Pulmonary Infectious Mortality Among Patients With End-Stage Renal Disease*

Mark J. Sarnak, MD; and Bertrand L. Jaber, MD

Background: Infection is the second-leading cause of death among patients with end-stage renal disease (ESRD). This is due in part to advanced age, comorbid conditions, and immune dysfunction observed in uremic states. Although one may hypothesize that pulmonary infectious mortality is higher among patients with ESRD compared with the general population (GP), no such data are currently available.

Methods: We compared annual pulmonary infectious mortality rates among patients with ESRD to those in the GP. The data were abstracted from the United States Renal Data System and the National Center for Health Statistics, respectively, and were stratified by age, gender, race, and presence or absence of diabetes mellitus (DM). In the GP, primary and multiple cause-of-death analyses were performed to account for potential limitations of the data sources.

Results: Overall, pulmonary infectious mortality rate was 14-fold to 16-fold higher in dialysis patients and approximately twofold higher in renal transplant recipients compared with the GP. After stratification for age, differences between groups decreased but retained their magnitude.

Conclusion: Patients with ESRD treated with dialysis have higher pulmonary infectious mortality rates compared with the GP, even after stratification for age, race, and DM. Consequently, this patient population must be considered at high risk for the development of lethal pulmonary infections.

(CHEST 2001; 120:1883–1887)

Key words: chronic renal failure; hemodialysis; infection; kidney transplantation; mortality; peritoneal dialysis; pneumonia

Abbreviations: DM = diabetes mellitus; ESRD = end-stage renal disease; GP = general population; HCFA = Health Care Financing Administration; ICD-9 = International Classification of Diseases, Ninth Revision; NCHS = National Center for Health Statistics; RTR = renal transplant recipient; USRDS = United States Renal Data System

Infection is an important cause of morbidity and mortality among patients with end-stage renal disease (ESRD). The United States Renal Data System (USRDS) registry indicates that infection is the second-leading cause of death among patients with ESRD, following cardiovascular disease. Furthermore, sepsis and pulmonary infections account for 75% and 20% of these infectious deaths, respectively.1 We have recently demonstrated2 that annual mortality rate due to sepsis is markedly elevated among patients with ESRD compared with the general population (GP). Although it is intuitive to believe that pulmonary infectious mortality rates may also be higher among patients with ESRD compared with the GP, no such data are currently available. An increased susceptibility to pulmonary infections may be ascribed, in part, to prevalent pulmonary dysfunction3,4 and impaired phagocytic cell function.5–7

In order to test this hypothesis, we analyzed the annual pulmonary infectious mortality rates among patients with ESRD treated by hemodialysis, peritoneal dialysis, and renal transplantation in the United States, and compared them with those in the GP.

Materials and Methods

Sources of Data

The ESRD patient mortality data were obtained through a special data request from the USRDS, which comprised a total of 50,227 deaths for the years 1994 through 1996. Pulmonary infectious deaths were stratified into deciles of age, according to race, gender, and presence or absence of diabetes mellitus (DM). Diabetic status was obtained from the Health Care Financing Administration (HCFA)-2728 Medical Evidence Form, which documents sociodemographic comorbid characteristics of all patients registering in the Medicare ESRD program. Death rates per 1,000 patient-years at risk were converted to annual percent mortality using the following equation:

\[
\text{fraction dead at 1 year} = 1 - e^{-\text{death rate}}
\]
The mortality data in the GP was obtained from the National Center for Health Statistics (NCHS) that comprised a total of 2.27 million deaths for the year 1993. Three data files were analyzed: (1) the NCHS “Multiple Cause-of-Death File,” which allowed the stratification of pulmonary infectious mortality into deciles of age, according to gender, race, and presence or absence of DM; (2) the NCHS “Health United States Population Statistics File,” which provided the population in each subgroup and, thereby in conjunction with the “Multiple Cause-of-Death File,” allowed the calculation of pulmonary infectious mortality rates in each subgroup; and (3) the NCHS “National Health Interview Survey,” which, in particular, provided estimates of the diabetic population in each subgroup, thereby permitting the calculation of pulmonary infectious mortality rates in subgroups with and without DM.

Case Definitions

ESRD was defined as a life-threatening reduction in glomerular filtration rate resulting in the requirement for hemodialysis, peritoneal dialysis, or renal transplantation to maintain life. For patients with ESRD, pulmonary infectious mortality was defined using the HCFA-2746 death notification form (#53–56). Bacterial, fungal, and other pulmonary infections were all included in this category.

For the GP, pulmonary infectious mortality was defined using the International Classification of Diseases, Ninth Revision (ICD-9) modification diagnosis code on the death certificate for the following pulmonary infections: Candida (112.4), coccidioidomycosis (115.0–115.9), histoplasmosis (115.0–115.9), all bacterial, viral and other fungal pneumonias (480.0–487.8), empyema with and without fistulae (510.0–510.9), and lung abscess (513.0) as the underlying cause of death. This classification for pulmonary infections was closely matched to the HCFA classification.

Analytical Approaches

Primary Cause-of-Death Analysis: In this analysis, mortality rates secondary to pulmonary infections were included only if they were the primary cause of death in both the NCHS and USRDS files.

Multiple Cause-of-Death Analysis: Because pulmonary infections may be underreported as the primary cause of death on death certificates, we performed multiple cause-of-death analyses in order to capture more pulmonary infectious deaths in the GP. In this analysis, we recalculated mortality rates in each subgroup of the GP using pulmonary infection ICD-9 codes documented anywhere on the death certificate. By performing this analysis, we attempted to honor the concept of multiple cause-of-death statistics.

In both analytic approaches, diabetic status in the GP was defined if ICD-9 code 250.0–250.9 was documented anywhere on the death certificate. All the results were presented as annual percentage mortality.

Characteristics of the Dialysis Patient Population

Because there is a clear inverse relationship between dose of dialysis, as measured by urea removal, and mortality among patients with ESRD, we have summarized the dialysis characteristics of this patient population. For patients receiving hemodialysis, the delivered dose of dialysis was near optimal; the average blood urea-reduction ratio was 65% and Kt/V (dialyzer clearance of urea [K] multiplied by the duration of dialysis treatment [V]) divided by the volume of distribution of urea in the body [V]) was 1.2, two measures of dialysis delivery. For patients receiving peritoneal dialysis, the average weekly Kt/V and creatinine clearance values were 1.95 and 62.9 L/wk/1.73 m², respectively. Throughout the period included in this analysis (from 1994 to 1996), these values met the minimum dialysis dose recommended by the Dialysis Outcomes and Quality Initiative guidelines.

Results

Primary Cause-of-Death Analyses

Prior to stratification for age, pulmonary infectious mortality was approximately 14-fold to 16-fold higher in hemodialysis and peritoneal dialysis patients compared with the GP (primary cause of death; Table 1). Compared to patients without DM, diabetic patients had higher mortality secondary to pulmonary infections, except in the population receiving hemodialysis. White race and male gender were associated with higher pulmonary infectious mortality in both hemodialysis and peritoneal dialysis patients, as well as renal transplant recipients (RTRs). The difference in pulmonary infectious mortality between patients treated by dialysis vs those in the GP was however much larger than the differences observed between male and female, white and black, or diabetic and nondiabetic persons in any particular population. Annual mortality rates in RTRs were approximately twofold higher than those in the GP, but lower than those in hemodialysis and peritoneal dialysis patients.

Table 1—Annual Mortality Rates (Percentage) Secondary to Pulmonary Infections Stratified by Gender, Race, and Diabetic Status in the GP Compared With the ESRD Population

<table>
<thead>
<tr>
<th>Study Population</th>
<th>All</th>
<th>Men</th>
<th>Women</th>
<th>White</th>
<th>Black</th>
<th>Diabetic</th>
<th>Nondiabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cause-of-death analysis</td>
<td>0.032</td>
<td>0.031</td>
<td>0.034</td>
<td>0.035</td>
<td>0.025</td>
<td>0.062</td>
<td>0.032</td>
</tr>
<tr>
<td>Multiple cause-of-death analysis</td>
<td>0.082</td>
<td>0.085</td>
<td>0.080</td>
<td>0.087</td>
<td>0.068</td>
<td>0.187</td>
<td>0.079</td>
</tr>
<tr>
<td>ESRD population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodialysis patients</td>
<td>0.519</td>
<td>0.508</td>
<td>0.469</td>
<td>0.668</td>
<td>0.339</td>
<td>0.509</td>
<td>0.519</td>
</tr>
<tr>
<td>Peritoneal dialysis patients</td>
<td>0.449</td>
<td>0.539</td>
<td>0.349</td>
<td>0.499</td>
<td>0.300</td>
<td>0.519</td>
<td>0.389</td>
</tr>
<tr>
<td>RTRs</td>
<td>0.070</td>
<td>0.070</td>
<td>0.060</td>
<td>0.070</td>
<td>0.070</td>
<td>0.090</td>
<td>0.060</td>
</tr>
</tbody>
</table>
After stratification for age, pulmonary infectious mortality was higher in dialysis patients compared with the GP, even among the old-age groups (Fig 1). For example, in the 65-year to 74-year age group, annual mortality was 0.06\% in the GP compared with 0.62\% in the dialysis population. Finally, compared with the GP, pulmonary infectious mortality remained higher in RTRs despite stratification for age (Fig 1).

**Multiple Cause-of-Death Analyses**

Pulmonary infectious mortality remained fivefold to sixfold higher in hemodialysis and peritoneal dialysis patients compared with the GP, after including all individuals with pulmonary infections documented anywhere on the death certificate (multiple cause of death; Table 1).

**Discussion**

Infection is a frequent cause of both morbidity and mortality among patients with ESRD receiving maintenance dialysis.\(^1\) An increased susceptibility to infections has partly been ascribed to old age,\(^17,18\) a high prevalence of DM,\(^19,20\) defective phagocytic function of granulocytes,\(^5,7\) and frequent exposure to potential infectious risk factors during the normal course of dialysis therapy.\(^21–23\) Although a prior study\(^21\) has suggested that pulmonary infection is the cause of as many as 25\% of all infections in patients with ESRD, others\(^24\) have suggested that patients receiving maintenance dialysis therapy do not have significantly increased morbidity or mortality from infectious diseases, with the exception of those related to dialysis access.

The results of our analyses suggest that pulmonary infectious mortality is approximately 10-fold higher in dialysis patients compared with the GP, despite stratification for age. The presence of ESRD, per se, acted as a greater risk factor for pulmonary infectious mortality compared with gender, race, or DM. In addition, stratification for the latter three factors did not significantly alter the magnitude of this difference.

There are several potential reasons why dialysis patients may be particularly susceptible to pulmonary infections. Alterations in respiratory drive, mechanics, muscle function, and gas exchange are frequent if not invariable consequences of uremia.\(^3\) Indeed, reduction in carbon monoxide transfer and decreased inspiratory muscle strength are almost universal findings.\(^3\) Furthermore, transient hypoxemia is commonly seen among patients receiving hemodialysis with dialyzers that have a high complement-activating potential and with the use of acetate dialysate.\(^25\) This has been ascribed to transient margination of leukocytes in the pulmonary vasculature and carbon dioxide losses, respectively. Finally, of patients treated with peritoneal dialysis, the infusion of dialysis solutions into the abdomen may reduce the functional residual capacity of the lungs, with consequent basilar atelectasis and altered respiratory muscle function.\(^26\) Consequently, the incidence of pulmonary infections may be greater in dialysis patients than in the GP due to these pulmonary functional abnormalities, in addition to depressed humoral and cellular immunity, and impaired phagocytic cell function. This may be particularly true in patients with preexisting lung disease.

In support of these suggestions are autopsy findings of dialysis patients documenting acute pulmonary infections in 37 to 45\% of cases.\(^4,27\) Interestingly, in these reports, chronic pulmonary abnormalities were also quite prevalent, including pulmonary interstitial fibrosis (40\%), pleural fibrosis (40\%), and pulmonary arteriosclerosis (24\%).\(^27\) Admittedly, these data are biased by the selection criterion to undergo autopsy, but they emphasize the magnitude of pulmonary abnormalities in dialysis patients. Parenchymal consolidation secondary to bacterial agents such as *Staphylococcus aureus* has also been reported as an important thoracic CT finding (38\%) in patients with pulmonary symptoms receiving maintenance hemodialysis.\(^28\)

In our analysis, we observed higher pulmonary infectious mortality rates in RTRs compared with the GP. The extent of these differences persisted after stratification for age. The use of immunosuppressive drugs and associated higher risk of opportunistic infections likely plays a part in these higher rates observed in RTRs. Our data are in agreement with an autopsy study\(^29\) of RTRs that has incriminated pulmonary infections as cause of death in 37\% of
cases. Lower mortality rates observed in RTRs compared with the dialysis population might be due in part to a combination of selection bias toward transplantation and disappearance of the uremic state and its associated immunosuppressive state. Our analyses also demonstrate that despite the use of multiple cause-of-death statistics, the magnitude of the difference in pulmonary infectious mortality between patients with ESRD and the GP remains extremely large (Table 1).

In the NCHS database, DM is frequently not recorded on death certificates of patients with a history of the disease. In fact, it has been shown that in the GP, DM is only documented on approximately 40% of death certificates of diabetic patients. This may result in an underestimation of the contribution of DM to overall mortality in the GP. Consequently, if mortality rates are recalculated after accounting for the underreporting of DM on death certificates in the GP, pulmonary infectious mortality remains approximately sixfold higher in diabetic patients with ESRD compared with diabetic patients in the GP (data not shown).

In addition, although the USRDS provides accurate data on the cause of death in >90% of patients with ESRD who are receiving dialysis, causes of death are only known in approximately 50% of RTRs. Consequently, if mortality rates are recalculated after accounting for the incomplete ascertainment of cause of death in RTRs, pulmonary infectious mortality remains approximately threefold higher in RTRs compared with the GP, and approximately fivefold lower compared with dialysis patients (data not shown). This analysis assumes that the proportion of patients who died from pulmonary infections was similar in the subgroup of patients with known and unknown causes of death. Although this may not be the most accurate representation, there is no reason to suspect that the groups would dramatically differ.

We suspect that our results actually underestimate the differences in pulmonary infectious mortality between patients with ESRD and the GP. Indeed, a proportion of deaths that are coded as pulmonary infections in both ESRD and the GP are likely misclassified as septic deaths. Due to an extremely high rate of sepsis in patients with ESRD,1 and assuming an equal proportion of misclassification in the two registries, accounting for this misclassification would even further increase pulmonary infectious mortality rates in ESRD compared with the GP.

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. We acknowledge the crude nature of our analyses and the inability to perform multivariate analyses. The latter limitation prevents us from ascribing the relative risk of various factors on pulmonary infectious mortality rate as well as the interactions between risk factors.

Studies have attempted to explore the accuracy of death certificates in the United States. In one such study, the death certificate had a sensitivity and specificity of 84% for coronary artery disease. Similar data are not available for pulmonary infectious mortality. A study examining the reliability of the HCFA-2746 death notification form in patients with ESRD has demonstrated a reasonable correlation between the HCFA-2746 death notification form and cause of death using an independent classification system. Nevertheless, comparisons of death certificate data (NCHS) with national registry data such as the HCFA-2746 death notification form need to be interpreted with great caution, and as suggested by Perneger et al, there is a need to increase compatibility between these two information systems to optimize their usefulness.

In summary, our results show that annual pulmonary infectious mortality among patients with ESRD treated by dialysis is approximately 10-fold higher than in the GP. Consequently, patients with ESRD must be considered a high-risk group for the development of lethal pulmonary infections.

ACKNOWLEDGMENT: The authors thank the USRDS for providing the Special Data Request. The interpretation of the data is the sole responsibility of the authors.

REFERENCES
2 Sarnak MJ, Jaber BL. Mortality due to sepsis in patients with end-stage renal disease compared with the general population. Kidney Int 2000; 58:1758–1764
8 National Center for Health Statistics. 1993 Multiple Cause-Of-Death File. 1.22a ed. Hyattsville, MD: US Department of Health and Human Services, Centers for Disease Control and Prevention, 1997
9 National Center for Health Statistics. Health United States


17 Terpenning MS, Bradley SF. Why aging leads to increased susceptibility to infection. Geriatrics 1991; 46:77–80


