Kidney International, Vol. 54 (1998), pp. 1684–1689

DIALYSIS - TRANSPLANTATION

Incidence and outcome of *Staphylococcus aureus* bacteremia in hemodialysis patients

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Incidence and outcome of *Staphylococcus aureus* bacteremia in hemodialysis patients.

Background. *Staphylococcus aureus* bacteremia is frequently associated with metastatic complications and infective endocarditis (IE). The Duke criteria for the diagnosis of IE utilize echocardiographic techniques and are more sensitive than previous criteria. The documentation of IE in patients undergoing hemodialysis (HD) has become increasingly important in order to avoid the overuse of empiric vancomycin and the emergence of antibiotic resistance.

Methods. Patients who developed *S. aureus* bacteremia while undergoing HD at a tertiary medical center or one of four affiliated outpatient HD units were identified. Clinical outcome (death, metastatic complications, IE, and microbiologic recurrence) was assessed during hospitalization and at three months after discharge. Transthoracic and transesophageal echocardiograms were performed and the Duke criteria were used to diagnose IE. Pulse field gel electrophoresis was performed to confirm genetic similarity of recurrent isolates.

Results. Four hundred and forty-five patients underwent hemodialysis for 5431.8 patient-months. Sixty-two developed 65 episodes of *S. aureus* bacteremia (1.2 episodes/100 patient-months). Complications occurred in 27 (44%) patients. Bacteremia recurred in patients who dialyzed through polytetrafluorethylene grafts (44.4% vs. 7.1%, $P = 0.0.01$), and there was a trend to increased recurrence in patients who received only vancomycin (19.5% vs. 7.1%, $P = 0.4$). IE was diagnosed in 8 patients (12%), six of whom had normal transthoracic echocardiograms.

Conclusions. Sensitive echocardiographic techniques and the Duke criteria for the diagnosis of IE should be used to determine the proper duration of antibiotic therapy in hemodialysis patients with *S. aureus* bacteremia. This diagnostic approach, coupled with early removal of hardware, may assist in improving outcomes.

Infection continues to be a major cause of morbidity and mortality in hemodialysis patients. Bacteremia caused by *Staphylococcus aureus* is frequent, and the portal of entry involves prosthetic vascular access in approximately three-fourths of cases [1–3]. Despite improvements in aseptic technique and measures taken to decrease *S. aureus* carriage and colonization, *S. aureus* bacteremia remains a serious and frequent complication of hemodialysis [4].

Staphylococcus aureus bacteremia is commonly associated with the development of metastatic complications (osteomyelitis, abscess formation, septic arthritis), and infective endocarditis (IE). The reported incidence of IE in all patients with *S. aureus* bacteremia has varied from 0 to 64% [1, 5–19]. Since these studies were performed, the transesophageal echocardiogram (TEE) has been shown to increase the sensitivity of the detection of IE vegetations to greater than 90% [12, 20, 21]. The Duke diagnostic criteria for IE, which differ from previous criteria by utilizing echocardiographic findings, are more sensitive and specific than the previous Beth Israel criteria [22–24]. However, the actual incidence of IE in hemodialysis patients has been disputed because most case series have been small, retrospective, and the methods used to diagnose IE lacked sensitivity.

The ease of weekly dosing and low incidence of associated toxicities has made vancomycin the most attractive drug for the treatment of *S. aureus* bacteremia in hemodialysis patients [25]. The empiric administration of long courses (>1 month) of weekly vancomycin is common practice in patients in whom the diagnosis of IE is suspected but not confirmed. With the appearance of vancomycin-resistant organisms in hemodialysis units, this use of vancomycin has been discouraged [26, 27]. In addition, several authors have suggested that vancomycin alone for the treatment of IE is associated with suboptimal clinical outcomes and slower *in vitro* killing rates when compared with β-lactam antibiotics [28]. Thus, establishing the diagnosis of IE has become necessary in order to determine the proper drug and duration of therapy in hemodialysis patients with *S. aureus* bacteremia.

Key words: infective endocarditis, vancomycin, antibiotic therapy, metastatic complications, Duke criteria, morbidity in hemodialysis.

Received for publication March 17, 1998
and in revised form May 12, 1998
Accepted for publication June 1, 1998

We conducted a prospective study of hemodialysis patients at Duke University Medical Center (DUMC) to determine the incidence and outcome of *S. aureus* bacteremia, using transesophageal echocardiogram and the Duke criteria for the diagnosis of endocarditis.

METHODS

All adult patients (>18 years old) undergoing hemodialysis who had *S. aureus* bacteremia at DUMC between 15 September 1994 and 15 March 1996 were enrolled in this prospective observational study. All patients were undergoing hemodialysis for chronic renal failure at DUMC or one of four affiliated hemodialysis units. Patients were excluded from analysis if they had polymicrobial bacteremia, or if they were neutropenic ($<1.0 \times 10^9$ wbc/liter).

Patients with *S. aureus* bacteremia were identified by daily communication between the microbiology laboratory blood culture technician and one of the authors (K.M., V.F., A.G.). Demographic and clinical data (presence of diabetes, immunocompromised status, type of vascular access, organism sensitivity, and treatment) were recorded for each patient with *S. aureus* bacteremia. In addition, each patients' clinical course and outcome (recurrent bacteremia, death, metastatic complication) were assessed during treatment and three months after treatment. Patients with *S. aureus* bacteremia had repeat blood cultures taken two days after initial recognition of bacteremia, and thereafter when clinically indicated. Standard microbiological methods were used for blood culture and sensitivity studies. We recommended that transthoracic echocardiograms (TTEs) and transesophageal echocardiograms (TEEs) be performed on all patients five to seven days after the first positive blood culture. This advice was followed for 49 (79%) and 36 (58%) of 62 patients, respectively.

Clinical care of each patient, including antibiotic type and duration was determined by each patient's attending physician. Vancomycin (20 mg/kg) and β-lactamase resistant penicillins were dose-adjusted for underlying renal failure in all patients. Oral rifampin was recommended in conjunction with vancomycin, but this therapy was used at the discretion of the attending nephrologist. In addition, the necessity for surgical removal of an infected graft or catheter, and the need for echocardiographic evaluation was determined by the patient's attending nephrologist.

We defined bacteremia as growth of *S. aureus* in two blood cultures taken from peripheral sites, or from at least one culture drawn from a central line in patients who had fever ($T > 38°C$). Portal of entry was defined as skin if history and physical examination provided evidence of soft tissue infection or wound infection that did not involve the vascular access. Patients who did not have an apparent source of infection after history and physical examination were considered to have vascular access-related bacteremia. Bacteremia was considered to be outpatient dialysis-related if the culture result was obtained within two days of admission. Recurrent bacteremia was defined as growth of the same organism from cultures taken after one or more negative cultures had been obtained. Infective endocarditis was defined using the Duke diagnostic "major" (typical blood culture and positive echocardiogram) and "minor" (predisposition, fever, vascular phenomena, immunologic phenomena, suggestive echocardiogram, and suggestive microbiologic findings) criteria. Patients who had two major criteria (*S. aureus* bacteremia and echocardiographic findings consistent with IE), or one major criteria and three minor criteria, or five minor criteria were diagnosed with IE [22].

Pulse field gel electrophoresis (PFGE) was performed on recurrent isolates in order to confirm genetic similarity, as described by Kong et al [28]. Briefly, single isolates grown overnight at 37°C in broth medium were embedded into small agarose plugs, digested with lysotaphin and lysozyme, and deproteinized using a reagent kit (GenePath I; Biorad, Hercules, CA, USA). Restriction enzyme digestions with *Sma*I were electrophoresed on 1% agarose gels, stained with ethidium bromide, and interpreted according to published guidelines [29].

SAS statistical software (SAS Institute, Inc., Cary, NC, USA) was used for analysis of data. The outcome variables were recurrence of bacteremia, metastatic complications, and death. The association of demographic, clinical, microbiological and treatment variables with these outcomes was assessed using two-sample *t*-tests, chi-squared analysis, and Cochran-Mantel-Haenszel statistics.

RESULTS

From September 1994 to March 1996, 445 patients underwent hemodialysis for a total of 5431.8 patient-months. Sixty-two of these patients developed 65 episodes of SAB, accounting for an incidence of 1.2 episodes per 100 patient-months. Thirty-nine (63%) patients were female, and 46 (74%) patients were African-American. The mean age was 53.5 years (range 25 to 87 years). Twenty-six (42%) patients had diabetes mellitus, 6 (10%) had ongoing injecting drug use, 4 (6%) chronically used oral steroids, and 2 (3%) were infected with human immunodeficiency virus (HIV).

Fifty-eight (89%) episodes of bacteremia were considered to have originated in a vascular access device, and 7 (11%) episodes were associated with a concurrent soft tissue infection. Thirty-one (53%) patients with device related bacteremia were dialyzed through dual lumen, tunneled, cuffed catheters, 8 (14%) were dialyzed through temporary catheters, 10 (17%) were dialyzed through arteriovenous (AV) fistulas, and 9 (16%) were dialyzed through polytetrafluoroethylene (PTFE) grafts. Forty-six (71%) episodes were acquired in the outpatient dialysis center and 19 (29%) were acquired in the hospital. Most patients

Table 1. Serious systemic complications in hemodialysis patients with *Staphylococcus aureus* bacteremia (SAB; $N = 65$ episodes)

Complication	# Patients % *episodes SAB*
Osteomyelitis	7 (11%)
Septic joint	2 (3%)
Epidural abscess	2 (3%)
Infective endocarditis	1 (2%)
Multifocal infection	8 (13%)
Infective endocarditis with:	
septic arthritis	2
line vegetation	3
osteomyelitis	1
meningitis	1
soft tissue abscess	1
Death	9 (14%)

received antibiotics within two days of the development of fever. The mean duration from the onset of symptoms to the receipt of intravenous antibiotics was 1.5 ± 1.1 day (range 1 to 8 days).

Methicillin-sensitive *S. aureus* (MSSA) was the cause of bacteremia in 49 (75%) episodes and methicillin-resistant *S. aureus* (MRSA) was the cause in 16 (25%). Forty episodes (61%) were treated with intravenous vancomycin alone. An additional 13 (20%) episodes were treated with a combination of intravenous vancomycin and oral rifampin. Only 12 (19%) episodes were treated with a β-lactamase-resistant penicillin. Antibiotics were administered for a mean duration of 31 ± 14 days (range 7 to 90 days). Forty-eight patients (83% of patients with device-related bacteremia) had their vascular access removed at a mean of 11.6 ± 24.6 days after presentation (range 1 to 120 days).

Complications of *S. aureus* bacteremia developed in 27 (44%) patients (Table 1). As shown in the Table, infective endocarditis [8], osteomyelitis [8], and septic arthritis [4] were the most common metastatic complications. No patient characteristics (age, diabetes mellitus, immunosuppressed status, type of vascular access), bacteremia characteristics (organism sensitivity, portal of acquisition), or treatment parameters (type or duration of antibiotics, time to antibiotics or line removal) led to an increased risk for the development of complications.

The detection of IE was particularly difficult. Clinical characteristics such as the presence of a cardiac murmur or known predisposing valvular heart disease were not predictive of the development of IE ($P = 0.38$ and 0.5, respectively) and embolic phenomenon were rarely noted on physical examination. Transthoracic echocardiograms were performed on 49 (79%) patients who developed *S. aureus* bacteremia, and transesophageal echocardiograms were performed on 36 (55%) patients. Ten patients with normal findings on TTE did not subsequently undergo a TEE study. Results of both studies are shown in Figure 1. TEE was performed in 28 patients who had normal findings

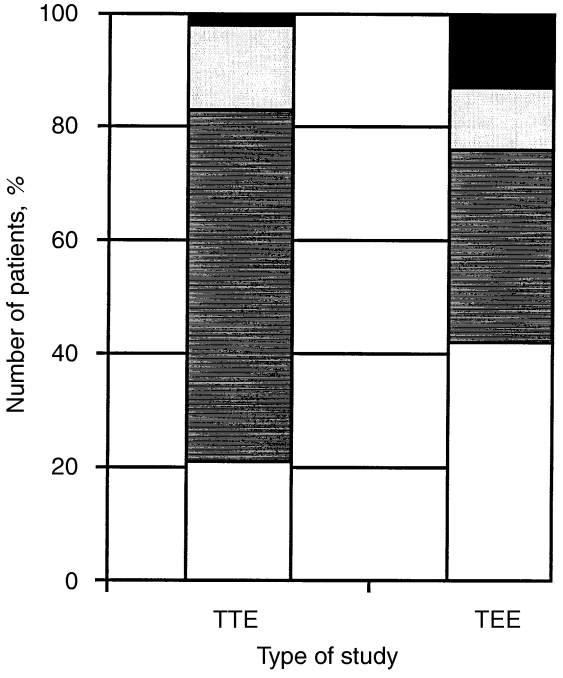

Fig. 1. Findings of transthoracic (TTE) and transesophageal (TEE) echocardiograms in 62 patients with *S. aureus* bacteremia. Symbols are: (■) valvular vegetations; (▨) anatomic abnormalities; (■) normal findings; (□) no study performed.

using TTE. Eight of these 28 patients (29%) had abnormalities detected by TEE that were not visualized by TTE. Two of the eight (25%) patients had anatomic abnormalities, and six (75%) patients had valvular vegetations. Thus, TEE was required for diagnosis of six of the eight patients with IE.

Bacteremia caused by a *S. aureus* with the same antibiotic sensitivity pattern recurred in 10 (15%) patients. Of the 10 pairs of isolates, nine pairs had identical banding patterns by PFGE analysis (data not shown), confirming a recurrence rate of 14%. Eight bacteremias recurred within one month of antibiotic therapy, and one bacteremia recurred within two months of antibiotic completion. Recurrent bacteremia developed more often in patients who were dialyzed through PTFE grafts compared to other forms of vascular access (44.4% vs. 7.1%, Table 2). More patients treated with vancomycin alone had recurrence of bacteremia when compared to patients treated with either β-lactamase-resistant penicillins or combination regimens (19.5% vs. 7.1%), even after controlling for the presence of a PTFE graft (21.4% vs. 5.5%), however, the difference was not statistically significant (Table 2).

Nine patients (14.5%) died as a consequence of infection. Eight patients died within one month of their bacteremia, and one patient died after the development of a cardiac valvular ring abscess within two months of presentation. Two of the patients that died had IE that was detected only by TEE.

Table 2. Risk factors (patient factor or treatment variable) for bacteremia recurrence ($N = 65$ episodes)

Patient factor	Number of patients	Risk of recurrent bacteremia: Patients with recurrence *(%)*	Risk of recurrent bacteremia: Relative risk	95% CI	*P* value[a]
Dialysis through PTFE graft					
yes	9	4 (44.4%)	6.22	1.9 to 20.5	(0.01)
no	56	4 (7.1%)			
Treatment with vancomycin only					
yes	41	8 (19.5%)	2.73	0.4 to 20	(0.4)
no	14	1 (7.1%)			
Treatment with vancomycin, controlled for PTFE graft					
yes	28	6 (21.4%)	1.29	0.2 to 8.8	(0.2)
no	18	1 (5.5%)			

[a] Fisher's exact 2-tailed *P* value reported

DISCUSSION

Staphylococcus aureus is the most common cause of bacteremia in hemodialysis patients [1–3]. In this prospective study, we used aggressive diagnostic methods and follow-up to demonstrate a surprisingly large incidence of metastatic complications (44%) and death (14%) in dialysis patients who develop bacteremia with *S. aureus*. Echocardiographic techniques, combined with the sensitive Duke Criteria for the diagnosis of IE, have enabled us to document that infective endocarditis occurs more frequently (14%) than previously described. *S. aureus* bacteremia recurs more frequently in patients who are dialyzed through PTFE grafts, and there is a trend to increased recurrence in patients who receive vancomycin as their only antibiotic.

Our population of hemodialysis patients had an incidence of *S. aureus* bacteremia (1.2 per 100 patient-months) that is consistent with previous results approximating 0.1 per patient-year [30]. In a recent literature review, Raad and Sabbagh concluded that serious complications of catheter-related *S. aureus* bacteremia occur at a frequency of 20% to 30% in the general population [9]. The authors of a prior retrospective study of *S. aureus* bacteremia in 30 hemodialysis patients suggested that the incidence of serious infectious complications in hemodialysis patients (27%) did not differ from the rate of complications in nonuremic patients [6]. The high incidence of noncardiac metastatic complications (17%) and recurrent bacteremia (14%) that we observed in our study confirms the results of these prior retrospective reports.

Documenting the diagnosis of IE has become important in order to avoid the overuse of long durations of empiric vancomycin in this patient population. The actual incidence of IE in patients with *S. aureus* bacteremia has been disputed, with rates ranging from 4% to 64% in the literature [8–19]. In a retrospective study of hemodialysis patients, Quarles, Rutsky and Rostand reported an incidence of IE of only 6.3% [1], and Francioli and Masur reported a similar incidence of 5.4% [6]. Both groups noted, however, that their findings might have been underestimated due to a lack of sensitivity of their diagnostic criteria for IE. Since those studies were performed, the Duke Criteria for the diagnosis of IE, which utilize echocardiographic findings, have been validated pathologically and found to be more sensitive and specific than previous criteria that rely on physical examination and laboratory results [23, 24]. In this study, the use of more sensitive diagnostic techniques allowed us to detect a two- to threefold increase (14% vs. 5 to 6%) in IE than found in previous studies. Since only 55% of our patients underwent TEE, the true incidence of IE may have been even higher. This high incidence of previously undetected IE may explain the high relapse rate in patients treated with short courses of antibiotic therapy [31].

Transesophageal echocardiogram appears to be more sensitive than TTE in detecting vegetations early (5 to 7 days) after bacteremia, as TTE detected only 25% of vegetations subsequently detected by TEE. This observation, which is consistent with our previous published findings [32], may be explained by enhanced visualization of "small" vegetations. However, since the present study was not designed to compare the two tests, further investigations are warranted to determine the sensitivity and specificity of these echocardiographic techniques performed early after bacteremia.

It is also important to note that history and clinical findings were of limited value as indicators of the presence or absence of IE, as we did not find that the presence of a murmur or history of pre-existing valvular disease at the time of first bacteremia were reliable predictors for the development of IE. Although evidence suggests that community-acquired *S. aureus* bacteremia results in an increased risk of IE when compared to nosocomial bacteremia [19], mode of acquisition is particularly difficult to assess in these patients who undergo hemodialysis several times a week in a hospital setting. In addition, the previously reported observations that patients with identifiable or removable portals of infection, and intravenous drug

users have more favorable prognosis were not supported by our findings [1, 12].

Our patients had a 44% complication rate and a 14% relapse rate despite the initiation of antimicrobial therapy within two days of the onset of symptoms. We found that patients who were dialyzed through PTFE grafts have a sixfold increased risk of bacteremia recurrence. This observation may be explained by the fact that it is difficult to completely remove PTFE grafts. Thus, the possibility exists that relapse is due to a persistent focus of infection remaining after partial resection. Another possibility for the high rate of relapse and complications is the frequent use of vancomycin as a sole antibiotic, a regimen that may be less effective than that including combinations of antibiotics or β-lactamase-resistant penicillins [19]. In this study, more patients treated with vancomycin (20%), had recurrence of bacteremia than patients who were treated with β-lactamase-resistant penicillins or combinations of antibiotics (7%). Although our sample size was not large enough to allow for statistical significance (CI 0.4 to 20), it is likely that patients with more severe infections would receive β-lactamase-resistant penicillins or combinations of antibiotics, biasing the results in the opposite direction. Though in the present study this trend may be explained by levels of vancomycin waning at the end of dosing intervals, several previous studies have documented similar suboptimal outcomes in vancomycin-treated patients despite adequate drug levels and susceptible strains [19]. This issue needs to be addressed in a larger prospective randomized trial.

Our study is limited by its observational design and relatively small sample size, which may have obscured small differences in patient groups predicting outcome. Also, not all patients were evaluated by echocardiogram, possibly resulting in an underestimated incidence of IE. Finally, we have no data on nasal carriage of *S. aureus* in our patients, which has been reported to result in an increased risk of infection in patients undergoing dialysis [30, 33].

Nearly half of our patients (44%) developed serious systemic complications, including osteomyelitis, infective endocarditis, and death following a bacteremia caused by *S. aureus*. By using sensitive diagnostic criteria for IE, we have documented a 14% incidence of IE in this setting, possibly explaining the frequent recurrence of bacteremia after short courses of antibiotic therapy. In light of the recent emergence of vancomycin-resistant *S. aureus* in patients with extensive exposure to vancomycin [27], we believe that hemodialysis patients with *S. aureus* bacteremia should undergo sensitive echocardiographic examination in order to determine the proper duration of antibiotic treatment instead of receiving long courses of empiric therapy. In addition, the trend of recurrent bacteremia associated with the use of vancomycin emphasizes the need for future prospective studies to evaluate the efficacy of other antibiotics in this setting. Suboptimal outcomes, combined with the recent emergence of resistance, emphasize that vancomycin should never be used simply for convenience of administration when other antibiotics are an option. Finally, the aggressive and complete removal of infected intravascular devices in patients with *S. aureus* bacteremia should be strongly considered in order to prevent metastatic and recurrent infection.

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APPENDIX

Abbreviations used in this article are: AV, arteriovenous; HD, hemodialysis; HIV, human immunodeficiency virus; IE, infective endocarditis; PFGE, pulse field gel electrophoresis; PTFE, polytetrafluoroethylene; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; *S. aureus*, *Staphylococcus aureus*; TEE, transesophageal echocardiograms; TTE, transthoracic echocardiogram; wbc, white blood cells.

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