A Prospective Multicenter Study of *Staphylococcus aureus* Bacteremia

Incidence of Endocarditis, Risk Factors for Mortality, and Clinical Impact of Methicillin Resistance

Feng-Yee Chang, Brent B. MacDonald, James E. Peacock, Jr., Daniel M. Musher, Patricia Triplett, Joseph M. Mylotte, Alice O'Donnell, Marilyn M. Wagener, and Victor L. Yu

Abstract: Our objectives were to determine the incidence of endocarditis in patients whose *Staphylococcus aureus* bacteremia was community-acquired, related to hemodialysis, or hospital-acquired; to assess clinical factors that would reliably distinguish between *S. aureus* bacteremia and *S. aureus* endocarditis; to assess the emergence of methicillin-resistant *S. aureus* (MRSA) as a cause of endocarditis; and to examine risk factors for mortality in patients with *S. aureus* endocarditis.

We conducted a prospective observational study in 6 university teaching hospitals; we evaluated 505 consecutive patients with *S. aureus* bacteremia. Thirteen percent of patients with *S. aureus* bacteremia were found to have endocarditis, including 21% with community-acquired *S. aureus* bacteremia, 5% with hospital-acquired bacteremia, and 12% on hemodialysis. Infection was due to MRSA in 31%.

Factors predictive of endocarditis included underlying valvular heart disease, history of prior endocarditis, intravenous drug use, community acquisition of bacteremia, and an unrecognized source. Twelve patients with bacteremia had a prosthetic valve; 17% developed endocarditis. Unexpectedly, nonwhite race proved to be an independent risk factor for endocarditis by both univariate and multivariate analyses. Persistent bacteremia (positive blood cultures at day 3 of appropriate therapy) was identified as an independent risk factor for both endocarditis and mortality, a unique observation not reported in other prospective studies of *S. aureus* bacteremia.

Patients with endocarditis due to MRSA were significantly more likely to have complicating renal insufficiency and to experience persistent bacteremia than those with endocarditis due to methicillin-susceptible *S. aureus* (MSSA). The 30-day mortality was 31% among patients with endocarditis compared to 21% in patients who had bacteremia without endocarditis ($p = 0.055$). Risk factors for death due to endocarditis included severity of illness at onset of bacteremia (as measured by Apache III and Pitt bacteremia score), MRSA infection, and presence of atrioventricular block on electrocardiogram.

Patients with *S. aureus* bacteremia who have community acquisition of infection, underlying valvular heart disease, intravenous drug use, unknown portal of entry, history of prior endocarditis, and possibly, nonwhite race should undergo echocardiography to screen for the presence of endocarditis. We recommend that blood cultures be repeated 3 days following initiation of antistaphylococcal antibiotic therapy in all patients with *S. aureus* bacteremia. Positive blood cultures at 3 days may prove to be a useful marker in promoting more aggressive management, including more potent antibiotic therapy and surgical resection of the valve in endocarditis cases. MRSA as the infecting organism should be added to the list of risk factors for consideration of valvular resection in cases of endocarditis.

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INTRODUCTION

Staphylococcus aureus is an increasing cause of bacteremia, both in the community and in the hospital setting. Bacteremia due to this organism poses a double threat: the bacteremia may result from a variety of deep-seated infections including endocarditis and, whatever its source, it may cause endocarditis secondarily. The goals of antibiotic therapy are to eradicate the bacteremia and prevent relapse or secondary infection on the heart valves and elsewhere. Controversy over the duration of therapy for *S. aureus* bacteremia has been debated for several decades.

A critical diagnostic question in patients with *S. aureus* bacteremia is whether endocarditis is also present. Acquisition of infection in the community, the presence of bacteremia with no apparent source (a primary bacteremia), and the occurrence of metastatic foci of infection have been thought to suggest the presence of endocarditis. However,

From University of Pittsburgh and Veterans Affairs Medical Center, Pittsburgh, Pennsylvania (FYC, MMW, VLY); Veterans Affairs Medical Center, Houston, Texas (BBM, DMM); Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina (JEP, PT); Erie County Medical Center, Buffalo, New York (JMM, AOD).

Dr. Chang's current affiliation is Division of Infectious Diseases, Tri-Service General Hospital, Taipei, Taiwan.

Address reprint requests to: Victor L. Yu, MD, VA Medical Center, Infectious Disease Section, University Drive C, Pittsburgh, PA 15240. Fax: 412-688-6950; e-mail: vly+@pitt.edu.

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the studies from which those predictors were derived were either small in size or retrospective in design. Since an increasing proportion of *S. aureus* bacteremias in both community-acquired and hospital-acquired settings is now due to methicillin-resistant *S. aureus* (MRSA), it is important to determine whether clinical features of endocarditis due to MRSA differ from those due to methicillin-susceptible *S. aureus* (MSSA).

To address those issues, we conducted a large-scale prospective, multicenter, observational study on *S. aureus* bacteremia. Our objectives were to determine the incidence of endocarditis in patients whose *S. aureus* bacteremia was community-acquired, related to hemodialysis, or hospital-acquired; to assess clinical factors that would reliably distinguish between *S. aureus* bacteremia and *S. aureus* endocarditis; to assess the emergence of MRSA as a cause of endocarditis; and to examine risk factors for mortality in patients with *S. aureus* endocarditis.

METHODS

Study Design

From August 1994 to March 1996, 505 consecutive patients in 6 hospitals (Presbyterian University Hospital; Montefiore University Hospital; Veterans Affairs Medical Center; Pittsburgh, PA; Veterans Affairs Medical Center; Houston, TX; Wake Forest University, Baptist Medical Center; Winston-Salem, NC; Erie County Medical Center, Buffalo, NY) from whom *S. aureus* was isolated from blood were followed prospectively. Institutional Review Board review was performed at all hospitals. Patients with *S. aureus* bacteremia were identified through a daily review of blood culture results in the microbiology laboratory. Thirty-four percent (173/505) had 1 positive blood culture for *S. aureus*, 47% (236/505) had 2 positive blood cultures, 11% (56/505) had 3 positive blood cultures, 7% (37/505) had greater than 3 positive blood cultures, and <1% (3/505) had an unknown number of positive blood cultures. These patients were then evaluated by an investigator who participated in the design of this study. The study was observational in that decisions regarding management were made by the primary physicians in accordance with their clinical judgment. Subsequent blood cultures were obtained as they were deemed clinically indicated by the primary physicians, usually when the patients had persistent or recurrent fever on therapy. All patients were monitored for at least 6 months after onset of bacteremia by review of clinic visits after discharge, discussion with managing physicians, and/or telephone interview. Patients with endocarditis were monitored for 3 years to determine whether valvular infection had recurred.

Bacteriology

Identification of bloodstream isolates as *S. aureus*, assays of antibiotic susceptibility, and determination if strains were MRSA or MSSA were done using standard techniques[54]. Susceptibility to oxacillin was screened by disk diffusion using a 1 μg oxacillin disk and standard zone size criteria[54]. Methicillin-resistance was verified by growth in broth supplemented with 2% sodium chloride containing 2 μg/mL oxacillin (Pos Combo Panel 4I, MicroScan R, West Sacramento, CA). The microdilution trays were inoculated with 10^5 cfu/mL and incubated at 35 °C for 24 hours. Following the National Committee for Clinical Laboratory Standards criteria, an isolate was considered to be resistant to oxacillin if the minimum inhibitory concentration (MIC) was greater than 2 μg/mL. Pulsed-field gel electrophoresis was performed as previously described[4,23,68].

Definitions

Onset of bacteremia was defined as the date when the first positive blood culture was obtained. Definitions of community-acquired and hospital-acquired infection were in accord with the Centers for Disease Control Guidelines[22].

Endocarditis was defined according to the 1994 Duke criteria and modification[39]. Cases were included that met definitions for both definite and possible endocarditis. ''New'' endocarditis, that is, development of endocarditis after the onset of bacteremia, was defined by fulfillment of the following 3 criteria: 1) the absence of clinical evidence of endocarditis at the time the bacteremia was first documented, 2) an interval of 1 week or more between the last positive blood culture and the earliest appearance of findings consistent with endocarditis, and 3) an identical pulsed-field gel electrophoresis pattern of the initial blood culture isolate and that obtained when endocarditis was diagnosed. These criteria are a modification of previously published criteria[15] with the addition of molecular subtyping results to identify recurring isolates. Nosocomial endocarditis was defined as endocarditis acquired more than 3 days from date of hospital admission with no clinical manifestations of endocarditis before admission. Persistent bacteremia was defined as the presence of positive blood cultures for *S. aureus* after $\geq$3 days of appropriate antistaphylococcal antibiotic therapy. Portal of entry was determined by the investigator based on clinical manifestations and positive cultures for *S. aureus* from extravascular sites. Catheter-related bacteremia was defined when a semiquantitative culture of the vascular catheter tip yielded greater than 15 colonies of *S. aureus*, and another source of bacteremia could not be identified[41]. Inflammation at the catheter insertion site was not a sufficient criterion for defining the catheter as a source. Severity of illness was assessed for each patient at the onset of bacteremia using APACHE III score[32] and Pitt bacteremia score[9]. The Pitt bacteremia score has been independently validated in a prospective study of 424 cases of *S. aureus* bacteremia[27].

Endpoints

Outcome (death versus survival) was recorded at 14 days, 30 days, and 60 days after the initial positive blood culture for *S. aureus* was obtained. Recurrence of valvular infection in patients with endocarditis was assessed at 3 months and 36 months after the initial blood culture for *S. aureus*.

Data Management and Analysis

Clinical and laboratory results were entered into a computer database (Prophet Systems, National Institutes of Health, Bethesda, MD). Categorical data were analyzed using a chi-square or Fisher exact test. Continuous variables were compared using the t test or the Mann-Whitney test. A step-wise regression model was used to examine the effects of multiple risk factors found to be significant by univariate analysis.

RESULTS

Incidence of Endocarditis

Of the 505 cases of *S. aureus* bacteremia, 13% (64/505) met the Duke criteria for endocarditis, including 51 with ''definite'' endocarditis (9 by pathologic and 42 by clinical criteria) and 13 patients with ''possible'' endocarditis[12]. Of these 64 patients, 67% (43/64) underwent echocardiography: transthoracic only (n = 10), transesophageal only (n = 6), or both (n = 27). Fifteen percent (4/27) had no evidence of endocarditis by either transthoracic or transesophageal echocardiogram when both procedures were performed. Our study was not designed to assess sensitivity, specificity, or interobserver variability in the 6 hospitals, so no further data are provided on echocardiography.

The prevalence of endocarditis in patients with community-acquired *S. aureus* bacteremia was 21% (43/206), 12% (11/95) in hemodialysis patients, and 5% (10/204) in patients with hospital-acquired bacteremia (Figure 1). Sixty-nine percent (44/64) and 31% (20/64) of cases of endocarditis were due to MSSA and MRSA, respectively. Oslerian manifestations were detected in 61% (39/64) patients with endocarditis including occurrence of new murmur (54%), evidence of emboli (41%), and presence of skin lesions (22%) including petechiae (11%) and Janeway lesions (11%).

New Endocarditis

Seven of 64 patients met the definition of new endocarditis as a complication of *S. aureus* bacteremia, as defined in the Methods (Table 1). An intravascular catheter was the most likely cause of new endocarditis: 3 patients had documented catheter-related bacteremia and 2 had suspected catheter-associated bacteremia, although confirmation was not available since dialysis catheters were not removed. In 5 of 7 patients, *S. aureus* bacteremia relapsed 17–87 days

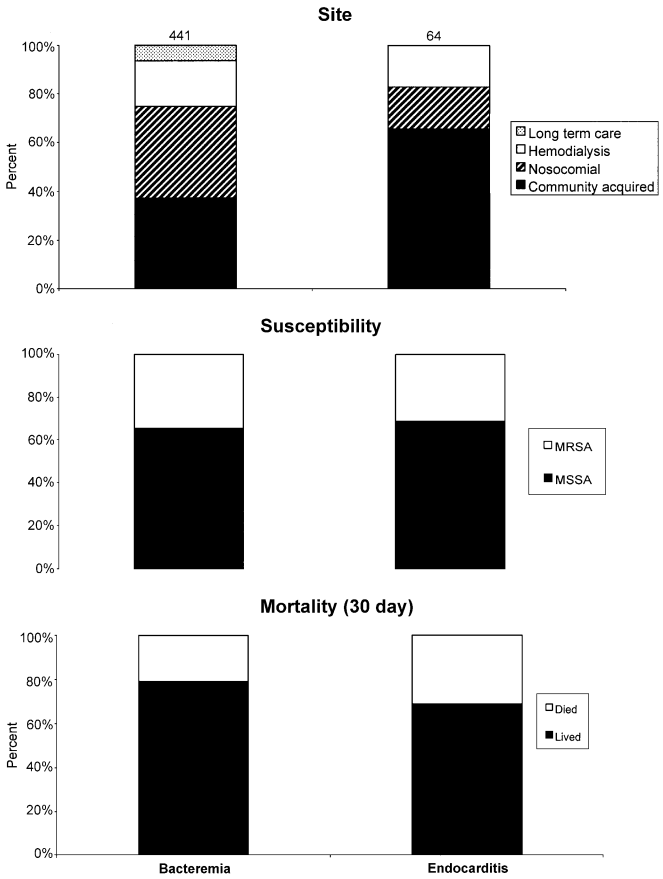

FIGURE 1. Comparison of site of acquisition, antibiotic susceptibility, and outcome for patients with *Staphylococcus aureus* bacteremia (n = 441) and endocarditis (n = 64). MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*. Community-acquisition was significantly more likely to occur in patients with endocarditis (see Table 2, $p > 0.04$, 3×2 chi-square test). Incidence of MRSA and mortality was similar for patients with bacteremia only and for patients with endocarditis.

(median, 32 d) after the discontinuation of antistaphylococcal antibiotics for treatment of the initial episode of bacteremia. The remaining 2 patients had persistent bacteremia for greater than 7 days during administration of active antistaphylococcal antibiotics. Of the 7 patients, 6 had severe arteriosclerotic heart disease or valvular disease, including 2 patients with prosthetic valves (see Table 1). All 7 patients had received therapy with vancomycin with appropriate dosing for the initial episode of bacteremia, and all received less than 4 weeks of therapy (see Table 1). In our patients with *S. aureus* bacteremia, 12 had prosthetic valves; 17% (2/12) developed ''new endocarditis'' as defined in the Methods.

In a more focused analysis of the impact of duration of therapy on development of new endocarditis, of 250 nosocomial bacteremias, new endocarditis developed in 4%

TABLE 1. Seven Patients with New Endocarditis*

Patient	Age/Sex (yr)	MRSA/ MSSA	Portal of Entry	Days Positive BC Before Endocarditis	Duration of Antibiotic Therapy (days)†	Heart Disease	Valvular Disease	Diagnostic Criteria	Outcome
1	70/M	MSSA	Peripheral IV, catheter-related thrombophlebitis	34	Vanco IV (15 d)	ASHD, CABG	Aortic stenosis, porcine aortic valve	Definite	IV Nafcillin (42 d) Cure
2	46/F	MRSA	Unknown	17	Vanco IV (10 d)	CHD	ASD	Definite	IV Vanco (42 d) Cure
3	47/M	MRSA	IV (artificial heart)	15	Vanco (15 d)	ASHD		Definite	Died (13 d)
4	79/M	MSSA	Unknown	16	Vanco IV (9 d) Oral TMP-SMZ (5 d)	ASHD, old MI		Definite	Died 58 d later
5	51/F	MSSA	Permacath (hemodialysis)	32	Vanco IV (27 d)	ASHD, CABG	Mitral prosthetic valve, AI	Definite	Valve replacement Cure
6	71/F	MSSA	Permacath (hemodialysis)	87	Vanco IV (21 d)		Mitral regurgitation, aortic stenosis	Possible	IV Vanco (42 d) Cure
7	77/M	MRSA	Uldall catheter	32	Vanco IV (14 d)			Definite	IV Vanco (42 d) Cure

Abbreviations: ASD = atrial septal defect; Vanco = vancomycin; AI = aortic insufficiency; IV = intravenous; TMP-SMZ = trimethoprim-sulfamethoxazole; ASHD = arteriosclerotic heart disease; CABG = coronary artery bypass graft; MI = myocardial infarction; CHD = congenitive heart disease; MSSA = methicillin-sensitive *S. aureus*; MRSA = methicillin-resistant *S. aureus*; BC = blood culture.

*Pulsed-field gel electrophoresis patterns of sequential isolates were identical for every patient except Patient 7 (isolates not available).

†Duration of antibiotic therapy for initial episode of bacteremia.

(4/101) who received 2 weeks or less of antistaphylococcal therapy, 4% (3/74) who received 15–27 days of therapy, and 0% (0/33) who received 4 weeks or greater of therapy. (Forty-two patients who died before 14 days after onset of *S. aureus* bacteremia were excluded because these patients would have had less opportunity to develop endocarditis.) These differences were not statistically significant (p = 0.5, chi-square for trend). In order to detect a difference of 4% at an alpha of 0.05 and power of 80%, 476 patients would have been required in a randomized trial.

Differentiation of *S. Aureus* Endocarditis from *S. Aureus* Bacteremia

Based on univariate analyses, valvular heart disease (native valve disease, prosthetic valve disease), prior endocarditis, intravenous drug use, community acquisition, and absence of a recognized portal of entry at the time of presentation were significant risk factors for endocarditis (Table 2). Nonwhite race was significantly associated with endocarditis. When race was subclassified, the frequency of endocarditis in each racial group was as follows: white 10% (35/336), black 16% (25/152), Hispanic 15% (2/13), and Asian 50% (2/4). Persistent bacteremia during the course of therapy was also significantly associated with endocarditis (27% (17/64), p < 0.0001, see Table 2).

Factors demonstrating an association with endocarditis by univariate analyses were then evaluated in a multivariate logistic regression model. Statistically significant associations were found with the following: native valve disease (odds ratio [OR] = 4.5; 95% confidence intervals [CI] = 2.0–9.9; p = .002), the presence of a prosthetic valve (OR = 10.5; 95% CI = 2.5–43.7; p = 0.0012), persistent bacteremia (OR = 7.4; 95% CI = 3.3–16.6; p = .0001), intravenous drug use (OR = 3.2; 95% CI = 1.2–8.6; p = .02), an unidentifiable portal of entry (OR = 3.3; 95% CI = 1.3–6.6; p = .008), a history of prior endocarditis (OR = 10.0; 95% CI = 2.0–50.0; p = .005), community acquisition (OR = 2.9; 95% CI = 1.4–4.9; p = .004), and nonwhite race (OR = 2.5; 95% CI = 1.2–5.3; p = .014).

MRSA Versus MSSA Endocarditis

Sixty-nine percent (44/64) of cases of endocarditis were due to MSSA and 31% (20/64) were due to MRSA (see Figure 1, Table 3), similar to the proportion of all bacteremias

that were MSSA (65%) or MRSA (35%) (see Figure 1 and Table 2). As anticipated, MSSA endocarditis was more likely to be community-acquired and to occur in intravenous drug users and in persons who had previously had endocarditis. MRSA endocarditis was more likely to be acquired in the hospital or to occur in patients with renal insufficiency and those on hemodialysis (see Table 3). Patients with MRSA endocarditis were also older than those with MSSA endocarditis (62.3 versus 51.4 yr, respectively), presumably reflecting the preponderance of nosocomial infection. Underlying diseases in each group were comparable and the severity of illness at the time bacteremia was documented (APACHE III score or Pitt Bacteremia Study) was not significantly different (see Table 3).

Patients with MRSA endocarditis were significantly more likely to experience persistent bacteremia than those

TABLE 2. Risk Factor Analysis for Factors that Might Distinguish Endocarditis and Bacteremia

			p Value	
Parameter	**Endocarditis (n = 64) (%)**	**Bacteremia (n = 441) (%)**	**Univariate**	**Multivariate***
Age (yr)	54.8	54.5	NS	
Nonwhite race	49	35	.027	0.01
Skin disease	22	26	NS	
Heart disease	58	36	.001	
Native valve	36	8	.0001	.002
Prosthetic valve	12	1	.0001	.001
Coronary artery disease	39	27	.05	
Prior endocarditis	13	1	.0001	.005
Diabetes mellitus	39	33	NS	
Diabetes, insulin dependent	27	19	NS (.13)	
HIV positive	10	7	NS	
Intravenous drug use	27	7	.0001	.02
Corticosteroids	11	21	NS (0.06)	
Hemodialysis	17	19	NS	
Portal				
Unknown	50	27	.001	.008
Wound/skin	14	20	NS	
Intravenous site	11	29	.004	
Urinary tract	3	5	NS	
Respiratory tract	2	10	NS	
Abdominal	3	1	NS	
Bone	0	2	NS	
MRSA	31	35	NS	
Critically ill[†]	51	46	NS	
Total APACHE III score	54.7	52.6	NS	
Community acquired	67	37	.0001	.004
Duration of fever[‡], mean [median]	5.3 [5]	3.9 [2]	.017	
Persistent bacteremia[§]	27	9	.0001	.001
Pitt score-continuous (mean)	3.98	4.0	NS	
Mortality				
14 d	20	17	NS	
30 d	31	21	.055	
60 d	34	25	.109	

Abbreviations: HIV = human immunodeficiency virus; MRSA = methicillin-resistant *S. aureus*; NS = Not significant, $p > 0.05$.

*Stepwise logistic regression analyses - see Results.

[†]Critically ill defined as Pitt bacteremia score ≥ 4.

[‡]Duration of fever in days after initiation of antistaphylococcal antibiotics.

[§]Persistent bacteremia defined as presence of positive blood cultures for *S. aureus* despite administration of antistaphylococcal antibiotics for at least 3 days. Patients who died before 3 days were excluded.

with MSSA endocarditis by univariate (p = 0.0001 in Table 3) and multivariate (p = 0.002) analyses. Risk factors entered into multivariate logistic regression analyses to assess differences between MRSA and MSSA endocarditis were those significant by univariate analysis (see Table 3). Only renal insufficiency as defined by creatinine >2 mg/dL at the time of presentation (p = 0.036) occurred significantly more often in MRSA endocarditis by both univariate and multivariate analyses. Prior antibiotic therapy within 2 weeks of the first positive blood culture and nosocomial acquisition were not significant risk factors (see Table 3). The following parameters were associated with persistent bacteremia by univariate analyses: hemodialysis, creatinine >2 mg/dL, total APACHE III score, intravenous drug use, and MRSA (data not shown). By multivariate analyses in a logistic regression model, only MRSA remained statistically significantly associated with persistent bacteremia (p = 0.001).

Mortality in Patients With Endocarditis

The mortality rate was 31% (20/64) and 34% (22/64) at the 30-day (see Figure 1) and 60-day follow-ups, respectively. Numerous logistic regression models were evaluated;

TABLE 3. Characteristics of Patients with MRSA versus MSSA Endocarditis (Persistent Bacteremia and Mortality Were Significantly Higher in MRSA Compared with MSSA Endocarditis.)

			p Value	
Parameter	**MRSA (n = 20) (%)**	**MSSA (n = 44) (%)**	**Univariate**	**Multivariate***
Age (yr)	62.3	51.4	.016	NS
Nonwhite race	45	48	NS	
Skin disease	20	23	NS	
Heart disease	75	50	.06	
Native valve	35	36	NS	
Prosthetic valve	15	11	NS	
Prior endocarditis	0	19	.046	NS
Diabetes mellitus	40	39	NS	
Diabetes, insulin dependent	30	25	NS	
HIV positive	10	7	NS	
IVDU	10	34	0.04	NS
Hemodialysis	25	14	NS	
Prior antibiotics (2 wk)	30	16	NS	
Critically ill[†]	63	45	NS	
Fever	95	88	NS	
Temperature (mean, °C)	39.3	39.1	NS	
White blood count	13,200/cc	15,500/cc	NS	
Creatinine >2 mg/dL	63	26	.009	.036
Community acquired	50	75	.048[‡]	NS
Nosocomial	25	11		
Hemodialysis	25	14		
Duration of fever (mean days)[§]	6.6	4.7	.056	
Persistent bacteremia (excludes pts died <3 d)	65	9	.0001	.002
Mortality				
14 d	40	11	.016	
30 d	50	23	.029	
60 d	55	25	.019	
Pitt bacteremia score	4.05	3.97	NS	
Total APACHE III (mean)	60.3	51.9	NS	

Abbreviations: See previous tables. IVDU = intravenous drug user.
*Stepwise logistic regression analyses.
[†]Critically ill defined as Pitt bacteremia score ≥4.
[‡]Chi-square 3 × 2 analyses (community-acquired, nosocomial, hemodialysis)
[§]Duration of fever after initiation of antistaphylococcal antibiotics.

TABLE 4. Factors Associated with Mortality (30 Days) in 64 Patients with Endocarditis*

Parameter	Deaths (%)	p Value
Insulin-dependent diabetes	47	NS (.10)
Nondiabetic	26	
Transplant recipient	100	.03
No transplant	28	
Persistent bacteremia	59	.004[1]
No persistence	21	
MRSA	50	.03
MSSA	23	
Hemodialysis	55	NS (.08)
No hemodialysis	26	
AV block on EKG	100	.002
No AV block	29	

Abbreviations: See previous tables. AV block = atrioventricular block; EKG = electrocardiogram.

*No significant association was seen with gender, race, presence of prosthetic valve, history of prior endocarditis, hospital acquisition, or vital signs at onset of bacteremia.

the parameters entered into the model were those significant by univariate analyses when assessing mortality at 30 days (Table 4) including age, MRSA as the bacteremic isolate, severity of illness (APACHE III or Pitt bacteremia score), and persistent bacteremia. Acquisition in the community was also inserted into the model because 5 studies suggested it as a risk factor for mortality[7,14,16,20,66]. APACHE III score and persistent bacteremia were significantly associated with mortality in all models, while MRSA bacteremia and presence of atrioventricular block on electrocardiogram were either significant ($p < 0.05$) or approached significance ($p = 0.08$) in various models (data not shown).

Of the 64 patients with endocarditis, only 6 patients underwent resection of the affected valve and all survived; in contrast, 50% (29/58) of patients who were treated with medical therapy only survived ($p = 0.02$). When 5 patients who died within 7 days of their first positive blood culture were excluded from the analyses, the association remained statistically significant ($p = 0.03$). No significant difference in severity of illness (APACHE score, Pitt bacteremia score) was found between those patients undergoing surgery versus those receiving medical therapy alone. When the 13 patients with possible endocarditis were excluded and the data reanalyzed, the results were essentially identical (data not shown).

DISCUSSION

To our knowledge, the current study is the largest prospective multicenter study on *S. aureus* endocarditis. Its strengths include the size and diversity of a multicenter study. Unlike the studies from an individual hospital conducted over a period of many years[18,57], our study was performed in less than 2 years in 6 hospitals. The epidemiology of *S. aureus* bacteremia is highly dependent on the patient population served by the facility, including the proportion of dialysis patients, intravenous drug users, and immunosuppressed hosts. Results from a multihospital study should be more generalizable than those from 1 hospital.

The clinical differentiation of *S. aureus* bacteremia from infective endocarditis has long been a vexing problem for clinicians and has obvious therapeutic and prognostic implications. In the absence of typical Oslerian manifestations (such as changing murmur, splenomegaly, embolic lesions), the clinical diagnosis of infective endocarditis among patients with *S. aureus* bacteremia can be challenging. Nolan and Beaty[57] reported 3 useful bedside criteria for predicting the presence of infective endocarditis in patients with *S. aureus* bacteremia: community-acquisition of bacteremia, unapparent primary focus, and metastatic foci. However, the latter 2 criteria may not be highly predictive risk factors for endocarditis. Several studies have documented the presence of *S. aureus* endocarditis in patients who have a detectable primary focus of *S. aureus* infection, usually from skin, soft tissue, or bone[10,47]. An increased incidence of endocarditis has been observed in populations with a large proportion of intravenous drug users[5,66] or with underlying valvular heart disease[76], or prior endocarditis[3,38,73].

Our study confirmed that valvular heart disease, intravenous drug use[66], community acquisition[5,10], prior endocarditis, and unknown source of infection are risk factors for endocarditis (see Table 2). Unexpectedly, nonwhite (black, Hispanic, Asian) race was also found to be a significant risk factor for endocarditis by both univariate and multivariate analyses, although the reason for this racial predilection is unclear.

The reported prevalence of infective endocarditis in patients with community-acquired *S. aureus* bacteremia has been quite variable, ranging from 6% to 64%[5,17,18,27,31,33,35,47–49,53,66,76]. In the current study, in which we precisely determined the denominator as well as the numerator, endocarditis was present in 21% (43/206) of patients with community-acquired *S. aureus* bacteremia. The incidence of endocarditis reported in intravenous drug users with *S. aureus* bacteremia has ranged from 38% to 67%[5,70]; in the current study, the incidence of endocarditis in intravenous drug users with *S. aureus* bacteremia was 35% (17/48).

Patients with hospital-acquired *S. aureus* bacteremia have a lower incidence of infective endocarditis (2%–17%) than those with community-acquired bacteremia[2,3,13,33,35,45,47,51,52,59,66,75]. In the current study, 5% (10/204) of hospital-acquired *S. aureus* bacteremias proved to be secondary to endocarditis. Fowler et al[18] diagnosed

endocarditis in 28% (17/61) of patients experiencing hospital-acquired *S. aureus* bacteremia. These results were biased by the exclusion of patients less likely to have endocarditis: 72/176 patients were excluded because of patient refusal to undergo transesophageal echocardiogram or failure of the attending physician to order the test. It is likely that those 72 patients were at lower risk for endocarditis, a point the authors also acknowledged. Therefore, the lower denominator of the remaining patients in the study by Fowler and colleagues may have led to an overestimate of the incidence of endocarditis in hospital-acquired *S. aureus* bacteremia.

Endocarditis may also develop as a sequela of staphylococcal bacteremia, as occurred in 7 patients in the current study (see Table 1). New endocarditis, as defined in the Methods, developed exclusively in patients with hospital-acquired bacteremia or in hemodialysis patients (see Table 1). An intravascular catheter was the portal of entry in 71% (5/7) of patients. All of the patients who developed new endocarditis had received vancomycin therapy for the initial episode of bacteremia (see Table 1). In 5 patients, a relapse of *S. aureus* bacteremia occurred at a median of 32 days (range, 17–87 d) following the previous episode of *S. aureus* bacteremia. In the remaining 2 patients, persistent bacteremia developed after 2 weeks of vancomycin. The pulsed-field gel electrophoresis patterns for the initial isolate and the recurrent isolate were identical for 6 patients; in the seventh patient, 1 of the 2 isolates was not saved. In a study by Fang et al[15], 11% of patients with a prosthetic valve developed endocarditis following an episode of bacteremia; both mitral valve location and staphylococcal etiology were significant risk factors. In the current study, the incidence of new endocarditis following *S. aureus* bacteremia in the subset of patients with a prosthetic valve was 17% (2/12). Thus, endocarditis must be strongly considered if *S. aureus* bacteremia develops in a patient with a prosthetic valve.

In a separate analysis published in this same issue[8], nafcillin proved to be superior to vancomycin for therapy of *S. aureus* bacteremia as measured by bacteriologic cures; persistent bacteremia occurred significantly more often in patients receiving vancomycin even when stratified by severity of illness. Fifteen percent (4/27) had endocarditis despite negative findings by both transthoracic or transesophageal echocardiography. Thus, consideration must be given to treating high-risk patients (see Table 2) with more potent antistaphylococcal therapy (for example, nafcillin rather than vancomycin) or with combination antibiotic therapy for long-term duration of at least 4 weeks, regardless of echocardiographic findings.

The current study failed to show that shorter duration of antibiotic therapy (2 weeks) was a significant risk factor for developing endocarditis, a subject that has been disputed for 2 decades and that was not answered definitively even by a Veterans Affairs Cooperative Study[29,60,61,70]. The strong association of persistent bacteremia despite active antibiotic therapy with higher mortality does suggest that more intensive therapy of some type is warranted.

Fowler et al[19] showed that the source of the *S. aureus* in endocarditis patients was the intravascular catheter in 40% (23/59) of cases. In the current study, the intravascular catheter was the source in only 11% (7/64). This higher incidence of a catheter source for endocarditis in the Duke study is perhaps due to differing definitions of catheter infections in the 2 studies: the criteria for an intravascular catheter as the source of infection in the Duke study were less strict since Fowler used the subjective criterion of ''inflammation'' at the insertion site but did not use the standard objective criterion of semiquantitative growth on culture[41]. Our stricter criteria may have resulted in underdiagnosis of catheter infection.

Hemodialysis patients are at notable risk for *S. aureus* endocarditis[25] because of the high proportion of such patients who are nasal carriers of *S. aureus*[77], the necessity for regular percutaneous access for dialysis, and the increased calcium deposition in cardiac valves predisposing to valvular dysfunction. Our study revealed endocarditis to be associated with 12% (11/95) of *S. aureus* bacteremias in hemodialysis patients, an incidence identical to the Duke study[46], but higher than the 3.3% reported in a Danish study[55].

Emergence of MRSA as a common pathogen has added new challenges in management. MRSA endocarditis was responsible for only 3% (16/559) of *S. aureus* in 9 large series of retrospective reviews of endocarditis reported before 1998[6,14,26,43,44,65,69,71], although an extremely high rate of MRSA was reported in young intravenous drug users from Detroit, Michigan[36,37]. In the current study, MRSA was the cause of 31% (20/64) of staphylococcal endocarditis, similar to data recently reported by Fowler et al[19]. Persistent bacteremia occurred significantly more frequently in endocarditis caused by MRSA compared with MSSA, as assessed by multivariate (see Results) and univariate analyses (see Table 3). In our study, MRSA endocarditis was more likely to be hospital acquired (including patients on hemodialysis), while MSSA endocarditis was more likely to be community acquired ($p < 0.05$, see Table 3). Patients with MRSA endocarditis had a longer duration of fever after active antibiotic therapy was initiated, were significantly more likely to have persistent bacteremia, and had a higher incidence of renal insufficiency (see Table 3).

The mortality in our study was significantly higher in MRSA endocarditis compared with MSSA endocarditis (see Table 3). This observation is consistent with the findings of other investigators[51], but is at variance with the study by Fowler et al, who found no differences in mortality between MRSA versus MSSA endocarditis[19,58,63]. In a logistic model

of multivariate analysis in which the age, total APACHE III score, MRSA, creatinine >2 mg/dL, and community acquisition were entered, only total APACHE III score (p = .004) was statistically significant in predicting mortality, although a trend for mortality was also seen for MRSA (p = .064).

Historically, *S. aureus* endocarditis has a higher mortality than endocarditis caused by most other microorganisms[42,56,65,67]. *S. aureus* bacteremia and endocarditis have a particularly bad prognosis in the context of old age[14,17,20,24,28,30,31,47,50,52,57,64,66,69,72], rapidly fatal underlying diseases[7,24,34,40,72], and preexisting cardiovascular disease[30,31]. An exception is *S. aureus* tricuspid valve endocarditis occurring in young intravenous drug users, which has a lower mortality[14,69]. Congestive heart failure[14,65,69], central nervous system involvement[14,21,62,69], embolic complications[14,69,74], atrial fibrillation[65], atrioventricular block, and renal failure[21] have been identified previously as other risk factors for increased mortality in patients with endocarditis. Most studies have shown that hospital-acquired *S. aureus* endocarditis was associated with higher mortality than that seen in community-acquired disease[7,14,16,66].

We found that severity of illness (total APACHE III score and Pitt bacteremia score) and persistent bacteremia were associated with mortality in patients with endocarditis by multivariate analysis. The presence of atrioventricular block on electrocardiogram was also a significant risk factor for mortality (see Table 4). Atrioventricular block may result from extension of infection on the heart valve into the conduction system, predisposing the patient to arrhythmias and myocardial damage. Heart block on electrocardiogram has been listed as a relative indication for surgery in native valve endocarditis[1]. The current study would likewise suggest that the presence of atrioventricular block should mandate consideration for surgical valve resection. Early surgery has been advocated for *S. aureus* endocarditis[11]. In our study, patients with *S. aureus* endocarditis had improved outcome if they underwent valvular resection (see Results).

Although we report 1 of the largest prospective series of *S. aureus* endocarditis, a weakness of the current study was that many patients with *S. aureus* bacteremia did not undergo echocardiography, which may have led to underdiagnosis of endocarditis.

Staphylococcal endocarditis continues to be among the most studied entities in clinical medicine. Although the technical advance of transesophageal endocardiography has revolutionized the diagnosis of endocarditis, similar advances in prevention and improvements in medical therapy have not kept pace. Furthermore, it appears that endocarditis is at least as prevalent today as it was in previous years; hemodialysis, nosocomial endocarditis resulting from invasive vascular procedures, and intravenous drug abuse have all conspired to push the incidence of endocarditis higher.

CONCLUSIONS

S. aureus bacteremia patients at higher risk for *S. aureus* endocarditis include those with community-acquired bacteremia, unknown portal of entry, underlying valvular heart disease, prior endocarditis, or injection drug use. Nonwhite race, as identified in this study, was also a risk factor, although confirmation of that finding is needed. The high-risk patients with *S. aureus* bacteremia should be screened for concurrent endocarditis by echocardiography. Persistent bacteremia following initiation of antibiotic therapy was identified as a statistically significant independent risk factor for both endocarditis and mortality, a unique observation to our knowledge not previously reported in other series on *S. aureus* bacteremia. Given the strength of that observation, strong consideration should be given to repeating blood cultures in all patients with *S. aureus* bacteremia 3 days after initiation of antistaphylococcal therapy. If persistent bacteremia is documented, the likelihood of underlying *S. aureus* endocarditis should be viewed as high, even if echocardiography is unrevealing. The necessity for changing the patient's antistaphylococcal therapy to a more ''potent'' regimen and/or prolonging the duration of therapy should then be addressed. Since persistent bacteremia has also been documented to occur in patients with metastatic foci of infection (that is, pulmonary emboli, septic arthritis, osteomyelitis), an investigation for occult foci should be undertaken as well.

Factors we identified as being associated with increased mortality in patients with *S. aureus* endocarditis were infections due to MRSA, persistent bacteremia, and atrioventricular block on electrocardiogram. In patients with *S. aureus* endocarditis, MRSA as the etiologic agent should be suspected in patients with hospital-acquired endocarditis and renal insufficiency. In those settings, empiric treatment with antibiotics active against MRSA would be justified. If patients with *S. aureus* endocarditis have any of the above risk factors for increased mortality, consideration should be given to ''optimizing'' the patient's antimicrobial regimen (either more ''potent'' therapy or possibly combination antibiotic therapy), and to exploring the advisability of early surgical intervention, since surgery appeared to improve survival.

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