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Septicemia, access and cardiovascular disease in dialysis patients: The USRDS Wave 2 Study[1]

AREEF ISHANI, ALLAN J. COLLINS, CHARLES A. HERZOG, and ROBERT N. FOLEY

Section of Nephrology, Department of Medicine, Minneapolis Veterans Affairs Medical Center, Minneapolis, Minnesota; Division of Renal Diseases and Hypertension, University of Minnesota, Minneapolis, Minnesota; and Cardiovascular Special Studies Center, United States Renal Data System, Minneapolis, Minnesota

Septicemia, access and cardiovascular disease in dialysis patients: The USRDS Wave 2 Study.

Background. Microinflammation is linked to cardiovascular disease, and is highly prevalent in dialysis patients. It is logical to postulate that septicemia, a common macroinflammatory occurrence in dialysis patients, contributes to their large burden of cardiovascular disease.

Methods. The Dialysis Morbidity and Mortality Wave 2 was a randomly selected prospective cohort of incident dialysis patients. Admission claims data were used to define and calculate rates of septicemia or bacteremia and cardiovascular events in those with Medicare as the primary payer. Utilizing Cox proportional hazard models we determined the association between baseline access and the development of bacteremia or sepsis, and also the association between bacteremia or sepsis episodes and subsequent cardiovascular events.

Results. The 2358 (59%) patients with Medicare as primary payer were older and more likely to have heart failure than those with other payers, but had similar comorbidity-adjusted mortality hazards. Rates of first septicemia, bacteremia, or either condition, were 7.0, 5.9 and 10.4 events per 100-patient years, respectively. Cox regression identified initial dialysis access as the main antecedent of septicemia or bacteremia. Hazards ratios for hemodialysis with permanent catheters, temporary catheters, and grafts were 1.95 (95% CI 1.47-2.57), 1.76 (95% CI 1.29-2.41), and 1.05 (95% CI 0.82-1.35), respectively, while that for peritoneal dialysis was 0.96 (95% CI 0.75-1.23) (reference arteriovenous fistula). After adjustment for baseline factors, septicemia or bacteremia, as a time-dependent covariate, was associated with subsequent death [hazards ratio (HR) 2.33, 95% CI 1.38-2.28], myocardial infarction (HR 1.78, 95% CI 1.38-2.28), heart failure (HR 1.64, 95% CI 1.39-1.95), peripheral vascular disease (HR 1.64, 95% CI 1.34-2.0), and stroke (HR 2.04, 95% CI 1.27-3.28).

Conclusion. Septicemia appears to be an important, potentially preventable, cardiovascular risk factor in dialysis patients.

Atherosclerosis and microinflammation are interrelated [1]. Infection is a classic macroinflammatory state and it is logical to postulate that infection may underpin the lethal synergy between inflammation and atherosclerosis. Cardiovascular disease is highly prevalent in those initiating dialysis. Dialysis patients have an excess of cardiovascular mortality that is poorly explained by traditional cardiovascular risk factors [2–4]. As in the general population, inflammatory markers have been demonstrated to be independent predictors of cardiovascular outcomes in hemodialysis [5] and peritoneal patients [6]. Access for dialysis is a significant source of infection and morbidity in those undergoing both hemodialysis and peritoneal dialysis [7–9]. It is unknown whether bacteremia or septicemia, clinical markers for a macroinflammatory state, has the same adverse association with cardiovascular disease as microinflammation.

We hypothesized that vascular access for dialysis is a source of infection for dialysis patients, leading to inflammation and cardiovascular disease. We aimed to determine rates of bacteremia or sepsis in incident dialysis patients and to quantify the associations between (*1*) access type and hospitalization for septicemia or bacteremia and (*2*) septicemia or bacteremia, cardiovascular events, and death.

METHODS

In temporal sequence, the objectives of the study were to determine, in incident dialysis patients: (*1*) hospitalized septicemia rates (referred to as "septicemia"), (*2*) bacteremia rates, not associated with hospitalization (referred to as "bacteremia"), (*3*) dialysis access type at dialysis inception and subsequent associations with septicemia or bacteremia, and (*4*) The association between

[1]The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the United States government

Key words: bacteremia, septicemia, death, vascular access, cardiovascular disease.

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septicemia and/or bacteremia and subsequent cardiovascular events and death.

Subjects

The Wave 2, Dialysis Morbidity and Mortality Study (DMMS), was a prospective study, including all incident peritoneal dialysis in the United States and one fifth of incident hemodialysis patients, during the years 1996 and 1997. Trained individuals recorded information on demographics, clinical variables (including access type), comorbidities, laboratory variables, and medication use through patient interviews and chart abstraction [10]. Dialysis access in use at study initiation was divided into five categories, peritoneal dialysis and the following four categories in hemodialysis patients: native fistula, graft [polytetrafluoroethylene (PTFE) or bovine], permanent catheter (tunneled), temporary catheter (nontunneled), and "other" type of access. To be included in the final analysis an individual was required to have complete baseline data, a valid United States Renal Data System (USRDS) identifier, and have Medicare as their primary payer source defined as: A threshold of Medicare claims submission totaling $675 or more in any of the 3 months after study initiation [11]. Individuals with dialysis claims less than this threshold amount are thought to have Medicare as a supplemental payer and consequently prone to misclassification bias as many events [I*nternational Classification of Diseases, Ninth Revision* (ICD-9 codes of interest)] would be missed by a Medicare only claims search. Blood pressure values utilized in all analyses were the mean of the last three clinically recorded blood pressures prior to the initiation of the study.

Outcomes

The participants of the Wave 2 Study were linked electronically to the USRDS through the use of a unique identifier to obtain subsequent Medicare claims and vital status. Claims data were available until December 31, 1999. With the exception of death, all outcomes in this study were obtained from Medicare claims data. Providers and facilities submit Medicare claims at the time of service and document, through the use of ICD-9 codes, the reason for the claim.

Outcomes were defined with the following *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) codes: (*1*) septicemia: codes 038.xx, where x is from 0 to 9 inclusive; streptococcal (038.0x), staphylococcal (038.1x), pneumococcal (038.2), anaerobic (038.3), aerobic gram-negative (038.4x), other specified septicemia (038.8) and unspecified septicemia (038.9) are defined by these terms; (*2*) bacteremia: code 790.7, defined as bacterial infection with no signs of infection; (*3*) myocardial infarction: codes 410.xx (except 410.x2); (*4*) congestive heart failure: codes 402.x1, 425.xx, 428.xx, 518.4, and 398.91; (*5*) stroke: codes 430.xx, 431.xx, 432.xx, 433.xx, 434.xx; and (*6*) peripheral vascular disease: codes 440.xx to 444.xx (except 443.0) and 447.xx (except 447.0, 447.6, 447.8, and 447.9).

Follow-up

Follow-up began at the study start-date, which was 60 days after the first dialysis treatment. The follow-up time for each event was defined as the time from initiation of the study until the date of the index event, the date of death, the date at which an individual was deemed lost to follow-up (defined as Medicare claims for dialysis below the threshold value of $675 in any 3-month period between study initiation and study end), or at the completion of the study, December 31, 1999. Individuals were considered censored if they were lost to follow-up or upon completion of the study without an index event. Deaths were ascertained through the end-stage renal disease (ESRD) death notification form (CMS-2746).

Analysis

To determine the effect of excluding non-Medicare recipients from our analyses we compared baseline data and survival in those with and without Medicare as their primary payer. Patients with and without Medicare as primary payer were compared using t tests for continuous parameters and $\chi 2$ analysis for proportions. Multivariate logistic regression was used, with Medicare as payer (yes/no) as the dependent variable and baseline patient characteristics as exploratory variables. Finally, the mortality hazards of patients with and without Medicare were compared using Cox regression, with adjustment for baseline characteristics.

In those with Medicare as primary payer, standard Cox regression was used to identify baseline covariates associated with septicemia or bacteremia, while actuarial survival analysis was used to calculate subsequent cumulative survival rates. Time-dependent Cox regression was used to quantify the association between septicemia or bacteremia and cardiovascular events. No screening was performed prior to a variable being entered into the final model. Reported P values are based on two-sided tests and were considered significant with $\alpha \leq 0.05$. All analyses were performed using the SAS system for Windows, version 8.02 (SAS Institute, Cary, NC, USA). The Hennepin County Medical Center Human Subjects Research Committee approved this study.

RESULTS

The Wave 2 Study included 4024 individuals, of these 94 were excluded as they lacked a valid USRDS identifier. As all of our outcomes utilized Medicare billing data we excluded 1572 individuals from our final analysis (leaving

Table 1. Baseline characteristic of those with and without Medicare as primary payer

	Medicare primary payer				
	No ($N = 1572$)	Yes ($N = 2358$)	P value[a]	Odds ratio (95% CI)[b]	P value[b]
Dialysis access%			<0.0001		
Temporary catheter	5.5	6.5		0.94 (0.65-1.37)	0.8
Permanent catheter	6.6	11.1		1.16 (0.83-1.64)	0.4
Graft	19.5	27.4		0.95 (0.71-1.26)	0.7
Fistula	7.5	9.9		1.0 Ref	Ref
Peritoneal dialysis catheter	60.8	45.0		0.63 (0.49-0.82)	0.0006
Baseline comorbidities%					
Myocardial Infarction	17.4	22.8	<0.0001	1.00 (0.82-1.22)	1.0
Congestive heart failure	31.9	44.9	<0.0001	1.16 (0.99-1.37)	0.06
Cerebrovascular accident	12.8	16.8	0.0006	1.11 (0.90-1.37)	0.3
Peripheral vascular disease	20.3	25.5	0.0001	0.93 (0.77-1.12)	0.4
Diabetes mellitus	48.6	54.0	0.001	1.16(0.89-1.54)	0.3
Primary renal disease%			<0.0001		
Diabetes mellitus	41.4	44.1		0.92 (0.68-1.24)	0.6
Hypertension	23.2	27.6		1.08 (0.88-1.33)	0.5
Glomerulonephritis	10.8	6.8		0.83 (0.63-1.10)	0.2
Other/unknown	24.6	21.5		1.0 Ref	Ref
Age *years* (SD)	52.6 (14.4)	62.5 (15.5)	<0.0001	1.04 (1.03-1.04)	<0.0001
Race%			0.001		
White	58.8	64.2		0.93 (0.72-1.21)	0.6
Black	30.7	27.8		0.88 (0.66-1.16)	0.4
Gender%					
Male	50.8	53.1	0.2	1.09 (0.94-1.25)	0.2
Blood pressure *mm Hg*					
Systolic 146.2 (20.4)		147.2 (21.7)	0.1	1.00 (1.00-1.01)	0.2
Diastolic	81.9 (12.0)	78.0 (12.1)	<0.0001	0.99 (0.98-1.00)	0.07
Serum albumin (<3.0 mg/dL)%	26.7	24.1	0.03	0.99 (0.84-1.16)	0.9
Adjusted mortality hazards ratio[c] (95% CI)	1[c] (Ref)	1.11[c] (0.996-1.23)	0.06[c]		

[a]Continuous parameters are compared using a t test. Categoric parameters are compared using the χ^2 test.
[b]Using logistic regression, with the presence (coded 1) or absence (coded 0) of Medicare as payer as dependent variable, with all the baseline parameters shown in the first column as exploratory variables.
[c]Using a Cox regression model, including Medicare as payer, with adjustment for all the baseline parameters shown in the first column.

$N = 2358$), as they had not generated sufficient dollar value claims to the Medicare system for dialysis within 3 months of initiation of the Wave 2 Study. Additionally, 47 individuals were excluded because baseline covariate information was missing. The final sample size included 2311, 57% of the original Wave 2 cohort.

Table 1 compares the baseline characteristics of those with and without Medicare as primary payer. On multivariate analysis, patients with Medicare as primary payer were older, and less likely to use peritoneal dialysis. Table 1 also shows that there was a trend toward higher adjusted mortality hazards in patients with Medicare as primary payer.

Further outcome analysis was restricted to those with Medicare as primary payer. The median follow-up was 3.2 years. A total of 527 patients had a first hospital-associated episode of septicemia, 446 had a first episode of bacteremia not associated with hospitalization, and 791 patients had at least one of the two events, yielding an incidence of 7.0, 5.9, and 10.4 events per 100 patient years, respectively (Fig. 1). Table 2 shows associations between baseline characteristics of patients who either did or did not experience septicemia or bacteremia. Cox regression identified initial dialysis access as the main antecedent characteristic of developing either hospitalized

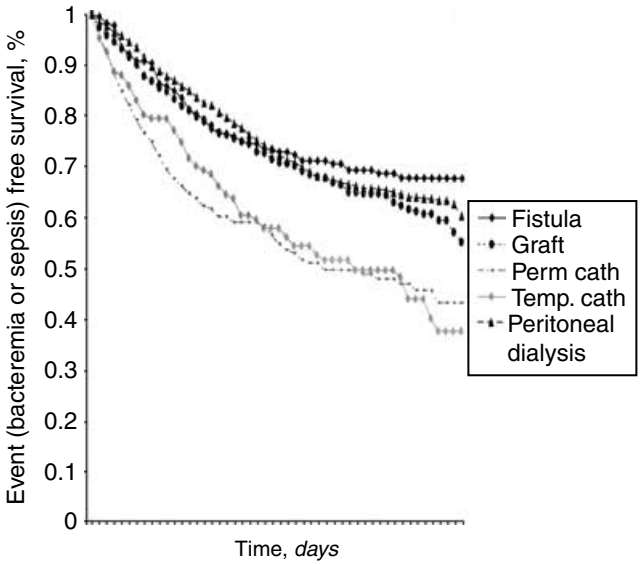

Fig. 1. Cumulative incidence of bacteremia or septicemia over time in the Wave 2 population.

septicemia or bacteremia. Using arteriovenous fistula as reference category, hazards ratios (HRs) for hemodialysis with permanent catheters, temporary catheters, and grafts and were 1.95 (95% CI 1.47-2.57) ($P = 0.0004$),

Table 2. Baseline characteristics associated with development of septicemia or bacteremia

	Bacteremia or hospitalized septicemia					
	No[a] ($N = 1533$)	Yes[a] ($N = 778$)	P value[a]	HR[b] ($N = 2311$)[c]	95% CI[b]	P value[b]
Dialysis access%			<0.0001			
Temporary catheter	5.1	9.3		1.76	1.29-2.41	0.0004
Permanent catheter	9.3	15.2		1.95	1.47-2.57	<0.0001
Graft	27.6	27.0		1.05	0.82-1.35	0.2
Fistula	10.5	8.5		1	Ref	Ref
Peritoneal dialysis catheter	44.9	37.2		0.96	0.75-1.23	0.8
Comorbidities%						
Myocardial infarction	23.2	21.9	0.5	0.99	0.82-1.19	0.9
Congestive heart failure	44.9	44.3	0.8	1.11	0.95-1.29	0.2
Cerebrovascular accident	16.2	17.9	0.3	1.06	0.87-1.28	0.6
Peripheral vascular disease	25.2	25.7	0.8	1.13	0.95-1.35	0.2
Diabetes mellitus	52.4	56.6	0.06	1.13	0.88-1.45	0.3
Primary renal disease%			0.6			
Diabetes mellitus	43.4	45.9		0.94	0.72-1.24	0.7
Hypertension	28.2	27.0		0.89	0.72-1.10	0.3
Glomerulonephritis	7.2	6.2		0.78	0.56-1.08	0.1
Other/unknown	21.1	21.0		1.0	Ref	Ref
Age *years* (SD)	63.1 (15.4)	61.3 (15.4)	0.01	1.00	0.97-1.01	0.7
Race%			0.0001			
White	66.9	59.8		1.14	0.85-1.52	0.4
Black	25.1	33.6		1.46	1.08-1.97	0.01
Other	8.0	6.7		1		
Male gender%	53.9	52.1	0.4	.96	0.84-1.11	0.6
Blood pressure *mm Hg*						
Systolic	146.8 (21.7)	148 (21.7)	0.2	1.00	0.99-1.00	0.08
Diastolic	77.6 (12.3)	78.8 (11.8)	0.03	1.00	1.00-1.01	0.4
Serum albumin (<3.0 mg/dL)%	23.0	25.3	0.2	1.20	1.01-1.41	0.03

[a]Continuous parameters are compared using a t test. Categoric parameters are compared using the χ^2 test.
[b]Using a Cox proportional hazards model with the time to developing a bacteremia or hospitalized septicemia episode as the dependent variable, with all the baseline parameters shown in the first column as covariates. The reference categories for categoric variables are dialysis access (fistula), absence of all comorbidities, primary renal disease (other/unknown), race (other), and gender (female).
[c]A total of 47 (2.0%) Medicare patients were excluded because of missing baseline data or absence of a follow-up interval greater than zero.

1.76 (95% CI 1.29-2.41) ($P < 0.0001$), and 1.05 (95% CI 0.82-1.35) ($P = 0.2$), respectively, while that for peritoneal dialysis was 0.96 (95% CI 0.75-1.23) ($P = .8$). Other significant associations included black race and low serum albumin (Table 2).

The occurrence of septicemia or bacteremia was associated with subsequent cardiovascular morbidity and mortality. Figure 2 shows adjusted survival estimates after septicemia and bacteremia, with survival after myocardial infarction, in the Wave 2 population, shown for comparison. One-year adjusted survival estimates after hospitalized septicemia, bacteremia, and myocardial infarction are demonstrated in Figure 2. Table 3 shows comorbidity-adjusted HRs for death and admission for cardiovascular events, with the first episode of septicemia or bacteremia treated as a time-dependent covariate. The occurrence of septicemia or bacteremia were associated with death (HR 2.33, 95% CI 2.08-2.61) ($P < 0.0001$), congestive heart failure (HR 1.65, 95% CI 1.39-1.95) ($P < 0.0001$), myocardial infarction (HR 1.78, 95%CI 1.38-2.28) ($P < 0.0001$), peripheral vascular disease (HR 1.64, 95% CI 1.34-2.00, $P < 0.0001$), and stroke (HR 2.04, 95% CI 1.27-3.28) ($P = .003$) (Fig. 3). The effect of

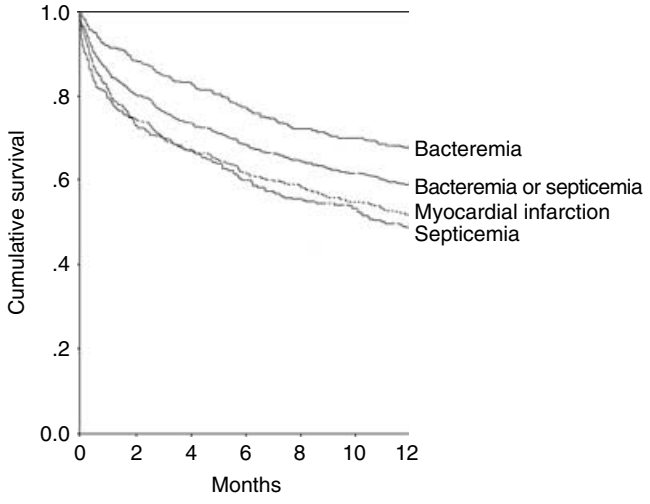

Fig. 2. Actuarial adjusted survival estimates after a diagnosis of bacteremia, septicemia, either septicemia or bacteremia and myocardial infarction in the Wave 2 population. Adjusted for the following variables: history of myocardial infarction, congestive heart failure, cerebrovascular accident, peripheral vascular disease, and diabetes, primary cause of kidney disease (diabetes, hypertension, glomerulonephritis, other), age, race (black, white, other), mean predialysis systolic and diastolic blood pressure, and an albumin <3.0 mg/dL).

Table 3. Cox proportional hazards demonstrating association between bacteremia or sepsis and various outcomes with adjustment for all the baseline variables shown in the first column

	Mortality		CHF events		MI events		PVD events		CVA events	
Variable	HR	95% HR CI	HR	95% HR CI	HR	95% HR CI	HR	95% HR CI	HR	95% HR CL
Time to bacteremia or sepsis *days*	2.33	2.08-2.61	1.65	1.39-1.95	1.78	1.38-2.28	1.64	1.34-2.00	2.04	1.27-3.28
Age *years*	1.03	1.02-1.03	1.01	1.01-1.02	1.00	0.99-1.01	1.00	1.00-1.01	0.99	0.97-1.01
Race										
White	1.49	1.19-1.87	1.44	1.10-1.88	1.32	0.86-2.02	1.40	1.01-1.93	1.62	0.64-4.11
Black	1.29	1.02-1.64	1.14	0.85-1.51	1.06	0.67-1.67	1.22	0.87-1.72	1.75	0.68-4.52
Gender, male%	1.02	0.92-1.14	1.01	0.88-1.15	1.21	0.97-1.50	1.12	0.95-1.31	1.27	0.82-1.96
Mean blood pressure										
Systolic *mm Hg*	0.99	0.99-1.00	1.00	1.00-1.00	1.01	1.00-1.02	1.00	1.00-1.01	1.00	0.99-1.02
Diastolic *mm Hg*	0.99	0.99-1.00	1.00	0.99-1.00	0.99	0.97-1.00	0.99	0.98-1.00	1.01	0.98-1.04
Low albumin (<3.0 mg/dL)%	1.20	1.07-1.36	1.12	0.96-1.31	0.96	0.74-1.24	0.96	0.80-1.16	0.80	0.46-1.39
Peritoneal dialysis%	1.23	1.10-1.37	0.88	0.77-1.01	1.40	1.12-1.76	1.88	1.59-2.22	0.66	0.41-1.07
Baseline comorbidities%										
Myocardial infarction	1.02	0.90-1.16	1.28	1.10-1.49	1.27	0.98-1.64	1.06	0.87-1.29	1.03	0.57-1.85
Congestive heart failure	1.19	1.07-1.33	1.75	1.52-2.01	1.37	1.09-1.73	1.22	1.03-1.45	1.14	0.72-1.82
Cerebrovascular accident	1.26	1.10-1.44	0.86	0.72-1.03	1.16	0.88-1.54	0.91	0.73-1.13	0.67	0.33-1.36
Peripheral vascular disease	1.16	1.02-1.30	1.13	0.97-1.31	1.12	0.87-1.44	1.67	1.40-2.01	0.69	0.37–1.26
Diabetes	0.90	0.75-1.09	1.02	0.81-1.28	1.16	0.79-1.68	1.29	0.98-1.71	1.25	0.62-2.54
Primary cause of renal disease%										
Diabetes	1.27	1.04-1.56	1.34	1.03-1.73	1.05	0.70-1.59	1.08	0.79-1.46	0.65	0.30-1.42
Hypertension	0.87	0.74-1.02	1.10	0.90-1.34	0.88	0.63-1.23	0.93	0.73-1.20	0.59	0.32-1.09
Glomerulonephritis	0.57	0.43-0.75	0.99	0.73-1.36	0.63	0.36-1.11	0.85	0.58-1.24	0.78	0.34-1.83
Other/unknown	1.0	Ref	1.0	Ref	1.0	Ref	1.0	Ref	1.0	Ref

Abbreviations are: HR, hazards ratio; CI, confidence interval; CL, confidence limits; CHF, congestive heart failure; MI, myocardial infarction; PVD, peripheral vascular disease; CVA, cerebrovascular accidents.

bacteremia or sepsis on subsequent death, or cardiovascular events differed by the presence or absence of cardiovascular disease (presence of either a history of myocardial infarction, congestive heart failure, peripheral vascular disease, or cerebrovascular accident) at baseline (Table 4). Individuals without a history of cardiovascular disease who developed bacteremia or sepsis were more likely to have a subsequent death or cardiovascular disease event as compared to those with a previous cardiovascular disease history ($P < 0.0001$ for the interaction).

DISCUSSION

We found that septicemia and bacteremia were common events after starting dialysis therapy and that catheter use for hemodialysis access was the most obvious antecedent association. Also we have demonstrated that an episode of either bacteremia or hospitalized septicemia was a harbinger of future cardiovascular events and death especially in those without a previous history of cardiovascular disease.

Infection is the second leading cause of death in dialysis patients. Death rates from septicemia have been estimated to be between 100 and 300-fold higher than in the general population [12–14]. Some retrospective studies have demonstrated lower rates of catheter infection than what we are reporting [15, 16]. These lower infection rates may have been the results of meticulous catheter care, similar to care provided to a peritoneal dialysis catheter and are not associated with increased mortality [17]. Alternatively several other studies have shown that septicemia rates are high in dialysis populations, that the presence of dialysis catheters, and grafts are dominant associations, and that septicemia is associated with higher than expected mortality rates [7, 18–25]. It has been hypothesized that this increased risk stems from generalized immunosuppression of dialysis patients, interruption of the skin barrier, and the increased age of those undergoing dialysis. Other studies have demonstrated that use of catheters as vascular access was a significant predictor of both all-cause mortality and infection-specific mortality [7, 26, 27]. Our study suggests that cardiovascular disease may be an intermediate stage in this process. Stated differently, it suggests that septicemia plays a role in the excessive burden of cardiovascular disease in dialysis patients. This phenomenon has recently been demonstrated in the general population where Smeeth et al [28] showed that an acute infection episode was associated with an increased short term risk of myocardial infarctions and stroke.

The mechanism by which septicemia and bacteremia could lead to cardiovascular disease is not fully understood. The full-blown sepsis syndrome has significant effects on endothelial function, as well as the coagulation and redox systems and overall cardiac function [29]. We found that bacteremic episodes, not admitted to hospital, were also associated with poor outcomes (Fig. 3). It is tempting to speculate that bacteremic episodes elicit an inflammatory response, which predisposes to overt cardiovascular dysfunction. Transmission

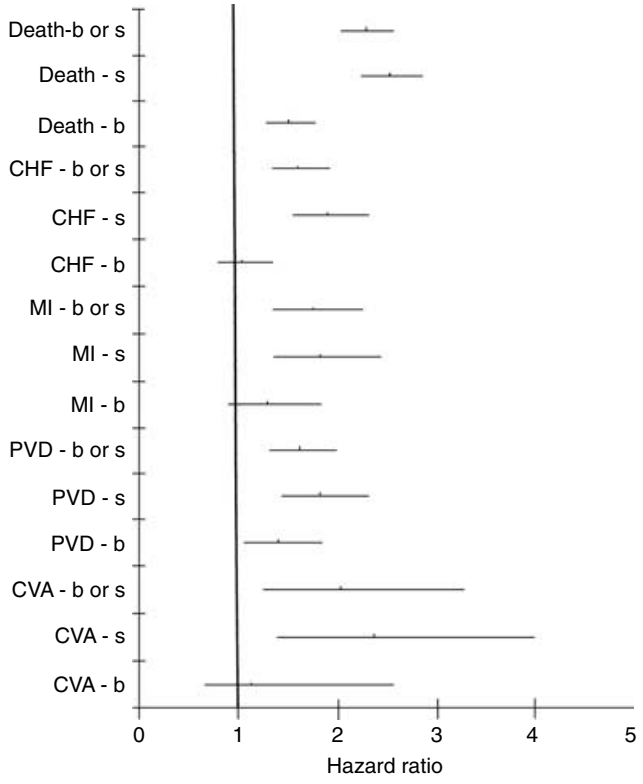

Fig. 3. Hazards ratios for death, hospitalized congestive heart failure (CHF), myocardial infarction (MI), peripheral vascular disease (PVD) and cerebrovascular accident (CVA). The results are reported for the occurrence of bacteremia or septicemia (b or s), bacteremia alone (b), or septicemia alone (s). In each model the outcome of interest was modeled as a time-dependent covariate, with adjustment for baseline dialysis access, comorbidities, primary renal disease, age, race, gender, systolic blood pressure, diastolic blood pressure, and serum albumin.

and scanning electron microscopy studies have demonstrated that almost all indwelling catheters are colonized with microorganisms, even when culture negative [30]. These organisms survive in a biofilm, and appear to be metabolically active and viable [31]. Skin organisms migrate from the catheter insertion site and colonize the external surface of the catheter. Pathogens, even when subclinical, can induce a host inflammatory response [32]. Inflammation has been linked to the future development of cardiovascular disease [33]. In addition, cohort studies in the general population suggest a dose response relationship between the number of previous pathogen exposures and the current inflammatory burden [34]. Both inflammation and the previous cumulative infectious exposure are significant predictors of atherosclerosis extent [35], myocardial infarction, and all-cause cardiovascular morbidity and mortality [36–38]. In those undergoing dialysis, markers of inflammation are elevated eightfold to tenfold compared with healthy controls [5, 39]. It is possible that the use of a catheter is associated with a subclinical infectious state, with resulting increases in serum inflammatory markers, and a more rapid rate of atherosclerosis progression. These changes are subsequently associated with an increased cardiovascular morbidity and mortality rate. This hypothesis is supported by a recent study by Lok et al [40], who showed, in a randomized controlled trial, that prophylactic treatment of dialysis catheter exit sites with polysporin ointment reduced the risk of bacteremia events and all-cause mortality.

Our study has several limitations. First, many individuals from the original study cohort are excluded from the current analysis, limiting the generalizability of this study. Also, we have performed a secondary analysis of an existing data set that was not originally designed to address this specific issue as such, there may be other unknown, or unmeasured factors that may explain the association we have demonstrated between septicemia and cardiovascular disease such as biocompatibility of dialyzers membranes and purity of dialysate which may independently lead to an enhanced inflammatory state [41, 42]. Additionally, our study only included individuals undergoing dialysis therapy in the United States, the applicability of these results to areas outside of the United States is unknown, as the recent Dialysis Outcomes and Practice Patterns (DOPP) Study demonstrated that the percentage of dialysis initiations with a catheter are significantly lower outside of the United States [43]. The underlying condition resulting in the coding of a septicemia event is an important issue. While the clinical definition of septicemia is well defined, the definition of septicemia from Medicare ICD-9 codes is unclear, but likely represents a spectrum of disease from true septicemia to bacteremia. The ICD-9 codes utilized are likely to be specific for infection, but not very sensitive [44, 45]. Also, they are poor markers for the severity of underlying disease. It is quite possible that serious medical conditions lead to admission, which were followed by septicemia. As such, some of the associations between septicemia and bad outcomes could represent an innocent bystander effect. It is interesting that estimates of hospitalized septicemia in this study were quite similar to those reported from the HEMO Study, where outcomes were classified by a committee [46]. Finally, we found an association between the baseline vascular access and subsequent hospitalizations for septicemia. Vascular access in hemodialysis patients changes over time and many of those classified as utilizing a given access may have changed to a different form of access through the course of the study. The Wave 2 Study categorized initial dialysis access; the associations between time-integrated access status, septicemia, cardiovascular events, and death could not be assessed. Regarding initial dialysis access, it is plausible that hemodialysis catheters account for a smaller proportion of overall follow-up, in a given patient, than fistulas or grafts, so that the HRs presented here may be an underestimate of the real association.

Table 4. Cox proportional hazards demonstrating association between bacteremia or sepsis and various outcomes with adjustment for all the baseline variables stratified by a history of cardiovascular disease (CVD) [congestive heart failure (CHF), myocardial infarction (MI), peripheral vascular disease (PVD), or cerebrovascular accidents (CVA)] at baseline

	Mortality		CHF events		MI events		PVD events		CVA events	
Variable	HR	95% HR CI	HR	95% HR CI	HR	95% HR CI	HR	95% HR CI	HR	95% HR CL
No Previous CVD ($N = 876$)	3.48	2.82-4.29	2.25	1.69-3.00	0.3.31	2.15-5.10	1.75	1.23-2.51	2.58	1.33-5.02
Time to bacteremia or sepsis *days*										
Previous CVD ($N = 1435$)										
Time to bacteremia or sepsis *days*	2.03	1.77-2.32	1.49	1.21-1.84	1.36	0.99-1.85	1.66	1.31-2.11	1.84	0.92-3.66

CONCLUSION

We found that hemodialysis catheter use was highly prevalent in United States dialysis patients and strongly associated with septicemia; septicemia, in turn was associated with cardiovascular morbidity and mortality. If this sequence of events is true, strategies leading to maximizing the use of arteriovenous fistula as hemodialysis access could lower infection risk, and ultimately lower cardiovascular event rates. When catheter use is unavoidable, other approaches show potential. To date, topical mupirocin, *Staphylococcus aureus*–conjugate vaccine, and topical antibiotic solutions have been shown to lower bacteremia rates in hemodialysis patients using catheters [47–49].

Reprint requests to Areef Ishani, Division of Nephrology (111J), Department of Medicine, Veterans Affairs Medical Center, One Veterans Drive, Minneapolis, MN 55417.
E-mail: areef.ishani@med.va.gov

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