Kidney International, Vol. 58 (2000), pp. 1758–1764

DIALYSIS – TRANSPLANTATION

Mortality caused by sepsis in patients with end-stage renal disease compared with the general population

MARK J. SARNAK and BERTRAND L. JABER

Division of Nephrology, Department of Medicine, New England Medical Center, Tufts University School of Medicine, Boston, Massachusetts, USA

Mortality caused by sepsis in patients with end-stage renal disease compared with the general population.

Background. In the United States, infection is second to cardiovascular disease as the leading cause of death in patients with end-stage renal disease (ESRD), and septicemia accounts for more than 75% of this category. This increased susceptibility to infections is partly due to uremia, old age, and comorbid conditions. Although it is intuitive to believe that mortality caused by sepsis may be higher in patients with ESRD compared with the general population (GP), no such data are currently available.

Methods. We compared annual mortality rates caused by sepsis in patients with ESRD (U.S. Health Care Financing Administration 2746 death notification form) with those in the GP (death certificate). Data were abstracted from the U.S. Renal Data System (1994 through 1996 Special Data request) and the National Center for Health Statistics. Data were stratified by age, gender, race, and diabetes mellitus (DM). Sensitivity analyses were performed to account for potential limitations of the data sources.

Results. Overall, the annual percentage mortality secondary to sepsis was approximately 100- to 300-fold higher in dialysis patients and 20-fold higher in renal transplant recipients (RTRs) compared with the GP. Mortality caused by sepsis was higher among diabetic patients across all populations. After stratification for age, differences between groups decreased but retained their magnitude. These findings remained robust despite a wide range of sensitivity analyses. Indeed, mortality secondary to sepsis remained approximately 50-fold higher in dialysis patients compared with the GP, using multiple cause-of-death analyses; was approximately 50-fold higher in diabetic patients with ESRD compared with diabetic patients in the GP, when accounting for underreporting of DM on death certificates in the GP; and was approximately 30-fold higher in RTRs compared with the GP, when accounting for the incomplete ascertainment of cause of death among RTRs. Furthermore, despite assignment of primary cause-of-death to major organ infections in the GP, annual mortality secondary to sepsis remained 30- to 45-fold higher in the dialysis population.

Conclusions. Patients with ESRD treated by dialysis have higher annual mortality rates caused by sepsis compared with the GP, even after stratification for age, race, and DM. Consequently, this patient population should be considered at high-risk for the development of lethal sepsis.

Key words: chronic renal failure, hemodialysis, peritoneal dialysis, kidney transplantation, bacteremia, mortality.

Received for publication December 27, 1999
and in revised form March 16, 2000
Accepted for publication April 18, 2000

Infection is an important cause of morbidity and mortality among patients with end-stage renal disease (ESRD). In fact, the national U.S. Renal Data System (USRDS) registry indicates that infection is the second leading cause of death in patients with ESRD following cardiovascular disease, and septicemia accounts for more than 75% of these infectious deaths [1].

Patients with ESRD have a high incidence of bacterial infections [2–4]. This increased susceptibility to bacterial infections is due in part to the acquired immune deficiency state of uremia, advanced age, and comorbid conditions such as diabetes mellitus (DM), as well as the frequent and repetitive exposure of patients to potential infectious risk factors during the normal course of dialysis therapy. One such example is repeated disruption of the skin barrier. Consequently, although it is intuitive to believe that mortality secondary to sepsis may be higher in patients with ESRD compared with the general population (GP), no such data are currently available.

In order to examine whether ESRD, per se, is associated with higher mortality secondary to sepsis, we analyzed annual mortality rates secondary to sepsis of patients with ESRD treated by hemodialysis (HD), peritoneal dialysis (PD), and renal transplantation in the United States and compared them with those derived from the GP. These analyses were stratified by age, race, gender, and the presence of DM, and sensitivity analyses were performed to account for potential limitations of the data sources.

METHODS

Sources of data

The ESRD patient mortality data were obtained from a special data request from the USRDS for the years 1994

through 1996 and comprised a total of 50,227 deaths. This special data request allowed the authors to divide septic deaths into deciles of age, according to gender, race, and presence or absence of DM in the various target populations, that is, HD, PD, and renal transplant recipients (RTRs). To allow direct comparison with death rates generated from the GP, for patients with ESRD, death rates per 1000 patient years at risk were converted to the annual percentage mortality using the following formula:

$$\text{Fraction dead at one year} = 1 - e^{-\text{death rate}}$$

Since there is a clear inverse relationship between dose of dialysis, as measured by urea kinetic modeling, and mortality among patients with ESRD [5], we summarized the dialysis characteristics of the patient population. For patients on maintenance HD, the mean urea reduction ratio (URR) was 65.4% and delivered "single pool" Kt/V 1.19 [6]. For patients on maintenance PD, the average weekly Kt/V was 1.95, and the weekly creatinine clearance was 62.9 L/week/1.73 m^2 [6]. The overall national trends in dose of dialysis in both the HD and PD patient population increased steadily throughout the period included in this analysis (1994 through 1996). The U.S. distribution of dialyzers for the year 1996 consisted of synthetic (59%), modified cellulose (20%), and unmodified cellulose (21%) membranes [6].

The GP mortality data were obtained from the National Center for Health Statistics (NCHS) for the year 1993 and comprised a total of 2.27 million deaths. The NCHS data consisted of three sources: (*1*) the NCHS "Multiple Cause-of-Death File," which allowed the authors to stratify the number of deaths secondary to sepsis into deciles of age according to gender, race, and the presence or absence of DM [7]; (*2*) the NCHS "Health United States Population Statistics File," which provided the number of patients in each subgroup, and thereby, in conjunction with the "Multiple Cause-of-Death File," allowed the calculation of mortality rates caused by sepsis in each subgroup [8]; and (*3*) The NCHS "National Health Interview Survey," which allowed estimation of the diabetic population in each subgroup, thereby permitting the calculation of mortality rates in subgroups with and without DM [9].

Case definitions

In patients with ESRD, mortality secondary to sepsis was defined using the U.S. Health Care Financing Administration (HCFA) 2746 death notification form (#49-52). In the GP, mortality secondary to sepsis was defined using the death certificate's International Classification of Diseases-9th (ICD-9) Modification diagnosis codes for sepsis (#038.0-038.9) and bacteremia (#790.7) as the underlying causes of death [10]. Mortality secondary to sepsis was included in the analyses only if sepsis was the primary cause of death in both the NCHS and USRDS files. Diabetic status in the GP was defined if ICD-9 codes #250.0-250.9 were documented anywhere on the death certificate. It is important to note that the planned analyses did not compare mortality rates among patients presenting with sepsis who subsequently succumbed to their illness, but rather annual percentage mortality secondary to sepsis.

Sensitivity analyses

Mortality secondary to sepsis may be underestimated in the GP (relative to patients with ESRD), primarily because of under-reporting of sepsis as the primary cause of death in the GP. Consequently, sensitivity analyses were performed to capture more septic deaths in the GP by combining "sepsis" or "bacteremia" ICD-9 codes documented anywhere on the death certificate and recalculating mortality rates in each subgroup of the GP (multiple cause-of-death data). In addition, since many infectious diseases are confined to specific organ systems, the use of the ICD-9 system does not readily allow assessment of the aggregate impact of infectious diseases on health statistics. Consequently, we performed additional sensitivity analyses to evaluate the overall burden of infectious diseases on mortality rates in the U.S. population. In doing so, we minimized the risk of potential underreporting of mortality caused by sepsis in the GP due to assignment of primary cause of death to specific organ system diseases despite their infectious etiologies (for example, pneumonia, pyelonephritis, cholecystitis, and diverticulitis). The analyses were limited to ICD-9 codes that were considered to be or result from an infectious disease in all cases. We used a comprehensive list of infectious disease syndromes that was previously proposed and categorized by Pinner et al [11]. We modified the list by capturing more ICD-9 codes in each category (**Appendix**).

Furthermore, there is known under-reporting of diabetic status on death certificates in the NCHS database [12]. Consequently, sensitivity analyses were also performed in the diabetic and nondiabetic GP, and mortality rates were recalculated assuming that DM was only documented on approximately 40% of diabetic patients' death certificates [12].

Finally, mortality secondary to sepsis may be underestimated in RTRs because of incomplete ascertainment of cause of death in these patients. In fact, the USRDS has near complete ascertainment of cause of death in patients currently receiving dialysis; however, causes of death in RTRs are only known in approximately 50% of patients [1]. Consequently, mortality secondary to sepsis in RTRs was recalculated in each subgroup, assuming that the proportion of patients who died from sepsis was similar in the subgroup of patients with unknown and

Table 1. Annual mortality rates (%) secondary to sepsis stratified by gender, race and the presence or absence of diabetes mellitus in the various target populations

	All	Men	Women	White	Black	Diabetic	Nondiabetic
GP	0.008	0.007	0.009	0.008	0.011	0.020	0.008
GP-S_1	0.041	0.040	0.043	0.040	0.057	0.141	0.038
GP-S_2	0.067	0.074	0.060	0.065	0.091	0.112	0.065
GP-DM-S	—	—	—	—	—	0.050	0.007
HD	2.117	1.921	2.332	2.332	1.951	2.732	1.725
PD	3.023	2.586	3.488	3.227	2.703	4.343	2.313
RTR	0.160	0.160	0.160	0.150	0.230	0.250	0.130
RTR-S	0.241	0.243	0.238	0.226	0.347	0.368	0.197

Abbreviations are: GP, general population; HD, hemodialysis; PD, peritoneal dialysis; RTR, renal transplant recipients; GP-S_1, sensitivity analysis of mortality due to sepsis (multiple cause-of-death data); GP-S_2, sensitivity analysis of mortality due to infectious disease syndromes (including sepsis) in the general population (**Appendix A**); GP-DM-S, sensitivity analysis of mortality due to sepsis of diabetic patients in the general population due to under-reporting of diabetes mellitus on death certificates; RTR-S, sensitivity analysis of mortality due to sepsis in renal transplant recipients due to incomplete ascertainment of cause of death.

known causes of death. All of the results are presented as annual percentage mortality.

RESULTS

Stratification analyses

As shown in Table 1, prior to stratification for age, mortality secondary to sepsis was approximately 100- to 300-fold higher in HD and PD patients compared with the GP. DM was associated with higher mortality caused by sepsis across all populations. In the GP and in RTRs, black race was associated with higher mortality rates caused by sepsis, whereas female gender and white race were associated with more septic deaths in both HD and PD patients. However, gender, race, and DM were associated to a lesser degree with mortality caused by sepsis when compared with "dialysis status" per se. Annual mortality rates in RTRs were approximately 20-fold higher than those in the GP, but were much lower than those in HD and PD patients.

After stratification for age, mortality secondary to sepsis remained approximately 100-fold higher in patients with ESRD treated by dialysis compared with the GP, even among the old age groups (Fig. 1). Indeed, in the 65 to 74 age group, annual mortality was 0.02% in the GP compared with 2.88% in the dialysis population.

After stratification for gender, race, and age, the presence of DM was associated with higher mortality rates caused by sepsis in patients with ESRD treated by dialysis compared with patients without DM (Fig. 2). This effect was magnified in the PD compared with the HD patient population. Indeed, in the 65 to 74 age group, the annual mortality rate was 3.19 and 2.21% in diabetic and nondiabetic HD patients, respectively. This contrasted with an annual mortality rate of 5.91 and 3.69% in diabetic and nondiabetic PD patients of the same age group, respectively (data not shown).

Finally, compared with the GP, mortality secondary to sepsis remained higher in RTRs despite stratification for age (Fig. 3).

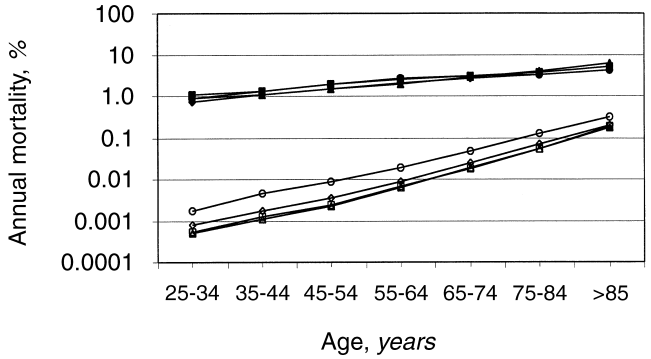

Fig. 1. Mortality caused by sepsis of patients with end-stage renal disease (ESRD) treated by dialysis compared with the general population (GP). Data are stratified by age, gender (◆, dialysis male; ■, dialysis female; ◇, GP male; □, GP female), and race (▲, dialysis black; ●, dialysis white; △, GP black; ○, GP white), and are shown as annual percentage mortality on a logarithmic scale.

Sensitivity analyses

Mortality secondary to sepsis remained approximately 50-fold higher in HD and PD patients compared with the GP, despite accounting for the extreme case, where all individuals with documented sepsis or bacteremia anywhere on the death certificate (multiple cause-of-death data) were included in the analyses (GP-S_1; Table 1). Furthermore, despite assignment of primary cause of death to major organ infections, annual mortality rates secondary to sepsis remained 30- to 45-fold higher in the dialysis population compared with the GP (GP-S_2; Table 1).

Mortality secondary to sepsis remained approximately 50-fold higher in diabetic patients with ESRD compared with diabetic patients in the GP, despite accounting for the under-reporting of DM on death certificates in the GP (GP-DM-S; Table 1).

Finally, after accounting for the incomplete ascertainment of cause of death in RTRs, mortality secondary to sepsis remained approximately 30-fold higher in RTRs compared with the GP and approximately 10-fold lower compared with HD or PD patients (RTR-S; Table 1).

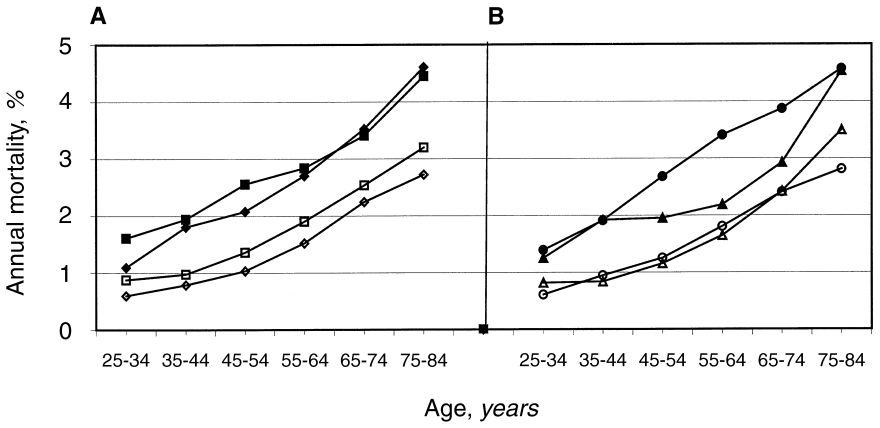

Fig. 2. Mortality caused by sepsis of diabetic (DM) and nondiabetic (no DM) patients with ESRD treated by dialysis. (*A*) Data are stratified by age and gender (◆, male DM; ■, female DM; ◇, male no DM; □, female no DM). (*B*) Data are stratified by age and race (▲, black DM; ●, white DM; △, black no DM; ○, white no DM). Data are shown as annual percentage mortality.

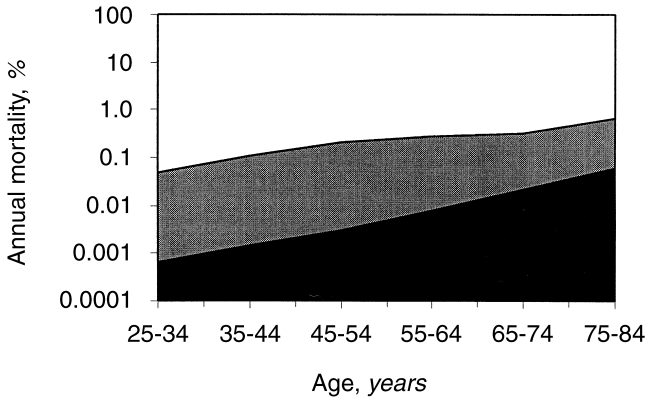

Fig. 3. Mortality caused by sepsis of renal transplant recipients (RTRs) compared with the general population (GP). Data are shown as annual percentage mortality on a logarithmic scale and are stratified by age (▒, RTR; ■, GP).

DISCUSSION

It is well recognized that infection is a frequent cause of both morbidity and mortality in patients with ESRD on maintenance dialysis. In fact, most studies suggest that infection is the second leading cause of death in patients with ESRD [1, 13]. This increased susceptibility to infections has partly been ascribed to defective phagocytic function of granulocytes [14, 15], old age, and a high prevalence of DM. In addition, dialysis patients have frequent and repetitive exposure to potential infectious risk factors during the normal course of dialysis therapy, which further predispose them to bacterial infections [2–4]. In a longitudinal cohort study of an incident ESRD patient population, Powe et al recently demonstrated that older age and the presence of DM were the strongest predictors of risk for developing septicemia in HD or PD patients [16].

In our study, we evaluated the extent of the difference in mortality caused by sepsis in patients with ESRD compared with the GP, after stratifying the analyses for age, gender, race, and DM. The results suggest that mortality rates secondary to sepsis are one to several hundred fold higher in HD and PD patients compared with the GP, despite stratification for age. The presence of ESRD, per se, acted as a greater risk factor for septic deaths compared with gender, race, or DM. In addition, stratification for the latter three factors did not significantly alter the magnitude of this difference. It is important to note, however, that the difference in mortality between the two groups cannot be solely ascribed to dialysis access-related infections. Indeed, HD- and PD-related access infections account for only 11 and 35% of deaths secondary to sepsis, respectively [1]. Therefore, the presence of "uremia" and its associated comorbid conditions, including older age and DM, may partly account for these differences. In addition, in HD patients, dialysis-related factors, including dialysis membrane biocompatibility [17] and iron overload [18], may also be incriminated in a higher incidence of bacterial infections.

Mortality secondary to sepsis in RTRs was also higher compared with the GP but was lower compared with HD and PD patients. The extent of these differences persisted after stratification for age (Fig. 3). The lower mortality rates observed in RTRs compared with dialysis patients may be due in part to a combination of selection bias toward transplantation (that is, patients who are transplanted are more likely to be healthy and have less comorbid conditions), disappearance of the uremic state and its associated immunosuppressive state, and resolution of dialysis access-related infections.

Although the USRDS provides accurate data on the cause of death in more than 90% of patients with ESRD who are currently on dialysis, causes of death are only known in approximately 50% of RTRs [1]. To account for this limitation, we performed a broad sensitivity analysis assuming that the causes of death in RTRs without documented causes were similarly proportioned as in those with documented causes. Although this may not be the most accurate representation, there is no reason

to suspect that the groups would dramatically differ. After performing these sensitivity analyses, mortality rates in RTRs remained significantly higher and lower compared with the GP and dialysis patients, respectively. The use of immunosuppressive drugs may account in part for the higher septic death rates observed in RTRs compared with the GP.

Age and DM were associated with a higher rate of septic deaths in both the GP and patients with ESRD. This was true across all subgroups of patients with ESRD regardless of dialysis modality, gender, or race (Figs. 1–3 and Table 1). These findings are consistent with the known impairment of host defense mechanisms in old and/or diabetic patients.

Diabetes mellitus is frequently not recorded on death certificates of persons with a history of the disease, which may result in an underestimation of the contribution of DM to overall mortality. This has particularly been demonstrated by Bild and Stevenson in the NCHS data [12]. Consequently, to account for this known underreporting of DM, we performed a sensitivity analysis using the aforementioned data generated by Bild and Stevenson. Although a higher percentage of deaths caused by sepsis was observed in diabetic patients in the GP (GP-DM-S; Table 1), the overall trends in comparison to patients with ESRD remained unaffected.

Our findings are in agreement with those outlined by Powe et al [16]. However, as shown on Figure 2A, female nondiabetic ESRD patients had higher mortality rates compared with male nondiabetic patients across all age groups. These observations were unadjusted. Interestingly, a more recent study by Jaar et al found similar trends in nondiabetic females; however, after adjustment for demographic, comorbid, and laboratory parameters, these analyses lost their statistical significance [19].

The major concern with the validity of our results is the accuracy of mortality statistics in general, and in particular, the comparative analyses between death certificates obtained from the GP with those of the HCFA-based ESRD registries. The latter tend to use customized cause of death-reporting procedures. Few studies have attempted to explore the accuracy of death certificates in the United States. One such study by Lloyd-Jones et al examined more than 2500 deceased Framingham Heart Study participants, primarily for coding heart disease as the cause of death [20]. A panel of three physicians reviewed all available medical information about each death, including the study records, hospitalization records, and when available autopsy results. In the hands of these authors, the death certificate had a sensitivity of 83.8% and a specificity of 84.1% for coronary heart disease. Similar studies have been attempted to examine the reliability of the HCFA 2746 death notification form among patients with ESRD. Indeed, Rocco et al have argued that there is an overall good correlation between the HCFA 2746 death notification form and cause of death using a classification system designed for the HEMO Study (abstract; Rocco et al, *J Am Soc Nephrol* 10:254A, 1999). In this comparative model, however, the disease-specific agreement was best for malignancy, followed by infectious and cardiovascular disease, respectively.

It has been suggested that comparisons of death certificate data with national registry data such as the HCFA 2746 death notification form need to be interpreted with great caution. Indeed, Perneger, Klag, and Whelton demonstrated that the overall degree of agreement for cause of death between death certificates and HCFA death notification forms was only 31% [21]. Furthermore, disease-specific agreement was good for cancer, moderate for infectious disease, and poor for cardiovascular disease. One reason for this less-than-perfect agreement was that as many as 40% of primary causes of deaths were classified as renal failure on the death certificate. This compared with only 8% of deaths that were indirectly attributed to renal failure on the HCFA death notification form, including hyperkalemia, pericarditis, and withdrawal from therapy [21]. Perneger, Klag, and Whelton argued that these sources of data should not be used interchangeably and suggested that there was a need to increase compatibility between these two information systems to optimize their usefulness [21].

One could argue that causes of death reported on HCFA 2746 death notification forms may be more reliable than death certificates, as patients with ESRD are under more continuous medical follow-up compared with patients in the GP. By contrast, the accuracy of the death certificate's completion is more likely to depend on the availability of the patient's primary care physician, who is most informed about the patient's medical condition(s), and who should ideally be the one to complete the death certificate [22]. Unfortunately, these scenarios are not always encountered in clinical practice, as the primary physician's input may not always be obtained.

Since infectious disease deaths may be underclassified as primary cause of death on the death certificate, we performed a sensitivity analysis in which we assumed that all patients who had sepsis documented anywhere on the death certificate (whether it be the underlying cause of death or not) died of sepsis. Furthermore, to minimize the risk of underreporting mortality secondary to sepsis in the GP, we ran additional sensitivity analyses to evaluate the overall burden of infectious diseases on mortality by globally analyzing the ICD-9 codes of a comprehensive list of infectious disease-related syndromes reported on death certificates (**Appendix**). Despite these two "extreme" sensitivity analyses, the magnitude of the difference in mortality caused by sepsis in patients with ESRD compared with the GP remained extremely large (GP-S_1, GP-S_2; Table 1).

The USRDS collapses ESRD infectious causes of

death into several categories, mainly septicemia followed by pulmonary infections. To examine whether organ-specific infectious death rates followed a similar trend, we ran additional analyses in which the annual mortality rates caused by pulmonary infections in dialysis patients were compared with those in the GP. Overall, annual mortality secondary to pulmonary infections remained 17-fold higher in the dialysis population compared with the GP. These results suggest that despite classifying infectious disease deaths according to specific organ systems, the magnitude of difference was maintained.

Deaths secondary to chronic disease such as ESRD are often not well characterized by a single cause, but are more likely to result from a number of intricate coexisting conditions, which do not facilitate the identification of a single underlying cause [23]. In fact, Israel, Rosenberg, and Curtin proposed that there is a need to shift emphasis from reliance on the primary cause of death to complementing the data with the multiple cause-of-death statistics [24]. By combining sepsis anywhere on the death certificate, we have attempted to honor this concept of multiple cause-of-death statistics. Nevertheless, we acknowledge that in the absence of a multivariate analysis, our overall results do not reflect the independent relationship of each risk factor to mortality caused by sepsis. Furthermore, this crude analysis is unable to ascribe the relative risk of each factor to sepsis mortality as well as the interactions between the various risk factors.

In summary, our results suggest that mortality rates secondary to sepsis in dialysis patients are several hundred-fold higher than those observed in the GP. RTRs have sepsis-associated mortality rates that are approximately 20-fold higher than the GP, but approximately 15-fold lower than dialysis patients. After stratification for race, gender, and DM, ESRD remains highly associated with mortality secondary to sepsis. These findings are robust despite a wide range of sensitivity analyses. Consequently, patients with ESRD should be considered a high-risk group for the development of lethal sepsis.

ACKNOWLEDGMENTS

The authors thank the U.S. Renal Data System for providing the Special Data Request. The interpretation of the data is the sole responsibility of the authors. This work was presented in part at the 32nd Annual Meeting of the American Society of Nephrology, Miami, FL, USA, November 5–8, 1999.

Reprint requests to Mark J. Sarnak, M.D., Division of Nephrology, New England Medical Center, 750 Washington Street, Box 391, Boston, Massachusetts 02111, USA.
E-mail:msarnak@lifespan.org

REFERENCES

1. United States Renal Data System: *USRDS 1998 Annual Data Report.* Bethesda, National Institutes of Health, Diabetes and Digestive and Kidney Diseases, April, 1998
2. Keane WF, Shapiro FL, Raij L: Incidence and type of infections occurring in 445 chronic hemodialysis patients. *Trans Am Soc Artif Organs* 23:41–46, 1977
3. Hoen B, Kessler M, Hestin D, Mayeux D: Risk factors for bacterial infections in chronic haemodialysis adult patients: A multicentre prospective survey. *Nephrol Dial Transplant* 10:377–381, 1995
4. Hoen B, Paul-Dauphin A, Heston D, Kessler M: EPIBACDIAL: A multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. *J Am Soc Nephrol* 9:869–876, 1998
5. Owen WFJ, Lew NL, Liu Y, Lowrie EG, Lazarus JM: The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. *N Engl J Med* 329:1001–1006, 1993
6. United States Renal Data System: *USRDS 1999 Annual Data Report.* Bethesda, National Institutes of Health, Diabetes and Digestive and Kidney Diseases, 1999
7. National Center for Health Statistics: *1993 Multiple Cause-of-Death File.* Hyattsville, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, CD-ROM Series 20, No. 11, version 1.22a, 1997
8. National Center for Health Statistics: *Health United States 1995.* Hyattsville, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, DHHS Pub. No. (PHS) 96-1232, 1996
9. National Diabetes Data Group: *Diabetes in America* (2nd ed). Hyattsville, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, NIH Publication No. 95-1468, 1995
10. *International Classification of Disease 9th Revision Clinical Modification.* Salt Lake City, Medicode, Inc., 1998
11. Pinner RW, Teutsch SM, Simonsen L, Klug LA, Graber JM, Clarke MJ, Berkelman RL: Trends in infectious diseases mortality in the United States. *JAMA* 275:189–193, 1996
12. Bild DE, Stevenson JM: Frequency of recording of diabetes on U.S. death certificates: Analysis of the 1986 national mortality followback survey. *J Clin Epidemiol* 45:275–281, 1992
13. Mailloux L, Bellucci A, Wilkes B, Napolitano B, Mossey R, Lesser M, Bluestone P: Mortality in dialysis patients: Analysis of the causes of death. *Am J Kidney Dis* 18:326–335, 1991
14. Himmelfarb J, Hakim RM: Biocompatibility and risk of infection in hemodialysis patients. *Nephrol Dial Transplant* 9:138–144, 1994
15. Vanholder R, Ringoir S: Infectious morbidity and defects of phagocytic function in end-stage renal disease: A review. *J Am Soc Nephrol* 3:1541–1554, 1993
16. Powe NR, Jaar B, Furth SL, Hermann J, Briggs W: Septicemia in dialysis patients: Incidence, risk factors, and prognosis. *Kidney Int* 55:1081–1090, 1999
17. Bloembergen WE, Hakim RM, Stannard DC, Held PJ, Wolfe RA, Agodoa LY, Port FK: Relationship of dialysis membrane and cause-specific mortality. *Am J Kidney Dis* 33:1–10, 1999
18. Patruta SI, Edlinger R, Sunder-Plassmann G, Hörl WH: Neutrophil impairment associated with iron therapy in hemodialysis patients with functional iron deficiency. *J Am Soc Nephrol* 9:655–663, 1997
19. Jaar BG, Hermann JA, Furth SL, Briggs W, Powe NR: Septicemia in diabetic hemodialysis patients: Comparison of incidence, risk factors, and mortality with nondiabetic hemodialysis patients. *Am J Kidney Dis* 35:282–292, 2000
20. Lloyd-Jones DM, Martin DO, Larson MG, Levy D: Accuracy of death certificates for coding coronary heart disease as the cause of death. *Ann Intern Med* 129:1020–1026, 1998
21. Perneger TV, Klag MJ, Whelton PK: Cause of death in patients with end-stage renal disease: death certificates vs. registry reports. *Am J Public Health* 83:1735–1738, 1993
22. Messite J, Stellman SD: Accuracy of death certificate completion: The need for formalized physician training. *JAMA* 275:794–796, 1996
23. Dorn HF, Moriyama IM: Uses and significance of multiple cause tabulations for mortality statistics. *Am J Public Health* 54:400–406, 1964
24. Israel RA, Rosenberg HM, Curtin LR: Analytical potential for multiple cause-of-death data. *Am J Epidemiol* 124:161–179, 1986

Appendix. Comprehensive list of infectious disease syndromes and related ICD-9 codes

Infectious disease syndromes	ICD-9 codes
Septicemia; bacteremia	0.38.0–0.38.9; 790.7
Respiratory tract infections	460.0–466.1; 475.0; 480.0–487.8; 510.0–510.9; 513.0–513.1
Gastrointestinal tract infections	540.0–542.0; 566.0; 567.1–567.2; 569.5
Infections of the kidney and urinary tract	590.0–590.9; 599.0
Bacterial meningitis	027.0; 036.0–036.9; 320.0–324.9
Infections of the heart	391.0–391.9; 393; 394.1; 395.0–395.2; 397.9–398.9; 421.0–421.9; 422.9; 424.9
Tuberculosis	011.2–018.9; 137.0–137.3
Human immune deficiency virus infection	042.0–044.9; 279.1
Hepatobiliary infections	070.0–070.9; 576.1
Perinatal infections	090.2–090.9; 770.0; 771.0–771.8
Mycoses	110.0–117.9