

# *Staphylococcus aureus* and Other Bacteremias in Hemodialysis Patients: Antibiotic Therapy and Surgical Removal of Access Site

J.R. Lentino, L.M. Baddour, M. Wray, E.S. Wong, V.L. Yu

## Summary

**Background:** Bacteremia is commonplace in patients undergoing hemodialysis since the vascular access site is a ready source of infection. Mortality is notably high. However, uncertainties exist with respect to therapy including indications for surgical removal of vascular access site and duration of therapy. We therefore conducted a large-scale collaborative study of bacteremia in hemodialysis patients in six US academic medical centers to define the epidemiology of such infections and to address issues of management.

**Patients and Methods:** We conducted a prospective observational study over 2 years. Severity of illness at onset of bacteremia was defined by objective criteria. Patients were followed for 90 days to assess late complications including endocarditis and mortality. Univariate and multivariate analyses were used to assess risk factors for mortality.

**Results:** Patients experiencing 127 consecutive episodes of bacteremia were enrolled. The most common cause of bacteremia was *Staphylococcus aureus* (31%), followed by aerobic gram-negative bacilli (28%) and coagulase-negative staphylococci (13%). Polymicrobial bacteremia occurred in 6% of patients. The most frequent focus of infection was the access site for hemodialysis, although urinary tract, gastrointestinal tract and lung were also implicated. Aerobic gram-negative bacilli and enterococci usually originated from the urinary tract. *S. aureus* was significantly more likely to cause infection of the access site than other bacteria ( $p = 0.0001$ ). *S. aureus* endocarditis was diagnosed in two patients who were receiving antibiotic therapy for *S. aureus* bacteremia.

Removal of the infected access site (shunt, fistula, catheter) was performed for 86% of the patients (95% of the intravenous catheters and 80% of the arteriovenous fistulas/shunts). Overall mortality was 33% at 90 days and was significantly associated with severity of illness at onset of antibiotic therapy and age > 60 years. Mortality was not significantly different in patients undergoing surgical removal of infected access site versus those treated with antibiotics alone.

**Conclusion:** When *S. aureus* was isolated from the blood, the access site was the most frequent source. Surgical removal

of the access site did not have a notable impact on mortality. Until a randomized trial proves otherwise, it appears that surgical removal of the access site can be individualized. Selected patients who are less severely ill (based on objective criteria) can maintain their hemodialysis access site and be treated with 2 weeks of antibiotic therapy.

## Key Words

*Staphylococcus aureus* · Bacteremia · Hemodialysis patients

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## Introduction

Since its implementation more than 30 years ago, hemodialysis has proved to be lifesaving for thousands of patients. Given the compromised immune status of these patients, the presence of a persistent foreign body and the frequent invasive procedures directed at the bloodstream, vascular access site infection is a common complication. In fact, bacteremia is now the second most common cause of death in the population [1, 2].

For catheter-related infections, removal of the foreign body is accepted as a cornerstone for successful therapy. However, removal of a hemodialysis vascular access site is

### J.R. Lentino

Loyola University Stritch School of Medicine, Hines VA Hospital, Hines, IL 60141-5000, USA

### L.M. Baddour

Dept. of Medicine (U-114), UT Medical Center - Knoxville, Knoxville, TN 37920-6999, USA

### M. Wray

Dept. of Medicine (U-114), University of Tennessee - Memphis, Memphis, TN 38163, USA

### E.S. Wong

Medical College of Virginia, McGuire VA Hospital, Richmond, VA 23249, USA

### V.L. Yu (corresponding author)

Infectious Disease Section (111E-U), VA Medical Center, University Drive C, Pittsburgh, PA 15240, USA; Phone: (+1/41) 2688-6179; Fax: -6950, e-mail: vly+@pitt.edu

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a more complex issue given the absolute necessity for renal function and the limited number of sites available for access [3]. The optimal duration of antibiotic therapy is also uncertain. We therefore conducted a prospective observational study of hemodialysis patients experiencing bacteremia. Our objectives were to survey the demographics of hemodialysis patients experiencing bacteremia and the microbiology of the isolates involved. We also sought to access the impact of duration of antibiotic therapy and approach to the vascular access site (i.e. removal or nonremoval) on the presence of complications (endocarditis), bacteriologic response and patient outcome.

### Patients and Methods

#### Patients

We conducted a prospective observational study of consecutive episodes of bacteremia occurring over 2 years concluding in 1988. This study was conducted at six university affiliated teaching hospitals in the United States: Pittsburgh VA Medical Center; Presbyterian University Hospital; Pittsburgh, PA; Hines VA Hospital, Hines, IL; Hunter-McGuire VA Medical Center, Richmond VA; University of Tennessee Medical Center, Memphis, TN; and Hennepin County Medical Center, Minneapolis, MN.

Patient demographic, microbiological and treatment data were prospectively collected by an infection control practitioner in collaboration with a physician. All data were then entered into a computer data bank housed on the Prophet System (Division of Research Resources, National Institute of Health). Patients were followed until hospital discharge and then at 30 and 90 days following the date the first positive blood culture was drawn. The study was observational in that decisions concerning choice of an-

timicrobial therapy and vascular access intervention were made by the patients' attending physicians.

### Definitions

Bacteremia was defined as isolation of an organism from one set of blood cultures (aerobic and anaerobic) with the exception of *Staphylococcus epidermidis* in which isolation from two sets of blood cultures obtained by separate venipunctures was required. Bacteremia was considered polymicrobial if more than one bacterium was isolated from blood. Vascular access site infection was defined according to the Centers for Disease Control criteria [4]. Severity of illness was assessed for each patient at the time of first positive culture using the Pitt Bacteremia Score, a previously validated index based on mental status, vital signs, requirement for respiratory support and occurrence of cardiac arrest [5]. Patients were defined as "critically ill" if they accumulated four or more points.

### Statistical Analyses

Univariate analyses were performed using the chi-square test for categorical variabilities and the Student's t-test or Fisher's exact test for continuous variables. Potential risk factors for bacteremia and for mortality were evaluated. Those that reached a 20% significance level were entered into a multiple regression analysis and significance was set at the 5% level.

### Results

#### Episodes of Bacteremia

127 consecutive episodes of bacteremia occurring in 118 patients were evaluated over 24 months. Seven patients had two episodes of bacteremia and one patient had three separate episodes of bacteremia. The mean age of patients was

53 years, range 21–76 years. The most common underlying diseases were: diabetes mellitus (34%), liver disease (8%), chronic obstructive pulmonary disease (8%), solid organ malignancy (6%). Corticosteroids or other immunosuppressive chemotherapies were received by 24% and 13% of patients, respectively.

#### Microorganisms

The most frequent indication for obtaining blood cultures was the presence of fever. 26% (33/127) of the isolates were isolated from a single set of blood cultures, and 74% (94/127) were isolated from two or more sets. 138 isolates were recovered from 127 episodes of bacteremia on

Table 1

The etiology of 127 bacteremia episodes involving 138 microorganisms in hemodialysis patients.

Microorganism	Frequency % (no.)	Primary Focus % (no.)	Mortality/30 days % (no.)
<i>Staphylococcus aureus</i>	31 (43)	Fistula/shunt IV-associated	51 (22) 23 (10)
<i>Staphylococcus epidermidis</i>	13 (18)	Fistula/shunt	50 (9) 11 (2)
<i>Escherichia coli</i>	8 (11)	Urinary tract	36 (4) 18 (2)
<i>Enterococcus faecalis</i>	6 (8)	Urinary tract	38 (3) 38 (3)
<i>Pseudomonas aeruginosa</i>	5 (7)	Wound	43 (3) 43 (3)
<i>Klebsiella pneumoniae</i>	4 (5)	Urinary tract	20 (1) 20 (1)
<i>Enterobacter</i> spp.	4 (6)	Pneumonia	38 (2) 50 (3)
<i>Viridans streptococci</i>	4 (5)	Fistula/shunt Endocarditis	40 (2) 0 (0)
<i>Streptococcus pneumoniae</i>	4 (5)	Pneumonia	80 (4) 40 (2)
<i>Streptococcus agalactiae</i>	3 (4)	Fistula	50 (2) 20 (10)
<i>Bacteroides fragilis</i>	1 (2)	Gastrointestinal	25 (1) 25 (1)
<i>Proteus mirabilis</i>	2 (3)	IV-associated	50 (1) 50 (1)
<i>Staphylococcus warnerii</i>	1 (2)	Unknown	100 (2) 0 (0)
<i>Candida</i> spp.	3 (4)	Gastrointestinal	50 (2) 75 (3)
Miscellaneous <sup>a</sup>	10 (14)	-	-

<sup>a</sup>Miscellaneous includes various *Streptococcus* spp. (6); *Citrobacter diversus* (1); *Pasteurella multocida* (1); *Pseudomonas putida* (1); *Haemophilus parainfluenzae* (1); *Pseudomonas* spp. (1); *Clostridium* spp (1); *Listeria monocytogenes* (1); *Providencia stuartii* (1)

Table 2

Etiology, access site and outcome of infection at 30-day follow-up for eight patients with polymicrobial bacteremia.

Organism 1	Organism 2	Organism 3	Primary focus	Outcome 30 days
<i>Staphylococcus epidermidis</i>	<i>Streptococcus agalactiae</i>		Fistula	Survived
<i>Staphylococcus epidermidis</i>	<i>Viridans streptococcus</i>		Fistula	Died
<i>Pseudomonas aeruginosa</i>	<i>Enterobacter cloacae</i>		Pneumonia	Died
<i>Escherichia coli</i>	<i>Enterococcus faecalis</i>		Unknown	Survived
<i>Enterobacter cloacae</i>	<i>Candida</i> spp.		Unknown	Died
<i>Viridans streptococcus</i>	<i>Enterococcus</i>	<i>Providencia stuartii</i>	UTI	Survived
<i>Enterococcus faecalis</i>	<i>Pseudomonas</i>	<i>Candida albicans</i>	GI	Died
<i>Enterococcus faecalis</i>	<i>Pseudomonas</i>	<i>Klebsiella pneumoniae</i>	Unknown	Survived

one or more occasions (Table 1). Gram-positive cocci were the predominant organisms with 31% of isolates identified as *S. aureus* (14%, 6/43 were methicillin resistant), followed by *S. epidermidis* (13%) and *Enterococcus faecalis* (6%) (Table 1). Among gram-negative bacilli, *Escherichia coli* (8%) and *Pseudomonas aeruginosa* (5%) were the most common. In the eight patients with multiple episodes of bacteremia, four had recurrent bacteremia with the same isolate: one each with *E. coli*, *Klebsiella pneumoniae*, *S. epidermidis* and *S. aureus*. The other four patients had different isolates with each episode of bacteremia. Polymicrobial bacteremias occurred in 6% (8/127) of episodes (Table 2). *S. aureus* was not recovered from any patients with polymicrobial bacteremia.

### Sites of Infection

112 patients had fistulas or shunts (101 with fistulas and 11 with shunts); 42 patients had other intravascular access for dialysis. 26 had both a fistula/shunt and an intravenous access catheter. Of the 42 catheters, 38 were Uldall or subclavian catheters, 17 of these became infected, nine with *S. aureus*, four with coagulase-negative staphylococci and four with gram-negative bacilli. Three patients with femoral catheters had infections, two with *S. aureus*, one with *Proteus mirabilis*. The one patient with an access catheter in the arm developed an *S. aureus* infection. Access sites were identified as the portal of entry for 39% of the bacteremias among this hemodialysis population (Tables 1 and 3).

Four patients developed endocarditis, two due to *Streptococcus* spp. and two due to *S. aureus*. The two patients with *S. aureus* endocarditis are described herein. One patient was a 73-year-old man admitted for dizziness, chills, fever and hypotension. The left forearm fistula was warm and was the presumed site of infection; all four blood culture sets yielded methicillin-sensitive *S. aureus*. The infection progressed despite therapy with gentamicin and vancomycin. The patient developed a loud systolic murmur and numerous subconjunctival petechiae. He died 7 days after the positive cultures. Autopsy confirmed presence of a mitral valve vegetation and pericarditis. The second patient was a 46-year-old intravenous drug user. He was admitted with abdominal pain, lethargy and weakness. Methicillin-sensitive

*S. aureus* was isolated from both sets of blood cultures, a gortex graft for hemodialysis access and a pericardial effusion. The graft was surgically removed. Echocardiogram demonstrated tricuspid valve vegetations. He developed right-sided hemiparesis from cerebral emboli. After 1 month of therapy with vancomycin and an aminoglycoside, he was discharged home.

### Antibiotic therapy

29 episodes of bacteremia/fungemia were treated with a single agent, which was vancomycin in 69% (20/29) of cases. 29 episodes of bacteremia were treated with two antibiotics: 51% (15/29) received vancomycin and an aminoglycoside, 10% (3/29) received a beta-lactam plus an aminoglycoside, 18% (5/29) received both a beta-lactam plus vancomycin and 21% (6/29) had other miscellaneous combinations. Vancomycin was the most commonly used antibiotic and was used in 55% (70/127) of episodes as the initial choice either alone or in combination with another agent, or as an addition to a two-drug regimen in 16% (20/127) of additional episodes of bacteremia.

### Duration of Antibiotic Therapy and Outcome

We arbitrarily defined short-term therapy as less or equal to 2 weeks and long-term therapy as greater than 2 weeks. Of the 127 patients followed, 17 died within 2 weeks of initiating antibiotics, and two patients received no antibiotic

Table 3.

***Staphylococcus aureus* bacteremia was significantly associated with access site infection.**

Isolate:	Noninfected % (no.) (n = 76)	Infected % (no.) (n= 51)	Total no.
<i>S. aureus</i>	17 (13)	59 (30)	43
Other organisms	83 (63)	41 (21)	84
Total	100 (76)	100 (51)	127

p = 0.0001 (Fisher's exact test, 2-tailed)

*S. aureus* was significantly more likely than other microorganisms to cause infection of access site

Table 4  
**Mortality of bacteremia.**

	30 days	90 days <sup>b</sup>
All episodes	25% (32/127)	33%(41/123)
All <i>S. aureus</i>	23% (10/43)	30% (13/43)
<i>S. aureus</i> from access site	27% (8/30)	30% (9/30)
Gram-negative aerobic bacilli	17% (5/30)	39% (11/28)
Non- <i>S. aureus</i> gram-positive cocci	18% (6/34)	18% (6/34)
Critically ill <sup>a</sup>	68% (13/19)	79% (15/19)
Not critically ill	18% (19/108)	25%(26/104)

<sup>a</sup> critically ill defined in Patients and Methods. Patients who were critically ill were significantly more likely to die compared to patients who were not critically ill,  $p < 0.001$ ; <sup>b</sup> four patients were lost to 90-day follow-up

therapy, leaving 108 evaluable patients. 65 received short-term therapy and 43 were given long-term therapy.

Outcome of therapeutic intervention was assessed at both 30 and 90-day follow-up. At 30 days, survival was no better in the long-term therapy group than in the short-term group (79% vs 91%,  $p > 0.05$ ). At 90 days, the survival rate in the long-term group was 63% compared to 86% in the short-term group ( $p > 0.05$ ). This reflects the bias for administering long-term therapy in patients with increased severity of illness. Outcome of antibiotic therapy was assessed for 43 episodes of *S. aureus* bacteremia. One patient received no therapy and eight patients died within 2 weeks of initiating therapy. The remaining 34 patients were evaluated: 12 received long-term and 22 short-term antibiotic therapy. No patient receiving short-term therapy died within 30 days, while 17% (2/12) of the patients receiving long-term therapy died at 30-day follow-up. By 90 days, 4.5% (1/22) of short-term patients had died vs 33% (4/12) long-term patients ( $p = 0.03$ ). Mortality was significantly higher in those patients who were critically ill (68%) compared to those who were less ill (18%,  $p = 0.001$ ) and older ( $> 60$  years vs  $< 60$  years,  $p = 0.05$ ) at the onset of therapy (Table 4).

Patients classified as critically ill were significantly more likely to die than those not critically ill by both univariate analyses ( $p = 0.001$ , Table 4) and multivariate analyses ( $p = 0.07$ ). In two models of assessing mortality by logistic regression analyses, the following factors were not significantly associated with mortality: age, presence of liver disease or chronic obstructive pulmonary disease.

### Surgical Intervention

Removal of infected shunts/fistulas or intravenous dialysis access catheters was required to treat most hemodialysis bacteremic patients. Overall, 86%

(44/51) of infected sites/devices were removed; 95% (20/21) of the intravenous catheters and 80% (24/30) of the arteriovenous fistulas/shunts. No significant improvement in outcome was seen with surgical removal of the access site compared to antibiotic therapy alone (Table 5). However, the statistical power with this sample size was low. Assuming the same distribution of surgery/no surgery (Table 5), approximately 1,200 patients would be needed to detect a significant difference at a beta error of 0.8 and an alpha error of 0.05.

For *S. aureus* bacteremia, 73% (19/26) of patients with access removal survived compared to 75% (3/4) without access removal. Comparison of vancomycin with other therapies was not feasible, because too few patients with *S. aureus* bacteremia were treated with antibiotics other than vancomycin. However, for the 38 patients with *S. aureus* bacteremia who were given vancomycin, survival at 30 and 90 days was 79% (30/38) and 70% (26/37), respectively. The majority of survivors (65%, 22/34) had received short-term vancomycin therapy.

### Discussion

We report one of the largest prospective studies of bacteremia in hemodialysis patients ever conducted; the multicenter nature of the study allowed inclusion of a wide diversity of patients so that the results might be more applicable. We not only monitored the patients throughout their hospital course, but for 90 days after documentation of bacteremia to capture long-term complications including endocarditis. Over a 2-year period, we studied 127 consecutive episodes of bacteremia. Gram-positive cocci were responsible for 70% of all bacteremic episodes in our investigation (Table 1). *S. aureus* was the single most common isolate recovered from bacteremic hemodialysis patients (31%).

Table 5  
**Effect of surgical removal of infected access site on 30-day mortality.**

	Surgery	Died % (no.)	Survived % (no.)	Total % (no.)
A) All bacteremias		n = 11		n = 51
	No	9 (1)	15 (6)	14 (7)
	Yes	91 (10)	85 (34)	86 (44)
	Total	100 (11)	100 (40)	100 (51)
B) <i>S. aureus</i> bacteremias		n = 8		n = 30
	No	13 (1)	14 (3)	13 (4)
	Yes	87 (7)	86 (19)	87 (26)
	Total	100 (8)	100 (22)	100 (30)

No significant difference in mortality at 30 days was seen for patients undergoing surgery vs those receiving antibiotic therapy only ( $p > 0.05$ )

Aerobic gram-negative bacilli accounted for 28% of isolates. The primary focus of infection was identified in 80% of the bacteremic patients in our study with the most frequent focus being the intravascular access sites – the majority of which were infected with *S. aureus* (Table 3). Aerobic gram-negative bacilli and enterococci usually originated from the urinary tract (Table 1). Eight patients experienced polymicrobial bacteremia (Table 2). *Enterococcus faecalis* was the most common isolate implicated in these patients. The fistula was the primary focus for the two patients with bacteremia caused by two different gram-positive cocci. Mortality at 30 days for polymicrobial bacteremia was 50% (4/8) which was not significantly different from that of bacteremia of monomicrobial etiology, 24% (28/119).

Complications of *S. aureus* bacteremia are common. Numerous studies published over the past 25 years have addressed the incidence of infective endocarditis as a complication of hemodialysis-associated bacteremia [6–11]. The incidence of infective endocarditis may be 21 to 54 times higher in hemodialysis patients than in the general population [9]. Factors accounting for the increased risk in hemodialysis patients include vascular invasion with frequent needlesticks, the presence of arteriovenous fistulas, and calcium deposition in valve structures that result in valvular dysfunction. Gram-positive cocci have accounted for the majority of endocarditis cases and *S. aureus* is the most common pathogen causing this hemodialysis-associated complication. In our study, two cases of *S. aureus* endocarditis were discovered at onset of bacteremia. The incidence of endocarditis in bacteremic patients in our study (3%) was similar to that demonstrated in smaller investigations conducted in Alabama (4%) [6] and New York (7%) [10].

Mortality was notable at 30 days (25%) and 90 days (33%) and was significantly higher in older patients (> 60 years vs < 60 years,  $p = 0.05$ ) and in patients classified as critically ill (Table 4). Duration of therapy was unrelated to outcome irrespective of the pathogen isolated, probably because more severely ill patients tended to receive antibiotic therapy of longer duration. The mortality was generally lower for those microorganisms emanating from the vascular access site and the urinary tract and generally higher for those microorganisms emanating from the lung and gastrointestinal tract (Table 1). With the exception of *E. coli* and *K. pneumoniae*, bacteremias due to enteric microorganisms (*P. aeruginosa*, *Enterobacter* spp., *P. mirabilis*, *Candida* spp.) resulted in the highest mortality (Table 1). The majority of bacteremias were treated with vancomycin (71%, 90/127), reflecting the prominence of *S. aureus* in access site infections (Table 3).

The optimal method for evaluating duration and choice of therapy would be a prospective randomized trial, which was not done in this observational study. Nevertheless, we noted that long-term antibiotic therapy defined as greater than 2 weeks did not appear to be superior to short-term therapy. For patients with less severe illness, 2 weeks of therapy was as effective as longer courses of therapy. However,

we note that severity of illness at onset of bacteremia and removal of infected access site would also affect outcome in addition to antibiotic therapy and duration; since these factors were not controlled, no definitive conclusions can be drawn on this issue.

We have performed two other prospective observational studies of bacteremia in which development of endocarditis was an endpoint [12, 13]. The first study involved 171 patients with prosthetic valves experiencing bacteremia [12], and the second was a large-scale study of 505 patients with *S. aureus* bacteremia [13]. In all three studies including this one, duration of antibiotic therapy was not a factor in development of subsequent *S. aureus* endocarditis. The first positive blood culture was often the initial clinical manifestation of endocarditis. For example, in both of our patients with *S. aureus* endocarditis, the diagnosis was confirmed during initial administration of antibiotic therapy.

Our study was performed in an era when arteriovenous fistulas were more commonly utilized for hemodialysis access. We found no difference in survival days for the cohort who underwent surgical removal of arteriovenous fistula or access catheter as compared to those who did not undergo surgery (Table 5). Other authors have suggested that arteriovenous fistulas can be left undisturbed but that prosthetic shunt material must be removed [14]. In a prospective study of dual-lumen cuffed catheters in patients undergoing hemodialysis, Marr et al. [15] found that catheter removal was usually necessary for successful eradication of bacteremia, although this remains controversial [16]. However, they also found that complications did not occur any more frequently in patients whose catheters were left in place and treated with antibiotic therapy only [15]. We found that shunt/fistula removal was not always required for bacteriologic cure, and thus, the decision for surgical removal of the access site can be individualized. Since preservation of an access site for hemodialysis is necessary for survival and since sterile preparation of the access site is traditionally wellmanaged by patients and healthcare personnel, other novel measures to minimize bacteriologic failure or prevent subsequent development of endocarditis must be developed [3, 17].

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