Septicemia in the United States Dialysis Population, 1991 to 1999

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Abstract. The clinical epidemiology of septicemia in dialysis populations remains poorly defined. In this historical cohort study of 393,451 U.S. dialysis patients, *International Classification of Disease, Ninth Revision, Clinical Modification* discharge diagnosis codes were used to compare first-year septicemia admission rates in annual incident cohorts from 1991 to 1999 and to calculate subsequent cardiovascular event and mortality rates. Hemodialysis (compared with peritoneal dialysis) as initial therapy and starting dialysis in more recent years were the principal antecedents of septicemia. In hemodialysis patients, adjusted first admission rates (expressed throughout as first episodes per 100 patient-years) rose by 51%, from 11.6 in 1991 to 17.5 in 1999. In peritoneal dialysis patients, rates rose from 5.7 in 1991, peaked at 9.2 in 1997, and declined to 8.0 in 1999. Mortality rates after septicemia were similar to mortality rates after major cardiovascular events. Septicemia was associated with developing myocardial infarction, congestive heart failure, stroke, and peripheral vascular disease with adjusted risk ratios of 4.1, 5.5, 4.1, and 3.8 in the initial 6 mo after admission for septicemia and 1.7, 2.0, 2.0, and 1.6 after 5 yr, respectively. Septicemia, which is associated with increased cardiovascular and death risk, has become more common in dialysis patients in the United States.

Septicemia is a common problem in dialysis patients. Dialysis patients tend to be older and often have other conditions that can impair their ability to combat infection, including diabetes and chronic kidney disease itself (1). Sepsis ranks second behind cardiovascular disease as cause of death in dialysis patients (2). In the general population, inflammation is strongly associated with atherosclerotic disease (3–5). Similar associations have been shown in dialysis populations, a group at considerable cardiovascular risk (6,7). Bacterial infection is a paradigmatic inflammatory state. The sepsis syndrome has profound effects on endothelial function, oxidant defense mechanisms, the equilibrium between procoagulant and anticoagulant systems, overall cardiac function, and cellular oxygen availability (8).

The clinical epidemiology of septicemia in dialysis populations remains poorly defined. One study, using information from death certificates, found that death from sepsis was 30 to 45 times more common in dialysis patients than in the general U.S. population (9). Findings from the Case-Mix Severity Study, a retrospective study of patients who started dialysis therapy in the United States in 1986 and 1987, showed that 11% of patients had a primary hospitalization diagnosis of septicemia over 7 yr of follow-up; septicemia was associated with a doubling of mortality rates (10). The Canadian Hemodialysis Morbidity Study reported that septicemia rates were >11% in the first year of dialysis therapy (11). Higher rates were also reported in a study of U.S. patients who initiated dialysis between 1992 and 1997 (12). In the latter study, septicemia was clearly higher in hemodialysis than in peritoneal dialysis patients. In the currently available literature, septicemia is consistently associated with the type of vascular access used for hemodialysis, the lowest rates being associated with native arteriovenous fistulas, followed by synthetic grafts and central venous catheters (10–13).

Very few studies have tried to define temporal trends in incidence rates and risk factors or to quantify associations between septicemia and outcomes such as major cardiovascular disease and death in dialysis patients. This study attempted to address partly this information gap.

Materials and Methods

The objectives of the study were to examine, in U.S. dialysis patients,

1. The comparative incidence of septicemia hospitalization in patients who started dialysis treatment between 1991 and 1999
2. The inception characteristics associated with septicemia
3. The association between septicemia and survival
4. The association between septicemia and subsequent cardiovascular events

Study Population

The Renal Beneficiary Utilization System identification and death notification files and Centers of Medicare & Medicaid Services

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(CMS) Institutional Inpatient Standard Analytical Files were used. Thirty percent of the 558,772 incident patients on dialysis at day 90 were excluded from this analysis because Medicare was not the sole primary payer at the beginning of the study, yielding a sample size of 393,451 patients. Patient characteristics at dialysis inception were obtained from the CMS Medical Evidence Report (Form 2728). This form changed effective April 1, 1995; in addition to information on age, gender, race, and Hispanic ethnicity, the form began to gather information on comorbidity and laboratory test results immediately before the first dialysis. Specifically, the revised form also gathered information on congestive heart failure, atherosclerotic heart disease, cardiac arrest/dysrhythmia, stroke/transient ischemic attack, peripheral vascular disease, diabetes, chronic obstructive pulmonary disease, current smoking, cancer, addiction to drugs/alcohol, and inability to ambulate or transfer, as well as hemoglobin, serum albumin, and serum creatinine values and height and weight data.

Definitions

Medicare hospital claims were used to define clinical events, based on discharge diagnoses, using the following *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) codes:

1. Septicemia: codes 038.xx (x = 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. Myocardial infarction: codes 410.xx (except 410.x2).
3. Congestive heart failure: codes 402.x1, 425.xx, 428.xx, 518.4, and 398.91.
4. Stroke: codes 430.xx, 431.xx, 432.xx, 433.xx, and 434.xx.
5. 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).

Estimated GFR was calculated from serum creatinine values immediately before the first dialysis using the Modification in Diet and Renal Disease Study formula (14): GFR = $186 \times (\text{serum creatinine in mg/dl})^{-1.154} \times \text{age}^{-0.203} \times (1.210 \text{ if black race}) \times 0.742$ (if female gender).

Outcome Analysis

Follow-up intervals and event rates. We studied first admission rates for septicemia, second admission rates for septicemia, admission rates for cardiovascular events, and mortality rates. Follow-up started after 90 d of dialysis therapy. In comparing the incidence of septicemia according to year of dialysis inception for the years 1991 through 1999, a follow-up period of 1 yr was used so that identical follow-up intervals would be available in each annual incident cohort; follow-up was censored at any modality change, including transplantation. For all other outcomes, follow-up ended on December 31, 2000, or at transplantation.

Models. Logistic regression models were used to compare patients who were included in the study and those who were excluded from the study because they did not have Medicare as sole, primary payer. Poisson regression was used to test the association between septicemia rates and baseline characteristics, including year of dialysis inception. The associations between first septicemia episode, cardiovascular events, and mortality were tested with interval Poisson models, in intervals of 6 mo. All patients from 1991 to 1999 were included when the association between year of dialysis inception and septicemia rates was tested. All other analyses were restricted to patients who started dialysis after 1995, because baseline comorbidity characterization was more extensive for these patients. Associations in the 1991-to-1995 cohort were very similar to those in the later cohort for the variables common to both cohorts and are not presented here. Septicemia-related associations were very similar with and without adjustment for baseline comorbidity; only adjusted rates are presented here. Finally, we performed analyses in which septicemia was the primary admission hospitalization diagnosis, which was the case in 46.5% of cases. Temporal trends, associations, and outcomes were very similar using septicemia as primary diagnosis and are not presented here.

Results

Table 1 shows the patient characteristics at dialysis inception for the years 1991 to 1995; Table 2 refers to the years 1996 to 1999. Thirty percent were excluded because Medicare was not their sole primary payer at the start of dialysis therapy. The following baseline characteristics distinguished included from excluded patients: hemodialysis as initial therapy, older age, female gender, black race, Hispanic ethnicity, dialysis inception in earlier calendar years, several comorbid conditions (including diabetes), anemia, low serum albumin value, high estimated GFR, and low body mass index.

Of the 393,451 patients, 44,972 (11.4%) had an admission with septicemia in the first year of dialysis therapy. Of these, septicemia was the primary hospitalization diagnosis in 46.5%. The readmission rate for septicemia was 40.5 per 100 patient-years. Figure 1 shows adjusted overall first hospitalization rates, expressed throughout per 100 patient-years, for septicemia in patients who started hemodialysis and those who started peritoneal dialysis between 1991 and 1999. Also shown are the rates for staphylococcal species, streptococcal species, aerobic Gram-negative organisms, and unspecified septicemia. In hemodialysis patients, overall rates rose by 51%, from 11.6 in the 1991 cohort to 17.5 in the 1999 cohort; this increase was predominantly in the staphylococcal species and unspecified septicemia categories, which rose by 39.4 and 89.7%, respectively. In peritoneal dialysis patients, rates were much lower in each annual cohort, increasing from 5.7 in 1991 to a peak of 9.2 in 1997, followed by rates of 7.1 in 1998 and 8.0 in 1999.

Table 3 shows the baseline characteristics associated with first-year septicemia hospitalization in patients who started dialysis between 1996 and 1999. These characteristics included hemodialysis as mode of therapy, Hispanic ethnicity, previous congestive heart failure, stroke, peripheral vascular disease, diabetes, chronic obstructive pulmonary disease, cancer, alcohol or drug dependence, inability to ambulate or transfer, anemia, low serum albumin value, higher estimated GFR, and low body mass index. Septicemia rates were lower among those of Asian race. The association between septicemia rates and age group was nonmonotonic in nature. Ranked by age group, septicemia rates were lowest in those aged 0 to 19 yr, followed by those aged 54 to 64, 20 to 44, 65 to 74, and 75 yr or older.

Figure 2 shows mortality rates, in 6-mo intervals, in patients with and without septicemia, adjusted for the following baseline characteristics: age, gender, race, ethnicity, year of dialysis

Table 1. Baseline characteristics 1991 to 1995, comparing those included and those excluded because Medicare was not the sole, primary payer[a]

Dialysis Inception 1991 to 1995	Included (%; n = 197,095)	Excluded (%; n = 69,245)	P[b]	Odds Ratio for Exclusion[c]	95% CI[c]	P[c]
Mode of dialysis			<0.0001			
hemodialysis	85.6	80.5		0.88	0.86 to 0.90	<0.0001
peritoneal dialysis	14.4	19.6		1	—	—
Age, y[d]			<0.0001			
0 to 19	0.9	2.0		1.29	1.20 to 1.39	<0.0001
20 to 44	15.0	25.9		1	—	—
45 to 64	30.0	50.2		0.93	0.91 to 0.96	<0.0001
65 to 74	33.1	14.7		0.23	0.23 to 0.24	<0.0001
≥75	21.0	7.2		0.17	0.17 to 0.18	<0.0001
Gender			<0.0001			
male	54.2	57.4		1	—	—
female	45.8	42.6		0.94	0.93 to 0.96	<0.0001
Race			<0.0001			
white	61.7	64.5		1.23	1.16 to 1.31	<0.0001
black	33.6	28.7		0.75	0.71 to 0.80	<0.0001
Asian	2.6	4.4		1.79	1.65 to 1.93	<0.0001
other	2.2	2.4		1	—	—
Hispanic ethnicity			<0.0001			
yes	5.2	4.8		0.60	0.58 to 0.63	<0.0001
no	94.8	95.2		1	—	—
Year of dialysis inception			<0.0001			
1991	17.8	15.2		1	—	—
1992	19.5	16.4		1.01	0.98 to 1.04	0.6
1993	19.8	17.3		1.08	1.05 to 1.12	<0.0001
1994	20.7	24.3		1.47	1.43 to 1.52	<0.0001
1995	22.2	26.8		1.54	1.49 to 1.58	<0.0001

[a] CI, confidence interval.
[b] Using the χ^2 test.
[c] Using a multiple logistic regression model including the variables shown in the first column. The reference categories were peritoneal dialysis, age 20 to 44 yr, male gender, other race, non-Hispanic ethnicity, and 1991 as year of dialysis inception.
[d] Age data were missing in 0.007% of patients and 0.049% of excluded individuals.

inception, congestive heart failure, atherosclerotic heart disease, cardiac arrest or dysrhythmia, stroke or transient ischemic attack, peripheral vascular disease, chronic obstructive pulmonary disease, tobacco use, cancer, alcohol or drug dependence, inability to ambulate or transfer, hemoglobin value, serum albumin value, and estimated GFR. For comparison, the equivalent adjusted rates after first myocardial infarction, congestive heart failure, stroke, and peripheral vascular disease episode are also illustrated. Adjusted mortality rates after septicemia were high, exceeding rates after all cardiovascular events, with the exception of myocardial infarction. Although mortality rates decreased as time elapsed since septicemia increased, they remained more than twice those of patients without septicemia throughout the 5 yr of follow-up.

Figure 3 shows adjusted cardiovascular event rates in patients after septicemia, compared with patients who remained free of septicemia. Septicemia was associated with each event, especially in the first 6 mo. In this time interval, adjusted risk ratios of 4.1 (95% confidence interval, 3.8 to 4.5) were observed for myocardial infarction, 5.5 (5.3 to 5.7) for congestive heart failure, 4.1 (3.8 to 4.4) for stroke, and 3.8 (3.6 to 3.9) for peripheral vascular disease. Although adjusted cardiovascular event rates decreased as time elapsed since septicemia increased, they were at least 50% higher through 5 yr of follow-up for each cardiovascular event.

Discussion

We found that the incidence of septicemia climbed throughout the 1990s among U.S. dialysis patients, especially in patients who started hemodialysis therapy. In hemodialysis patients, increased rates of septicemia as a result of staphylococcal species (and, to a lesser extent, streptococcal species) were seen, whereas septicemia as a result of Gram-negative organisms seemed to peak in 1997 and then decline. Among peritoneal dialysis patients, overall rates and rates according to a specified organism declined after 1997. The magnitude of the other associations, including older age, diabetes, and comorbid conditions at dialysis inception, was small

Table 2. Baseline characteristics 1996 to 1999, comparing those included and those excluded because Medicare was not the sole, primary payer

Dialysis Inception 1996 to 1999	Included (%; n = 196,356)	Excluded (%; n = 96,076)	P[a]	Odds Ratio for Exclusion[b]	95% CI[b]	P[b]
Mode of dialysis			<0.0001			
hemodialysis	89.6	86.0		0.92	0.90 to 0.94	<0.0001
peritoneal dialysis	10.4	14.0		1	—	—
Age (yr)[c]			<0.0001			
0 to 19	0.8	2.0		1.47	1.37 to 1.57	<0.0001
20 to 44	13.2	21.6		1	—	—
45 to 64	30.7	47.4		0.98	0.96 to 1.00	0.07
65 to 74	30.6	17.7		0.36	0.35 to 0.37	<0.0001
≥75	24.7	11.4		0.28	0.27 to 0.29	<0.0001
Gender			<0.0001			
male	52.9	54.9				
female	47.1	45.1		0.96	0.95 to 0.98	<0.0001
Race			<0.0001	1	—	—
white	61.4	60.6		0.93	0.89 to 0.97	0.001
black	32.1	30.4		0.70	0.67 to 0.74	<0.0001
Asian	3.1	4.6		1.26	1.18 to 1.33	<0.0001
other	3.4	4.4			—	—
Hispanic ethnicity			<0.0001			
yes	11.5	12.8		0.89	0.87 to 0.91	<0.0001
no	88.5	87.2		1	—	—
Year of dialysis inception			<0.0001			
1996	23.5	21.3		1	—	—
1997	24.2	24.2		1.13	1.10 to 1.16	<0.0001
1998	25.5	26.2		1.18	1.15 to 1.21	<0.0001
1999	26.8	28.2		1.22	1.19 to 1.24	<0.0001
Congestive heart failure	34.1	26.1	<0.0001	0.91		<0.0001
Atherosclerotic heart disease	27.3	20.4	<0.0001	0.95	0.93 to 0.97	<0.0001
Cardiac arrest or dysrhythmia	6.6	4.5	<0.0001	0.97	0.94 to 1.01	0.1
Stroke or transient ischemic attack	9.5	6.7	<0.0001	0.87	0.84 to 0.90	<0.0001
Peripheral vascular disease	15.3	11.3	<0.0001	0.91	0.88 to 0.93	<0.0001
Diabetes	46.7	44.2	<0.0001	0.92	0.91 to 0.94	<0.0001
Chronic obstructive pulmonary disease	7.4	4.9	<0.0001	0.90	0.87 to 0.93	<0.0001
Current tobacco use	5.6	5.2	<0.0001	0.78	0.75 to 0.81	<0.0001
Cancer	5.0	4.0	<0.0001	1.00	0.96 to 1.04	1.00
Alcohol or drug dependence	2.3	2.5	<0.0001	0.91	0.87 to 0.96	0.0009
Inability to ambulate or transfer	4.3	3.1	<0.0001	0.96	0.91 to 1.00	0.05
Hemoglobin (g/dl)			<0.0001			
missing	6.3	5.0		0.77	0.74 to 0.81	<0.0001
<11	76.3	76.2		0.92	0.90 to 0.94	<0.0001
11 to 12	10.9	11.5		1	—	—
>12	6.6	7.4		1.04	1.00 to 1.08	0.05
Serum albumin (g/dl)			<0.0001			
missing	22.6	21.6		1.01	0.99 to 1.04	0.4
≤3.0	30.8	30.0		0.98	0.96 to 1.01	0.1
3.1 to 3.4	19.0	18.0		1	—	—
≥3.5	27.7	30.4		1.08	1.05 to 1.11	<0.0001
Estimated GFR (ml/min per 1.73 m^2)			<0.0001			
missing	2.5	1.7		0.67	0.63 to 0.71	<0.0001
≤5.0	16.8	20.1		1.01	0.99 to 1.03	0.6
5.1 to 10.0	56.9	58.0		1	—	—
>10.0	23.8	20.2		0.94	0.92 to 0.96	<0.0001
Body mass index (kg/m^2)			<0.0001			
missing	2.9	2.2		0.78	0.73 to 0.82	<0.0001
<18.5	6.6	6.0		0.95	0.92 to 0.98	0.004
18.5 to 24.9	42.1	40.1		1	—	—
25 to 29.9	26.7	27.3		1.01	0.99 to 1.03	0.2
≥30	21.7	24.4		0.99	0.97 to 1.01	0.4

[a] Using the χ^2 test.

[b] Using a multiple logistic regression model including the variables shown in the first column. The reference categories were peritoneal dialysis; age 20 to 44 yr; male gender; other race; non-Hispanic ethnicity; 1996 as year of dialysis inception; absence of congestive heart failure, atherosclerotic heart disease, cardiac arrest or dysrhythmia, stroke or transient ischemic attack, peripheral vascular disease, chronic obstructive pulmonary disease, current tobacco use, cancer, alcohol or drug dependence, inability to ambulate or transfer; hemoglobin 11 to 12 g/dl; serum albumin 3.1 to 3.4 g/dl; estimated GFR 5.1 to 10 ml/min per 1.73 m^2; and body mass index 18.5 to 24.9 kg/m^2.

[c] Age data were missing in 0.007% of patients and 0.008% of excluded individuals.

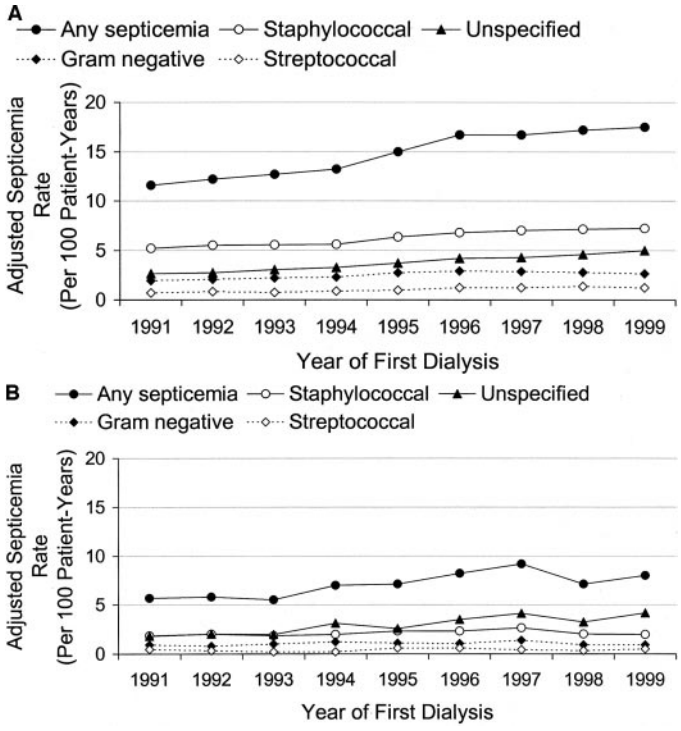

Figure 1. Adjusted rates of hospitalization with septicemia in the first year of dialysis therapy. (*A*) Hemodialysis patients. (*B*) Peritoneal dialysis patients. For the years 1991 to 1995, rates are adjusted for the baseline age, gender, race, and Hispanic ethnicity. For the years after 1995, rates are adjusted for age, gender, race, Hispanic ethnicity, congestive heart failure, atherosclerotic heart disease, cardiac arrest or dysrhythmia, stroke or transient ischemic attack, peripheral vascular disease, chronic obstructive pulmonary disease, current tobacco use, cancer, alcohol or drug dependence, inability to ambulate or transfer, hemoglobin value, serum albumin value, estimated GFR, and body mass index. For 1991 to 1995, $P < 0.0001$ for incident year in hemodialysis, $P = 0.002$ for incident year in peritoneal dialysis, and $P < 0.0001$ for the comparison of hemodialysis patients and peritoneal dialysis patients. For 1996 to 1999, $P = 0.02$ for incident year in hemodialysis, $P = 0.02$ for incident year in peritoneal dialysis, and $P < 0.0001$ for the comparison of hemodialysis patients and peritoneal dialysis patients.

compared with the dominant associations of year of inception and mode of dialysis therapy. Mortality rates after septicemia were high. Finally, we found that septicemia was an association of cardiovascular events.

The sepsis syndrome has become more common in the general population. In 1995, approximately 750,000 cases were seen in the United States, with a case fatality rate of 28.6%; it is likely that the increased disease burden partly reflects societal aging and more comorbid conditions (15). Temporal trends regarding the incidence of hospital admission for septicemia, as opposed to the sepsis syndrome, are unknown in the general population. It is difficult to know whether the trends seen in our study reflect trends in the general population, because we studied septicemic episodes without stipulating the coexistence of acute organ dysfunction. This being said, the antecedent associations and prognosis of what we labeled septicemia in our study were similar to those seen with sepsis in the general population.

In this study, the major associations of septicemia were hemodialysis (as opposed to peritoneal dialysis) and dialysis inception in more recent years. It is plausible that our findings reflect changes in hemodialysis vascular access. There is little clinical doubt that the type of vascular access is a major factor in the development of bloodstream infections in hemodialysis patients. Observational studies suggest that the use of central venous catheters increases the risk of bacteremia in dialysis patients (10,11). For example, in the study of Powe *et al.* (10), temporary catheters and arteriovenous grafts were associated with septicemia rates between 34 and 48% higher than rates that occurred with use of native fistulas; septicemia was associated with a relative risk of 2.74 for all-cause mortality and 9.62 for mortality from septicemia. Other recent studies have linked vascular access to death from any cause, death from infection, and death from cardiovascular causes (16,17). It is notable that catheter use for hemodialysis almost doubled between 1995 and 2000 in the United States. During this time, a more modest relative increase in fistula use and decrease in synthetic graft use was seen; by 2000, 24% of hemodialysis patients had catheters, 28% had fistulas, and 48% had grafts (2).

This study has limitations. The study was limited to the 70% of patients with Medicare as primary payer, which limits generalizability. No information was available on the type of hemodialysis access in use at baseline or at the time of admission for septicemia. Comorbidity at dialysis inception relied on the CMS Medical Evidence Report (Form 2728). The sensitivity and specificity of this instrument have been tested using a prospective cohort study, the Choices for Healthy Outcomes in Caring for ESRD, as the gold standard. The sensitivity of Form 2728 averaged across all 17 comorbid conditions examined was 0.59, whereas the specificity was >0.95 for 16 conditions, the exception being hypertension (specificity, 0.91). Thus, although comorbid conditions are significantly underreported on the Medical Evidence Report, diagnoses do not seem to be falsely attributed (18). We did not have a way to cross-validate the ICD-9-CM diagnosis of septicemia with a reliable gold standard, in terms of measuring its performance as a diagnostic test. Our study did not document the other illnesses that may have precipitated admission. It is likely that other serious illnesses precipitated admission to the hospital, which were then followed by septicemia. We attempted to estimate this effect by repeating our analyses using cases in which septicemia was the primary admission diagnosis. Temporal trends, associations, and outcomes were very similar using either approach. Admission for septicemia could be a marker of poor predialysis care, a relatively rapid decline in renal function, unmeasured comorbidity at dialysis inception, or more severe levels of measured comorbidity. Consistent with this possibility is our finding that known comorbidity at baseline was associated with septicemia. It is worth reiterating that the associations of septicemia with baseline age and comorbidity were far weaker than the associations with dialysis mode and year of dialysis inception. It is conceivable that the threshold for admission may have increased, all things being

Table 3. Associations between baseline characteristics and septicemia hospitalization in the first year of dialysis therapy in the 1996-to-1999 cohort

Factor	Relative Risk[a]	95% CI[a,b]	*P*[a]
Mode of dialysis			
hemodialysis	2.09	1.97 to 2.22	<0.0001
peritoneal dialysis	1	—	—
Age (yr)			
0 to 19	0.71	0.59 to 0.86	0.0003
20 to 44	1	—	—
54 to 64	0.85	0.81 to 0.89	<0.0001
65 to 74	1.02	0.98 to 1.07	0.4
≥75	1.21	1.15 to 1.26	<0.0001
Gender			
male	1	—	—
female	1.02	0.99 to 1.05	0.09
Race			
white	0.97	0.90 to 1.03	0.3
black	1.07	0.99 to 1.14	0.06
Asian	0.61	0.55 to 0.68	<0.0001
other	1	—	—
Hispanic ethnicity	1.09	1.05 to 1.13	<0.0001
Congestive heart failure	1.14	1.11 to 1.18	<0.0001
Atherosclerotic heart disease	0.98	0.95 to 1.01	0.1
Cardiac arrest or dysrhythmia	1.02	0.97 to 1.07	0.5
Stroke or transient ischemic attack	1.16	1.11 to 1.21	<0.0001
Peripheral vascular disease	1.11	1.08 to 1.15	<0.0001
Diabetes	1.11	1.08 to 1.14	<0.0001
Chronic obstructive pulmonary disease	1.09	1.05 to 1.15	<0.0001
Current tobacco use	0.95	0.90 to 1.00	0.06
Cancer	1.20	1.14 to 1.27	<0.0001
Alcohol or drug dependence	1.18	1.09 to 1.28	<0.0001
Inability to ambulate or transfer	1.65	1.57 to 1.73	<0.0001
Hemoglobin (g/dl)			
<11	1.05	1.01 to 1.09	0.03
11 to 12	1	—	—
>12	0.99	0.93 to 1.06	0.9
Serum albumin (g/dl)			
≤3.0	1.24	1.20 to 1.28	<0.0001
3.1 to 3.4	1	—	—
≥3.5	0.84	0.80 to 0.87	<0.0001
Estimated GFR (ml/min per 1.73 m^2)			
<5	0.89	0.86 to 0.93	<0.0001
5 to 10	1	—	—
>10	1.22	1.19 to 1.26	<0.0001
Body mass index (kg/m^2)			
<18.5	1.18	1.13 to 1.24	<0.0001
18.5 to 24.9	1	—	—
25 to 29.9	0.95	0.92 to 0.98	0.0007
≥30	1.01	0.97 to 1.04	0.68

[a] Using a Poisson regression model including the variables shown in the first column. The reference categories were peritoneal dialysis; age 20 to 44 yr; male gender; other race; non-Hispanic ethnicity; 1996 as year of dialysis inception; absence of congestive heart failure, atherosclerotic heart disease, cardiac arrest or dysrhythmia, stroke or transient ischemic attack, peripheral vascular disease, chronic obstructive pulmonary disease, current tobacco use, cancer, alcohol or drug dependence, inability to ambulate or transfer; hemoglobin 11 to 12 g/dl; serum albumin 3.1 to 3.4 g/dl; estimated GFR 5.1 to 10 ml/min per 1.73 m^2; and body mass index 18.5 to 24.9 kg/m^2.

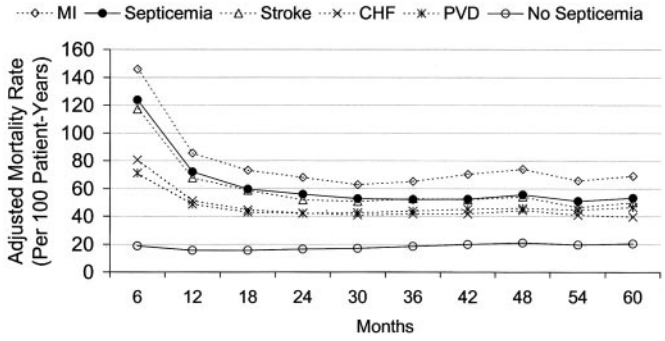

Figure 2. Interval Poisson model of adjusted mortality rates in 1996 to 1999 patients, with and without an admission for septicemia in the first year of dialysis therapy. Adjustment was made for the baseline variables shown in Table 2. $P < 0.0001$ for mortality rate comparisons in patients with and without septicemia. For illustration, the adjusted mortality rates after first admission with myocardial infarction (MI), congestive heart failure (CHF), stroke, and peripheral vascular disease (PVD) are also shown.

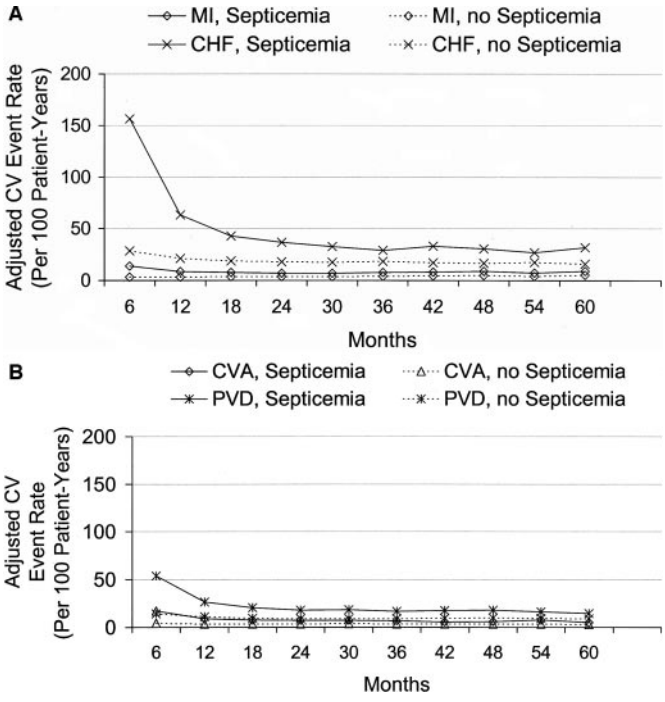

Figure 3. Interval Poisson model of cardiovascular (CV) event rates in 1996 to 1999 patients. (*A*) Myocardial infarction (MI) and congestive heart failure (CHF), with and without an admission for septicemia. (*B*) Cerebrovascular accident (CVA) and peripheral vascular disease (PVD), with and without an admission for septicemia. Adjustment was made for the baseline variables shown in Table 2. $P < 0.0001$ for comparisons in patients with and without septicemia for each event.

equal, between 1991 and 1999. If this is the case, then we may have underestimated temporal trends in event rates, which are already disturbing. It is possible that the higher rates of septicemia in hemodialysis patients could partly be related to ascertainment bias. For example, providers may be more likely to code peritonitis with systemic symptoms as "peritonitis" than "sepsis." Similarly, many illnesses in hemodialysis patients with catheters may have been wrongly attributed to septicemia. Hospitalization claims were used to define septicemia. It is plausible that septicemia with a defined organism is a real event and more objective than subjective. Staphylococcal species were the major named organisms. Unfortunately, the ICD-9-CM coding system does not allow further definition of the particular species involved. It was not possible in this study to determine whether a finding of "septicemia" with a specified organism was based on single or multiple blood cultures. The nature of the unspecified organisms cannot be determined. Similarly, it was not possible to address the contribution of antibiotic-resistant organisms, another emerging area of concern (19). Despite these limitations, an event labeled "septicemia" in this study clearly had grave prognostic connotations.

We believe that our study has some useful features and important implications. The sample studied represents the entire U.S. Medicare dialysis population. Mortality rates in dialysis patients declined in the early and mid-1990s but subsequently reached a plateau. Data from 1998 to 2000 suggest that mortality rates may have started to rise again (2). Our findings suggest that septicemia rates climbed steadily throughout the last decade, especially in hemodialysis patients. It is tempting to speculate that rising septicemia rates may have contributed to the leveling off in mortality. If true, then these findings suggest challenges and opportunities in the realms of prevention and treatment of bacterial infections. For example, it is likely that maximizing the use of arteriovenous fistula as hemodialysis access would lower infection risk. Alternative prevention strategies show promise when catheter use is unavoidable, including topical mupirocin and *Staphylococcus aureus* conjugate vaccine (20,21). A recent controlled trial showed that topical antibiotic solutions could prevent bacteremia in hemodialysis patients for whom catheter use was unavoidable. A secondary outcome analysis also showed lower mortality rates in the experimental group (22). Although these findings need confirmation, they suggest that septicemia, cardiovascular disease, and short survival are not predetermined destinies for latter-day dialysis patients. At a minimum, recognition that septicemia is a common occurrence with grave cardiovascular risk should lead to enhanced diagnostic suspicion. This may serve as a point from which we can begin to address the problem.

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