Infectious Complications in Chronic Kidney Disease

Sakina B. Naqvi and Allan J. Collins

Infectious complications in individuals with chronic kidney disease (CKD) pose a significant source of morbidity and mortality. The overall scope of major infectious complications has, however, received little attention even though some of these events may be preventable. We reviewed infectious hospitalization rates in the CKD and end-stage renal disease (ESRD) populations, comparing them with the non-CKD and non-ESRD groups. We also reviewed preventive vaccination rates for influenza, pneumonia, and pneumococcal pneumonia to assess areas of potential improvement. We reviewed the medical literature and present findings based on hospitalization rates for pneumonia, sepsis/bacteremia, and urinary tract infections in the Medicare CKD, ESRD, and non-CKD populations. Vaccination rates were determined from submitted claims for services with specific codes for the vaccinations. Regardless of the primary cause for the development of CKD, primary kidney disease or secondary to hypertension, diabetes mellitus, or other chronic condition, patient outcomes after the development of infections were 3 to 4 times worse than in the non-CKD population. Influenza vaccination rates were 52%, far less than the target of 90%. Pneumococcal pneumonia vaccination rate was only 13.5%, far less than recommended. CKD is associated with significant major infectious complications, which occur at rates 3 to 4 times the general population. Providers can improve prevention by using fewer dialysis catheters and increasing vaccination rates for influenza and pneumococcal pneumonia.

© 2006 by the National Kidney Foundation, Inc.

Index Words: Chronic kidney disease; Infectious complication; Vaccination

Chronic kidney disease (CKD) is fast emerging as a major public health problem in the 21st century. According to the National Kidney Foundation, 4.5% of the United States population (more than 14 million people) suffer from CKD. New classification systems standardize categories for the various stages of kidney damage. The National Kidney Foundation Disease Outcomes Quality Initiative guidelines define CKD as kidney damage or a glomerular filtration rate of less than 60 mL/min per 1.73 m² for at least 3 months. Three intermediary stages follow, with kidney failure or end-stage renal disease (ESRD), as the final stage, defined by a glomerular filtration rate of less than 15 mL/min per 1.73 m².

Many people within the large group of CKD patients are also affected by cardiovascular disease (CVD) as well as infectious complications. CVD is in fact twice as common in CKD patients as in the general population, and it advances at twice the rate. Although a great deal of attention has been paid to CVD, not enough has been said about infectious complications, which closely follow CVD in frequency and seriousness. The 2 complications appear to be closely linked; infection is an inflammatory state and as such may be implicated in the development of atherosclerotic disease, and the risk of the developing CVD is increased in the 6 months after an infection (Fig 1).

The CKD population is predisposed to adverse infectious events because of overwhelming uremia, which is associated with alterations in primary host defense mechanisms and increases the risk of bacterial infections. Neutrophils exhibit impaired chemotaxis, oxidative metabolism, phagocytic activity, degranulation, intracellular killing, and dysregulated programmed cell death. Factors contributing to neutrophil dysfunction include malnutrition, trace element deficiencies, iron overload, impaired glucose metabolism, hyperparathyroidism, dialysis, and uremic retention solutes. These immunologic abnormalities are complicated by the use of immunosuppressive drugs to treat and control
underlying diseases and exacerbated by nutritional deficiencies, the dialysis procedure, and the disruption of cutaneous and mucosal barriers to infection. Epidemiological studies suggest that ESRD patients have a higher risk of contracting bacterial infections and that the 3 most commonly seen infectious complications are urinary tract infections (UTI), pneumonia, and sepsis.

This article sets out to review literature related to CKD and the incidence of these complications in pre- and postintervention populations. Within the CKD population, we discuss patients who reach ESRD and receive hemodialysis, peritoneal dialysis or kidney transplantation. Patients in each of these groups are susceptible to similar infections; however, the different modalities lead to complications that vary in magnitude. The infectious complications in the non-ESRD population will also be discussed and compared with the event rates for dialysis patients and the non-CKD population.

**Infectious Complications**

The incidence of the commonly seen infectious complications is approximately 3 times greater among CKD patients who have not yet initiated dialysis than in the general population, with UTI, pneumonia, and sepsis in descending order of prevalence. Notably, raw death rates after infection follow a different pattern in the CKD and non-CKD patient groups, with sepsis, pneumonia, and UTI in descending order of prevalence for both (Fig 2). The higher UTI susceptibility in the CKD group may be explained, in part, by a greater incidence of urinary obstructions, which in turn leads to infections, commonly seen in those with benign prostatic hypertrophy, kidney stones, and urinary tract cancers. Patients with ESRD treated by dialysis have higher annual mortality rates caused by sepsis com-
pared with the general population, even after stratification for age, race, and diabetes.

Overall, the annual percentage of mortality secondary to sepsis is approximately 100- to 300-fold higher in dialysis patients. The urinary tract, which may not be recognized as an important source of infection among dialysis patients because of their minimal urine output, is responsible for the highest rates of hospitalization followed by pulmonary infections (Fig 3). Other potential sources of infection include the skin, the dialysis water treatment system, and dialyzer reuse, which can cause septicemia in a small minority of patients.

Hemodialysis patients, during the normal course of treatment, are exposed to several infectious risks, and the majority of patients require at least 1 hospitalization every year for treatment of infections. The type of vascular access in use plays an important role in the subsequent development of bloodstream infections. Central venous catheters significantly increase the risk of bacteremia in hemodialysis patients; those with temporary catheters have been shown to have a 50% higher risk of septicemia than patients with a native fistula. Maximizing the use of arteriovenous fistula as hemodialysis access is likely to lower infection risk.

Old, nonfunctional, clotted prosthetic arteriovenous grafts have recently been recognized as a frequent cause of bacteremia and morbidity among hemodialysis patients. Infected grafts should be surgically excised without delay and systemic antibiotics delivered. At present, there are no prospective data to address the question of routine excision of old grafts; a high-risk population should be identified and actively managed.

Chronic hemodialysis has been recognized as a risk factor for the development of infective endocarditis (IE) since the early 1960s, and mortality rates for IE in the hemodialysis population are high. The study by Strom et al put the relative risk of IE in dialysis patients compared with the general population at 16.9. Prevention and early detection of this complication are imperative.

Compared with hemodialysis patients, in whom the predominant morbidity is from cardiovascular complications, peritoneal dialysis patients are more often hospitalized for infections, with peritonitis secondary to catheter tunnel infections as the most common cause of morbidity. Peritonitis usually results from decreased host phagocytic efficiency with depressed phagocytosis and bactericidal capacity of peritoneal macrophages. During episodes of peritonitis, fluid movement is reversed, away from the lymphatics and peritoneal membrane and toward the cavity. As a result, bloodstream infections are rare, yet there is no mistaking the impact of these infections on peritoneal membrane function with the loss of ultrafiltration capacity and subsequent difficulties in fluid removal.

Most peritonitis episodes are caused by gram-positive bacteria. Staphylococcus aureus or epidermitis are common, and often associated with a catheter infection, frequently requiring catheter removal for resolution. S. aureus infections in peritoneal dialysis patients are especially common in nasal carriers, as the bacteria move from the nasal reservoir to the hands and skin and from there to the access site.

Compared with hemodialysis and peritoneal dialysis patients, kidney transplant recipients are at the lowest risk for infection, although United States Renal Data System data indicate that the annual percentage of mortality secondary to sepsis is 20-fold higher in kidney transplant recipients than in the general population.

Factors contributing to a higher incidence of infection among transplant patients include extremes of age, low body mass index, and the presence of diabetes. Interestingly, the infection
rate is also higher for recipients of deceased-donor organs than for recipients of live-donor organs. Over the last 10 years, the risk of infection status posttransplant has remained lower than in the population on dialysis (Fig 4), most likely because of better transplant techniques and improved immunosuppression.

Infections in CKD Patients

Although studies have addressed host defense abnormalities in the CKD population, the magnitude of the morbidity has received less attention than in the ESRD population. Figure 5 shows infectious hospitalization rates for pneumonia, bacteremia/sepsis, and UTI in the non-CKD, CKD, and dialysis populations. Compared with the non-CKD population, the rates of pneumonia are 3 times greater in the CKD population and 5 times greater in the dialysis population. Of particular interest, the length of hospital stays for pneumonia in the CKD and dialysis populations are very similar and 4 to 6 times longer than those in the non-CKD population (Fig 5). In fact, pneumonia as a complication in the CKD population appears to be more severe than previously appreciated.

Bacteremia/sepsis patterns are also quite different when comparing the non-CKD, CKD, and dialysis populations. Admission rates for this infectious event are 4 times greater in the CKD population than in the non-CKD population but almost 10 times greater in the dialysis population than in the non-CKD population. These complication rates highlight the extraordinary risk of infections that CKD patients, especially dialysis patients, face, placing them in an environment of repeated inflammatory stimulation.
Preventive Approaches to Major Infections in the CKD Population

The problem of infections in CKD patients may need greater attention, particularly related to vaccinations. Because a randomized trial of influenza or pneumococcal vaccination is unlikely to occur and the complication rates from these vaccines is very low, addressing this major risk with more intensive effort seems reasonable. Currently, only 56% of dialysis and transplant patients receive influenza vaccinations each year despite the Centers for Disease Control and Prevention (CDC) Healthy People 2010 target objective of 90%.

Equally surprising are the low rates of influenza vaccinations in those less than 65 years old. In light of a recent study by Gilbertson et al21 showing significantly lower risk of infectious hospitalizations and infectious death in patients who receive influenza vaccinations, perhaps performance measures for providers should be implemented to address this gap in a potentially effective treatment.

Rates of pneumococcal vaccination are also surprising low, at only 13.5% per year.17 Tracking these vaccinations is very difficult because no integrated set of information is transmitted to dialysis units from hospitals, nursing homes, or skilled nursing facilities, or from primary care physician offices. Pneumococcal vaccinations may be more important than previously considered. Recent reports indicate reduced rates of severe pneumococcal infections in the general population during a period of increased vaccinations of children with new pneumococcal vaccine, a so-called herd immunity.22 Repeated pneumococcal vaccination may be nonproblematic; the CDC has not reported adverse effects of vaccinations given within 2 years, although the package insert labeling recommends revaccination every 5 years.23 There is little doubt that the CKD and ESRD populations are at substantial risk for pneumonia, yet it appears little is being done to prevent this major source of morbidity and mortality with known vaccinations.

Acute hepatitis B virus (HBV) infection in uremic patients on dialysis is generally mild or asymptomatic, but these patients have a higher incidence of chronic HBV infection compared with immunocompetent persons.24,25 Infection control measures and the use of hepatitis B vaccine have significantly reduced the annual incidence of HBV infection among patients on dialysis, from 3.0% to 0.05% between 1976 and 1997.26

Preventive strategies to reduce the future incidence of IE in long-term dialysis patients should be used and include scrupulous attention to asepsis in line insertion and toileting, antibiotic locks in dialysis catheters,27 vaccination against staphylococci (though uremic patients characteristically respond poorly to this immunization),28 and consideration of using antibiotic-impregnated dual-lumen tunneled catheters when available.29

The incidence of diabetes mellitus as a cause of ESRD has increased, as have related complications. Preventive techniques that may be used by dialysis centers include foot assessments, laboratory testing and maintenance of strict glycemic control, diabetes self-management education, nutritional counseling, and annual eye examinations.

Conclusion

Despite improvements in infection-control practices and dialysis techniques, bacterial and viral infections are a major cause of morbidity and mortality among patients on long-term hemodialysis or peritoneal dialysis; many of these deaths may be vaccine preventable.6,30 The Advisory Committee on Immunization Practices currently recommends a single 0.5 mL dose of the 23-valent pneumococcal polysaccharide vaccine administered intramuscularly or subcutaneously to all dialysis patients 2 years of age or older,22,31 and the influenza vaccine administered annually, before the beginning of the influenza season, for all dialysis patients 6 months of age or older. Topical mupirocin and S. aureus conjugate vaccine use have shown promise as alternative prevention methods in those patients for whom catheter use is unavoidable.32 The need for preventive measures to reduce pneumonia seems obvious, and they can be implemented in the dialysis units.

Patients, families, and caregivers should be educated on infectious risks through raised general public awareness and awareness
within the CKD community. More meticulous patient management by medical professionals and increased attention to infections and their prevention may reduce at least 1 source of inflammatory stimulation in the CKD population, which may affect CVD and high mortality rates.

References