin disease	41	26	NS (.16)	

*Excludes patients with polymicrobial bacteremias (n = 57), deaths before day 14 (n = 71), patients with endocarditis (n = 49), patients reinfected with *S. aureus* of a different PFGE pattern (n = 6), and patients with no isolates available for PFGE testing (n = 3).

Nafcillin Versus Vancomycin Therapy for MSSA Bacteremia

We compared characteristics of patients who received nafcillin with those who received vancomycin for MSSA bacteremia. Patients with MSSA bacteremia who received nafcillin treatment were significantly more likely to be male (85% versus 61%, p = 0.015), and to have community acquisition (67% versus 31%, p = 0.001) or to be intravenous drug users (30% versus 7%, p = 0.002), but were less likely to have a catheter-related infection (12% versus 48%, p = 0.0002) than patients who received vancomycin therapy. Patients on hemodialysis were significantly more likely to receive vancomycin for MSSA bacteremia (46% versus 12%, p = 0.0007). No significant differences were seen between patients receiving nafcillin versus those receiving vancomycin for the following parameters: presence of native valve cardiac disease or prosthetic valve, diabetes mellitus, hepatic cirrhosis, malignancy, or severity of illness (as measured by the Pitt bacteremia score or APACHE III score).

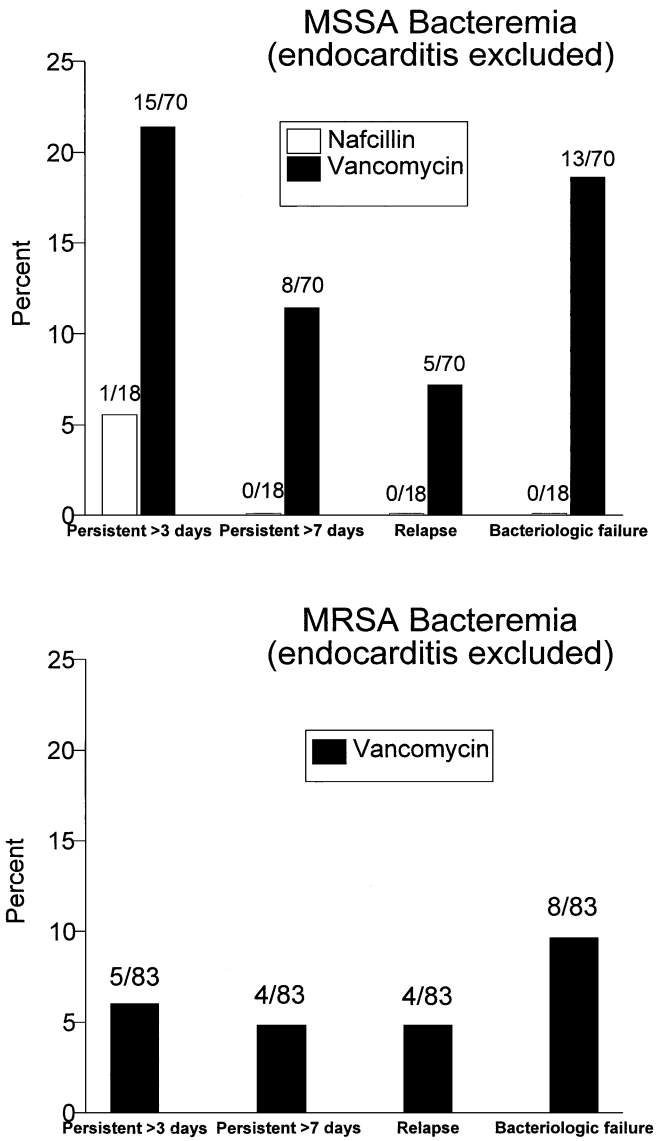

FIGURE 1. Efficacy of nafcillin versus vancomycin in preventing persistent bacteremia and relapse for methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia (**top**) and methicillin-resistant *S. aureus* (MRSA) bacteremia (**bottom**). Bacteriologic failure was defined as persistent bacteremia >7 days and/or relapse. Multivariate analysis showed that treatment with vancomycin predisposed to relapse (p < 0.048, see Results). Excludes patients with endocarditis and patients who did not receive at least 10 days of either vancomycin or nafcillin within the first 14 days of positive blood culture drawn (129 MSSA and 24 MRSA).

In all patients with MSSA bacteremia, nafcillin therapy was superior to vancomycin with respect to preventing bacteriologic failure (persistent bacteremia >7 d and/or relapse) (0% failure [0/18] versus 19% [13/70], respectively; p = 0.058) (Figure 1). In patients with *S. aureus* bacteremia only, without endocarditis, only 5 patients experienced relapse; although this number is too small for meaningful statistical analysis, all 5 had received vancomycin. Factors predisposing to relapse were further evaluated in a logistic model multivariate analysis. The following factors were entered: nafcillin (versus vancomycin), endocarditis, and hemodialysis. Presence of endocarditis (p < .009; OR = 7.6; 95% CI = 2.5-22.8) and treatment with vancomycin (p < .048; OR = 6.5; 95% CI = 1.0-52.8) were predictive of relapse. For those patients with designated catheter-related bacteremia, 90% had the catheter removed.

DISCUSSION

Recurrence of *S. aureus* bacteremia after treatment is a well-described phenomenon; 8 earlier reports described a total of 35 recurrences in 321 cases (11%)[1,6,11,15,17,18,21,24]. The number of patients with recurrence of *S. aureus* bacteremia from individual reports ranged from 1 to 9 patients[1,6,11,15,17,18,21,24]. These studies were usually retrospective and small. Chambers et al[1] reported a prospective study of 9 patients with 10 episodes of recurrence in 53 patients with *S. aureus* bacteremia. Data on recurrences are inherently difficult to collect given the follow-up period required for observation. In the current study, all patients were followed for 6 months, and patients with endocarditis were followed for 3 years. We present the results of, to our knowledge, the largest prospective study ever conducted of recurrences of *S. aureus* bacteremia following discontinuation of antistaphylococcal therapy. We utilized chromosomal DNA genotyping (pulsed-field gel electrophoresis) to differentiate relapse from reinfection. One previous study[11] addressed this issue using plasmid DNA analysis (8 patients with 10 episodes of recurrent *S. aureus* bacteremia). Other

studies have used antimicrobial susceptibility patterns, phage typing, and plasmid profile[1]. Fowler et al[7] also used pulsed-field gel electrophoresis to define relapses in a study of 29 patients with recurrent *S. aureus* bacteremia. In 79% (26/33) of cases of recurrent bacteremia in the current study for which the original and recurrent *S. aureus* were available for analyses, molecular subtyping showed that both isolates were identical, indicating a relapsing infection, although the possibility of reinfection by a resident colonizing strain cannot be excluded.

In the current study, 9.4% (42/448) of patients experienced recurrence of their bacteremia. Native heart valve disease was an independent risk factor for relapse of bacteremia (see Table 2), a factor not previously linked to relapse. One possible explanation for the link between native valve disease and subsequent relapse of bacteremia in the current study might be the presence of occult endocarditis that was not detectable according to the Duke criteria. Thirty-five patients with native valve disease in the current study did not have endocarditis by Duke criteria. The recent documentation by transesophageal echocardiogram of a substantial rate of endocarditis in patients thought to have only bacteremia by Duke criteria supports this hypothesis[8]. Thus, all patients experiencing relapse with *S. aureus* bacteremia should undergo transesophageal echocardiography.

Cirrhosis of the liver was an independent risk factor for relapse if endocarditis and reinfection were excluded from analysis. *S. aureus* infection has been linked to nasal carriage in cirrhotic patients[3]. Patients with cirrhosis of the liver often require hospitalizations that may increase their risk of acquiring staphylococcal nasal carriage with subsequent infection. Moreover, pruritus, a common symptom in patients with hepatic failure, may lead to excoriation of the skin which may, in turn, provide a portal of entry for *S. aureus*. Clearance of microorganisms from the bloodstream is impaired in these patients, partly as the result of a diminished hepatic blood flow[13,16,23].

The relapse rate was higher in Category 1 infections (likely to have endocarditis) than in Category 2 infections (with removable foci) as would be expected (see Table 1). Somewhat surprisingly, the duration of antibiotic treatment was not associated with relapse (see Table 1). A possible bias of this analysis was that physicians might prefer to give a longer duration of treatment in patients with prolonged fever who are Category 1 patients; however, the relapse rate was not significantly different in Category 1 patients receiving 28 days of antistaphylococcal antibiotics after defervescence (14% in optimal group) versus less than 10 days of antistaphylococcal antibiotic therapy (9.9% in suboptimal group, see Table 1). Similarly, for Category 2 patients (mostly patients with catheter-related bacteremia), the relapse rate was similar in patients who received 28 days of antibiotics after defervescence (6%) compared with those who received less than 10 days of antibiotics after defervescence (4%).

Relapse of *S. aureus* bacteremia occurred earlier (median, 36 d) than reinfection (median, 99 d). In a retrospective study, Hartstein et al[11] showed that relapse usually occurred before 2 months after completion of antistaphylococcal therapy for an episode of *S. aureus* bacteremia. In our 7 patients with reinfection, repeated exposure to vascular manipulation via hemodialysis or breaks in the epidermal barrier via insulin injections or a nephrostomy tube likely provided the portal of entry for *S. aureus*.

Relapse of *S. aureus* bacteremia has been linked to treatment with vancomycin (as opposed to a β-lactam agent) in anecdotal reports[1,6,17,18,24]. One retrospective review showed that 75% (6/8) of patients experiencing recurrent *S. aureus* bacteremia had received prior vancomycin therapy for the initial episode of *S. aureus* bacteremia[11]. Although Fowler et al[7] showed that vancomycin therapy was a risk factor for relapse of *S. aureus* bacteremia, they failed to exclude patients with MRSA infection. This study provides the strongest support to date for the concept that vancomycin is inferior to nafcillin in treating bacteremic *S. aureus* infection due to MSSA. Bacteriologic failure occurred more frequently with vancomycin (19%, 13/70) than with nafcillin (0%, 0/18; $p = 0.058$) (see Figure 1). Multivariate analysis also showed that vancomycin (as opposed to nafcillin) administration predisposed to relapse ($p < 0.05$). One potential weakness of this conclusion is that patients on hemodialysis were more likely to receive vancomycin, and the access site was rarely removed, such that evaluation of vancomycin might be confounded by persistent foci of infection. However, by multivariate analysis, treatment with vancomycin remained significantly associated with relapse when the statistical model adjusted for use of hemodialysis. Likewise, persistent bacteremia also occurred significantly more often as assessed by multivariate analyses in patients receiving vancomycin and independent of severity of illness or any other clinical variables, such as the need for hemodialysis. Treatment with vancomycin was also more likely to be associated with progression to endocarditis as found in our companion study published in this issue[2] than was treatment with nafcillin.

These findings provide support for the recommendation that *S. aureus* bacteremia should be treated with antistaphylococcal β-lactam antibiotics rather than vancomycin whenever possible, especially in patients with risk factors, such as the presence of an abnormal valve, that are associated with a high rate of relapse and/or subsequent endocarditis. When vancomycin must be used, consideration might be given to adding another antistaphylococcal antibiotic or a more prolonged course of treatment regardless of echocardiographic findings, or both. In a previous multicenter study of MSSA endocarditis, the combination of nafcillin and gentamicin (for

the first 2 weeks of therapy) did not significantly improve the cure rate, although clearance of *S. aureus* from the blood and defervescence were more rapid[15]. The fact that patient data are not available to support the role for antibiotic synergy in treatment for *S.aureus* bacteremia underscores the need for prospective clinical studies, especially in light of the widespread practice of administering vancomycin for access-related bacteremia in hemodialysis patients, a practice that presumes equivalent efficacy where none may exist. Comparative evaluation of newer antimicrobial agents for MRSA bacteremia and endocarditis, such as quinupristin-dalfopristin, linezolid, and daptomycin, is indicated given the suboptimal results with vancomycin in our study.

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