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Septicemia in dialysis patients: Incidence, risk factors, and prognosis

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Septicemia in dialysis patients: Incidence, risk factors, and prognosis.

Background. Infection is second to cardiovascular disease as a cause of death in patients with end-stage renal disease (ESRD), and septicemia causes a majority of these infectious deaths. To identify patients at high risk and to characterize modifiable risk factors for septicemia, we examined the incidence, risk factors, and prognosis for septicemia in a large, representative group of U.S. dialysis patients.

Methods. We conducted a longitudinal cohort study of incident ESRD patients in the case-mix study of the U.S. Renal Data System with seven years of follow-up from hospitalization and death records. Poisson regression was used to examine independent risk factors for hospital-managed septicemia. Cox proportional hazards analysis was used to assess the independent effect of septicemia on all-cause mortality and on death from septicemia. Separate analyses were performed for patients on peritoneal dialysis (PD) and hemodialysis (HD).

Results. Over seven years of follow-up, 11.7% of 4005 HD patients and 9.4% of 913 PD patients had at least one episode of septicemia. Older age and diabetes were independent risk factors for septicemia in all patients. Among HD patients, low serum albumin, temporary vascular access, and dialyzer reuse were also associated with increased risk. Among PD patients, white race and having no health insurance at dialysis initiation were also risk factors. Patients with septicemia had twice the risk of death from any cause and a fivefold to ninefold increased risk of death from septicemia.

Conclusions. Septicemia, which carries a marked increased risk of death, occurs frequently in patients on PD as well as HD. Early referral to a nephrologist, improving nutrition, and avoiding temporary vascular access may decrease the incidence of septicemia. Further study of how race, insurance status, and dialyzer reuse can contribute to the risk of septicemia among ESRD patients is indicated.

Infection is an important cause of mortality among patients with end-stage renal disease (ESRD). Using regional and national data, epidemiologic studies within the United States indicate that infection is second to cardiovascular disease as the leading cause of death in ESRD patients, occurring in approximately 12 to 22% of patients [1, 2]. Infections are also a leading cause of morbidity. They are responsible for a significant proportion of hospital admissions and total hospital days for patients with ESRD [2].

One of the most serious and life threatening infections in dialysis patients is septicemia. It accounts for over three fourths of deaths caused by infections [1]. Several clinical, treatment, and sociodemographic characteristics make ESRD patients particularly susceptible to septicemia. Uremia often results in immune deficiency [3, 4]. Malnourishment and older age may interact with uremia to impair the immune system further and to increase the risk of infection in patients with ESRD [5]. Risk may also vary according to the presence of comorbid conditions such as diabetes mellitus (DM) and disruptions of dermal barriers to gain access for dialysis [6, 7]. In peritoneal dialysis (PD), infection may occur through either the catheter entrance through the skin or the peritoneal cavity [8]. In hemodialysis (HD) patients, infection may occur from the need for intravascular catheters to perform dialysis [9, 10]. Infection may also depend on the type of vascular access used to conduct HD, reuse practices, and membrane selection [11–14].

Despite these acknowledged pathophysiological precepts, risk factors for septicemia have not been well characterized in large, representative incident populations of dialysis patients in the United States. Recent studies of septicemia in prevalent dialysis patients may overlook risk factors that may be unique to the first few months of dialysis and may also omit the highest risk patients with relatively short survival on dialysis [15]. Additionally, as the racial distribution and causes of ESRD differ among nations, the risk for septicemia among U.S. ESRD patients may differ from those reported in other populations. Furthermore, although several studies have addressed risk factors for septicemia

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among HD patients, few have addressed the risk of septicemia in PD patients and compared the risk factors for sepsis in patients on PD and HD. Because prior reports have shown that the percentage of deaths attributable to infection are higher in PD-treated than in HD-treated patients [2], we conducted a study of septicemia in a large population of incident U.S. dialysis patients in order to define its incidence, risk factors, and natural history in patients on PD as well as HD. The relatively large sample size and long period of follow-up of this study population allowed for simultaneous adjustment of many potential confounding variables, such as patient age, race, and socioeconomic factors, that might influence the risk of sepsis in this population.

METHODS

Study design and patient population

We conducted a national longitudinal cohort study of the incidence, risk factors, and prognosis for hospitalized cases of septicemia in ESRD patients. We used baseline data from a special case-mix study [16] of the U.S. Renal Data System (USRDS) and follow-up data from hospitalization and death records in the USRDS. Patients were randomly selected for this study from the national population of ESRD patients in the Medicare ESRD registry using a two-stage cluster sampling procedure. The criteria for selection were initiation of chronic maintenance dialysis for ESRD in 1986 or 1987, Medicare-entitlement for dialysis services, no transplantation as initial renal replacement therapy, and treatment at a dialysis facility that was within one day of travel of the ESRD network office. To be eligible for this analysis, we required patients to be age 18 years or older, of white or black race, and have a documented dialysis treatment modality.

Data collection

During 1991, abstractors from the ESRD Network offices visited each dialysis facility and abstracted data elements from the medical record into a standardized form. The window for data collection was defined as the period spanning from one month before to one month after the patient's first dialysis service in 1986 or 1987. Baseline data collected include patient demographic information (age, gender, race), socioeconomic information (for example, insurance status just before the start of ESRD and education), laboratory data (for example, serum albumin, hematocrit), comorbid disease (for example, prior diagnosis of DM, neoplasm, congestive heart failure, peripheral vascular disease), and dialysis modality (HD or PD). For HD patients, information was collected on up to two types of vascular access in use (native arteriovenous fistula, gortex graft, bovine graft, permanent central venous catheter, and temporary catheter) and reuse of dialyzers in each patient. We used hospitalization records in the USRDS to assess hospital admissions for septicemia over the seven-year follow-up period. We used data from the U.S. Health Care Financing Administration (HCFA) 2746 death notification form (date and cause of death) to assess survival over the follow-up period [16].

Construction of analytic variables and outcome measures

The outcome variable was admission to the hospital for septicemia. We defined this as patients having a primary International Classification of Diseases-9th Modification diagnosis code of 038.xx (septicemia) or 790.7 (bacteremia) on the discharge abstract. Because we were interested in septicemia acquired in the outpatient setting, we limited the outcome variable to patients with a primary diagnosis code of septicemia. Thus, patients with a secondary diagnosis of septicemia were excluded to avoid including cases with hospital-acquired infection in the definition of our outcome variable. We also required that repeat hospital admissions for septicemia be separated by at least 30 days.

Patient characteristics and treatment factors were those obtained at the start of ESRD. Many of these were relatively fixed or nonmodifiable (age, gender, race, education, presence of DM), and some could vary over time (serum albumin, hematocrit, treatment modality, vascular access). Analyses examined the relationship of these risk factors at baseline (onset of ESRD treatment) to subsequent outcomes. To address the issue of change in baseline variables over the follow-up period, in selected analyses, we assessed the relationship between risk factors and early (within the first 6 months of onset of dialysis) versus late outcomes (after the first 6 months).

Because 40% of patients undergoing HD had more that one type of vascular access reported in the first six weeks after the start of dialysis treatment, vascular access was classified according to a hierarchy of perceived highest risk of septicemia (temporary catheter $>$ permanent central venous catheter $>$ goretex or bovine graft $>$ native fistula; Table 4). When two types of access were reported, the patient was assigned the one with the highest risk. For example, 507 patients who had both a temporary catheter and a native fistula in the baseline period were classified as having a temporary catheter, and 198 patients who had both a goretex or bovine graft and a native arteriovenous fistula in the baseline period were classified as having a goretex/bovine graft.

Analysis of risk factors for septicemia

First, the crude rate of septicemia (episodes per 100 patient years) between HD patients and PD patients over the follow-up period was compared using the Wilcoxon rank sum test. Then differences in the rate of

septicemia between HD and PD patients were examined in multivariate analyses (Poisson regression) adjusting for age, gender, race, education, insurance status, region of the country (as defined by ESRD network), the presence of DM, serum albumin, hematocrit, and the presence of a neoplasm. All subsequent risk factor analyses were stratified by dialysis modality.

Second, the crude (or unadjusted) association between patient factors and the risk of septicemia over a seven-year period following the initiation of dialysis was examined using Poisson regression. Then, the independent association of each patient factor with hospital-managed septicemia was examined, controlling for potential confounders, including age, gender, race, education, insurance status, region of the country, DM, serum albumin, hematocrit, and the presence of a neoplasm. Finally, the independent association of treatment factors (type of vascular access and reuse of dialyzers) with hospital-managed septicemia was examined, controlling for the potential confounders listed earlier here. Because vascular access was ascertained at the initiation of dialysis, the risk of septicemia within the first six months after the start of dialysis as well as at later periods was calculated. Alternative analyses modeling the risk of at least one episode of septicemia were done using logistic regression with an adjustment for days at risk. Because the results were robust across the different types of analyses, only the results from the Poisson regression are presented.

Selection of risk factors for septicemia was guided by our review of the literature and clinical knowledge. For completeness in the mortality analyses (discussed later here), in addition to potential risk factors for survival in the ESRD population, such as age, DM, and serum albumin, other important factors known to impact on mortality in the general population were added, such as cholesterol, smoking status, and the presence of cardiovascular diseases.

Mortality analysis

To examine the prognosis of patients who developed septicemia, Kaplan-Meier survival analyses and Cox proportional hazards analysis were used. The risk of death from all causes and from septicemia for patients who had experienced an episode of septicemia was compared with the risk of death for patients who did not have an episode of septicemia. In this analysis, we controlled for age, gender, race, education, insurance at onset of ESRD, serum albumin, hematocrit, cholesterol, blood pressure at onset of ESRD, smoking status, and comorbid disease (presence of DM, congestive heart failure, neoplasm, left ventricular hypertrophy, coronary heart disease, cerebral vascular disease, and peripheral vascular disease). All analyses were performed using the Statistical Analysis System [17].

RESULTS

Characteristics of patients

Of the 5255 patients in the USRDS case-mix study, 4918 met the eligibility criteria: 186 patients who were neither black nor white race were excluded, as were 82 patients who were less than 18 years old or were not incident in 1986 or 1987. Sixty-nine patients had no documented dialysis treatment modality. Of the remaining patients, 4005 were HD patients and 913 were PD patients (Table 1). Hemodialysis patients were older and more likely to be black, whereas PD patients were more likely to be high school graduates. At the onset of ESRD, PD patients were more likely to have DM, higher hematocrit levels, and lower serum albumin levels than HD patients. Patients were represented from all areas of the United States. There were more PD patients in the Southeastern and Midwestern United States and more HD patients in the Southwestern and Western United States.

Nearly 40% of HD patients had more than one type of vascular access during the first six weeks of dialysis. Among those with only one type of vascular access, 24.4% had a native fistula, and 27.3% had a goretex or bovine graft. Dialysis membranes were reused in 57% of patients.

Episodes of septicemia

Over the seven-year period of follow-up, overall, 11% of patients (HD, 11.7%; PD, 9.4%) had at least one episode of septicemia that was managed in the hospital. Most of these patients had only one episode of hospital-managed septicemia (Table 2). Although the rate of septicemia was always higher for HD patients than for PD patients over the period of follow-up (Fig. 1), the difference was not statistically significant for any time period. In addition, after controlling for age, gender, race, education, insurance status, DM, serum albumin level, and hematocrit level using Poisson regression, there was still no difference in the rate of septicemia between HD patients and PD patients.

In HD patients, the following potential sources of infection were listed as secondary diagnosis codes among all episodes of septicemia: infection/inflammation caused by internal prostheses (18%), suggesting septicemia secondary to vascular access infection, other complications of internal prosthetic device (8%), decubitus ulcer (6%), urinary tract infections (5%), pneumonia (5%), gangrene (3%), endocarditis (2%), and cellulitis and abscess of foot (1%), which is possibly related to diabetic peripheral vascular disease. In PD patients, the potential infectious sources listed as secondary diagnosis codes were infection/inflammation caused by internal prosthetic devices or peritoneal catheter infection (12%), pneumonia (12%), peritonitis (5%), urinary tract infection (8%),

Table 1. Characteristics of patients ($N = 4918$)

Characteristic	Hemodialysis	Peritoneal dialysis	P value[b]
N	4005	913	
Age (mean ± SD) years	60.0 (15.9)	55.2 (16.5)	<0.0001
Female gender %	47.7	47.8	NS
Black race %	39.2	27.3	0.001
High school graduate %	56.1	65.7	0.001
No insurance prior to ESRD onset %	7.2	9.2	0.058
Diabetes mellitus %[a]	40.0	44.6	0.01
Serum albumin (mean ± SD) *g/dl*	3.50 (0.54)	3.39 (0.56)	<0.0001
Hematocrit (mean ± SD)%	26.1 (4.5)	28.2 (5.2)	0.0001
Access *within 6 weeks of start of dialysis*			
temporary catheter %	4.9	—	
permanent catheter %	4.9	—	
goretex or bovine graft %	27.3	—	
native AV fistula %	24.4	—	
more than one %	38.4	—	
Dialyzer reuse %	57.0	—	
Geography of treatment facility [Network]			
Northeast [1–5] %	37.1	35.7	NS
Northeast [6–8] %	18.2	27.8	0.001
Mideast [9–12] %	20.4	24.0	0.018
Southwest [13–15] %	12.3	7.1	0.001
West [16–18] %	11.9	5.4	0.001

[a] Represents diabetes mellitus as a comorbid condition, not diabetes mellitus as the cause of ESRD; NS = not significant $P \geq 0.05$
[b] t-test for continuous variables (age, serum albumin, hematocrit); χ^2 for categorical values

Table 2. Episodes of hospital managed septicemia during the seven year follow-up period in patients with onset of ESRD treatment in 1986–1987

Number of episodes of septicemia per person	Hemodialysis $N = 4005$	Peritoneal dialysis $N = 913$
None %	88.3	90.6
One %	9.7	8.8
Two %	1.5	0.7
Three or more %	0.4	0

endocarditis (2%), and cellulitis and abscess of foot (2%).

Patient characteristics associated with septicemia

In both HD and PD patients, crude and adjusted analyses indicated that older age was associated with a 60 to 90% higher risk of hospital-managed septicemia (Table 3). Black PD patients had a lower risk of septicemia than did white PD patients. For HD patients, the point estimate suggested a lower risk of septicemia in black versus white patients; however, the result was not statistically significant.

When compared with PD patients with private insurance at baseline, uninsured PD patients and those with Medicaid insurance at the onset of ESRD were at greater risk of septicemia. However, the association of insurance status and increased risk of septicemia did not hold for HD patients.

In both unadjusted and adjusted analyses, the presence of DM was associated with a higher risk of hospital-managed septicemia in both HD and PD patients. Among PD patients, the risk was twofold. Hemodialysis patients with a serum albumin level of less than 3.5 mg/dl had a 66% higher risk of hospital-managed septicemia than patients with higher albumin levels. Female gender, educational status, hematocrit level, and the presence of cancer were not associated in this analysis with hospital-managed septicemia.

Treatment factors associated with septicemia

Type of vascular access. Table 4 shows that over the entire period of follow-up, HD patients with a temporary catheter had a 50% higher risk of septicemia than patients with a native fistula. Patients with a gortex or bovine graft had a 33% higher risk of septicemia than patients with a native fistula during the entire seven years of follow-up. During the first six months after the onset of ESRD, patients with permanent central venous catheters also had an increased risk of septicemia compared with patients with native fistulae.

Reuse of dialyzers. We assessed the relationship between reuse of dialysis membranes in individual patients undergoing HD and the risk of septicemia. Patients who reused dialyzers had a 28% higher risk of septicemia than patients who did not reuse membranes over the entire follow-up period.

Prognosis of patients with septicemia

We examined the natural history of patients who had experienced an episode of septicemia (Table 5). In the Cox proportional hazards model analyses, both HD and PD patients who experienced an episode of hospital-

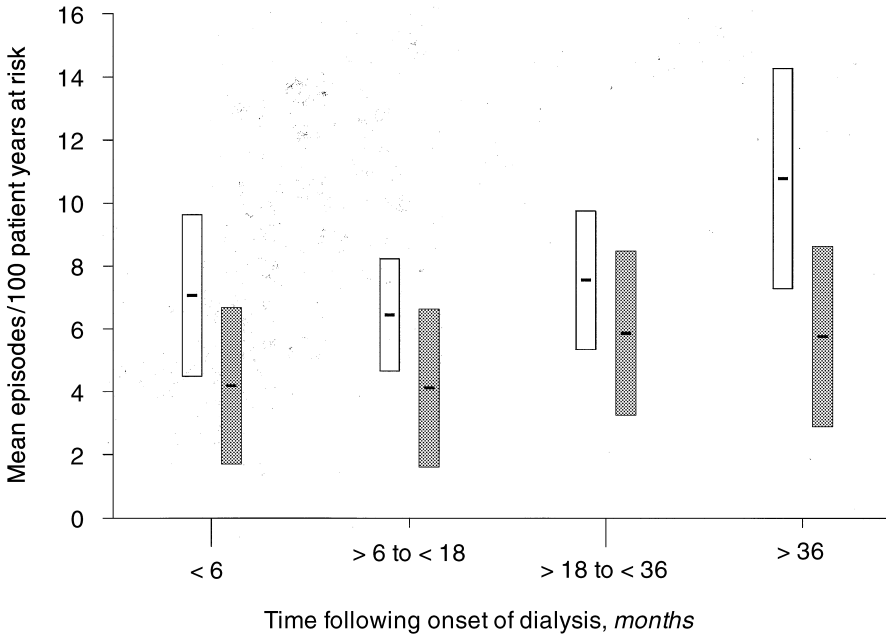

Fig. 1. Episodes of septicemia per 100 patient-years at risk differing follow-up time periods after dialysis initiation. Symbols are: (□) hemodialysis patients; (■) peritoneal dialysis patients. Upper and lower limits of the boxes at each time point represent 95% confidence intervals, and (−) represents the point estimate.

managed septicemia had more than a twofold higher risk of death from any cause than patients who had not experienced an episode of hospital-managed septicemia. This effect persisted even after adjusting for age, gender, race, education, insurance at the onset of ESRD, serum albumin, hematocrit, cholesterol, blood pressure at the onset of ESRD, smoking status, and comorbid disease (presence of DM, congestive heart failure, neoplasm, and peripheral vascular disease). Hemodialysis patients who experienced an episode of hospital-managed septicemia had a ninefold greater risk of death from septicemia than patients who had not experienced an episode of hospital-managed septicemia after adjustment. Although the risk of death from septicemia for PD patients was also high following an episode of septicemia, it was almost half of that for HD patients, after adjustment for case mix.

DISCUSSION

This national study of incident U.S. ESRD patients demonstrates that septicemia, which requires hospital admission, is a common event for both HD and PD patients, occurring in more than 10% of patients over seven years of follow-up. Few medical conditions, except for chemotherapy-induced neutropenia, immunosuppression, and intravenous drug abuse, are associated with higher rates of septicemia than those we observed for dialysis patients in this national study. Our findings on the incidence of septicemia in U.S. HD patients with ESRD is comparable to that reported by Churchill et al in the Canadian Hemodialysis Morbidity Study [18]. The rate we observed for patients on HD for more than 36 months was comparable to that recently reported by Hoen et al in their study of septicemia in prevalent HD patients in France [15]. Although many reports have described rates for exit-site infections and peritonitis for patients on PD, to our knowledge, few have addressed the incidence of septicemia in patients on PD, which we found to be comparable to that of patients on HD.

Age and diabetes as risk factors for septicemia

Our study documents that, as one might expect, older patients and patients with diabetes, who made up 40% of the incident ESRD population in the case-mix study, are at increased risk of septicemia, regardless of dialysis modality. Diabetes is well known as a general risk factor for infection because of impaired immunologic defense mechanisms and deficient phagocytic function, which has been observed in diabetics with poor metabolic control [6]. Combined with the impaired immune defenses in uremia, the increased risk in this patient group should alert clinicians to be vigilant for signs of infection.

In contrast to our findings, in the EPIBACDIAL Study, which focused on determining risk factors for bacteremic in chronic HD patients, Hoen et al did not find age and DM to be independent risk factors for septicemia [15]. The difference between the results of these two studies could be related to differences in sample size and case mix. The number of patients studied in the EPIBACDIAL study was smaller than the U.S. population we studied. In their multivariate analyses, Hoen et al studied only 44 episodes of bacteremia in 865 patients, whereas we studied 559 episodes in 4918 patients. Fur-

Table 3. Association between patient factors and septicemia episodes in dialysis patients

Characteristic	Hemodialysis patients		Peritoneal dialysis patients	
	Unadjusted risk ratio	Adjusted[a] risk ratio	Unadjusted risk ratio	Adusted[a] risk ratio
Age > 65 years	1.75(1.48–2.06)[b]	1.61(1.35–1.92)[b]	1.63(1.06–2.50)[b]	1.90(1.17–3.08)[b]
Female gender	1.09(0.92–1.28)	0.96(0.81–1.14)	1.26(0.84–1.90)	1.17(0.77–1.79)
Black race	0.83(0.70–0.97)[b]	0.91(0.76–1.08)	0.56(0.34–0.90)[b]	0.53(0.31–0.90)[b]
High school grad	1.12(0.90–1.40)	1.20(0.95–1.50)	0.72(0.42–1.25)	0.82(0.46–1.45)
Insurance status:				
None	0.66(0.46–0.96)[b]	0.89(0.61–1.32)	1.59(0.90–2.81)	2.69(1.43–5.05)[b]
Medicaid	1.01(0.82–1.24)	1.00(0.80–1.25)	1.27(0.73–2.21)	1.83(1.00–3.36)[b]
Medicare or private insurance	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Diabetes mellitus	1.28(1.08–1.51)[b]	1.26(1.06–1.50)[b]	1.92(1.28–2.90)[b]	2.21(1.43–3.40)[b]
Serum albumin < 3.5 g/dl	1.79(1.50–2.14)[b]	1.66(1.38–1.99)[b]	1.44(0.93–2.23)	1.22(0.77–1.91)
Hematocrit >25%	0.93(0.78–1.12)	0.92(0.77–1.11)	0.86(0.53–1.40)	0.66(0.40–1.11)

[a] Adjusted for age, gender, race, education, insurance status, diabetes, serum albumin, hematocrit, neoplasm and geographic location, except for the characteristic of interest, using Poisson regression. For the hemodialysis population, also adjusted for vascular access and reuse of dialyzers
[b] $P < 0.05$

Table 4. Association between treatment factors and septicemia episodes in hemodialysis patients

Treatment factor	Entire follow-up period (up to 7 years)	Early (first 6 months after start of dialysis)	Late (after 6 months or more after start of dialysis)
	Adjusted[a] RR(95% CI)		
Type of vascular access (first 6 weeks after start of dialysis treatment[b]			
Temporary catheter	1.48 (1.16–1.89)[c]	2.26 (1.15–4.46)[c]	1.37 (1.06–1.78)[c]
Permanent subclavian catheter	1.35 (0.95–1.92)	2.38 (0.997–5.66)	1.22 (0.82–1.80)
Goretex or bovine graft	1.34 (1.04–1.71)[c]	1.63 (0.79–3.38)	1.29 (0.99–1.69)
Native fistula	1.00 (reference)	1.00 (reference)	1.00 (reference)
Reuse of dialysis membranes	1.28 (1.05–1.56)[c]	1.40 (0.87–2.25)	1.23 (0.99–1.53)

RR is risk ratio.
[a] Adjusted for age, gender, race, education, insurance status, diabetes, serum albumin, hematocrit, geographical location and neoplasm using Poisson regression
[b] For patients who had more than one type of vascular access, access was classified as the one with the presumed higher risk, (that is, temporary catheter (33.7%) > permanent central venous catheter (9.1%) > goretex or bovine graft (32.9%) > native arteriovenous fistula (24.4%)
[c] $P < 0.05$

thermore, only 12% of the population of the EPIBACDIAL study were diabetic compared with more than 40% of our U.S. population. Our study therefore had greater power to detect an increased risk of septicemia among diabetics. Although a statistically significant increased risk of septicemia in diabetics was not observed in the EPIBACDIAL study, more than 7% of their patients with DM had an episode of septicemia with an increased relative risk of 1.63. Other studies corroborate our evidence of an association between DM and septicemia in dialysis patients. In another French prospective study, Roubicek et al found that diabetic HD patients were at significantly higher risk of bacteremia than nondiabetic patients [19].

Although Hoen et al did not find a statistically significant increased risk of sepsis with increased age, patients with bacteremia in their study were older than those who did not experience bacteremia, and this approached statistical significance. We found a statistically significant association between age and sepsis when we used age as a categorical variable (an age of more than 65 years), rather than as a continuous variable, as was done in the EPIBACDIAL study. This finding is in accordance with previous knowledge that the function of the immune system declines with age, putting the older population at greater susceptibility to infections [20, 21].

Effect of hematocrit on risk of sepsis

Although the EPIBACDIAL study suggested a protective effect of an increased hematocrit against septicemia, we did not find a significant protective effect against septicemia associated with an increase in hematocrit. This difference may be related to the populations studied, differences in the measurement of anemia, and the impact of recombinant human erythropoietin (rHuEPO). The EPIBACDIAL study reported that an increase of 1 g/dl hemoglobin was associated with protection against bacteremia. Although the point estimate for the relative risk in our analysis did suggest a protective effect for a hematocrit of more than 25% against risk of septicemia,

Table 5. Association of septicemia with death

Type of death	Hemodialysis patients risk ratio (95% CI)		Peritoneal dialysis patients risk ratio (95% CI)	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Death from all causes	2.74 (2.44–3.07)[b]	2.40 (2.12–2.72)[b]	2.66 (2.02–3.50)[b]	1.73 (1.23–2.44)[b]
Death from septicemia	9.62 (6.75–13.73)[b]	9.79 (6.49–14.76)[b]	7.25 (3.40–15.48)[b]	4.81 (1.56–14.81)[b]
Death from other causes	2.44 (2.16–2.76)[b]	2.14 (1.87–2.45)[b]	2.46 (1.82–3.32)[b]	1.77 (1.23–2.55)[b]

[a] Adjusted for age, gender, race, diabetes mellitus, serum albumin, hematocrit, education, insurance at onset of ESRD, cholesterol, blood pressure, smoking, obesity and comorbid disease (neoplasm, congestive heart failure, LVH, coronary disease, cerebrovascular disease and peripheral vascular disease). Septicemia is modeled as a time dependent covariate

[b] $P < 0.01$

the association was not statistically significant. The reasons for this difference are not completely clear. The study populations differed in their baseline hematocrit levels. At the time when the patients were enrolled in the case-mix study, rHuEPO was not available. This is in contrast to the EPIBACDIAL study, in which over half of the study participants were receiving rHuEPO. The use of rHuEPO has dramatically reduced the severity of anemia and the need for blood transfusions in dialysis patients. It has also been associated with a fall in serum ferritin levels, suggesting that a reversal of secondary hemosiderosis may be the mechanism through which the frequency of bacterial infection decreases in HD patients on rHuEPO. Although in our study we do not have data on ferritin levels, *in vitro* studies suggest that iron overload may increase the dialysis patient's susceptibility to infection by two mechanisms. The first mechanism is the enhancement of bacterial growth in an iron-enriched medium. The second mechanism is impairment of phagocytic function [22, 23]. Several authors have shown an increased risk of septicemia in HD patients with a serum ferritin level above 1,000 μg/liter [24, 25]. EPIBACDIAL study patients are likely to have had higher hematocrits, lower serum ferritin, and fewer blood transfusions than patients in our analysis. Few patients in the case-mix study (pre-rHuEPO) had hematocrits of more than 25%, and those that did most likely received frequent blood transfusions. It is possible that we did not see a protective effect associated with increased hematocrit because of the possible confounding effect of elevated serum ferritin levels, which were unmeasured in our analysis. Further suggestive evidence of the potential benefits of rHuEPO and increased hematocrit in dialysis patients, consistent with the finding in the EPIBACDIAL study, has recently been presented by Collins, Ma and Ebben in work demonstrating that hospital length of stay and the risk of hospitalization in general significantly decrease as patients' hematocrits increase [26, 27].

Risk factors for septicemia in hemodialysis patients

Vascular access. As in the Canadian Hemodialysis Morbidity Study [18], we found that among U.S. HD patients, low serum albumin and vascular grafts rather than native fistulae conferred increased risk for septicemia. Although the estimate of risk for sepsis associated with permanent central venous catheters was twice that of patients with native fistulae in the first six months after dialysis initiation in our study, we did not see the marked sevenfold increased risk of septicemia associated with permanent central venous catheters recently reported by Hoen et al in the EPIBACDIAL study [15]. The difference between our estimate of permanent central venous catheter risk and the estimate from the EPIBACDIAL study may be due to our examining incident dialysis patients who frequently had temporary access, whereas the EPIBACDIAL study included prevalent patients, with an average five-year duration of ESRD. Patient demographic differences and differences in practice patterns between the United States and France may also play a role.

In this incident ESRD patient group, we observed a 50% increased risk of septicemia associated with temporary catheters for vascular access compared with native fistulae. The higher risk may be inherent to the temporary catheter or may be confounded by the type of patient who would need a temporary catheter at first dialysis. Having a surgically created graft or native fistula for HD access within six weeks of initiation of dialysis suggests a patient with long-term medical involvement prior to ESRD. This involvement may confer a protective effect against septicemia. Of note, our analysis of vascular access risk was complicated by the large number of patients who had more than one access when baseline data collection occurred. Additionally, calculating the risk of a particular access type with risk of septicemia at time points distant from when the access information was obtained is limited by the potential for misclassification.

Low serum albumin. Among HD patients, low serum albumin at baseline was also an identifiable risk factor for septicemia. Low serum albumin may represent nutritional deficiency in dialysis patients and has previously been shown to be a strong predictive risk factor for death [28, 29]. Our findings suggest that prevention and

treatment of dialysis associated malnutrition through nutritional counseling, avoiding low-protein diet months before implementation of renal replacement therapy, and increasing the dose of dialysis to improve appetite and correct acidosis may eventually decrease the risk of septicemia in this vulnerable population.

Membrane reuse. Among HD patients, membrane reuse was also an independent risk factor for septicemia in this analysis. One of the major concerns with dialyzer reuse is the risk of infection. Recently, several case reports in the medical literature have cited an association between reuse and individual patient's infections [30–33], but there have been no large representative cohort studies linking reuse with the risk of septicemia. Reuse has been associated with lower survival among HD patients in prior studies [12, 14], but the reasons for this increased mortality have not been clear. Although it has been proposed that infectious causes of death might be more common if reused dialyzers were improperly disinfected, the mortality risks associated with reuse are reportedly similarly elevated for infectious, cardiovascular, and other causes of death [14]. Our finding of an association of reuse and septicemia again raises the possibility that decreased survival with some types of reuse may be mediated through infection. Recently, Collins et al also reported on the effect of reuse of dialyzers on survival of HD patients at free-standing facilities. They found that for patients who entered HD in 1991 to 1993, there was no association between the reuse germicide used and survival, but patients who entered HD in 1988 to 1990 had a higher risk of death with peracetic acid [34, 35]. Because patients in the case-mix study were incident in 1986, they may be more similar to the earlier cohort in Collins et al's analysis. This suggests that potential changes in reuse practices over time could explain the variability in risk associated with reuse between our study and other studies in different time periods. Further analyses of potential interactions between secular trends in reuse of dialyzers and risk of infection-related morbidity, including septicemia, are warranted.

Risk factors for septicemia among PD patients.

Risk factors for hospital-managed septicemia and its outcome among U.S. PD patients have not been previously reported. We found that in U.S. PD patients, white race is a risk factor for septicemia even after taking into account other factors, including health insurance and education. Although a racial difference was also suggested among HD patients, the protective effect of black race against sepsis was not statistically significant in the adjusted analysis. The association of increased risk for sepsis for white PD patients is the opposite of that seen in the general population [36], but analogous racial differences have been described previously in ESRD. In comparing causes of death in dialysis patients by race, Bloembergen et al found an increased risk of death from infection in white females and in white patients with diabetes [2, 37]. The explanation for a lower risk of septicemia in black PD patients remains unclear. Possible explanations include selection bias, as only healthier black patients may be selected for PD. Also, white patients may more readily go on to transplant, leaving "sicker" whites and relatively "healthier" blacks on dialysis [16].

In examining possible socioeconomic factors that may increase risk of septicemia, we found that among PD patients, having no insurance prior to the onset of ESRD is a strong marker for septicemia. We found an apparent stepwise increase in risk of septicemia for patients with Medicare or private insurance at baseline (reference) to those covered by Medicaid (RR 1.83), to patients with no insurance at baseline (RR 2.69). This finding could be explained if patients without insurance present for dialysis services with more advanced renal disease and have already suffered adverse effects from long-standing uremia, hypertension, and hyperparathyroidism due to limited access to health care.

Limitations

In interpreting the risk factors for sepsis enumerated in this study, it is important to note that we examined only hospital-managed septicemia listed as the primary International Classification of Diseases-9th Modification code for a hospital admission. Certainly, some cases of bacteremia may be managed on an outpatient basis, and others may be reported as secondary diagnoses. We therefore analyzed for risk of more severe cases of septicemia, or cases more likely to be hospitalized, possibly underestimating the frequency of disease in both HD and PD patients. Furthermore, the management of "bacteremia" may differ significantly between HD patients, who have ready vascular access and might be cultured and treated at outpatient HD, and PD patients, who do not have vascular access and are less frequently seen on a routine outpatient basis by medical personnel.

A second limitation of our study is that most patient and treatment factors assessed as potential risk factors were ascertained at the initiation of dialysis. For nonmodifiable characteristics such as age, gender, and race, this is not a limitation. However, for patient factors that may change over time, such as vascular access, insurance status, serum albumin, hematocrit, and even dialysis modality, assessing the risk of septicemia several years after these data were obtained may lead to misclassification and may bias our results. Because data in our analysis were abstracted from a single chart review, there was no opportunity to track individual changes in albumin, hematocrit, or vascular access over time. Therefore, to address the changes in the laboratory values or vascular access over the follow-up period, we assessed the rela-

tionship between risk factors for septicemia within the first six months after the start of dialysis as well as later periods. We found that the results were unchanged across the different time periods. Insurance status is another baseline variable that changes over time, as almost all patients with ESRD become eligible for Medicare. Our analysis of risk during the first six months of treated ESRD would most closely approximate the risk of the individual who was uninsured prior to dialysis.

For the issue of reuse, we examined only whether an individual patient reused dialyzers for HD. We did not have access to information on the type of disinfectant process used prior to reuse. In prior studies, increased risk of mortality has been suggested with only certain reuse practices. As this information was not available in the current study, we are unable to relate our findings of increased risk of septicemia with any particular dialyzer disinfectant or reuse process [14].

A potential weakness of our analysis of mortality caused by septicemia is our necessary reliance on HCFA form 2746 for cause of death. Standard death certificate and ESRD registry information in the same ESRD patients do not always agree. The discrepancy could stem from insufficient reliability or validity of either or both reporting systems. In their study of cause of death, comparing death certificates versus registry reports, Perneger et al found a moderate agreement (κ 0.44) for infectious disease, which represented 16% of the causes of death in the death certificates and 22% of the causes of death in the registry reports [38]. It is therefore possible that causes of infectious death in our patients were misclassified. If the misclassification was random, we would actually be underestimating the risk of death from sepsis. If, however, as suggested by the study of Mailloux et al, many "noninfectious deaths" in dialysis patients are actually caused by sepsis, misclassification may have been systematic [39]. To address this possibility, we also studied the risk of death by looking at all causes of death, death due to septicemia, and death attributed to other causes. It is possible that the increased risk of death because of other causes in patients with septicemia was due to misclassification, and deaths attributed to other causes were actually infectious deaths. Recent changes in HCFA form 2746 may improve the reporting of infectious causes of death, and future analyses may be less subject to this possible reporting bias.

Conclusions and implications

Septicemia remains a frequent cause of death in patients with ESRD. In this U.S. study, it is not surprising that patients with an episode of septicemia had a very high risk of death from septicemia. What was perhaps more significant in this analysis was that patients with an episode of septicemia had an increased risk of death from other causes as well. The risk factors that we have outlined for septicemia are older age, diabetes, low serum albumin, temporary vascular access, and reuse, and also in PD patients, white race and no insurance, which are factors that identify a particularly vulnerable group of patients with ESRD. Several of the risk factors identified in this study are modifiable risk factors (for example, serum albumin, temporary vascular access). Early referral to a nephrologist, as emphasized in recent Dialysis Outcomes Quality Initiative guidelines, might help ameliorate the risk of septicemia, by improving the nutritional status of the patients, correcting the anemia of chronic renal failure by starting rHuEPO even before dialysis when necessary, assisting with better insurance coverage before dialysis, and more importantly, minimizing use of temporary catheters at the start of dialysis by insertion of permanent fistula in the pre-ESRD period [40, 41]. Further analyses to elucidate potential mechanisms for variations in risk for septicemia according to race, access to health insurance, and dialyzer reuse practices over time are warranted.

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