

Research Paper

Incidence, Clinical, Microbiological Features and Outcome of Bloodstream Infections in Patients Undergoing Hemodialysis

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Abstract

Objectives: Infection is a common cause of death among hemodialysis patients. The study investigated incidence, risk factors, clinical features and outcome of bloodstream infections (BSIs) in haemodialysis patients.

Methods: The records of haemodialysis patients from 1999 to 2005 were reviewed. Risk factors were investigated by multivariate analysis.

Results: There were identified 148 bacteremic episodes, in 102 patients. The BSI rate was 0.52 per 1000 patient-days. Of the 148 episodes, 34 occurred in patients with permanent fistulae (0.18/1000 patient-days); 19 in patients with grafts (0.39/1000 patient-days); 28 in patients with permanent tunneled central catheters (1.03/1000 patient-days); and 67 in those with temporary-catheter (3.18/1000 patient-days). With fistula as reference, the BSI ratio was 1.84 with arteriovenous graft ($P=.029$), 4.85 with permanent central venous catheter ($P<.001$), and 14.88 with temporary catheter ($P<.001$). Catheter related were 41 episodes (28%). Gram positive organism were responsible for 96 episodes (65%), with *S. aureus* (55%) the most frequent, followed by *S. epidermidis* (26%) and Gram-negative for 36 (23%), with *E. coli* (39%) the most frequent. Infection was polymicrobial in 14 (9.5%). Diabetes ($p<0.001$), low serum albumin ($p=0.040$) and low hemoglobin ($p<0.001$) were significant risk factors. During hospitalization 18 patients (18%) died. Septic shock ($p<0.001$) and polymicrobial infection ($p=0.041$) were associated with in-hospital mortality.

Conclusion: The risk of BSI in patients undergoing hemodialysis is related to the catheter type and vascular access. Septic shock and polymicrobial infection predispose to unfavourable outcome.

Key words: Antimicrobial Resistance, Sepsis, Vascular Catheter-Related Infections, Epidemiology

Introduction

Patients with end-stage renal disease (ERSD) requiring dialysis are at increased risk for bloodstream infection (BSI). This type of infection repre-

sents a main cause of morbidity, as well as a preventable cause of death, along with increased costs and hospitalization [1-5].

Impaired immunity due to renal failure, comorbidities, malnourishment that increase the virulence and the adherence properties of hospital bacteria as well as the breakdown of the protective anatomical barriers due to repeated intravascular intervention required for haemodialysis, represent the main reasons for the high prevalence of bloodstream infection in those patients [3,6-8].

Previous studies suggested that the vascular access for hemodialysis is the major risk factor for bacteremia in patients with ESRD [9-12]. The infection risk has been found to be lower when the vascular access occurs through arteriovenous graft or fistula and higher when it occurs through central venous catheter (CVC), either permanent or temporary [9-12].

Chronic dialysis patients are at risk for infections caused by nosocomial multidrug resistant (MDR) pathogens exhibiting decreased susceptibility to many antimicrobials. Hence, empirical administration of such antimicrobials may be inappropriate resulting in increased morbidity, mortality and cost to the health care system [13]. Gram positive organisms are the most common etiologic agents of bacteremia in this setting; however, infections may also be caused by gram-negative pathogens [14-16]. The latter are of particular concern due to the absence of new drug development against them.

We, therefore, conducted a retrospective study in order to identify and compare the incidence of bacteremias associated with different types of vascular and non-vascular access and to determine risk factors, microbiological features and outcome of bacteremia among patients undergoing hemodialysis.

Patients and Methods

Study Population

The medical records of 239 patients undergoing hemodialysis at the Department of Nephrology of the University Hospital of Heraklion, Crete, Greece over a 7-year period (1999 to 2005) were retrospectively reviewed. Each patient was evaluated by both nurses and medical staff during each dialysis session for the presence of bloodstream infection (BSI) using CDC case definitions [17]. Only outpatients undergoing chronic hemodialysis were studied. Patients receiving short-term dialysis were excluded.

Hemodialysis patients with a documented BSI, defined as the isolation of a bacterial or fungal pathogen from at least one blood culture in the presence of clinical signs of infection, were selected as "cases". If potential skin contaminants (e.g., coagulase-negative *Staphylococci* (CNS), *Corynebacteria*, *Propionibacterium* spp., *Bacillus* spp., or *Micrococci*) were isolated, the episode was included in the study only when at least

2 blood culture sets yielded the same microorganism and the patient was showing clinical signs of infection. Since any given patient could have a BSI more than once, we used the term "episode of BSI" for each separate event.

All patients who underwent chronic hemodialysis during the study period and did not experience a bloodstream infection were considered "controls".

In the case-control study, only the first episode of bacteremia in a given patient was included in the analysis as case in order to preserve the independence of the values.

Rates of bloodstream infections

The patients were categorized into 1 of 4 current vascular access types: arteriovenous fistula, arteriovenous graft, temporary central venous catheter (CVC) or permanent tunneled central catheter. The total number of dialysis sessions was recorded on daily basis and grouped according to the 4 vascular access types.

For the calculation of the BSI incidence rates, the number of the BSI episodes during the study period were used as numerator and the total cumulative number of hemodialysis days for the same period (patient-days) as denominator. Rates were calculated separately for each type of vascular access. Rates of BSI were expressed as the number of infections per 1,000 patient-days.

Data collection

Clinical variables collected were age, gender, underlying diseases, cause of renal failure, comorbidities, length of time on renal replacement therapy, vascular access type, history of bacteremia, previous and current erythropoietin treatment, any iron supplementation, history of blood transfusions and dialysis procedures, risk factors for bacteremia (presence of central venous catheters, prior invasive procedures, surgical procedure within the past month, urinary tract catheter) and source of bacteremia.

White blood cell count, haemoglobin, serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum ferritin, serum albumin, serum calcium and phosphate product and serum parathyroid hormone concentration were the laboratory values collected at the study entry.

Data on duration of hospital stay, empirical treatment (appropriate or inappropriate) and outcome (cure or death due to bacteremic episode) were also carefully collected.

Definitions

Catheter-related bacteremia was defined as the occurrence of a positive blood culture from the cath-

eter with or without a positive peripheral blood culture, in the presence of systemic symptoms of infection with no other source of infection identified. Bacteremia was classified as primary in the absence of an identified source growing the same organism(s) as that recovered from blood. When the organism isolated from blood was the same as the organism causing an infection at another site, the BSI was classified as secondary. Exceptions to this were intravascular device-associated BSIs, all of which were classified as primary even if localized signs of infection were present at the access site [18].

Established definitions for sepsis and septic shock were followed [19].

Antimicrobial therapy was considered appropriate if the bacteria isolated were sensitive to at least one of the antimicrobials used as empirical therapy.

A bacteremic episode was considered polymicrobial if more than one organism was isolated in the same blood culture.

Established definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pan-drug-resistant (PDR) bacteria were followed [20].

Regarding outcome, an episode was considered cured if resolution of the infection was noted, the patient had been discharged. Relapse was defined as recurrence of the infection due to the same organism occurring during the following four weeks after completion of antimicrobial therapy. A second (new) BSI episode was considered if a blood culture meeting the case definition criteria grew a different bacterial species or, in the case of same species, if sufficient time (more than 4 weeks) had elapsed without antimicrobial therapy, so that a relapse of the previous infection to be extremely unlikely.

Death was attributed to the infectious process if the patient died after a clinical course suggesting persistent infection and/or if the patient died during the phase of acute infection and death could not be clearly attributed to any other cause.

Statistical analysis

The incidence of infection rates, in terms of 1,000 patient-days, were calculated for each type of vascular access based on the collected data from the device-days monitoring forms and the confirmed BSIs.

A Poisson regression model was used to determine the incidence rate ratios and associated 95% confidence intervals, with fistula used as the reference access category.

Categorical variables were evaluated using chi-square or Fischer's exact test for comparisons between groups. Continuous variables were compared using Student's t-test or Mann-Whitney U test for not normal distributions.

Multivariate analyses were performed using logistic regression model to test for: (i) an independent association with the development of bacteraemia; and (ii) an independent association with mortality. Variables found to be statistically significant ($P < .05$) in the bivariate analysis were entered into the multivariable model.

Statistical analysis was performed using SPSS 16 (SPSS Inc, Chicago, IL); $P < .05$ was used to determine statistical significance.

Results

Patient demographics

During the 7-year study period, 148 bacteremic episodes, occurring in 102 patients, were identified. Their median age was 70 years (range 20-90). There were 53 (52%) women. Seventy one out of 102 patients (69%) had only one bacteraemic episode, 20 (20%) two and 11 (11%) three or four.

The aetiology of ESRD for the study population was diabetic nephropathy (20%), glomerulonephritis (13%), polycystic kidney disease (9%), and/or unknown (46%).

Table 1 shows characteristics of patients with BSIs.

Table 1. Demographics of 102 patients with bloodstream infection

Characteristic	Number of patients (%)
Sex	
Male	49 (48)
Female	53 (52)
Median age [range]	70 [20-90]
Cause of ESRD	
Diabetic nephropathy	20 (19.6)
Glomerulonephritis	13 (12.7)
Polycystic kidney disease	9 (8.9)
Obstructive nephropathies	8 (7.8)
Hypertensive nephropathy	4 (3.9)
Familial kidney disease	1 (1)
Unknown	47 (46.1)
Underlying disease	
Hypertension	67 (66)
Diabetes Mellitus	40 (39)
Heart Failure	21 (21)
Coronary Disease	18 (18)
Anemia	11 (11)
Chronic Obstructive Pulmonary Disease	11 (11)
Secondary Hyperparathyroidism	11 (11)
Cancer	11 (11)
Depression	5 (5)

Infection rates and comparisons between access types

Regarding the type of vascular access, 107 patients (37,5%) had AV fistulas, 32 (11%) AV graft, 104 (36.%) temporary and 42 (15%) permanent catheter.

The 148 BSIs detected represent an incidence rate of 0.52 per 1,000 patient-days. Of the 148 episodes, 34 (23%) involved permanent fistulae (0.18/1,000 patient-days); 19 (13%) grafts (0.39/1,000 patient-days); 28 (19%) permanent tunneled central catheter (1.03/1,000 patient-days); and 67 (45%) temporary-catheter (3.18/1,000 patient-days).

With fistula as the reference vascular access type, results has shown that the incidence rate ratio for BSI was 1.84 with arteriovenous (AV) graft access ($P=.029$), 4.85 with permanent central venous catheter access ($P<.001$), and 14.88 with temporary catheter access ($P <.001$).

The incidence rate ratios associated with different types of vascular access are summarized in Table 2.

BSI was strongly associated with central venous catheter access. Only 24 (16%) BSI episodes occurred in patients with an arteriovenous fistula or graft, compared with 124 (84%) BSI episodes in patients with a catheter access ($P <.001$).

The mean time to BSI from the beginning of the observation period were for AV fistula 48 ± 33 months, for AV graft 41 ± 33 months, for permanent catheter 28 ± 32 months and for temporary catheter 18 ± 28 days.

Table 2. Risk of bloodstream infection according to the type of vascular access

Type of access	Number of bloodstream infections	IRR (95% CI)	P-value
Temporary CVC	67	14.88 (10.18-22.20)	<0.001
Permanent CVC	28	4.85 (3.0-7.85)	<0.001
AV graft	19	1.84 (1.06-3.16)	0.029
AV fistula	34	1	

Source of bacteremia and microbiology

The BSI was considered to be primary in 76 (51%) episodes, catheter-related in 41 (28%), while 31 (21%) episodes were secondary to other sources. The most frequent diagnoses were urinary tract infections (12 episodes; 39%), respiratory tract infections (8; 26%), and skin/soft tissue infections (6; 19%).

In 134 episodes (90.5%) a single microorganism was isolated. In 96 of them (65%) a single gram-positive organism was involved; more than half (55%) of these episodes were caused by *Staphylococcus*

aureus and 26% by *Staphylococcus epidermidis*. In 36 (33%) episodes a single Gram-negative bacillus was involved. *Escherichia coli* accounted for more than one-third (39%) of them followed by *Klebsiella* spp. (17%), *Acinetobacter* spp. (14%) and *Enterobacter* spp. (14%). A gram-negative anaerobe (*Bacteroides fragilis*) was the cause of 1 episode, and *Candida albicans* of another one. Bacteremia was polymicrobial in 14 cases (9.5%). The predominant strains isolated from polymicrobial events were *Staphylococcus aureus* (7 isolates; 50%), *Enterobacter* spp. (3; 21%), *E. coli* (3; 21%), *Enterococcus faecalis* (3; 21%) and *Pseudomonas aeruginosa* (3; 21%).

The organisms isolated are shown in Table 3.

Table 3. Organisms isolated from 148 bacteremic episodes

Pathogens	No. of BSI episodes (%)
Gram-positive bacteria	96 (65)
<i>Staphylococcus aureus</i>	53 (36)
<i>Staphylococcus epidermidis</i>	25 (17)
<i>Enterococcus faecalis</i>	6 (4)
<i>Streptococcus</i> spp.	4 (3)
<i>Staphylococcus lugdunensis</i>	2 (1)
<i>Streptococcus agalactiae</i>	2 (1)
<i>Staphylococcus coag.-negative</i>	1 (1)
<i>Staphylococcus haemolyticus</i>	1 (1)
<i>Staphylococcus simulans</i>	1 (1)
<i>Enterococcus faecium</i>	1 (1)
Gram-negative bacteria	36 (24)
<i>Escherichia coli</i>	14 (9)
<i>Klebsiella</i> spp.	6 (4)
<i>Acinetobacter</i> spp.	5 (3)
<i>Enterobacter</i> spp.	5 (3)
<i>Pseudomonas aeruginosa</i>	3 (2)
<i>Stenotrophomonas maltophilia</i>	3 (2)
Anaerobes	1 (1)
Fungi	1 (1)
Polymicrobial	14 (9)
<i>Staphylococcus aureus</i>	7
<i>Escherichia coli</i>	3
<i>Enterococcus faecalis</i>	3
<i>Enterobacter</i> spp.	3
<i>Pseudomonas aeruginosa</i>	3
<i>Staphylococcus epidermidis</i>	3
<i>Staphylococcus haemolyticus</i>	2
<i>Klebsiella pneumoniae</i>	1
<i>Corynebacterium</i> spp.	1
<i>Streptococcus pneumoniae</i>	1
<i>Proteus mirabilis</i>	1
<i>Candida albicans</i>	1
Total	162

The total number of pathogens isolated, including both uni- and polymicrobial episodes was 162. Forty out of 60 (67%) *Staphylococcus aureus* isolates and 19 out of 28 (68%) of *Staphylococcus epidermidis* exhibited resistance to methicillin. Of the 48 gram-negative bacteria isolated 20 (42%) exhibited resistance to piperacillin-tazobactam, 18 (38%) to cefepime, 14 (29%) to ceftazidime, amikacin and ciprofloxacin and 12 (24%) to imipenem-cilastatin. Additionally, 3 out of 17 (18%) *Escherichia coli* isolates produced extended spectrum β -lactamase. Finally, 3 out of 8 isolated (37.5%) *Enterobacter* spp. strains, 4 out of 5 (80%) *Acinetobacter* spp. strains, and 2 out of 7 (29%) *Klebsiella* spp. strains were sensitive only to colistin.

Risk factors for bacteremia

There were 239 patients enrolled in the case-control study; 102 cases and 137 controls. Bivariate analysis of categorical variables identified that female gender [53 cases (52%) vs. 52 controls (38%)], presence of diabetes mellitus [40 (39%) vs. 25 (18%)] and absence of fistula [81 (79%) vs. 64 (47%)] were more common among patients with BSI. Considering continuous variables, lower serum protein, albumin and serum haemoglobin levels, and higher white blood cell count were more frequently associated with BSI (Table 4).

Table 4. Bivariate analysis of risk factors for bloodstream infection in patients receiving hemodialysis

Characteristic	Patients without bacteremia (N=137)	Patients with bacteremia (N=102)	P-value
Age, years (SD)	65.9 (15.9)	66.4 (14.7)	0.925 (NS)
Male gender	85 (62)	49 (48)	0.031
Comorbidity			
Diabetes Mellitus	25 (18)	40 (39)	< 0.0001
Malignancy	6 (4)	11 (11)	0.057 (NS)
Vascular access			
A/V fistula	73 (53)	21 (20)	< 0.0001
A/V graft	13 (10)	10 (10)	
Temporary catheter	37 (27)	53 (52)	
Permanent catheter	14 (10)	18 (18)	
Current erythropoietin treatment	86 (63)	66 (65)	0.759 (NS)
Current iron therapy	106 (77)	71 (70)	0.176 (NS)
Surgical procedure within 1 mo.	9 (7)	9 (9)	0.500 (NS)
Serum protein	6.61 (0.77)	6.40 (0.85)	0.011
Serum albumin	3.69 (0.40)	3.43 (0.65)	< 0.0001
WBC on admission	7233 (3294)	15780 (6496)	< 0.0001
Serum ferritin	219,4 (255.4)	360.8 (410.0)	0.062 (NS)
Serum Ca	9,04 (1.19)	8.96 (1.10)	0.482 (NS)
Serum P	4.72 (1.63)	4.82 (1.69)	0.472 (NS)
Hb	11.14 (1.53)	10.51 (1.58)	0.001

In the multivariable logistic regression model, presence of diabetes mellitus (OR: 2.651; $P < 0.001$), absence of fistula (OR: 2.933; $P = 0.047$), low serum albumin (OR: 1.976; $P=0.040$) and low serum haemoglobin levels (OR: 1.354; $P < 0.001$) were all independently associated with occurrence of a BSI.

Outcome and Predictors of Mortality

One hundred thirty out of 148 episodes (88%) have been cured, whereas death attributed to the BSI occurred in 18 episodes (12%). Five episodes (3%) relapsed.

The initial empirical antimicrobial therapy was appropriate in 116 episodes (78%), resulting in an infectious mortality rate of 6% and inappropriate in 32 episodes (22%) resulting in an infectious mortality rate of 34% ($p < 0.001$).

After multiple logistic regression, only 2 variables had been found to be independently associated with death in hemodialysis patients with BSI: the presence of septic shock on admission (OR: 174.446, 95% CI: 24.360-1249.245, $P < 0.001$) and a polymicrobial episode (OR: 8.934, 95% CI: 1.039-73.029, $P=0.041$).

Discussion

In the present retrospective study, diabetes mellitus, temporary CVC vascular access, low serum albumin and hemoglobin levels all were risk factors for occurrence of a BSI in patients with ESRD, while septic shock upon admission and polymicrobial BSI were associated with poor outcome. It is worth noting that 25 % of the bacteremic episodes were caused by gram-negative pathogens and a substantial proportion of them were sensitive only to colistin.

Infection is an important cause of morbidity and mortality among patients with ESRD [1-5]. In the HEMO study an infectious etiology was responsible for 23% of all deaths among 1846 chronic hemodialysis patients, while the annual rate of the infection related hospitalization was 35% [4]. Furthermore, data from the United States [Renal Data System (USRDS)] showed that infection was the leading cause of death among patients with ESRD, while the majority of deaths in these patients were due to bacteremia/sepsis [1].

Bacteremia is common in patients undergoing hemodialysis, and the CVC is the most common source of the infection [4,6,7,17]. In the HEMO study patients with bacteremia or sepsis represented 45% of those hospitalized due to infection, while 23% of them were considered having access related infection [4].

Since the number of patients that need renal replacement therapy continues to grow, the prevalence of BSIs is expected to rise as well. In the present study

arteriovenous fistulas and grafts were associated with the lowest cumulative rates of infection, followed by permanent catheters, while temporary central venous catheters were associated with the highest ones. These results are consistent with findings reported in the literature [3,9-12]. It has been demonstrated recently that hemodialysis via catheter, compared with that via fistula or graft, increases not only the infection rates, but also mortality [21,22]. However, in the present series we could not reveal any significant difference in mortality between vascular access types probably due to the small number of deaths.

The majority of the present BSIs were caused by gram positive micro-organisms, while the two most common pathogens isolated were, not surprisingly, the skin-derived *Staphylococcus aureus* and *Staphylococcus epidermidis*, a finding consistent with other investigators' experience [8,9,14,15,22].

Considering other BSI risk factors, diabetes mellitus, low serum albumin and low haemoglobin levels have all been significantly associated with increased risk for bacteremia in the present series. All three have been identified as risk factors of bacteremia in a number of other studies [3,6,7]. It is well-known that diabetes mellitus leads to impaired immunologic defense [23] and in combination with the immunosuppression caused by uremia, may lead to increased risk for bacteremia [24]. In addition, in the present study low albumin level on admission has been shown also to be a risk factor for bacteremia. Low serum albumin may represent patient's malnutrition, a common problem in dialyzed populations, causing immune defect and facilitating bacteremia [25,26]. These data suggest that careful clinical evaluation, improved nutrition and diabetes management in hemodialysis patients may decrease the incidence of bacteremia.

The role of low haemoglobin level as risk factor is more difficult to be explained. However, a lower hemoglobin level may potentially be associated with risk of iron overload, which may lead to enhancement of bacterial growth and impairment of phagocytic function [24,26]. Previous studies have shown that iron overload, render hemodialysis patients more susceptible to bacteremia [24,26]. Furthermore, the potential role of haemoglobin in hemodialysis patients is supported by the study of Ma et al., which demonstrated the negative effect of low hematocrit on overall and infection-related survival in hemodialysis patients [27]. However, in the present study we did not find any difference between bacteremic and non-bacteremic patients regarding ferritin levels.

Infections in patients receiving hemodialysis are often caused by resistant pathogens, due to frequent hospital admissions and the also frequent need for

antimicrobial therapy [28,29]. In the present study more than two thirds of the *S. aureus* and *S. epidermidis* isolates were methicillin-resistant. It is of note that the proportion of methicillin-resistant pathogens in our study is remarkably higher compared to other studies, suggesting that the use of vancomycin as first-line therapy may be necessary in our unit with regard to local patterns of resistance [9,10,15]. However, no vancomycin resistant staphylococci or enterococci have been isolated from the present series of patients.

One fourth of the bacteremic episodes were caused by gram-negative pathogens resistant to common antimicrobial agents, a proportion consistent with prior studies [9,10,15,22]. It is worth noting that a substantial percentage of the gram-negative isolates (25%) were sensitive only to colistin.

Polymicrobial infections, represented 10% of the present bacteremic episodes.

The present mortality rates are consistent with those previously reported [2,5,30]. Septic shock on admission and a polymicrobial episode were predictors of poor outcome. Polymicrobial bacteremia has been suggested as predictor of adverse outcome in several studies [31,32], including immunocompromised patients [33] but this is the first study which outlines its predictive value in hemodialysis patients and this should be taken into account when empirical antimicrobial therapy is undertaken.

The present study has some limitations: its retrospective nature makes it vulnerable to collection bias and to potential inaccuracy in data collection. Additionally the number of deaths was relatively small, leading to wide confidence intervals.

In conclusion, the risk of bacteremia in hemodialysis patients can be stratified according to vascular access type. Diabetes mellitus, low albumin and haemoglobin levels upon admission are independent risk factors for BSI, while the presence of septic shock and polymicrobial bacteremia predispose to unfavourable outcome. Hence, careful clinical evaluation, limitation of the catheter use, improvement of nutritional status, correction of anemia and successful management of diabetes mellitus considerably reduce the incidence of BSIs. Finally, surveillance of local microbiology is of utmost importance for appropriate empirical antimicrobial treatment.

Competing Interests

The authors have declared that no competing interest exists.

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